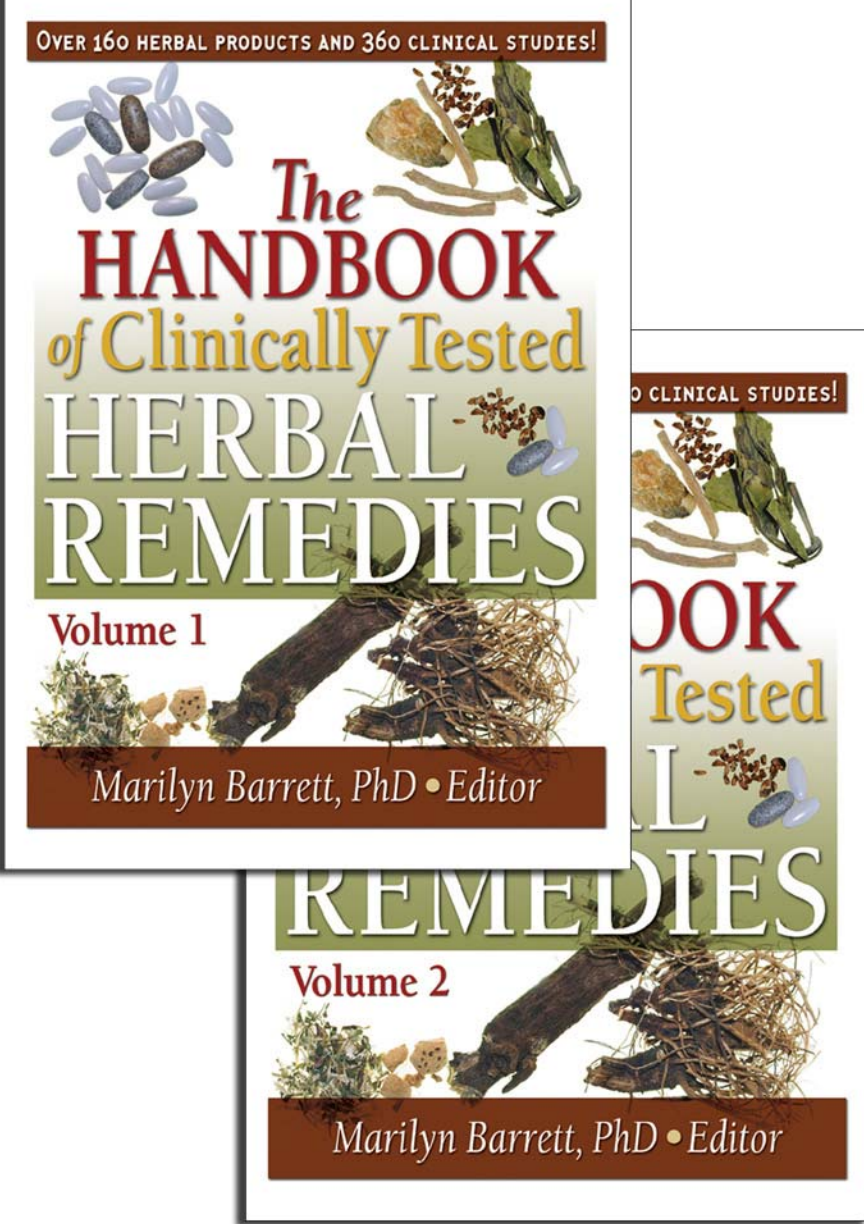
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The Handbook of Clinically Tested Herbal Remedies
Volume 1

Pre-publication REVIEWS, COMMENTARIES, EVALUATIONS . . .

"*The Handbook of Clinically Tested Herbal Remedies* is an important addition to the modern clinical literature on herbs."

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REVIEWS, COMMENTARIES, EVALUATIONS . . .

"This book includes profiles on thirty-two individual herbal medicines and ten combination formulas. These profiles include descriptions of most of the major published clinical studies, which have been analyzed by a panel of authoritative reviewers. It is obvious that great care was taken to ensure completeness and accuracy of information, and the reviewers' comments regarding study quality are especially informative and helpful.

Clinicians searching for detailed and accurate information on herbal clinical trials will find much in this text that is useful. It is a significant achievement in the field of evidence-based analyses of herbal medicine. It should be of most help to clinicians or researchers who want specific details on herbal clinical studies that are not readily available, or who are interested in clinical-trial-quality assessments by authoritative reviewers."

Michael Rotblatt, MD, PharmD
Associate Clinical Professor of Medicine, UCLA; Co-author,
Evidence-Based Herbal Medicine

"The purpose of this book is to provide both consumers and health care providers with concise, evidence-based information on the most widely used herbs and herbal formulas tested in clinical trials. The focus is on what preparations have been studied in clinical trials and how good the evidence is as assessed by preset criteria applied by botanical experts.

The book is broken down into three parts. The first section is very informative and sets the stage nicely for a discussion of individual herbs. The second part describes the process of evidence gathering, sorting, grading, and peer review. Those readers familiar with the Natural Standard database of natural products will recognize the editor's use of 'levels of evidence' criteria as a useful tool to distill the information available from clinical trials. In the third part, the authors provide monographs on the various herbals listed alphabetically. These are concise and cover basic questions of whether the trial was randomized and whether the methods were clearly described. One unique feature is a detailed description of specific products used in clinical trials. These are very helpful to both clinicians interested in recommending specific products and to patients interested in finding these same products at their local health food stores.

This book provides valuable information to providers and patients looking to sort out which commonly used herbs are evidence-based and particularly which specific products they should be looking for."

Philippe O. Szapary, MD
Assistant Professor of Medicine,
Division of General Internal Medicine,
University of Pennsylvania School
of Medicine

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The Handbook of Clinically Tested Herbal Remedies

Volume 1

Haworth Series in Evidence-Based Phytotherapy
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The Handbook of Clinically Tested Herbal Remedies

Volume 1

Part I: Fundamentals of Herbal Medicine
Part II: Methods
Part III: Botanical Profiles—
Product and Clinical Trial Information
(Artichoke–Ginseng)

Marilyn Barrett, PhD
Editor

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To Dr. Varro (Tip) Tyler, who believed in my abilities and sold the idea of this book to the publisher of The Haworth Press

To my parents, Geoffrey and Elizabeth Barrett, whose faith and confidence in me has enabled me to embark on this book, and many other adventures

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PART III: BOTANICAL PROFILES— PRODUCT AND CLINICAL TRIAL INFORMATION (Grape Seed–Valerian and Herbal Formulas)

ABOUT THE EDITOR

Marilyn Barrett, PhD, is founder and principal of Pharmacognosy Consulting, whose mission is to provide a scientific foundation for botanical medicine. She was awarded a PhD in pharmacognosy from the School of Pharmacy, University of London, UK, in 1985 and a BA in botany from the University of California, Berkeley, CA, in 1977.

Since 1994, Dr. Barrett has provided scientific information and technical expertise to manufacturers, associations, and government concerning medicinal plant products through her consulting business. She is a member of the United States Pharmacopeia Committee of Experts for Dietary Supplements Information, an external advisory board member for the University of California at Los Angeles Center for Dietary Supplements (an NIH-funded center) and a consultant to the Office of Dietary Supplements in preparation of their botanical fact sheets. Dr. Barrett served on a working group for the Institute of Medicine of the National Academy of Sciences Committee developing a Framework for Evaluating the Safety of Dietary Supplements. She is a member of the American Botanical Council Advisory Board, the American Herbal Pharmacopoeia and Therapeutic Compendium Technical Advisory Board, and the American Herbal Products Association's Scientific Advisory Board.

Dr. Barrett has published over 30 publications in peer-reviewed journals and a booklet titled *Reference on Evaluating Botanicals* for the Council for Responsible Nutrition, in 1998. More information is available on her Web site at <www.pharmacognosy.com>.

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Tieraona Low Dog, MD, currently serves as chair of the U.S. Pharmacopeia Dietary Supplements/Botanicals Expert Panel and was a member of the White House Commission on Complementary and Alternative Medicine. A former president of the American Herbalists Guild, she has researched, practiced, and taught about herbs for more than twenty years. Dr. Low Dog is in private practice and serves on the executive advisory board for the National Institutes of Health National Center for Complementary and Alternative Medicine (NCCAM).

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Varro E. Tyler, PhD, was Editor in Chief of The Haworth Herbal Press and Distinguished Professor Emeritus of Pharmacognosy in the School of Pharmacy and Pharmacal Sciences at Purdue University before his recent passing in 2001. A recognized authority on plant drugs (herbs) and their uses, he was a co-author of *Pharmacognosy and Pharmacobiotechnology,* the standard U.S. textbook in the field. Dr. Tyler authored over 300 scientific and educational publications, including more than two dozen books. He served as Purdue University's Executive Vice President for Academic Affairs for five years, and for 20 years as dean of its School of Pharmacy and Pharmacal Sciences.

Roy Upton, RH, is the executive director and editor of the American Herbal Pharmacopoeia, an organization dedicated to the development of quality control standards for botanical medicines. Mr. Upton is also vice president of the American Herbalists Guild, serves on the board of directors of the Botanical Medicine Academy, is general manager of the herbal company Planetary Formulas, and is a member of the Standards Committee of the American Herbal Products Association. Mr. Upton has also authored several books, including *St. John's Wort* and *Echinacea,* in the Good Herb series of Keats Publishing and the *Botanical Safety Handbook* published by CRC Press.

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Richard Aranda, MD, obtained his degree from Stanford University School of Medicine and is board certified in internal medicine and gastroenterology. He also obtained advanced training in immunology at UCLA where he was on the faculty in the Division of Digestive Diseases. Currently, he holds the position of Associate Director, Clinical Design and Evaluation, Immunology, Bristol-Myers Squibb Co., Princeton, New Jersey. Dr. Aranda reviewed trials on dragon's blood, ginger, milk thistle, and the formulas Gastrim and Iberogast in conjunction with Dr. Ali.

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Hannah L. Kim, MD, is board certified in both child/adolescent psychiatry and adult psychiatry and is in private practice in Honolulu.

She is also clinical assistant professor at the Department of Psychiatry, John A. Burns School of Medicine, University of Hawaii. She and colleagues previously published a review of St. John's wort clinical studies. For this book, Dr. Kim reviewed trials on St. John's wort in conjunction with Dr. Goebert.

Tieraona Low Dog, MD, currently serves as chair of the U.S. Pharmacopeia Dietary Supplements/Botanicals Expert Panel and was a member of the White House Commission on Complementary and Alternative Medicine. A former president of the American Herbalists Guild, she has researched, practiced, and taught about herbs for more than 20 years. Dr. Low Dog is in private practice and serves on the Executive Advisory Board for the National Institutes of Health National Center for Complementary and Alternative Medicine. Dr. Low Dog reviewed trials on black cohosh, chaste tree, red clover, and the formula Geriforte.

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Barry S. Oken, MD, has been a member of the faculty at Oregon Health and Science University (OHSU) since 1985, where he is currently Professor in the Departments of Neurology and Behavioral Neuroscience and Director of the Oregon Center for Complementary and Alternative Medicine (CAM) in Neurological Disorders (www.ohsu.edu/orccamind) whose mission is to facilitate research and education on the effectiveness and mechanisms of action of CAM therapies in the treatment of neurological disorders. Dr. Oken reviewed trials on kava and valerian in conjunction with Dr. Shinto.

Lynn Shinto, ND, received a degree in naturopathic medicine from Bastyr University, Kenmore, Washington. She is currently a research assistant professor in the Department of Neurology at Oregon Health and Science University and a clinical research professor at the National College of Naturopathic Medicine, Portland, Oregon. Dr. Shinto reviewed trials on kava and valerian in conjunction with Dr. Oken.

Keith Wesnes, PhD, founded Cognitive Drug Research in 1986, which has since grown to be the world's leading provider of automated cognitive function testing facilities for clinical trials. The company was honored to receive the Queen's Award for Enterprise for International Trade in 2002, and the Queen's Award in Innovation in 2003. Professor Wesnes has published over 100 peer-reviewed research articles and chapters and holds several university appointments, including a visiting professorship at the Human Cognitive Neuroscience Unit, University of Northumbria. He is a member of numerous advisory boards and frequently speaks at national and international meetings. Dr. Wesnes reviewed trials on ginkgo and ginseng.

Gloria Y. Yeh, MD, is a faculty member of the Harvard Medical School Division for Research and Education in Complementary and Integrative Medical Therapies. She has a research interest in complementary approaches to diabetes and cardiovascular disease. She received her MD from the University of Maryland School of Medicine and completed a Master's in Public Health at Harvard. She is board-certified in internal medicine and practices at an integrative health clinic in Cambridge, Massachusetts. Dr. Yeh reviewed the American ginseng trials.

Assistants

Eva Boyd, AB, worked with me in the summer of 2000. She searched scientific literature databases for clinical trials, retrieved those studies, and entered the information into the database.

Julie Dennis, BA, worked with me at the beginning of this project, from June 1999 to January 2000. She made the initial contact with U.S. manufacturers and gathered product information from them. She was also instrumental in establishing the electronic database that was used to collect the trial and product information included in this book.

Eva Dusek, BS, worked with me in 2001. She also collected and summarized information from clinical studies and entered it into the database.

Clea Lopez, BA, worked with me during the last year and a half on this project, from January 2002 through June 2003. She conducted scientific literature searches, reviewed and extracted information from clinical trials, and obtained product information from manufacturers. Clea compiled the pharmacopoeial therapeutic information in the summary sections in Part III of the book. She also assisted in editing the chapters in Part I, Part II, and the summary sections in Part III.

Preface

> I believe that if herbal medicine is to play a significant role in future health care, the therapeutic effects of the individual herbs must be carefully evaluated by well-designed, randomized, double-blind, placebo-controlled studies involving a significant number of human subjects.
>
> Varro E. Tyler (1999)
> "Phytomedicines: Back to the Future"
> In *Journal of Natural Products*

Background of the Project

The genesis of the idea for this book came from a conversation with my childhood physician, Larry Posner, MD, at a party in September 1998. He told me of his interest in botanicals due to the number of patients he had taking dietary supplements and of the limited knowledge he had of those products. He knew of my work with medicinal herbs and asked me to speak to him in his language regarding the evidence for these herbs. I inquired what language that might be and he replied, "double-blind, controlled, randomized clinical trials." My response was that quite a few studies have been conducted on herbal remedies, probably more than he realized. Thus, the idea of this book was born.

Purpose and Scope of the Book

This book provides consumers and health professionals with a means to distinguish those herbal products that have the backing of clinical evidence to substantiate claims of efficacy. It includes product descriptions provided largely from label information. In addition, this book describes in detail the trials associated with those products and provides an assessment of the quality of those trials.

Only products that have undergone controlled clinical trials are included, as this research design is considered the most persuasive and is generally given the most weight by researchers and practitioners. Many herbal preparations commonly sold on the market are not included in this text, as they have not been subjected to controlled clinical trials.

The book lists products, made with 32 herbs and ten formulas, that have been studied in a total of 369 clinical trials. Attempts were made to be systematic and inclusive in gathering products and trials; however, due to the magnitude of the effort and the amount of time required to complete the project, I acknowledge that it is essentially a snapshot—a sampling of the existing products and their clinical trials at the time when we were doing research for the book.

It is my hope that this snapshot will assist in the evaluation of the clinical science behind botanical medicine and will help with the evaluation of the evidence for herbal product efficacy. I also hope that this book will help to bridge the gap between herbal medicine and standard Western therapies by using the language of the latter to describe the former. Ultimately it is my desire that this book will assist in establishing an appropriate place for botanical medicine alongside standard Western therapies in the medicine cabinet.

The chapters in *Part I: Fundamentals of Herbal Medicine* provide background as well as context for the product and trial summaries that follow. These chapters provide information on the regulatory status of botanicals in the United States, the characterization and standardization of products, as well as the means to establish bioavailability, efficacy, and safety. Also included is a discussion on the "borrowing" of science from one product to support claims of efficacy for another. In addition, there is a discourse on the motives for conducting trials in the United States and in Europe, particularly in Germany. Finally, a chapter on pharmacopoeial monographs describes what they are and what information they provide.

Part II: Methods describes the methods used to gather information on products and clinical studies. It includes the criteria for entry into the book and the means used to evaluate the efficacy of the individual trials.

Part III: Botanical Profiles contains information on products and clinical trials. Products are grouped according to the principal botanical ingredient. If the products are multi-ingredient formulas, without

a primary ingredient, then they are listed separately. Each botanical section is headed by a summary review of the products and trials. This summary section contains an at-a-glance table listing the products included in that section, the indications addressed by the clinical studies, and the number and quality of those studies. The summary section also includes information from therapeutic monographs with use information for that herb. The summary section is followed by details on the products, which is in turn followed by a detailed account of the clinical trials for each product.

Indexes allow for easy access to the product and trial information through the botanical common and scientific names, as well as by product and manufacturer names and therapeutic indication.

Acknowledgments

This book was a long time in the making, and like many large projects, it has gone through several stages. Many people have given me advice and/or assistance over that time and to mention all of them would be prohibitive. I will therefore mention a few and hope that those whose names do not appear will forgive me.

When I embarked on this book, I had only a vague sort of notion as to what it would entail. Initial encouragement from Joerg Gruenwald regarding the idea of this book resulted in a joint attempt to contact U.S. manufacturers. We asked manufacturers if they had products whose efficacy was supported by clinical studies. The scant response revealed to us that it would not necessarily be easy to obtain this product information and the project was abandoned.

However, Dr. Varro (Tip) Tyler approached me regarding a contract with The Haworth Herbal Press in June 1999, starting the process anew. With the assistance of Julie Dennis, we expanded our mailing list and contacted approximately 200 manufacturers, initially asking only for a sign of interest. This time, with the publisher's name clearly on the letterhead, we got better results. We set out to collect not only those products which had been tested in clinical studies, but also those which had similar specifications. Julie tirelessly collected information on 300 products, designed and established a database for that information, and entered the information into the database. Her enthusiasm and positive attitude were a boon throughout this stage of the project.

In the meantime, conversations with Loren Israelsen, Ulrich Mathes, and others revealed to me the complexity of evaluating product equivalency and the issues behind "borrowing" the science for one product to support the efficacy of another. I soon realized that I could include only products that had themselves been tested in clinical trials. However, now I was seven months into the project, had spent most of the generous grant from The Haworth Press, and, in some ways, was starting over. I began to concentrate on the clinical trials themselves: retrieving studies from scientific databases and

then specifically contacting manufacturers who made those products. Both Eva Boyd and Eva Dusek helped tremendously with the massive job of identifying and collecting clinical trials as well as entering them into the database.

Conversations with Marie Mulligan, MD, and others helped me with ideas regarding the evaluation of the quality of clinical studies. Paramount in these conversations were those methodological qualities required by the medical community for a trial to be considered credible. Thankfully, Tieraona Low Dog, MD, stepped in and designed the checklist used to evaluate the trials. Her guidance was also instrumental in the overall concept and design of the book.

With the trials gathered and the checklist in place, I began to send those trials out to MDs for review. I am deeply indebted to all those who reviewed trials, for this is not a quick process. Concurrent with the gathering and evaluation of trials was the writing of Part I of the book, encompassing the fundamentals of herbal medicine. I am indebted to the authors of those chapters for their contributions. In addition, I am grateful to Mitch Bakos for his computer advice and assistance with the database. Also, the advice of Cathirose Petrone, who taught me how to juggle many tasks at the same time with a minimum of stress, was a blessing.

Thinking that I had only a few months left before finishing the book, I asked Clea Lopez to assist me. Those several months turned into a year and a half. Clea assisted with just about every aspect of the book during that time. With her help, we again conducted literature searches, looking for trials that had been published since our initial search. Her editing skills were a very pleasant surprise to me, with a wonderful ability to spot where the text needed to be clearer or where I needed to provide additional information. Her excellent editorial advice and attention to detail has made this book a much better one than it would have been without her.

EDITOR'S NOTE

The purpose of this book is informational. It is not intended as a guide to self-medication or as a substitute for the advice of a health practitioner.

The production of this book was partially supported by a grant from The Haworth Press. No monetary assistance was provided by any manufacturer whose product is, or is not, included in the book.

This book is not meant to promote any product(s) in particular. The purpose of the book is to examine the scientific data supporting the efficacy of herbal preparations. As therapeutic equivalence of these products has not been proven, examining the clinical evidence cannot be done without profiling individual products.

Manufacturers who wish to submit their product(s) for inclusion in future editions of this book should contact the editor via e-mail at <marilyn@pharmacognosy.com> or via the Internet at <http://www.pharmacognosy.com>.

PART I: FUNDAMENTALS OF HERBAL MEDICINE

Chapter 1

History and Regulation of Botanicals in the United States

Loren D. Israelsen
Marilyn Barrett

INTRODUCTION

At least four regulatory classifications are now possible for botanicals in the United States: (1) food, (2) dietary supplement, (3) over-the-counter (OTC) drug, and (4) prescription (Rx) drug. However, most botanical products are regulated as dietary supplements according to provisions in the Dietary Supplement Health and Education Act (DSHEA) of 1994. This chapter gives a brief description of how botanicals were historically regulated in the United States, the subsequent genesis of DSHEA, and the means that DSHEA provides to regulate herbs and other botanicals. It also briefly covers the regulations regarding botanicals as drugs, either sold without a doctor's prescription over-the-counter or requiring a doctor's prescription.

HISTORY

Plants have, at one time, supplied virtually all cultures with food, clothing, shelter, and medicines. It is estimated that approximately 10 to 15 percent of the roughly 300,000 species of higher plants have a history of use in traditional medicine. By contrast, only 1 percent of plant species have a history of food use (McChesney, 1995).

One hundred years ago, herbs were well established as medicines in the United States. They were widely listed in the *United States*

Pharmacopeia (USP) and prescribed by physicians. Herbal tinctures, extracts, salves, and so forth, were the materia medica of the day.

Regulation of medicines in this country began when the authority to set and enforce drug safety standards was given to the Food and Drug Administration (FDA) in 1938. The passage of the Food, Drug, and Cosmetic Act gave the FDA the responsibility to prosecute the adulteration or misbranding of foods, drugs, and cosmetics.

Herbal preparations soon gave way to single-entity chemical drugs. World War II created a demand for more powerful drugs of all kinds, particularly antibiotics and trauma treatment agents. The federal government urged drug companies, then largely botanical crude-drug houses, such as Merck, Lily, and Parke-Davis, to invest in new synthetic chemistry-based research. Single-entity chemicals were more consistent, easier to measure, and judged more specific in their therapeutic focus than botanical preparations.

In 1951, Congress passed the Durham-Humphrey Act which defined a prescription drug as any drug that because of its toxicity or other potential for harmful effect or method of use is not safe for use except under the supervision of a practitioner licensed by law to administer such a drug (Young, 1995). Manufacturers at that time had to position their drugs as either Rx or OTC.

In 1962, the Food, Drug, and Cosmetic Act was expanded to require all drugs marketed at that time to be proven *both* safe and effective. The FDA then issued guidelines for safety and efficacy testing requirements for new drugs. As a result, new drugs now required the FDA's approval before marketing. Old drugs were permitted to remain on the market as long as their ingredients and labeling remained unchanged.

In 1972, the FDA began a comprehensive review of all OTC drug products to assess their safety and efficacy. Drug ingredients found to be generally recognized as safe and effective (GRASE) were placed into Category I and approved for marketing. Those determined to be unsafe or ineffective were placed in Category II and banned from use in any OTC drug. If safety and efficacy could not be determined due to a lack of information, then the ingredient went into Category III. With few commercial sponsors to conduct safety and efficacy studies, many botanicals, listed as possible or known ingredients in OTC products, were relegated to Category II status and some were placed in Category III. With few herbs retaining drug status after the OTC re-

view, the botanical industry had no other regulatory option but to offer their products as foods.

In the late 1970s, the FDA began to apply the food additive provisions of the Food, Drug, and Cosmetic Act to botanicals. Under provisions added to the Federal Food, Drug, and Cosmetic Act of 1958, food additives already on the market in 1958 were accepted without FDA review. However, substances added to the food supply after this date were required to gain FDA approval prior to marketing, unless they were considered GRAS (generally recognized as safe). A fair number of herbs were included on a list of GRAS food additives that had been prepared by the Flavor and Extract Manufacturers Association as flavorings for alcoholic beverages. However, the FDA viewed commonly used herbs as unapproved food additives and therefore subject to FDA approval prior to marketing. This interpretation led to a series of bitterly fought court cases and several herbs being taken off the market.

Congress passed the Nutrition Labeling Education Act of 1990 (NLEA) to reform food labeling and to allow, for the first time, a new class of health claims based on disease-nutrient relationships. For the most part, this legislation did not apply to botanicals because of the way it was written and the way it was interpreted by the FDA.

With lawsuits between herbal manufacturers and the FDA commonplace, a group of leading herb companies met with Senator Orrin G. Hatch (R-Utah) and Congressman Bill Richardson (D-New Mexico) who drafted legislation that became the Dietary Supplement Health and Education Act of 1994. This law was passed by Congress and signed into law by President Clinton on October 25, 1994. This was the first time a U.S. law defined the terms *herb* or *botanical*.

DSHEA EXPLAINED

As with most federal laws, the legislative language of DSHEA is arcane, if not mystifying. The core provisions of the act, however, are straightforward and create an expansive framework for all dietary supplements. The following summary of DSHEA is an "herbs-only" interpretation which provides a useful tool for those wishing to see how DSHEA creates a new architecture for the manufacture, sale, and promotion of herbs.

Definition

DSHEA defines the term *dietary supplement* as an herb or other botanical or concentrate, constituent, extract, or combination of any botanical that is intended for ingestion as a tablet, capsule, or liquid, is not represented for use as a conventional food or as a sole item of a meal or the diet, and is labeled as a dietary supplement. This includes new drugs that were marketed as botanicals prior to such approval; it does not include a botanical approved as a new drug, or authorized for investigation as a new drug, and not previously marketed as a dietary supplement. Botanicals are not classified as food additives.

Safety

Dietary supplement products are allowed to contain botanicals that have been present in the food supply and in a form in which the food (botanical) has not been chemically altered. Dietary supplement ingredients marketed in the Unites States before October 15, 1994, are regarded as safe because of their long history of use. Those ingredients not marketed before then are "new" ingredients. At least 75 days before introduction into commerce, manufacturers must provide the FDA with information that shows the new botanical can reasonably be expected to be safe under conditions of use or labeling.

DSHEA states that a botanical is considered unsafe under one of two conditions: (1) it presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or (2) it is a new botanical for which inadequate information exists to provide reasonable assurance that it does not present a significant or unreasonable risk of illness or injury. In any case, the FDA shall have the burden of proof to show that a botanical is unsafe.

Good Manufacturing Practices

A botanical is also considered unsafe if it is prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations (GMPs). For the moment, the preparation and packaging of dietary supplements is covered by the same GMPs that apply to conventional foods. However, DSHEA authorizes the FDA to establish separate GMPs for dietary supplements, and rule making by the FDA is imminent.

Labeling

The label must identify the product by the term *dietary supplement*. Botanical dietary supplement labels must list the name of each ingredient, the quantity of such ingredients, or, if a proprietary blend, the total quantity of all ingredients. The label must also identify any part of the plant from which the ingredient is derived.

Botanical dietary supplements are misbranded if they are represented as conforming to such official compendium as *USP* and fail to do so, fail to have the identity and strength which they represent to have, or fail to meet the quality, purity, or compositional specifications, based on validated assays or other appropriate methods, which they are represented to meet.

Literature, including an article, a chapter in a book, or an official abstract of a peer-reviewed scientific publication which appears in an article shall not be defined as labeling when used in connection with the sale of botanicals to consumers provided that it is not false or misleading, does not promote a particular manufacturer or brand of botanical, is displayed or presented with other items on the same subject matter so as to present a balanced view of the available scientific information on a botanical, and, if displayed in an establishment, is physically separate from the botanical and does not have appended to it a sticker or other method that associates it with the product.

Claims of Benefit or "Statements of Nutritional Support" Allowed in Labeling

Under DSHEA, a statement for a botanical dietary supplement may be made if the statement describes how a botanical is intended to affect the structure or function of humans, characterizes the documented mechanism by which a botanical acts to maintain such structure or function, or describes general well-being from consumption of a botanical. The statement must contain, prominently displayed and in bold-faced type, the following: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease."

The FDA published a final rule in the Federal Register on February 7, 2000 (docket No. 98N-0044), which describes how the agency will distinguish disease claims from structure/function claims. The rule

permits health maintenance claims ("maintains a healthy circulatory system"), other nondisease claims ("for muscle enhancement," "helps you relax"), and claims for common, minor symptoms associated with life stages ("for common symptoms of PMS," "for hot flashes"). It does not allow for claims regarding diseases ("prevents osteoporosis") or implied disease claims ("prevents bone fragility in postmenopausal women") (FDA, 2000).

As with all food labeling, statements must be truthful and not misleading. Statements of nutritional support may be made without prior FDA review, but the manufacturer must notify the FDA within 30 days of marketing a product with a new claim and must have substantiation for the claim. Criteria for substantiating a claim are not yet defined by the FDA. However, advertising guidelines for benefit statements for dietary supplements have been published by the Federal Trade Commission (1998) and can be found on their Web site (www.ftc.gov).

DSHEA establishes that a botanical is not a drug solely because its label or labeling contains a statement of nutritional support. Also, a botanical shall not be deemed misbranded if its label or labeling contains directions or conditions of use or warnings.

Commission on Dietary Supplement Labels

DSHEA established a presidential commission to study and provide recommendations for the regulation of label claims and statements for botanicals, including the use of literature in connection with the sale of botanicals, and procedures for evaluation of such claims. The seven members of the Commission on Dietary Supplement Labels were appointed by the president to evaluate how best to provide truthful and scientifically valid information about dietary supplements to consumers. The commission's final report, which was submitted to the president and Congress in November 1997, included guidance regarding statements of nutritional support and the substantiation of such claims. The commission recognized that under DSHEA, botanical products should continue to be marketed as dietary supplements, when properly labeled. However, they recommended that a review panel be established to review claims for OTC drug uses (Commission on Dietary Supplement Labels, 1997).

Office of Dietary Supplements

DSHEA also established an Office of Dietary Supplements (ODS) within the National Institutes of Health (NIH). The purposes of the office are to explore the potential ability of botanicals to improve health care and to promote scientific study of the benefits of botanicals in maintaining health and preventing chronic disease.

The director of the ODS is to conduct and coordinate scientific research relating to botanicals that can limit or reduce the risk of diseases such as heart disease, cancer, birth defects, osteoporosis, cataracts, or prostatism, collect results of scientific research related to botanicals and compile a database, and serve as a principal advisor to the NIH, the Centers for Disease Control and Prevention (CDCP), and the commissioner of the FDA on issues relating to botanicals and scientific issues arising in connection with the labeling and composition of botanicals.

Currently the ODS, in collaboration with the National Center for Complementary and Alternative Medicine (NCCAM), sponsors six botanical research centers. The ODS Web site hosts two databases: one containing information regarding federally funded research on dietary supplements (CARDS, "Computer Access to Research on Dietary Supplements") and the other containing scientific literature regarding dietary supplement ingredients (IBIDS, "International Bibliographic Information on Dietary Supplements") (http://dietary-supplements.info.nih.gov). The ODS is also conducting systematic reviews of the literature in order to determine areas needing research and to assist in the development of clinical guidelines. Fact sheets with information on the most commonly used botanicals are in preparation. The ODS, again in conjunction with NCCAM, has sponsored clinical trials on St. John's wort and ginkgo. Several dozen other trials on botanicals are currently listed on the NCCAM Web site (nccam. nih.gov). The ODS is also currently supporting the development of validated analytical methods, standards, and reference materials for the most commonly used botanicals.

DRUGS: OTC AND Rx

Before a botanical product is marketed as a drug with a claim to diagnose, treat, cure, or prevent a disease, it must first be approved by the FDA. The revision of the Food, Drug, and Cosmetic Act in 1962 required all drugs marketed after that time to be proven both safe and effective. This revision presented the FDA with the challenge of updating its approval of hundreds of drugs already on the market that had not been proven effective. The FDA set up panels of experts to review the active ingredients of these drugs, many of which were sold over-the-counter. However, many herbal products were found to be either unsafe, ineffective, or simply lacking sufficient evidence to evaluate (Tyler, 1993).

In order to obtain drug status for a new botanical product, or for one that failed a previous evaluation, manufacturers must submit a New Drug Application (NDA) to the FDA. This requirement holds whether the new drug is to be sold as an OTC or Rx drug. The NDA must contain evidence of the product's safety and efficacy. This evidence is usually in the form of pharmacological studies, ranging in scope from in vitro assays and small animal studies to randomized, double-blinded clinical trials in humans, with an emphasis on the clinical studies. The benefit to pharmaceutical firms which manufacture synthetic chemical drugs is that their research is rewarded by patent protection for a substantial period of time. However, as most herbs have previously been marketed in a traditional form, and thus are not new or unique, they are not eligible for patent protection. There are some exceptions when a botanical is prepared in a unique form (for example, the ginkgo extract EGb 761) or for a previously unknown use. Without patent protection, most manufacturers are unwilling to spend the money necessary to conduct the research required for a new drug application. In addition, manufacturers may find it easier to forego scientific studies as they can easily sell their products as dietary supplements.

The Commission on Dietary Supplement Labels (1997) recommended that the FDA establish a "review panel for OTC claims for botanical products that are proposed by manufacturers for drug uses" (p. 57). However, in April 1998 the FDA published a notice responding to the commission report, indicating that the agency considers

such a review to be "premature" at this time. The FDA did not give an explanation for their decision (FDA Notice, 1998).

Petitions formally requesting that valerian and ginger be recognized as old OTC drug ingredients were filed with the FDA in 1994. Nearly six years later, the agency issued a response provisionally accepting the supporting data, which was largely European, but only under very stringent conditions. Valerian and ginger have yet to become OTC drugs.

Numerous experts agree that a select number of botanicals are proper candidates for OTC drug status. Although this would mean that some plant extracts would be available both as dietary supplements and OTC drugs, it is likely that many American consumers who currently would not use a certain herb as a dietary supplement would accept and use that same herb if it were offered as a drug that has received FDA (government) approval. Likewise, physicians, pharmacists, and other health care providers would be far more inclined to recommend, or at least not discourage, the use of an herbal OTC drug. The reasons being that OTC drugs are manufactured under stricter good manufacturing practices, and OTC products have mandatory labeling which includes dosage recommendations, cautions, and warnings. Although manufacturers of botanical products are welcome to submit their products for review under the new drug approval process, it does not appear that the FDA is prepared to actively welcome OTC applications for botanicals as old drug ingredients. That is, for a botanical to achieve OTC status, it must have all the scientific research required for a new drug. It is unlikely to be "grandfathered in" as an old drug without that documentation.

PROSPECTUS

Canada has created a natural health products category, which is intermediate between the formal OTC drug review process and the less formal dietary supplement regime in the United States. Many in the herbal industry now feel that such a category would be beneficial for the United States as well. However, this would require a new regulatory category to be created.

In the meantime, it is entirely possible for a botanical to be marketed and sold as a food, a dietary supplement, and a drug at the same

time, depending on its label claim. For example, ginger root can be sold as a food ingredient, as a dietary supplement "to maintain a calm stomach," or (if approved by the FDA) as an OTC drug "to prevent and treat nausea or motion sickness."

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Chapter 2

Product Definition Deficiencies in Clinical Studies of Herbal Medicines

Varro E. Tyler

Clinical studies and case reports of herbal medicines have recently begun to appear in major medical journals of the United States. The clinicians responsible for these publications are apparently unaware that no standards of quality exist for herbal products in this and many other countries. Accustomed to working with drugs that must conform to official specifications, these authors often fail to define adequately the botanicals employed, and their failure to do so raises more questions than are answered. The following examples, some of them selected from the special November 11, 1998, alternative medicine issue of the *Journal of the American Medical Association,* will illustrate this problem.

One of the major clinical trials published in that issue was a study conducted in Australia by Bensoussan et al. (1998), involving the treatment of irritable bowel syndrome with a multi-ingredient Chinese herbal formula. None of the 20 botanicals employed was identified by its correct Latin binomial (genus, species; followed by author citation) nor was any assurance provided that the identification given only as a Latin drug title was confirmed in any way (botanical or chemical characterization).

The quantities of the herbs were provided only as a percentage basis (presumably by weight), and the amount administered was stated only as five capsules (size not specified) three times daily. On the basis of the data provided, the study could never be replicated or its pur-

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ported results verified. Further, no follow-up was conducted to determine which of the herbs contributed to the reported positive effects and which were merely adjuvants, correctives, or flavors.

A letter to the editor by Grush et al. (1998) in the same issue warns against the use of St. John's wort during pregnancy as a result of observations on two gravid women. Both of them were said to be consuming 900 mg/day of the herb. Because the dose of St. John's wort ranges from 2 to 4 g, what is probably being referred to here is 900 mg of a St. John's wort concentrated extract standardized to contain 0.3 percent hypericin. There is a considerable difference between this and the crude herb. Further, no botanical or chemical studies verifying that the herbal product labeled St. John's wort was indeed *Hypericum perforatum* L. were apparently conducted.

Garges, Varia, and Doraiswamy (1998) attribute a case of cardiac complications and delirium to the withdrawal of valerian root extract, even though the patient was consuming seven other medications plus minerals and vitamins. Although the designation valerian root is commonly misused to described both the rhizome (underground stem) and roots of the plant, no data were presented to assure readers that the extract was prepared from *Valeriana officinalis* L. as specified. Several species of valerian are commonly employed as central nervous system depressants.

Further, the preparation involved is defined only as an "extract," without specifying the solvents used to prepare it or the degree of concentration. It was apparently consumed in substantial quantities, ranging from 30 mg to 2 g per dose five times daily. The authors conclude that in view of the multiple factors involved (e.g., numerous other drugs, surgery) "we cannot causally link valerian root to his symptoms." This statement contradicts an earlier one, which reported "a case of serious cardiac complications and delirium associated with the withdrawal of valerian roots." It also renders inaccurate the similarly worded title of the publication. In actuality, information provided in the paper is inadequate to allow any firm conclusion as to what herbal product was being consumed.

A letter from Lawson (1998) in the same issue of *JAMA* commented on the negative results achieved with a steam-distilled garlic oil (*Allium sativum* L.) preparation tableted in combination with beta-cyclodextrin. The author pointed out that the prepared garlic oil has little hypocholesterolemic activity in the first place and that only

about 25-40 percent of it was ever released from the binder. Some of the tablets were compressed so compactly that they passed through the intestinal tract of human intact or in large pieces.

Although the authors of the original paper replied that the binding of the oil to the beta-cyclodextrin was intentional, thus providing a slow release of activity, they failed to address the more difficult problem of whether therapeutic levels of allyl sulfides were ever attained (Berthold, Sudhop, and von Bergmann, 1998). In their minds, this was considered unnecessary because "convincing evidence of lipid-lowering effects of any garlic preparation is still lacking." No reference in support of this assertion is provided. The 17 positive of 20 total studies cited by Lawson are dismissed as lacking rigorous design, but the defects are not specified. They do concede that "conclusions of our study apply only to the preparation we used. . . ." Unfortunately, that was not the way it was reported in the popular press, which labeled all garlic preparations ineffective for blood lipid reduction.

Berthold and colleagues (1998) could have precluded much of the concern about their original study simply by including in it a better definition of the product utilized. Characterization of the proven activity (or lack thereof) of allyl sulfides, quantitative figures regarding the slow release of these principles from the beta-cyclodextrin binder with estimates of predictable blood levels, and data on tablet disintegration time under controlled conditions should certainly have been presented. This study is an excellent example of the pronounced effect dosage form design can have on the purported activity of an herbal product.

In the report of their clinical trial on *Garcinia cambogia* Desr. for weight loss, Heymsfield et al. (1998) made more than the usual effort to define the product utilized. However, something went awry. The authors indicate that caplets containing the plant extract (50 percent hydroxycitric acid) plus added hydroxycitric acid were administered in daily doses totaling 3000 mg of extract and 1500 mg of hydroxycitric acid. The problem here is that hydroxycitric acid (HCA) does not exist in that form in nature. Instead, it occurs as a lactone which lacks the ability to inhibit ATP-citrate lyase (Clauatre and Rosenbaum, 1994). That enzyme is responsible for the formation of acetyl-CoA, the metabolite necessary for fatty acid and cholesterol biosynthesis. Lacking this inhibiting activity, the plant extract could not

be expected to have any antiobesity activity and, of course, none was found.

However, the authors state that the extract used was found to contain 50 percent hydroxycitric acid by analysis. This is almost certainly inaccurate because HCA is an unstable hygroscopic compound that reverts to the inactive lactone over time. Probably the HCA was present in the extract as a more stable salt of some type. This raises concerns about the absorbability and ultimate activity of the undefined salt. Presumably the HCA administered with the plant extract was also in the form of a salt rather than the free acid.

Once again, failure to define precisely the nature of the herbal extract utilized has resulted in confusion. Replication of the study on the basis of the published data would be impossible.

Confusion in the medical literature due to inadequate herbal product definition is certainly not confined to one journal, nor is it of recent origin. In 1989, MacGregor et al. published a report in the *British Medical Journal* of four women who suffered hepatotoxic effects after consuming two different proprietary herbal remedies. Both of these remedies presumably contained scullcap (*Scutellaria lateriflora* L.) and valerian *(Valeriana officinalis),* and the authors concluded that the deleterious effects noted probably resulted from the consumption of these two herbs. This assumption was based in part on the reported toxicity of valepotriates in valerian. No analysis of the products was conducted to determine if they actually contained the two herbs in question.

Since that time, it has been determined that the unstable iridoid compounds known as valepotriates are not found in significant amounts in commercial valerian preparations. Further, in Britain the known hepatotoxic herb germander (*Teucrium chamaedrys* L.) is often substituted for scullcap, and this substitution was, in all likelihood, the cause of the observed effects (Tyler, 1993). Once again, failure to characterize an herbal product properly resulted in a false report of potential toxicity of two herbs.

Probably more confusion has been produced in the herbal literature by so-called Siberian ginseng, better designated eleuthero, than any other herb. Eleuthero is not a true ginseng, a designation properly reserved for species of *Panax*. Botanically, it is *Eleutherococcus senticosus* (Rupr. and Maxim.) Maxim., and although it belongs to the same family as ginseng, the *Araliaceae,* its constituents are very

different. Family relationships of botanicals do not necessarily reflect similar constituents or activities. Potatoes (*Solanum tuberosum* L.) and the deadly nightshade (*Atropa belladonna* L.) are both members of the Solanaceae.

Eleuthero is seldom obtainable in this country in the form of pieces sufficiently large to allow identification by means of organoleptic evaluation. Instead, it is usually seen either as a powder, which is more difficult to identify, or as an extract. In China, where much of the herb originates, it is known as *wujia,* a name also applied to entirely different plants, especially Chinese silk vine (*Periploca sepium* Bunge) (Keville, 1992). Eleuthero is utilized in various herbal mixtures touted to enhance athletic performance, so it is also subject to adulteration with stimulants.

In 1990, Koren et al. published a report of a mother whose newborn infant suffered from neonatal androgenization. They attributed the effect to the mother's consumption of "pure ginseng" and discussed the literature on ginseng's (*Panax ginseng* C.A. Mey.) effect on hormones. In fact, the product consumed was labeled Siberian ginseng, but the authors failed to recognize the difference between it and ginseng.

Unfortunately, the product actually consumed was no longer available for analysis, but additional samples of the same lot from the original supplier were subsequently shown to be Chinese silk vine (Awang, 1991). Additional analyses of various specimens revealed one that was actually eleuthero, but it contained caffeine, which is not a normal constituent of that herb (Tyler, 1994). Moreover, none of the natural constituents of either species is known to induce androgenization. The hairy baby case has thus become an infamous example of poor herbal quality. One herb, eleuthero, was mistaken for another, ginseng, but eleuthero was replaced by Chinese silk vine, which in turn was almost certainly adulterated with an androgen. This entire muddle could have been avoided if the dosage form initially utilized had been properly analyzed and defined prior to publication.

Eleuthero substituted with Chinese silk vine has also been implicated in a case involving elevated digoxin levels in a cardiac patient. McRae, the attending physician, reported that eleutherosides in Siberian ginseng may have been converted to digoxin in vivo, thus causing the increased serum levels (McRae, 1996).

No eleutheroside is known to be related chemically to digoxin or to have cardiotonic properties, but Chinese silk vine has related compounds with such properties. Therefore, as Awang has surmised, the apparent rise in serum digoxin levels was probably due to the substitution of *P. sepium* for *E. senticosus* (Awang, 1996). The erroneous attribution of digitalis-like effects to constituents of eleuthero could have been avoided if the dosage form utilized had been tested for the presence of eleutherosides, thus assuring its identity before publication.

A particularly egregious case of inadequate product definition appeared in a 1998 article by DiPaola et al. in the *New England Journal of Medicine*. An eight-herb formula designated PC-SPES, promoted for the treatment of prostate cancer, was defined as consisting in part of five plants designated by common names only. These included chrysanthemum, licorice, scutellaria (scullcap), isitis, and saw palmetto. Of these, the first three may be obtained from at least two different species, so the composition of the formula is unclear. The remaining three botanicals in the formula were designated by Latin binomials but without author citations.

The formula was said to have been purchased from a commercial source in four different batches, each of which was analyzed. Exactly what the products were analyzed for, how they were analyzed, and the results of the analyses are not stated in the paper. The concentration of each of the eight herbs in the total formula is likewise not mentioned. Stock solutions of the formula and other herbs studied were prepared by exposing them to alcohol for 24 hours. Nowhere is the method of "exposure" explained.

Rather than continuing to describe examples of inadequate herbal product characterization in the medical literature, it seems more profitable to review exactly what is necessary to provide adequate herbal product definition. First of all, the botanical should be identified by its Latin binomial, followed on the first citation by the name of the author who assigned that designation. This latter specification, often overlooked by those unfamiliar with botanical nomenclature, is nevertheless important because it increases the clarity and accuracy of the designation (Laurence, 1995).

Plants often have more than one scientific name, each assigned by a different author. The long-used medicinal herb chamomile has at least 12 scientific names, each more or less accurate depending on

one's interpretation of its characteristics. *Matricaria recutita* L. (the L. is an abbreviation of Linnaeus) is now considered the most appropriate binomial, but other authors have assigned it to different genera and utilized different specific epithets. The genera include *Chamomilla, Chrysanthemum, Leucanthemum,* and *Athemis,* in addition to *Matricaria* (List and Hörhammer, 1976). Unless the author's name is cited, it is impossible for a reader to know that *Matricaria recutita* L. and *Chamomilla vulgaris* K. Koch, for example, refer to the same plant, specifically, chamomile. Chamomile, which is also commonly referred to as German chamomile, Hungarian chamomile, or genuine chamomile, is distinct from Roman or English chamomile, an altogether different plant. Common names also cause serious problems because the same one may be applied to several different plants.

Correctly written, a Latin binomial includes a genus name that is capitalized and a species epithet in lower case; both words are italicized. Such scientific names should not be confused with the seldom-used (in the United States) Latin drug names, which in the case of chamomile is Matricariae flos (Matricaria flowers).

Following the proper name of the herb, the part used should be specified (root, rhizome, bark, leaves, flowers, seeds, etc.) and the method of identification (botanical, chemical) specified. Next, a profile or fingerprint of the principal constituents, particularly if an extract is employed, obtained by HPLC, CG-MS, or some appropriate analytical methodology, should be reported. If the product tested is a mixture of herbs, the above information should be specified for each.

The appropriate data concerning the identity of the herbs and their composition are available from any quality producer of botanical products. It is essential, however, that they be reported in a clinical study on a particular dosage form because they vary greatly from product to product. Further, the composition of a particular product may change from time to time without notice.

Herbal mixtures, particularly the complex formulas utilized in Asiatic traditional medical systems, require special consideration. Clinicians need to remember that determination of the activity of the entire formula is not an end point but simply the beginning of the study. The Old Woman of Shropshire's dropsy formula is a good example. The astute physician William Withering was able to narrow down her secret remedy of some 20 plants to a single effective herb, foxglove (digitalis) (Mann, 1992). In almost all such cases, the significant ac-

tivity of such remedies can ultimately be attributed to a single herb and the remaining botanicals, whether called adjuvants, correctives, or flavors, are found to be more or less window dressing. Clinical studies of complex mixtures must eventually determine what is active and what is not, in order to be truly useful.

Finally, the composition of the dosage form and the method of administration must be specified. Diluents used in capsules and tablets may have a decided influence on the availability of the active constituents. Likewise, appropriate data concerning such important factors as the dissolution time of compressed tablets, the properties of tablet or capsule coatings, and the like need to be specified.

Inclusion of the above information may at first seem superfluous to clinicians accustomed to working with drugs for which standards covering such matters are in place. However, no such standards exist for herbal products, and it is necessary to include sufficient information to allow the study to be reproduced. Many of the problem studies reviewed in the initial section of this paper could never be replicated because the necessary data are not provided in the original publication.

Authors and editors also have the responsibility to assure that titles of papers accurately describe the specific nature of the study and the conclusions reached. A paper dealing with the activity or inactivity of a particular herbal dosage form should not be titled so broadly as to allow the inference, especially by the popular media, that all dosage forms of that herb have the same properties.

While applicable to all clinical trials, this caveat is most important for herbal studies, which in the past have often utilized ill-defined dosage forms, and the results of which are of extreme interest to the popular press. Just because a particular dosage form of garlic oil did not show antihypercholesterolemic activity does not in any way invalidate the utility of other garlic preparations. Similarly, data indicating that a specific preparation of echinacea did not prevent colds following prophylactic administration does not necessarily invalidate the results of studies indicating that some echinacea preparations ameliorated the symptoms of colds following remedial use.

Most clinical studies involve participation of a relatively large number of investigators with different areas of expertise. It seems obvious that any future studies will find it necessary to involve individuals with experience in the broad field of phytotherapy ranging from

botanical nomenclature to analytics to dosage form design, if the investigation is to be conducted in such a way as to produce meaningful, reproducible results. Editors of clinically oriented journals have an important responsibility to utilize referees capable of judging whether herbal dosage forms have been adequately defined in submitted manuscripts.

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Chapter 3

Identifying and Characterizing Botanical Products

Marilyn Barrett

When referring to a botanical product in a scientific report, details such as the scientific name of the plant, plant part, preparation, formulation, and dose must be included as the basis of any discussion of therapeutics. Without a full description of the test material, there can be no assurance of a reproducible effect.

In Chapter 2, Dr. Varro Tyler addresses the lack of proper characterization of botanical materials in clinical study publications. The omissions he describes are still more common than not, even in the most prestigious medical journals. The need for guidelines in the characterization of botanicals has been acknowledged by the National Center for Complementary and Alternative Medicine of the U.S. National Institutes of Health (NCCAM). NCCAM recently added a description of characterization parameters expected of botanical products to the grant application guidelines on their Web site (http://nccam.nih.gov).

An unfortunate recent example of an inadequately described product was a report of a trial studying the effectiveness of echinacea for the prevention of experimental rhinovirus colds. The authors acknowledge in their report that three species of echinacea are used medicinally and that different echinacea preparations differ in their chemical composition. They therefore present chemical analysis of the test sample as 0.16 percent cichoric acid with almost no echinacoside or alkamides (Turner, Riker, and Gangemi, 2000). However, the paper does not state whether the echinacea preparation was powdered plant material or an extract. Further, we are not told the species or the plant part (the flowering tops and/or roots of echinacea are both

commonly used). When I contacted the lead author, Dr. Turner, it was apparent that he was not informed of the taxonomic identity of the material that he tested, although he did tell me it was powdered plant material. Further inquiries by Dr. Tyler of the supplier led to the information that the material was 85 percent *Echinacea purpurea* root and herb with 15 percent *E. angustifolia* root extract powder. However, Dr. Tyler and I were still puzzled, as the results of the chemical analysis did not fit the suggested identification. The combination of *E. purpurea* root and herb with *E. angustifolia* root would be expected to contain both alkamides and echinacoside, as alkamides are present in both species and echinacoside is present in *E. angustifolia* roots.

Lack of adequate identification can lead not only to scientific confusion, but also to substitutions that can have toxic consequences. In one incident the similar-looking leaves of a species of digitalis (*Digitalis lanata* Ehrhart) were accidentally substituted for plantain (*Plantago lanceolata* L.), thereby causing heart arrhythmia (Slifman et al., 1998). In several other incidents confusion over traditional Chinese names led to the substitution of guang fang-ji root, also known as fang-chi (*Aristolochia fangchi* Y.C. Wu ex L.D.), for han fang-ji (*Stephania tetrandra* S. Moore) root. Unfortunately, the use of the *Aristolochia* species caused liver failure and death in several individuals (Vanhaelen et al., 1994).

In the hope that this sort of confusion may be prevented in the future, this chapter describes the means for assuring the identity of plant material, common forms of botanical preparations, and the influence of the dosage form on the dose and bioavailability of the product.

IDENTIFYING PLANTS BY NAME

Purple coneflower, black samson, red sunflower, comb flower, cock-up-hat, Indian head, and Missouri snakeroot are all common names for the same plant as defined by its Latin binomial, *Echinacea purpurea* (L.) Moench (Hobbs, 1994). Another plant, also known locally in the U.S. Midwest as snakeroot, has a completely different Latin name: *Parthenium integrifolium* L. Confusion over the similar common names is thought to be the cause of exportation of *Parthenium* root as *Echinacea purpurea* root to Europe. The substitution of *Parthenium* for *Echinacea* has raised doubt over which plant material

was used in clinical trials conducted in Germany before 1986 (Awang and Kindack, 1991).

Common names are not definitive, as demonstrated in the previous example. Different plants may have the same common name, or the same plant may have different common names. Common names are given in the local language and often vary depending upon the region. In contrast, the scientific name, or Latin binomial, is a definitive name, and if used properly should eliminate confusion. The name is composed of the taxonomic categories of genus and species followed by the name of the scientific authority, or authorities, who officially described the plant. Thus in the binomial for garlic, *Allium sativum* L., the "L." at the end is an abbreviation for Linnaeus, the famous botanist of the 1700s.

Scientific names are based on guidelines laid down by the International Code of Botanical Nomenclature (ICBN). These rules were originally established in 1930 and are periodically revised (Greuter et al., 2000). According to the ICBN, the Latin binomial is accompanied by a published description and a "type" specimen upon which that description is based.

Although Latin names are definitive, they can be revised. All taxonomic revisions are conducted according to a detailed set of guidelines established by the ICBN. An old name can be replaced by a new one, or the definition of a name can be altered. When the definition is altered, but the name remains the same, both authorities are listed after the binomial, with the previous authority listed in parentheses. As an example, we have the name for milk thistle, *Silybum marianum* (L.) Gaertn.

Latin names are commonly listed with the taxonomic family to which they belong. Milk thistle is in the sunflower family, or Asteraceae. Thus, the complete name for milk thistle is *Silybum marianum* (L.) Gaertn., Asteraceae.

The American Herbal Products Association (AHPA) has attempted to solve the confusion over common names by establishing definitive common names to be used in trade. In a publication titled *Herbs of Commerce,* AHPA has defined common trade names by pairing them with their Latin binomials (McGuffin et al., 2000). The FDA, in its dietary supplement labeling regulations, has recognized the common names listed in *Herbs of Commerce* as official trade names (CFR 21 Part 101.36, 1997).

MEANS OF ASSURING PLANT IDENTITY

The primary way to identify plant material is through physical examination of the features of the entire plant, especially the flowers. Those features are compared to descriptions in plant taxonomy books and/or to specimens whose identity has already been established by a botanist. When a specimen is identified by a botanist, it is said to be authenticated.

Sensory information, referred to as organoleptic features (color, texture, smell, taste), can also yield information on the identity of whole, chopped, or milled plant material. Further information on identity of milled or powdered plant material is provided by microscopic examination that allows for viewing of tissue structures, organization, cell types, and cell contents.

Chemical constituents are also important in identification. Plants contain thousands of chemical components, including basic proteins and sugars necessary for metabolism and structure. They also contain secondary compounds that were originally thought not to be essential to the life of the plant, but have important medicinal qualities for mammals. The best known of these secondary components are the alkaloids, a group which includes nicotine, caffeine, morphine, and cocaine. Other classes of secondary compounds include phenolics, terpenoids, and steroids (Trease and Evans, 1978). Chemical analysis can be useful in identification even when physical examination of plant structures is not possible, such as with fine powders and extracts.

For any material studied scientifically, or sold in retail, a sample should be retained for a period of time. This sample could be examined in the future, should any questions arise regarding identity or quality. In the case of fresh plant material, this can be a voucher specimen that is pressed and dried. If the test material is milled or powdered, or even in final product form, a retained sample, in that form, may still be used to answer any possible inquiries that might arise regarding identity or quality.

Voucher Specimens

Voucher specimens include the whole plant, or representative parts of the plant (ideally including flowers and seeds), pressed, dried, and fastened to an 11.5" by 16.5" card. Included along with the plant ma-

terial is information as to the location and environment from which the plant was collected. Prepared in this way, the taxonomic identity of the specimen can be determined by a botanist. The specimen also serves as a lasting record.

Millions of plant specimens have been collected and stored in herbaria, to serve as reference collections of the world's flora. Most universities and many private organizations that work with plants house herbaria. The largest herbarium in the United States is the National Herbarium in Washington, DC, which houses 4.5 million specimens and contains collections from the exploration of North America in the 1800s (http://www.nmnh.si.edu/botany/colls.htm). The world's largest herbarium is the Royal Botanical Gardens in Kew, England, with over seven million specimens from all over the world, including 250,000 type specimens (specimens that define taxonomic species) (http://www.rbgkew.org.uk).

Voucher specimens are the most appropriate form of identification for primary suppliers of botanicals, i.e., farms, collectors, and those who have access to the entire plant.

Organoleptic Identification

Sensory, or organoleptic, information is very useful to those experienced with plant materials in establishing identity. Sight, touch, smell, taste, and sound can also assist in assessment of the quality of the material.

Organoleptic features are included in the following characterization of cinnamon bark (*Cinnamomum verum* J. Presl.):

> The matt pieces of bark, 0.2 to 0.7 mm thick, in the form of single or double compounds quills, light brown on the outside and somewhat darker on the inside; the surface longitudinally striated and the fracture is short and splintery. The odor is characteristic and pleasantly aromatic. The taste is pungently spicy, somewhat sweet and mucilaginous and only slightly sharp. (Wichtl, 1994, 148)

Microscopic Identification

Characteristic tissue structures, tissue organization, cell types, and cell contents can be viewed under magnification. For example, the

glandular (rounded, multicellular) hairs common to mint leaves are quite distinct from the stellate (star-shaped) hairs of witch hazel leaves when viewed under a microscope. The addition of chemical reagents to the microscope slide can verify the presence and location, or absence, of starch grains, calcium carbonate, and/or oxalate crystals, as well as lignin (a plant cell wall component). Starch grains will appear purple following the addition of iodine, and their size and pattern are indicative of certain plants. Lignin will appear red with the addition of acidic phloroglucinol solution and is present in the cell walls of woody plants. The appearance of uncharacteristic components is an indication of adulteration or substitution.

Chemical Identification

Simple chemical tests can be performed on milled or powdered plant material by adding a few drops of a particular chemical reagent to the plant material. These tests usually indicate the presence or absence of a characteristic class of chemical constituent, for example, steroids or alkaloids. The presence of alkaloids, for example, can be determined by a purple (reddish-brown) color reaction following addition of Dragendorff's reagent (a solution of potassium bismuth iodide).

Extracts of plant material can be analyzed in more detail for characteristic compounds using spectroscopic analysis and chromatographic techniques. Spectroscopic analyses employ light absorption techniques to analyze classes of compounds. They include ultraviolet (UV), infrared (IR), and Fourier-transfom infrared (FTIR) spectroscopy.

Chromatographic techniques allow for the isolation and quantification of individual compounds. Components of the mixture are separated through chemical affinity to either the mobile phase (liquid or gas) or the stationary phase (solid substance such as silica over which the mobile phase runs). These techniques include thin layer chromatography (TLC), high performance thin layer chromatography (HPTLC), gas chromatography (GC), capillary electrophoresis (CE), and high performance liquid chromatography (HPLC).

Plant extracts examined using either spectroscopic or chromatographic techniques will display a characteristic profile, or "fingerprint," which is useful in identification. Even without chemical identifi-

cation of all the individual components, a particular pattern accompanied with the identification of a few components can be an assurance of identity.

Chemical analysis is often offered as proof of identity of plant material, but it is not necessarily enough by itself. To prove this point, Dr. Alvin B. Segelman (1995) demonstrated that belladonna alkaloids added to sterilized cow dung could pass the *U.S. Pharmacopeia* chemical identification test. However, when the material was examined microscopically it was clear that it was neither belladonna leaves nor roots. Conversely, if plant material has been depleted chemically, through extraction, it may pass microscopic examination due to the remaining cell structure, but not chemical analysis. Therefore, both physical characterization (microscopic examination) and chemical analyses are needed for optimal identification.

When the results of chemical analysis are given as descriptors of a product, some indication of the test method must be provided. For example, extracts of St. John's wort (*Hypericum perforatum* L.) are often described as standardized to 0.3 percent hypericins. Hypericin is one of a group of biologically active dianthrones (phenolic compounds) in the herb that includes hypericin, pseudohypericin, protohypericin, and protopseudohypericin. The dianthrones in the extract can be measured using either UV spectroscopy or HPLC. UV spectroscopy will provide information as to absorption of light by compounds at a specific wavelength. Thus UV spectroscopy will indicate the total quantity of the dianthrones in the extract (as well as other compounds that absorb light at the tested frequency), and the results can be described as total hypericins. In contrast, HPLC analysis allows for the separation and quantification of the individual compounds. HPLC allows the quantities of hypericin, pseudohypericin, and other dianthrones to be determined individually. Therefore, the quantity of total hypericins as determined by UV will be different from the amount of the individual hypericin as quantified by HPLC.

As another example, the *U.S. Pharmacopeia* (2004) method of measuring the alkaloids in belladonna extract via HPLC will give a slightly different number from the European Pharmacopoeial (Ph Eur) method which measures total alkaloid content via titration (Ph Eur, 2002). Thus in describing the amount of any constituent in a botanical, the method of analysis must be indicated.

PREPARATIONS AND FORMULATIONS

Herbs are sold in many forms, as fresh plant material in the produce department of a grocery store, and as dried plant material in bulk, tea bags, capsules, or tablets. Fresh or dried plant material can be prepared as extracts, either sold in liquid form, or dried and formulated into tablets or capsules, both hard and soft. Some basic botanical preparations and formulations are described in the appendix to this chapter.

The diversity in plant preparations is illustrated by those available for commercially supplied Asian ginseng roots, which are graded according to their source, age, part of the root, and method of preparation (Bahrke and Morgan, 1994). The root can be used fresh, or prepared as "white" ginseng (peeled and dried) or "red" ginseng (steamed and dried). The fresh root is often thinly sliced and taken with or without honey, or it can be boiled in soup. White or red ginseng can be powdered, extracted, or made into a tea (Yun and Choi, 1998). The different ginseng root preparations differ in their chemical composition. As an example, we know that the heating process in the production of red ginseng converts the malonylginsenosides to their ginsenoside counterparts and also results in other chemical transformations (Chuang et al., 1995).

DOSE

The preparations described are, by definition, of different strengths and composition. Thus the type of preparation will have an influence on the recommended dose. Teas prepared with hot water are usually quite dilute in contrast with extracts that are more concentrated. So it follows that the type of preparation must be taken into account in determining the dose. For example, peppermint tea may be drunk by the cupful, while peppermint oil is administered in doses of five hundredths of a milliliter (Wren, 1988).

BIOAVAILABILITY

The type of preparation, and formulation of the preparation, will have an influence on the ability of the chemical components of the

herb to be assimilated into the body. This is especially a concern with tablets and capsules whose contents must first dissolve before being absorbed. Coatings on the surface of tablet or capsules may be designed to either accelerate or delay dissolution (release of chemical constituents) in the gastrointestinal tract.

As an example, garlic products often have enteric coatings to delay dissolution until the garlic preparation reaches the intestine. The reason for this is that garlic powder contains the enzyme allinase, which is necessary to produce the active constituent allicin, and that enzyme is destroyed by the acidic pH of the stomach. Studies on the effectiveness of Kwai garlic to reduce elevated serum cholesterol levels have been inconsistent. A review found a highly significant difference in effectiveness between studies conducted before 1993 and those conducted in 1993 and later. The authors found that the amount of allicin released under simulated gastrointestinal conditions correlated well with the success or failure of the tablets to lower serum cholesterol values. The sharp decline in the effectiveness of the tablets is paralleled by sharp declines in both the acid resistance and the allicin release from the tablets, apparently caused by a change in the coating of the tablet (Lawson, Wang, and Papadimitriou, 2001).

GUIDELINES

As demonstrated in this chapter, therapeutic effect is a result of the following variables: botanical identity, chemical profile, formulation, bioavailability, and dose. Therefore, characterization of botanical products, in publications and scientific studies, needs to include all of that information. An adequate description of botanical products is needed in order to ensure a consistent therapeutic effect. It is also needed to be able to compare products and to conduct statistical analyses on the results of multiple trials.

Editors of scientific, particularly medical, literature need to be cognizant of the breadth of information required. The *Journal of Natural Products,* published by the American Chemical Society and the American Society of Pharmacognosy, provides guidance to its authors in the characterization of botanical substances. It requires that experimental biological material be authenticated as to its identity and that the herbarium which holds the voucher specimen be given along with the voucher number. It further requires that the scientific

name (genus, species, authority citation, and family) be given. It also requires authors who purchase dried "herbal remedies" or other materials from companies to deposit a specimen in an herbarium, for future access. It requires that the extraction procedure be specified when studying a commercially available extract and that the identification of the extract be supported by an HPLC trace of known secondary metabolite constituents (*Journal of Natural Products,* 2003).

NCCAM, in its guidelines for clinical trial grant applications, suggests that when plant material is used in a trial, it be accompanied by a botanical description, extraction procedure, the quantity of any known active constituent(s), as well as identity and stability tests. When a product is used, information about the manufacturing process, analysis for impurities, and quality controls for manufacturing must be included. In addition, disintegration/dissolution rates are required to estimate bioavailability (NCCAM, 2003).

APPENDIX: PREPARATIONS AND FORMULATIONS

Preparations

Teas and Decoctions

A tea, or infusion, is made by pouring boiling water over finely chopped plant material (usually leaves and flowers). The mixture is allowed to stand for a period of time before straining. The usual ratio is 500 ml (1 pint) of water to 30 g (1 oz) plant material. A decoction is made by adding cold water to the plant material and then heating it to a boil. The mixture is allowed to simmer before cooling and straining. Decoctions are often made of roots, bark, and berries, which may require more forceful treatment than more fragile plant parts such as leaves and flowers. The same proportions of water to plant material apply, but it is best to start with 800 ml (1½ pints) to allow for evaporation. Teas and decoctions may be consumed either hot or cold.

Plant Juices

Freshly harvested plant parts can be pressed to release their juices. The shelf life of the expressed juice is usually extended by pasteurization or by rapid, ultra-high-temperature treatment. In addition, alcohol may be added as a preservative.

Tinctures

A tincture is made by soaking the plant material in a solution of alcohol and water for a period of time followed by filtering. Tinctures are sold in liquid form and are useful for both concentrating and preserving an herb. They are made in different strengths that are expressed as ratios. Traditionally, a ratio of 1 part herb to 5 or 10 parts liquid (1:5 or 1:10) has been used. These ratios represent 100 g (3½ oz) plant material in 500 ml (1 pint) of solvent, or 100 g plant material in 1000 ml (2 pints) solvent.

Extracts

Extracts are concentrated preparations that can be in liquid, viscous, or powdered form. They are prepared from fresh or dried plant material by distillation, maceration (soaking then filtering), or percolation. The extraction liquid or solvent is chosen for its chemical properties, as it will selectively extract components in the plant that match those chemical properties. Typical solvents include water-alcohol mixtures, glycerin (a colorless, odorless, syrupy, sweet liquid), oils, supercritical gases (carbon dioxide can be liquefied at certain temperatures and pressures), hexane, methylene chloride, acetone, and ethyl acetate. Some or all of the liquid solvent can then be evaporated to make a dry extract, which can be easily placed into capsules or made into tablets. This is often accomplished by evaporating the liquid in the presence of a carrier such as cellulose, lactose, maltodextrose, or even dried plant material.

Again, ratios are used to describe the strength of the extract. Most crude plant materials have a content of roughly 20 percent extractable substances which corresponds to an herb to extract ratio of 5:1. If the extract is further purified, even greater ratios can be obtained. However, this means that some components of the plant have been selected over other components. For example, the standardized ginkgo extracts, which are made in a multistep purification process, are highly purified extracts with an average ratio of 50:1. This ratio means that 50 parts of plant material went into producing one part extract. Essentially the extract is a concentration of certain flavonoids and terpenes present in ginkgo leaves.

Syrups

Medicinal syrups are viscous liquids that contain a minimum of 50 percent sugar, more typically 65 percent, added to a plant extract. This high concentration of sugar acts as a preservative.

Oils

Oils can be produced by pressing or extracting plant materials such as seeds and fruits. Crude oils can be refined by distillation. Alternatively, medicinal oils can contain plant substances dissolved in oil. These oil-based extracts are typically used as salves or in other topical applications.

Formulations

Tablets

Tablets are made by compressing powdered or granulated material. Besides the active ingredients, tablets may contain diluents, binders, lubricants, coloring, and flavoring agents. They also contain disintegrators that help the compressed tablet to dissolve when it comes in contact with water. Tablets can be coated with sugar, dyes, fat, wax, or film-forming polymers. The function of the coating may be to extend the life of the tablet by protecting the active ingredients. It also may be to control or delay the release of the active ingredient. Coated tablets may mask any unpleasant taste of the active ingredient and may make the tablet easier to swallow.

Capsules

Hard gelatin capsules consist of a two-part cylindrical shell. They usually enclose plant material or dried extracts. Soft gelatin capsules are spherical, oval, oblong, or teardrop shaped and consist of a gelatin shell enclosing semisolid or liquid contents. The composition of the capsule can be designed to control the release of the contents. For example, an enteric coating, which resists the acid in the stomach, will dissolve in the intestine when the pH rises above 7.

Lozenges

Lozenges have a tabletlike appearance but differ in that they are not made by compression. They are molded or cut from a gummy mass. Lozenges are designed to release the active ingredient slowly in the mouth while being sucked or chewed. They are often made with sugar, gums, gelatin, and water.

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Chapter 4

Standardization of Botanical Preparations: What It Does and Does Not Tell Us

Uwe Koetter
Marilyn Barrett

INTRODUCTION

Standardization is probably one of the most controversial terms used to describe herbal supplements. Most would agree that the goal of standardizing herbal products is to provide product consistency and thus a reliable health benefit. However, the term has been defined in several different ways. Standardization can mean the establishment of a consistent biological effect, a consistent chemical profile, or simply a quality assurance program for production and manufacturing.

How the process of standardization is applied depends, in part, on whether the active constituents in the botanical are well established. For that reason, the European Union has defined three categories of botanical products: (1) those containing constituents (single compounds or families of compounds) with known and acknowledged therapeutic activity that are deemed solely responsible for the clinical efficacy; (2) those containing chemically defined constituents possessing relevant pharmacological properties which are likely to contribute to the clinical efficacy; and (3) those in which no constituents have been identified as being responsible for the therapeutic activity (Lang and Stumpf, 1999).

This chapter will discuss how the extent of knowledge regarding the active constituents in the botanical relates to standardizing botanical products either to a consistent biological effect, a consistent chemical profile, or as part of a quality assurance program. The most

important point is that there is no one definition of standardization and that this term has been applied differently to different products in the marketplace. In addition, no legal or regulatory definition of standardization for herbal products has been established in the United States.

STANDARDIZATION OF THERAPEUTIC ACTIVITY

The standardization of active ingredients in botanical preparations is a well-established procedure that has been used for over a century. Before sophisticated chemical analytical methods were available, and when the active principles were unknown, preparations were standardized to biological activity. This was accomplished with the help of bioassays: measurements of activity in animals or animal tissues. Bioassays were especially important tools for normalizing the activity of powerful drugs, such as digitalis, in which small variances in the glycoside content could lead to sufficient differences in the cardiac stimulating effect that could be dangerous. Still today, the potency of digitalis preparations is determined using a pigeon assay, which compares the activity of the new preparation to that of a standard preparation (U.S. Pharmacopeia [USP], 2004b).

In those instances in which the chemical constituents deemed responsible for the clinical efficacy (active ingredients or active components) are known and easily measured, chemical analysis can indirectly determine biological activity. With the advent of more sophisticated chemical analytical techniques, it became more efficient to replace bioassays with the measurement of chemical constituents.

Standardization of a botanical product with established active components is achieved by adjusting the preparation to contain a defined level of active substance or group of substances in the dosage form. This can be achieved by adjusting the final amount of raw material (i.e., extract or powdered herb) in the dosage form so as to include a consistent amount of active constituent. It can also be achieved by including a consistent amount of raw material that contains a consistent amount of active ingredient. In the latter case, the consistency of the raw material is achieved by blending different lots of material. As an example, milk thistle preparations contain silymarin, which is accepted as the active component of the botanical. So, the amount of product in the dosage form could be either a fixed amount of sily-

marin in a variable amount of total extract, or a fixed amount of extract that has been adjusted to contain a fixed amount of silymarin.

Guidelines for the standardization of specific botanical preparations can be found in pharmacopoeial monographs. These guidelines include the methods used to determine the levels of active ingredients. As an example, the *United States Pharmacopeia* defines belladonna extract as containing not less than 1.15 g, and not more than 1.35 g, of alkaloids (measured as atropine [*dl*-hyoscyamine] and scopolamine via high performance liquid chromatography [HPLC]) in 100 g extract (USP, 2004a). The *European Pharmacopoeia* defines standardized belladonna leaf dry extract as containing not less than 0.95 percent, and not more than 1.05 percent, total alkaloids calculated as hyoscyamine measured via titration (European Pharmacopoeia [Ph Eur], 2002a).

An important distinction can be made between single chemical compounds that are *active ingredients* and *active components* of a mixture. For example, hyoscyamine as an isolated compound may be an active ingredient in a pharmaceutical formula. However, as a component of belladonna extract, and one of several alkaloids in the extract with activity, it is an active component of the extract.

Standardization to active constituents can ensure consistency between lots produced by the same manufacturer. However, it is just one step toward comparing a proprietary preparation that has been tested in clinical studies with another proprietary preparation of the same botanical. Even if the claimed level of constituents is accurate, the inherent variability in the undefined portion of the extract must be considered. In addition, different formulations or routes of administration may affect the bioavailability (levels of active components present at the site of action in the body).

STANDARDIZATION TO MEET A CHEMICAL NORM

Botanical products can be standardized to a norm that may or may not relate to the expected biological activity of the product. Usually this norm is a level of a constituent chemical or group of chemicals called marker compounds. The concept of determining levels of marker compounds was developed because it is not feasible to test for all compounds in an extract and final formula for content and consis-

tency. *Markers* are chemically defined constituents of an herbal drug, ideally specific to that herb, which are of interest for quality control purposes independent of whether they have any therapeutic activity (European Agency for the Evaluation of Medicinal Products [EMEA], 2000).

By providing product characterization, marker compounds can be used to facilitate botanical identification and detection of adulteration. They can also be used as indicators of consistency throughout manufacturing, handling, and storage. When marker levels are determined in the starting materials they can be used to calculate the quantity of herbal drug or preparation in the finished product. Setting minimum limits for marker compounds can be a useful indicator of quality in preparations in which there is little, or contradictory, knowledge regarding the active constituents.

As there is no established active ingredient in this class of botanicals, the whole preparation is considered to be the active principle. Standardization is achieved by including a consistent amount of raw material (i.e., extract or powdered herb) in the dosage form. Preparations that contain powdered herb are filled with a set amount of powder. The amount of marker compound in the powdered herb can be controlled through blending different lots of powder. Preparations that contain extracts can be made consistent by controlling the ratio of plant material to extract and including either a fixed amount of plant material or a fixed amount of extract.

For consistency, determinations regarding levels of markers in finished products should be made with validated methods for specific formulations. For some botanicals, detailed analytical procedures are provided by pharmacopoeial monographs. However, adherence to pharmacopoeial guidelines may be regional or voluntary, and compliance may not be apparent from product labels.

Analytical methods can be used to measure either classes of compounds or individual constituents. Thus the measurement can be general in nature or highly specific. Ultraviolet/visible light spectroscopy (UV/VIS) results in detection and quantification of a general class of compounds, compared to high performance liquid chromatography (HPLC), which allows for analysis of individual compounds. Thin layer chromatography (TLC) presents a general profile of the plant and can detect whether the product contains a full spectrum extract or a few isolated compounds.

As an example, some echinacea products are standardized to contain 4 percent phenolics. This measurement will mean something quite different if the determination is made using the Folin-Ciocalteu spectrophotometric (UV) method detecting phenolics as a class of compounds, than if it is made using an HPLC method detecting specific phenolics, i.e., cichoric acid, 2-caffeoyl tartaric acid, and echinacoside. In addition, two HPLC analyses can yield different results if different test parameters are used and/or if different phenolic constituents are measured.

In addition, the purity of chemical reference standards, as well as sampling methods, sample preparation, sample matrix (excipients used in formulation of the sample), solvents, and the equipment used, all contribute to the results achieved in chemical analysis.

Thus, it is important to realize that no global consensus has yet been made regarding standards or test methods for herbal products, although attempts are being made in this direction.

STANDARDIZATION AS A REFLECTION OF QUALITY ASSURANCE PROGRAMS

Standardization is also understood to be, and perhaps better described as, a quality assurance program. This type of standardization is the result of following guidelines that cover all aspects of production from seed selection, cultivation, collection, extraction, and formulation to production of the final product. Throughout this process, the measurement of a particular chemical or chemicals can be used to indicate the consistency of one lot throughout production and the consistency of numerous lots to one another.

The quality assurance process starts with the cultivation and/or harvesting of the plant material. The chemical profile of plant material can vary due to genetics, environmental factors, seasonal and/or diurnal variation, the age of the plant, selection of the plant part, the time of harvest, postharvest treatment (drying and storage conditions), and processing.

For example, there are 72 cultivars of the same species of kava growing in Vanuatu (South Pacific) with kavalactone contents ranging from 3 to 20 percent (Dentali, 1997). In another example, St. John's wort growing conditions are important for consistent chemical

profiling. Studies have shown that the phenolic content increases in dry climates and when the ambient temperature is above 57°F (Upton et al., 1997). Harvest time is important for ginseng roots. The content in American ginseng varies from 3 percent in the first year to 8 percent in the fourth year (Court, Reynolds, and Hendel, 1996).

Awareness of the possible variation of a particular botanical can be used to guide the control of each step of the process. Under controlled conditions, a plant variety can be bred for consistency, the growing environment can be carefully selected, and watering and the use or avoidance of pesticides, herbicides, and fertilizers can be directed and monitored. In addition, the plant can be harvested at the optimal time, and processing after harvest can take place in a controlled environment. Careful management of postharvest processing can prevent or control enzymatic processes and preserve the content of volatile oils.

As part of the standardization process, manufacturing protocols must be in place to guarantee consistency in the extraction process. Extraction of plant materials is a process of using a liquid or *solvent* to remove substances from the crude plant material. This is a process many of us use daily to make tea or coffee. As everyone knows from experience, the consistent quality of the raw material accounts only partly for the quality of the end product. Both the water temperature and the amount of water used will also influence the quality of the drink. In addition, there is consideration with coffee as to whether the beans are boiled in water, percolated with boiling water, or steamed under pressure. So, too, with commercial botanical extraction procedures, the quality of the extracts will vary depending upon the conditions of the extraction process, including solvent type, temperature, method of extraction, and the ratio of plant material to solvent.

The ratio of plant material (by weight) to solvent (by volume) is referred to as the *strength* of the extract. This ratio is sometimes listed on the product label as a description of the extract. For example, an extract made with 100 g of plant material in 1000 ml solvent would be described as having a ratio of 1 to 10 and might appear on a label as 1:10. The ratio can also appear as a range. For example, the German Commission E monograph for hawthorn leaf and flower extract allows for the ratio of plant material to extract to be from 4 to 7:1, with a defined flavonoid or procyanidin content calculated according to the *German Pharmacopoeia* (Blumenthal et al., 1998).

GUIDANCE

The lack of uniform understanding of the term *standardization* is reflected in a guidance note drafted by the European Agency for the Evaluation of Medicinal Products. Standardization, as defined in the note for guidance on the quality of herbal medicinal products, means adjusting the herbal drug preparation to a defined content of a constituent or group of substances with known therapeutic activity. However, the group further states that in some member states of the European Union the expression is used to describe all measures which are taken during the manufacturing process and quality control leading to a reproducible effect (EMEA, 2000).

The EMEA makes the distinction between constituents with known therapeutic activity, which can be used to standardize to a biological effect, and marker compounds, which allow standardization on a set amount of the chosen compound. Constituents with known therapeutic activity are defined as chemically defined substances that are generally accepted to contribute substantially to the therapeutic activity of a herbal drug or of a preparation. Examples given of known active constituents include the kava pyrones in kava kava (*Piper methysticum* G. Forst.); silymarin in milk thistle [*Silybum marianum* (L.) Gaertn.]; and aescin in horse chestnut (*Aesculus hippocastanum* L.) (EMEA, 2000).

The EMEA defines marker compounds as chemically defined constituents of a herbal drug which are of interest for control purposes, independent of whether they have any therapeutic activity or not. Examples of markers are the valerenic acids in valerian (*Valeriana officinalis* L.), ginkgolides and flavonoids in ginkgo (*Ginkgo biloba* L.), and flavonoids, hypericin, and hyperforin in St. John's wort (*Hypericum perforatum* L.) (EMEA, 2000).

In Europe, herbal preparations with known actives are standardized in reference to the pharmacopoeial monograph. Where the active compound is not known, the whole preparation is considered to be the active principle. In this case the monograph sets quality guidelines and measurement of marker compounds as a means of quality control.

Both the *European* and *United States Pharmacopoeias* set lower and upper limits for chemical constituents in an extract. As an example, the *European Pharmacopoeia* defines standardized senna leaf

(*Senna alexandrina* Mill.) extract as containing 5.5 to 8.0 percent hydroxyanthracene glycosides, calculated as sennosides (Ph Eur, 2002b). Since the level of active sennosides has been defined, the monograph can reasonably recommend a dose of the whole extract that is expected to produce the declared laxative effect.

In the United States, compliance with pharmacopoeial standards is required for drugs but is optional for dietary supplements.

SITUATION IN THE MARKETPLACE

Assumptions have been made about what the term standardized means when applied to herbal products. It is often incorrectly assumed that botanicals are similar to single-entity drugs, e.g., aspirin, in which one chemical listed on the label is responsible for the activity. This assumption has led consumers, retailers, and even extract manufacturers to presume that controlling the levels of a chemical constituent is equivalent to controlling the physiological effect. Furthermore, when examining the label of a botanical dietary supplement marketed in the United States, it is not possible to distinguish the listing of active constituents of a botanical preparation from marker compounds that may either be inactive or possess pharmacological activity unrelated to the therapeutic application.

Because of the assumed correlation with pharmaceutical agents with identified active ingredients, U.S. manufacturers and consumers often assumed that "more is better." This attitude has prevailed regardless of whether the identified chemical is an active component or a marker compound. On the market, ginseng product labels frequently claim anywhere from 2 to 10 percent ginsenosides. However, no evidence suggests that the effects are increased with higher levels of ginsenosides. In fact, one clinical study suggests that no additional increase in physical work capacity occurs when the ginsenoside content is increased from 4 to 7 percent (Forgo and Kirchdorfer, 1982).

Thus, enrichment of a chemical constituent does not necessarily result in an increase in potency. Even in the case of identified active constituents, other components of the botanical may be present which either increase or complement that action. Or components may decrease or oppose the principal action. The matrix of components in the botanical may also affect the bioavailability of the preparation by enhancing solubility, absorption, and/or stability. These complex in-

teractions are not well understood. Therefore, the entire plant material or herbal preparation should be regarded as the active substance.

Efforts to increase the amount of marker compounds used for standardization are usually driven by market forces and reveal a lack of understanding of the complexity of the issue. The only exception is when this increase is backed by product-specific clinical data and an established link to efficacy or consumer benefit has been identified.

When a preparation differs from the traditional or pharmacopoeial guidelines by enriching the concentration of a select constituent, it must be considered a novel preparation. As a new preparation, appropriate efficacy and safety data need to be collected. The product ought to be tested clinically. Data from established products demonstrating efficacy and tolerability do not necessarily apply to other products. For example, safety and efficacy data collected on kava products containing 30 to 40 percent kavalactones may not apply to products containing twice that percentage, and vice versa.

PERSPECTIVE

Regulatory requirements for the quality of botanical products vary depending on the country and the regulatory category. The same herbal product can be marketed as a drug in Germany and as a dietary supplement in the United States. In Germany, medicinal plant products are produced to quality standards typical for pharmaceutical products. This is especially true for potent herbals in which the active ingredients are defined, contribute substantially to the therapeutic activity, and allow standardization to a biological effect. Specifications for these products include standardization of a constituent, or constituents, within a set range supported by a pharmacopoeial monograph.

If the active components are not established, then markers are used to assure/measure quality. When there is no established link between the marker compound and consumer benefit or efficacy, the herbal drug or the herbal preparation *in its entirety* is regarded as the active substance.

Individual governments, the World Health Organization, and panels of academic experts and clinicians provide guidelines for manufacturing and quality control, as well as therapeutic use (indication, dose, and possible safety concerns). Many of these guidelines are

contained in pharmacopoeial monographs. Compliance with these guidelines is governed by regulations that cover all aspects from manufacturing to labeling and advertising of final products.

In the United States, compliance of dietary supplements to a pharmacopoeial monograph is optional. Therefore, it is difficult for consumers of dietary supplements to make informed decisions about self-medication based upon label information. The level of quality control used by different manufacturers varies widely. Claims of standardization are made without definition of the term, or indication of whether the chemicals used in standardization are responsible for the therapeutic effect. Often no indication is given of which test method was used to determine the marker levels. Without all this information, the consumer commonly makes purchasing decisions based upon price. Thus, regrettably, it appears that price, rather than quality or proven therapeutic effect, drives the market.

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Chapter 5

The Importance and Difficulty in Determining the Bioavailability of Herbal Preparations

Anton Biber
Friedrich Lang

Bioavailability is an important issue to consider in the evaluation of the therapeutic effects of a botanical (herbal) product. The biological effect of any substance is influenced by the extent to which it is absorbed into the body, metabolized (e.g., by gut flora and/or liver enzymes), distributed throughout the body, and finally excreted. A diverse array of factors influence bioavailability, including the route of administration (oral, IV, or topical), the age of the person, his or her particular genetics, other foods or drugs taken at the same time, whether the person smokes, and any relevant disease pathologies. The pharmacological effect of the drug can occur only if the drug, or an active metabolite, reaches and sustains an adequate concentration at the appropriate site of action in the body.

Studies on bioavailability are an integral part in the development of conventional drugs. One of the most basic considerations in determining bioavailability is the formulation of the drug. Formulation in liquid or solid form (pills, capsules, tablets) and with special coatings (e.g., delayed release) will influence the absorption of the product. The ability of solid products to dissolve is studied in disintegration and dissolution tests using solutions that mimic the conditions in the stomach or intestine. A disintegration test measures the extent to which the solid dosage form dissolves. A dissolution test is designed to detect the presence and quantity of the active principal in the dissolved media. Disintegration and dissolution tests for specific products are described in U.S. Pharmacopeia (USP) monographs. Pharmaco-

kinetic studies measure the metabolism, distribution, and excretion of the active substance in the bodies of animals and humans. Disintegration, dissolution, and pharmacokinetic data are required for most pharmaceutical drugs before marketing. These studies are important because the beneficial effects will not occur if doses are too small, and toxic effects can occur if doses are too large or if the drug accumulates in the body.

Data on the bioavailability of herbal medicinal products are not as common as they are for chemically defined synthetic drugs. Although disintegration studies would be fairly easy to carry out, dissolution and pharmacokinetics studies are inherently difficult. The reason for the difficulty is that these assays require the detection and quantification of isolated constituents. It is often difficult to decide which component(s) of a botanical should be used in these assays. Often the constituents responsible for the therapeutic activity are unknown or there is no scientific agreement on the probable active constituent(s). In this case, a surrogate, or marker compound, is chosen as a measuring tool. However, the extent to which the active constituent(s) is known determines the relevance of the bioavailability studies to the therapeutic effect.

Even when the active ingredient is established, it is often present in low concentrations, making quantification in plasma difficult. However, in the past ten years, sophisticated analytical techniques, such as high performance liquid chromatography (HPLC) or gas chromatography (GC) with sensitive detectors, including ultraviolet (UV), fluorescence, electrochemical (ECD), and mass spectrometry (MS), have become available. As a result, more pharmacokinetic data on herbal medicinal products have been published recently (De Smet and Brouwers, 1997). Some examples of studies are listed in Table 5.1.

In most cases in Europe, no pharmacokinetic data are necessary for the approval for marketing an herbal medicinal product as a drug. At present, dissolution tests are required only for standardized extracts in which the constituents solely responsible for the clinical efficacy have been identified. No data are required for nonstandardized extracts or extracts in which no constituent(s) is acknowledged as being solely responsible for the therapeutic effect (European Medicines Evaluation Agency [EMEA], 1999). Recently, however, it has been acknowledged that biopharmaceutic and pharmacokinetic aspects should be involved in the development of all herbal medicinal prod-

TABLE 5.1. Pharmacokinetic data on humans after administration of herbal medicinal products

Extract/product administered	Substance analyzed	Method	Reference
Horse chestnut, *Aesculus hippocastanum* L.	Aescin	Radioimmunoassay	Oschmann et al., 1996
Ginkgo, *Ginkgo biloba* L.	Ginkgolides A, B, bilobalide	GC/MS	Fourtillan et al., 1995
Milk thistle, *Silybum marianum* (L.) Gaertn.	Silibinin	HPLC	Schulz et al., 1995
Myrtle, *Myrtus communis* L.	Cineol	GC	Zimmermann et al., 1995
St. John's wort, *Hypericum perforatum* L.	Hypericin Hyperforin	HPLC/Fluorescence LC/MS/MS	Kerb et al., 1996; Biber et al., 1998
Buckwheat, *Fagopyrum esculentum* Moench	Quercetin	HPLC/ECD	Graefe et al., 2001

ucts (Blume and Schug, 2000). In this regard, the Herbal Medicinal Products working group of the FIP (Federation Internationale Pharmaceutique/International Pharmaceutical Federation) published recommendations on the biopharmaceutical characterization of herbal medicinal products (Lang et al., 2003).

In the United States, the U.S. Pharmacopeia Subcommittee on Natural Products produced a draft guideline suggesting that dissolution testing should be an integral part of the public standard for botanicals marketed as dietary supplements (USP Committee of Revision, 2000b). The USP Committee proposes that disintegration testing be only an interim standard for botanical formulations in which no dissolution test is feasible (USP Committee of Revision, 2000a). The members acknowledge that the index compound(s) or marker compounds selected for demonstration of dissolution may not be responsible for the therapeutic effect.

For companies applying for approval to market their botanicals as drugs in the United States, the Food and Drug Administration (FDA) *Guidance for Industry: Botanical Drug Products* requests that bio-

availability data be submitted when the companies file Investigational New Drug Applications (IND) (FDA/CDER, 2000).

Factors influencing the importance and ease of conducting bioavailability studies include the type of therapeutic activity and the extent to which the active constituents have been identified. Common sense tells us that bioavailability studies are more important for botanicals with immediate and strong activity. For those botanicals with mild or tonic actions (with a wide safety margin), fewer studies may be required (De Smet and Brouwers, 1997).

In the *European Pharmacopoeia,* botanical preparations are divided into three categories depending upon the degree to which the active components are known. In the first category (A) are extracts containing constituents (single compounds or families of compounds) with known and acknowledged therapeutic activity deemed solely responsible for the clinical efficacy. Extracts in this category are standardized by adjusting the amounts of the active constituents within acceptable minimum and maximum levels. This adjustment is achieved by mixing the extract with inert materials or by blending batches of extracts. Examples of category A botanicals in the *European Pharmacopoeia* are aloe dry extract, buckthorn bark dry extract, senna leaf dry extract, and belladonna leaf dry extract. Examples in the *German Pharmacopoeia* are ipecacuanha dry extract, rhubarb dry extract, milk thistle fruit dry extract, and horse chestnut seed dry extract (Lang et al., 2003).

In the second category (B) are extracts containing chemically defined constituents (single or groups) possessing relevant pharmacological properties that are likely to contribute to the clinical efficacy. However, proof that they are solely responsible for the clinical efficacy has not been provided. Quantified extracts are prepared by adjusting select constituents to defined upper and lower tolerance levels by blending batches of extracts. As there may be unidentified constituents with clinical efficacy in the extract, the use of inert material to standardize preparations is not appropriate. Examples of category B botanicals are ginkgo leaf dry extract and St. John's wort dry extract, listed in the *German* and *European Pharmacopoeia,* respectively (Lang et al., 2003).

Extracts that do not contain any constituents regarded as being responsible for the therapeutic activity are placed in category C. For these botanicals, chemically defined constituents (markers) may be

used for quality control purposes to monitor good manufacturing practices or to determine the contents in the product. These extracts are essentially defined by their production process specifications (e.g., the state of the herbal material to be extracted, the solvent, the extraction conditions, plant to extract ratio, etc.). An example of a category C botanical in the *German Pharmacopoeia* is valerian root dry extract (Lang et al., 2003).

In the European Medicines Evaluation Agency's "Note for guidance on the investigation of bioavailability and bioequivalence," it is stated that the bioavailability of an active substance from a pharmaceutical product should be known and be reproducible. This is especially the case if one product is to be substituted for another. Bioequivalence studies should be performed for all oral immediate release products intended for systemic action, unless in vitro data are sufficient (EMEA, 2001). This concept, originally developed for synthetic compounds, may be transferred to type A extracts without any modification.

In principle two parameters from in vitro data are essential in this context: solubility (the ability to dissolve as predicted through dissolution tests) and permeability through the intestinal wall according to the Biopharmaceutical Classification System (BCS) (a predictor of absorption rates) (Amidon et al., 1995). If both the solubility and permeability of a substance are good, there should be no problems with bioavailability. However, if one or the other is poor, bioavailability may be compromised. That is, if solubility is good (the rate of dissolution is relatively quick) and permeability is poor, then absorption is the limiting step for the appearance of drug substances in the blood. In this case, bioavailability would not be predicted by the in vitro dissolution rate. However, if the solubility is poor and permeability is good, then bioavailability will depend upon the in vitro dissolution rate and the substance will be absorbed as soon as it dissolves.

For example, Schulz and colleagues (1995) described the pharmacokinetics of silibinin after administration of different milk thistle extract-containing formulations with different dissolution profiles. As silibinin has a low solubility according to the BCS (Ihrig, Dedina, and Möller, 2000), there was, as expected, a correlation between the dissolution rate and the plasma levels. As seen in Figures 5.1 and 5.2, after administration of a product with a high dissolution rate (M9) higher plasma levels were achieved as compared to products M1 and

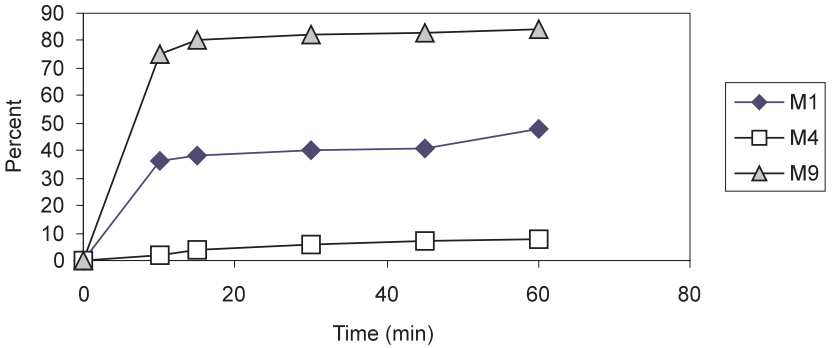

FIGURE 5.1. In vitro dissolution of silibinin from three different milk thistle extract-containing products (*Source:* Adapted from Schulz et al., 1995.)

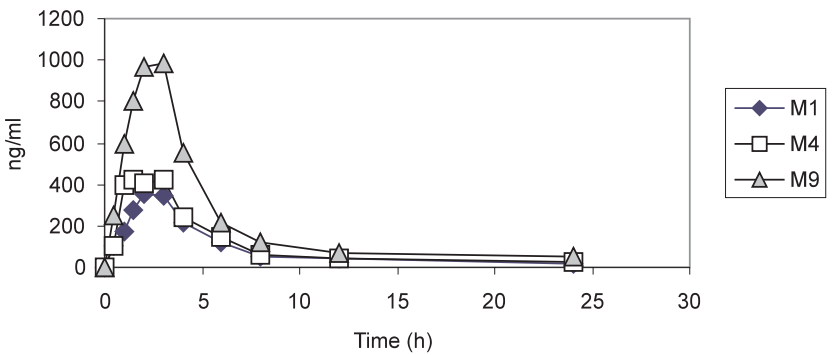

FIGURE 5.2. Plasma concentration of silibinin after oral administration of the products M1 to M4 (*Source:* Adapted from Schulz et al., 1995.)

M4 for which the dissolution rate was considerably lower (Schulz et al., 1995).

In consideration of these studies, the *United States Pharmacopeia–National Formulary* monographs on capsules and tablets containing milk thistle extract include the criteria for in vitro dissolution, that no less than 75 percent of the labeled amount of silymarin must be dissolved under specified conditions (United States Pharmacopeial Convention, 2002). This is especially important if another brand of product is substituted for a clinically tested brand of herbal medici-

nal product containing low-solubility substances. In these cases, bioavailability studies in human subjects should be performed, to the extent that is possible. However, certain restrictions may apply due to technical difficulties in measuring the desired marker compound(s).

For type B extracts, the solubility of both the markers likely to contribute to the clinical efficacy and the total extract should be studied in the pH of the gastrointestinal tract (pH 1 to 6.8). If the solubility of the extract and of the markers is good (>90 percent soluble from the highest dose strength), no problems with permeability through the intestinal wall and bioavailability are to be expected. If the solubility of the total extract and/or the markers is poor (<90 percent), bioavailability studies or clinical studies should be performed before bioequivalence with a clinically tested product can be determined.

A correlation between solubility and bioavailability was demonstrated for the ginkgolides (A, B) and bilobalide in two different ginkgo extract preparations. The reference preparation had an in vitro dissolution rate at pH 1 and 4.5 of over 99 percent after 15 minutes. In contrast, the test preparation had an in vitro dissolution rate of less than 33 percent after one hour. Bioavailability (plasma levels of constituents) of the two preparations was measured in 12 healthy volunteers in a crossover design. The reference preparation caused statistically significant greater maximum plasma concentrations and areas under the curve (amounts measured in the plasma) for all three constituents compared to the test preparation. Statistical analysis, using 90 percent confidence intervals, showed that these two products, with apparently similar chemical profiles, were not bioequivalent (Kressmann et al., 2002).

In the case of type C extracts, in which the constituents responsible for the therapeutic activity are unknown, no bioavailability problems are to be expected if solubility of the extract is high. In the theoretical case of poorly soluble type C extracts, clinical studies should be conducted on a case-by-case basis.

In bioavailability studies containing type B or C extracts, it would be desirable to measure not only (active) markers but also the total active principle of the extract. Chemical assays measure only a small percentage of botanical components, and in the case where the active components are not determined, they may not predict the pharmacological activity of the preparation. Therefore, bioassays that measure biological activity (pharmacodynamic effects) may be more suitable

end points. Recently, biochemical assays have been proposed for several plant extracts, as depicted in Table 5.2 (Rininger et al., 2000).

An ideal bioassay would be a measurement that correlated with the therapeutic activity of the extract. However, this ideal is difficult to achieve. In most cases biochemical assays do not reflect therapeutic effects as a whole but only selected pharmacological aspects caused by individual active markers. A disadvantage of biochemical assays is that they are generally not as reproducible as chemical analytical methods, and the variability in results may complicate evaluation of the bioavailability studies. Nevertheless, bioassays or biochemical assays may play an important role for future pharmacokinetic approaches if intelligent strategies can be found.

It should not be taken for granted that different brands of botanicals are equivalent in their bioavailability. The presence or absence of substances in the product other than the active ingredients may prevent, prolong, or enhance absorption. In the scramble to differentiate products in the U.S. dietary supplement market, some manufacturers have adopted novel delivery systems and/or innovative formulations. These innovations may be beneficial, but they need to be tested to determine the bioavailability of the ingredients.

In summary, further research is needed into the bioavailability of herbal products. This research is complicated by the need for identification of active constituents. However, technical advances have helped in this process, and there is movement toward the establishment of standards for the disintegration, dissolution, and bioavailability of herbal products.

TABLE 5.2. Bioassays for plant extracts

Extract	Extract type	Bioassay
Hypericum	B	Serotonin and dopamine reuptake inhibition
Ginkgo	B	Free-radical scavenging activity
Ginseng	C	Induction of corticosterone
Echinacea	C	TNF (tumor necrosis factor)-alpha production
Saw palmetto	B	5-alpha-reductase inhibition

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Chapter 6

"Borrowed Science" and "Phytoequivalence": Can Two Herbal Products Be Judged Equivalent?

Marilyn Barrett

When is it appropriate for a clinical trial conducted on one herbal preparation to be applied to another herbal preparation so as to support the indication of the second product? That is, when can a trial conducted on one ginkgo product be used to establish the efficacy of another ginkgo product? This is the question behind the concept known popularly as "borrowed science." The manufacturers of the second product "borrow" the clinical studies conducted on the first product to establish the efficacy of and to promote their own product.

The first issue to address in borrowed science is product equivalency, i.e., does the second product have the same therapeutic value as the clinically proven product? Substituting one product for another product with an apparently similar description appears reasonable. However, what about products made from different species, plant parts, or manufacturing processes? Often in the United States an herbal preparation is not specified beyond the common name of the plant. Simply "valerian," "echinacea," or "garlic" is used to describe the preparation. That might suffice if all valerian products were equivalent, all echinacea products were equivalent, and all garlic products were equivalent, but they are not. For example, valerian root preparations are available as teas (aqueous extracts) and aqueous alcoholic extracts (70 percent ethanol with an herb-to-extract ratio of 4 to 7:1). These two preparations are not chemically equivalent. It is also common to lump echinacea products together, but can it really be assumed that a preparation made from the expressed juice of *Echinacea purpurea* flowering tops is equivalent to an aqueous alcoholic

extract of the roots of *Echinacea angustifolia* roots? Garlic is available raw, dried, aged, and as an oil. None of these preparations are chemically equivalent.

It seems a first step in comparing products is to recognize the source of the knowledge regarding efficacy. For many herbs, the foundation of the evidence comes from traditional use. This evidence may or may not be supported by more recent pharmacological and/or clinical studies. In a few instances, products have been developed, apart from traditional uses or preparations, using pharmacological, toxicological, and clinical experiments.

Once the source of knowledge regarding efficacy has been identified, then the form of the material used to provide that evidence must be considered. Is the evidence regarding efficacy based upon raw plant material, a tea, a traditional tincture or other liquid preparation, or a solid oral formulation containing a dried or semipurified extract?

Duplication of each of these types of products raises slightly different issues. The quality of the raw material is dependent upon the identity and selection of the plant material as well as agricultural and/or harvesting practices. The chemical profile of an extract is, in addition, dependent upon processing methods.

The most common practice of borrowing science in the United States occurs when U.S. companies use the scientific data from European manufacturers to support statements regarding the benefit of their product. In other words, the reason for borrowing science is to aid in marketing and to support an allowable statement regarding the benefit of the product (a structure/function statement allowable under the Dietary Supplement Health and Education Act [DSHEA] of 1994). As noted in Chapter 10, "Motives for Conducting Clinical Trials on Botanicals in Europe," German manufacturers who wish to sell their herbal products as drugs or traditional medicines must provide documentation of efficacy and safety, or their product must conform to the quality specifications of a published monograph. Under DSHEA, dietary supplement structure/function statements must have evidence that the statement is truthful and not misleading. However, the extent of that evidence, and the strength of the link to the dietary supplement itself, have not been fully defined.

The practice in the United States of borrowing science allows for products to be sold more cheaply compared to their European counterparts, as the U.S. manufacturers are not forced to invest substantial

amounts of money into researching efficacy or safety. Consumers, for the most part, are unaware of which products have been tested in clinical studies and which have not. Thus price becomes the deciding factor in their purchase.

However, a rational approach to evaluating the phytoequivalence of herbal products does exist. An international group, the Herbal Medicinal Products Working Group of the FIP (Federation Internationale Pharmaceutique/International Pharmaceutical Federation) has taken such an approach in producing guidelines to be used in evaluating the equivalence of herbal medicinal products sold as solid oral formulations (Lang et al., 2003). This group declared that a medicinal product is essentially similar to an original product when it has the same qualitative and quantitative composition in terms of active ingredients, has the same pharmaceutical form, and has demonstrated bioequivalence (similar bioavailability of active ingredients).

CHEMICAL OR PHARMACEUTICAL EQUIVALENCY

In determining whether borrowing science is acceptable, the first issue to examine is whether the two products are pharmaceutically equivalent. Two products are pharmaceutically equivalent if they contain the same active ingredient, the same strength of that active ingredient, the same dosage form, and are intended for the same route of administration and labeled for the same conditions of use (United States Pharmacopeial Convention, 2002).

In the case of drugs that are single-entity chemicals, pharmaceutical equivalence is relatively easy to determine. Chemical analysis of most single-entity chemical ingredients is fairly straightforward. In fact, the idea of equivalency is the basis for the promotion of, usually cheaper, generic drugs. It is relatively easy to identify and quantify the acetylsalicylic acid in Walgreens generic aspirin and determine it to equivalent to that in Bayer Aspirin.

But what of botanical preparations that contain hundreds of chemical components? For a few herbs, the active components have been identified. For those herbs, it is accepted that the defined constituents are responsible for the therapeutic activity, independent of the other components in the herb. The *European Pharmacopoeia* places extracts of aloe, buckthorn, senna, and belladonna in this category,

while the *German Pharmacopoeia* includes extracts of ipecacuanha, rhubarb, horse chestnut, and milk thistle in this category (Lang et al., 2003). For these herbs characterization of the active ingredients is sufficient to establish chemical or pharmaceutical equivalency.

What about those herbs that contain several chemical components which are thought to contribute to the activity but do not necessarily account for all of the activity? St. John's wort and ginkgo standardized extracts are placed in this second category by the *European Pharmacopoeia* and *German Pharmacopoeia,* respectively (Lang et al., 2003). What about those herbs for which there is no agreement as to the active component(s)? The *German Pharmacopoeia* places valerian extracts in this third category (Lang et al., 2003). As all the active ingredients have not been identified in the herbs in these latter categories, theoretically all components in the preparations should be congruent for the products to be considered equivalent. However, this is impractical and difficult to demonstrate. Not all constituents may be identified, and even if identified, it would be difficult to quantify all of them. Practical steps in this direction would be to assure that the identities and qualities of the raw material, as well as the manufacturing processes, are similar. For extracts, the processing details would include the plant to extract ratio, the principal extraction solvent, and the extraction method.

BIOEQUIVALENCY OR THERAPEUTIC EQUIVALENCY

As described earlier, pharmaceutical equivalence is achieved if two products contain the same amount of the same active ingredient(s) in the same quantities in the same dosage form. However, chemical equivalence does not imply bioequivalence. Differences in the excipients and/or final formulation of the capsules or tablets may lead to faster or slower dissolution (release of chemical constituents) and/or absorption into the body.

For drugs, the disintegration of the tablet or capsule and the dissolution of chemical constituents are specified in pharmacopoeial monographs. U.S. federal law mandates that drugs comply with monograph specifications published in the *United States Pharmacopeia (USP).* Thus Walgreens aspirin must meet the same disintegration and dissolution specifications as Bayer Aspirin.

Measuring the disintegration of herbal tablets or capsules can be achieved using similar guidelines as those for drugs. However, measuring the dissolution (release of the active chemical constituents) of herbal preparations becomes problematic if the active ingredients are unknown. For those few herbs in which the active ingredients are known, dissolution guidelines are beginning to be drafted into the *United States Pharmacopeia–National Formulary (USP–NF).* For example, the *USP–NF* monographs on capsules and tablets containing milk thistle extract include criteria for in vitro dissolution of silymarin (United States Pharmacopeial Convention, 2002). However, these guidelines are not in place for the majority of herbs on the market, and no mandatory compliance to the specifications that do exist is enforced.

Once the dissolution of the active components is assured, absorption into the body is the next step. Measurement of the active component(s) or metabolite(s) in the plasma and/or urine is an indication of bioavailability. A bioequivalence study compares the bioavailability of two products. According to the FIP Herbal Medicinal Products Working Group, a bioequivalence study is the most widely accepted means of demonstrating that any apparent differences in the two products being compared have no impact on the rate of absorption and the extent of absorption. The working group adds the caveat that the products contain only excipients which are generally recognized as not having an influence on safety or efficacy (Lang et al., 2003).

APPLICATION OF THE CONCEPTS, GINKGO AS AN EXAMPLE

Ginkgo extracts meeting the specifications of the German Commission E monograph have been approved for use in cases of dementia syndromes, improvement of pain-free walking distance in peripheral arterial occlusive disease, vertigo, and tinnitus (Blumenthal et al., 1998). The product specifications for this indication are a dry extract of the dried leaf that is manufactured using acetone/water with subsequent purification steps, without addition of concentrates or isolated ingredients, and with a drug/extract ratio of 35 to 67:1, on average 50:1. The extract is characterized as containing 22 to 27 percent flavonol glycosides; 5 to 7 percent terpene lactones, of which approx-

imately 2.8 to 3.4 percent consists of ginkgolides A, B, and C and 2.6 to 3.2 percent bilobalide; and ginkgolic acids below 5 mg/kg. This detailed description of approximately 24 percent flavonol glycosides and 6 percent terpene lactones still accounts for only 30 percent of the extract, providing little information on the remaining 70 percent. Other components, yet unidentified, may also contribute to clinical efficacy. The variability of these unidentified components can be minimized using consistent agricultural and manufacturing practices.

Many U.S. dietary supplement products are sold with claims based upon the German Commission E monograph. However, studies have found that not all of them conform to the quality specifications of the monograph (ConsumerLab, 2000; Kressmann, Müller, and Blume, 2002). Analysis of 26 ginkgo products sold in health food stores and supermarkets in the United States found that 16 products conformed to the flavone glycoside specification but only nine and seven conformed to the terpene lactone and ginkgolic acid specifications, respectively. A further breakdown of the lactone content revealed that four conformed to the suggested level of total ginkgolides and nine to the bilobalide level (Kressmann, Müller, and Blume, 2002). It must be noted that this level of detail was not on the label of the tested products, so most manufacturers were not in violation of truthful ingredient labeling. However, questions arise as to whether the products on the market provide the same therapeutic benefit as the extract specified by the Commission E monograph.

Kressmann, Müller, and Blume (2002) further compared the in vitro dissolution of the ginkgo products. The dissolution rates of terpene lactones, specifically ginkgolide A, B, and C, as well as bilobalide, were tested. The dissolution rates for the products were comparable, with most brands releasing over 75 percent of the terpene lactones within 30 minutes. Only one product stood out, as it released merely 10 percent of its terpene lactone content in 30 minutes. (It should be noted here that the Commission E monograph does not specify dissolution parameters.)

Another study by this group compared the bioavailabilities of two ginkgo extracts, both characterized on their labels as containing 24 percent flavone glycosides and 6 percent terpene lactones. The reference product was Ginkgold, manufactured by Dr. Willmar Schwabe GmbH & Co. of Germany and distributed by Nature's Way Products, Inc. (Springville, Utah) in the United States. The extract in this prod-

uct, EGb 761, is the basis of a total of 32 controlled clinical studies reviewed in this book and is the basis for the Commission E monograph. Ginkgold was compared to "Ginkgo biloba extract" distributed by Whitehall-Robins Healthcare (Madison, New Jersey). Previous dissolution studies had indicated that the Whitehall-Robins product released less than 33 percent of its terpene lactone content in 60 minutes, whereas Ginkgold released over 99 percent in 15 minutes. These two products were given to 12 healthy volunteers using a crossover trial design, and the concentrations of ginkgolides A, B, and bilobalide were measured in their blood. The result of the study was that EGb 761 caused statistically significant greater maximum plasma concentrations and areas under the curve (amounts measured in the plasma) for ginkgolides A, B, and bilobalide compared to the test preparation. Statistical analysis, using 90 percent confidence intervals, showed that these two products were not bioequivalent (Kressmann et al., 2002).

META-ANALYSES

Another situation in which it is helpful to determine whether products are similar in therapeutic efficacy is in the pooling of clinical trials conducted on different products. A meta-analysis is a statistical review of multiple trials. It is a systematic way to pool data, often from numerous, small, randomized controlled studies, and examine the significance of their findings as a whole. But what is the significance of pooling data from different botanical preparations, possibly with different chemical profiles and without established bioequivalence?

Certainly there is a basis for comparing studies conducted on different powdered garlic products, but powdered garlic products do not have the same chemical profile as aged garlic or garlic oil. The Agency for Healthcare Research and Quality, an agency in the U.S. Department of Health and Human Services, sponsored a systematic review of garlic through one of its Evidence-Based Practice Centers (EPC). The evidence report separately summarized the effects of garlic on cardiovascular-related factors/disease and cancer. Studies on preparations ranging from dehydrated garlic, aged garlic extracts, and garlic oil macerates to distillates, raw garlic, and combination

tablets were all pooled together (Mulrow et al., 2000). This practice of attempting to collectively determine the evidence regarding an herb's efficacy by pooling all products, regardless of their different specifications, provides misleading results. It reinforces the idea that all garlic products are alike, a concept not supported by chemical analysis.

PERSPECTIVE

The appropriateness of borrowed science is not only a question regarding truthful advertising but also a question regarding therapeutic benefit for health practitioners and consumers. Often health practitioners and patients uncritically substitute one herbal product for another. The consequence of this action could be a lack of the expected therapeutic benefit.

For this situation to change, consumers and health care practitioners would need to be aware of the source of the information regarding the efficacy of a product. Is the source of evidence traditional use of a tea or tincture, or is it several clinical studies conducted on a specific type of extract? The next question is, does the form of the product being sold match that of the product with the direct evidence? Of course, certain differences may not influence efficacy, and further research is needed to determine what differences are acceptable or unacceptable. Further, health practitioners and consumers would have to be aware enough of the complexity of herbal preparations to realize that a generic form may provide the same activity, but it also may not. Without evidence of equivalency, health practitioners and consumers would have to be able to distinguish clinically researched products from those that have no direct evidence to support their claims.

At the moment, no regulatory pressure has been placed on manufacturers to conduct either their own efficacy studies or equivalency tests. Without additional regulation, it is unlikely that most manufacturers will invest money into such research.

As outlined in this chapter, the concept of herbal product equivalence can be approached in a rational and scientific manner. The FIP Herbal Medicinal Products Working Group is exploring the means to do just that. The examination of chemical equivalency is determined by the extent of knowledge regarding the active components. For most herbs, it begins with comparison of the botanical identities, the plant

parts, and agricultural practices and extends to manufacturing practices. Determination of in vitro disintegration and dissolution are first steps toward determining bioequivalency, which ultimately must be determined clinically. It is important to remember that the extent to which the active constituents are known will determine the degree of correlation between dissolution and bioequivalence tests and efficacy.

Until health practitioners and consumers demand more information on the source of the evidence for efficacy, or until additional regulation is in place, the current problem of borrowed science will continue in the United States. In other words, many U.S. companies will inappropriately attribute science conducted on other products as pertaining to their own.

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Chapter 7

Determining Efficacy of Herbal Preparations

Tieraona Low Dog

Herbal medicine has been used since prehistoric times and gave birth to the sciences of botany, pharmacology, and, in part, chemistry. The initial evidence for the efficacy of these medicines was derived from direct human experience and observation. Some of the most effective medicines in our recent past originated from plants, including aspirin (salicylic acid from willow bark and meadowsweet), quinine (from cinchona bark), digoxin (from foxglove), and morphine (from opium poppy). Although many health care practitioners recognize that a number of other botanicals may be of therapeutic benefit, there is an undeniable sense of skepticism given the amount and quality of information currently available.

New information about the safety and efficacy of botanicals is becoming available on a daily basis. For this reason, both patients and providers utilize the Internet to gather health information; 52 million American adults have used the Web for this purpose (Pew Internet and American Life Project, 2000). Most users like the convenience of using the Web and the fact that they can do their research anonymously, yet 86 percent of those using the Internet for medical information worry about getting information from unreliable sources. The Federal Trade Commission (FTC) is charged with enforcing laws that ban "unfair or deceptive acts or practices." In 1998, the FTC held a "health claims surf day," during which 80 organizations from 25 countries searched the Internet for treatment and/or cures for cancer, arthritis, heart disease, AIDS, diabetes, and multiple sclerosis. Unfortunately, during this one afternoon of searching they found 400 sites making unfounded claims (Rusk, 2001).

So how does a health care provider determine what evidence is available regarding a specific botanical product? How does one assess the strength and weight of the existing evidence and apply that to a given patient? Evidence on the efficacy of herbal medicines ranges from historical use data, pharmacological studies, case reports, and uncontrolled clinical studies to the gold standard of randomized, double-blinded, placebo-controlled clinical studies. The strengths and weaknesses of each type of evidence and the criteria for a quality clinical trial are presented in this chapter.

A long history of traditional use of an herb can be an important source of information about safety and efficacy, especially if the information is corroborated by similar uses in multiple cultures which have apparently discovered that use independently. Objective pharmacological measurements using isolated tissue or cell culture is a well-accepted first step for understanding the biological activity of a particular substance. Animal studies are often used, as they permit generous control over a number of variables and can help to explain potential mechanisms of action. In vitro and animal data can provide important information about both the effectiveness and the safety of an herb; however, they are limited in their ability to accurately predict physiological effects in humans. Special attention must be paid to the experimental concentrations used in in vitro studies. These amounts should correlate with the concentrations expected in the plasma (blood) following human use. Similar attention should also be paid to the doses used in animal studies. In addition, caution must be used in the extrapolation of an activity produced with an isolated constituent of a plant to the activity expected with a whole plant preparation. Especially in the case of in vitro studies, one must determine if the components in the plant material being studied are altered by gut flora, transported across the intestinal wall, or altered by hepatic first pass metabolism. In addition, any physiological effects due to secondary metabolites must be considered.

OBSERVATIONAL MEDICINE

Decision making in medicine, until very recently, has been based primarily upon observation, personal experience, and intuition. Early physicians observed the patterns of illness and effects of treatment, and many wrote extensively about their findings. Information based

upon personal observation by an individual is referred to as anecdotal. However, observations are seldom neutral, as they are based upon the preconceptions of the observer. Realizing the inevitable problem with anecdotal information, Aristotle called for the systematic observation of nature more than 20 centuries ago. Observational information was still an important source of information in early twentieth-century medical journals, and uncontrolled studies remained popular in the literature until their frequency diminished over the past 20 years. Uncontrolled studies do not include randomized groups, blinding of investigators, or a control group. Anecdotal information and uncontrolled studies can provide valuable hypothesis-generating information and assist in the identification of adverse events; however, they are extremely vulnerable to both bias and confounders. Thus, although helpful, these types of evidence should be considered supportive, not primary.

"EVIDENCE-BASED" MEDICINE

The decision-making process in medicine has been undergoing a dramatic shift toward "evidence-based" medicine that is based upon reviews of randomized, placebo-controlled, double-blinded studies which can be used to determine the degree of treatment effect, or lack thereof, of a particular intervention (Evidence-based medicine, 1995). Deciding what determines a high-quality study is complex and is the subject of great debate among researchers in conventional and complementary/alternative medicine. It is well recognized that certain study designs are more persuasive than others because they are less subject to bias. Although not a perfect mechanism for judging all interventions, at this time no other single study design provides a better level of safeguards against bias than a quality randomized, controlled trial (RCT). Three basic design protocols should always be considered when reviewing an RCT: randomization, blinding, and accounting of all participants, including those who withdraw or drop out.

An adequate randomization process assigns subjects that are similar to one another to either receive or not receive an intervention. Allocation of treatments can be either computer generated or through the use of a table of random numbers. The use of hospital numbers, date of admission, date of birth, or alternating numbers is not consid-

ered adequate. Selection bias is avoided by not preferentially selecting for the intervention arm those subjects most likely to experience a favorable outcome in the study. Every study participant must have an equal chance of receiving each intervention, and the investigators must not be able to predict which treatment a given participant will receive. Researchers have shown that trials with inadequately concealed allocation yielded larger treatment effects compared to trials in which the intervention assignments were hidden from all study participants (Schulz et al., 1995).

Blinding is achieved by matching the appearance of the placebo or standard treatment to the test substance. This may be somewhat problematic when studying liquid botanical products, as replication of taste and flavor with inert substances can be difficult. Masking of the treatment received by individual subjects (blinding) is adequate when neither the participants, the individuals doing the intervention, outcome assessors, nor the data analysts are able to identify which intervention is being assessed. This is the case for double-blind studies, but not for single-blind studies in which only the participants are blinded. Evidence should be provided that demonstrates successful blinding, and a detailed description of the characteristics of the product or treatment should be provided in the report (Schulz et al., 1996).

All participants included in the study must be properly accounted for at the conclusion of the trial. Those who fail to complete the trial, or who are not included in the analysis, must be described. The number of subjects that withdraw and reasons for withdrawal should be clearly stated. If participants in the active group drop out due to adverse events or because they perceived the treatment wasn't working, this information needs to be conveyed in the reporting of the trial. Many researchers now advocate for an intention-to-treat (ITT) analysis to be included in all randomized clinical trials. The ITT analysis is a strategy for analyzing data in which all participants are included in the group to which they were assigned, whether they completed the intervention given to the group or not (Begg et al., 1996). The ITT approach maintains the randomization originally sought at the beginning of the trial by fully accounting for all participants in both groups. Hollis and Campbell (1999) provide a clear example of the risk of not using an ITT approach. In a trial comparing medical and surgical treatment for stable angina pectoris, some patients allocated to surgical intervention died before being operated on. If these deaths were

not attributed to surgical intervention using an intention-to-treat analysis, the surgical intervention would appear to have a falsely low mortality. In addition, it is normal for some patients to discontinue treatment or fail to adhere to prescribed treatment, thus allowing studies with an ITT analysis to more accurately parallel routine clinical practice.

In addition to appropriate randomization, blinding, and accounting of participants, RCTs should state the estimated effect of the intervention on outcome measures. The treatment effect observed in the clinical trial is called the point estimate and provides the best estimate of the true effect size in the study. This statistical measurement (relative risk, reduction in relative risk, absolute risk reduction) is heavily emphasized in the research report, as clinicians and patients are most interested in the question, "What was the difference in outcome between the treatment group and the control group?" The point estimate is the best estimate of the true size of the effect demonstrated in the study and applicable to the larger population that the trial's randomized sample is meant to represent.

The paper should also include an adequate description of the statistical methods used and how they were applied, with the data summarized in a fashion which allows others to perform alternative analyses. One must be careful to limit the risk of an alpha error, the determination that a treatment is effective when it actually is not. Thus, the sample size must be large enough to provide statistical power to detect a significant, i.e., clinically relevant, effect.

The appropriate application of inclusion/exclusion criteria is also an important factor when considering the strength of a study. The criteria for the inclusion and exclusion of subjects must be clearly explained and relevant to the clinical condition being studied. For instance, a study for a cold treatment should clearly list appropriate exclusions for those with chronic illness and those taking antibiotics or over-the-counter cold/cough medications.

Due to the complex nature of botanicals, variation in constituents between species, plant part, and preparation, it is essential that authors clearly provide an adequate description of the product used in the clinical trial. Descriptions should include identification (Latin binomial and authority), plant part (root, leaf, seed, etc.), and type of preparation (tea, tincture, extract, oil, etc.). Tincture and extract descriptions should include the identity of the solvent and the ratio of

solvent to plant material. If the preparation is standardized to a chemical constituent, then that information should also be included. Precise and clear dose and dosage form should be provided. Papers that say, "three tablets of *Echinacea purpurea* were given two times per day" are simply unacceptable. How many milligrams were in each tablet? What part of the plant was used? How was it extracted? However, if a commercial product is used in a clinical trial, then information on preparation may be publicly available. Even so, characterization of the product is helpful as specifications can change over time.

Recently, the clinical evidence for efficacy of many herbal treatments has been subjected to systematic reviews (Ernst, 1999). These include reviews of garlic (Ackermann et al., 2001), kava (Pittler and Ernst, 2000a), ginkgo (Pittler and Ernst, 2000b), and St. John's wort (Linde and Mulrow, 2003), to name a few. A systematic review is a method of reviewing multiple clinical trials using a process that minimizes bias. The review includes all existing trials of a predefined quality, such as double-blind and controlled. If possible, statistical analyses are conducted on the end points of the trials, and a broad conclusion may be reached regarding efficacy and/or safety. These systematic literature reviews are becoming extremely important, as practitioners are overwhelmed with unmanageable amounts of information. Single studies are not usually sufficient for providing definitive answers to clinical questions. Recently two systematic reviews were published by the governmental Agency for Healthcare Research and Quality on garlic and milk thistle. These are available online at <http://www.ahrq.gov/clinic/epcix.htm>. Another excellent resource is the Cochrane Database of Systematic Reviews available online at <www.cochrane.org/reviews/index.html>.

SUMMARY

Decision making in medicine, until very recently, has been based primarily upon observation, personal experience, and intuition. Much of the historical information available on herbs is based upon these types of evidence. While recognizing that this type of evidence is valuable and certainly should not be discarded, decision making in medicine is undergoing a shift toward evidence-based medicine, based upon reviews of well-done randomized, placebo-controlled, double-blind studies which can be used to determine the degree of

treatment effect, or lack thereof. Herbal preparations can also be evaluated in this manner.

Clinical trials included in this book have been reviewed for their level of evidence according to a template included in the methods section. These levels of evidence provide the reader with an assessment of the strength of the evidence presented in the trial.

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Chapter 8

Evaluating Safety of Herbal Preparations

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A substance is generally considered to be safe if it does not cause harm or risk of harm. Unfortunately, nothing is *absolutely* safe, and substances ingested for their beneficial effect may in some cases also be expected to exhibit undesirable effects. There is an amount (dose or concentration) and time interval (duration) beyond which we should not consume any substance, even one as safe as water. The sixteenth-century alchemist Paracelsus put it best when he stated that the dose makes the poison. Safety is thus a relative term best evaluated in terms of expected benefit weighed against the likelihood the substance will cause harm and the severity of the expected harm.

Undesirable effects can occur at recommended (therapeutic) doses and are called adverse reactions or side effects. The terms adverse reaction and side effect are not synonymous. *Adverse reaction* is used to describe undesirable effects that are not extensions of the known pharmacology of the substance. Adverse reactions may, or may not, be attributed to the product in question. They are usually unexpected until their origin is understood. A typical mild adverse effect is nausea and vomiting after taking a product. *Side effects* are undesirable effects that could be predicted or described based on the known pharmacology of the substance. Examples of side effects are dry mouth observed after taking decongestants such as pseudoephedrine and sleeplessness after taking ephedra. Aspirin may have the side effect of causing direct gastric damage by topical irritant effects and indirect damage via systemic inhibition of cyclooxygenase enzymes and microcirculation injury. An adverse reaction to aspirin may be hives or even anaphylaxis caused by unpredictable hypersensitivity in cer-

tain individuals. Both adverse effects and side effects can be mild, moderate, or severe.

If an undesirable effect occurs at a much higher dose than the therapeutic dose, it is considered an intoxication. An example of a toxic effect is a poisonous condition caused by too great a dose of salicylate. Salicylates are ubiquitous in nature and occur in low levels in a range of plants used as foods and flavorings. High blood levels can be obtained through ingestion of large amounts of aspirin (acetylsalicylic acid). Salicylism is characterized by rapid breathing, vomiting, headache, irritability, low blood sugar, and, in severe cases, convulsions and breathing problems. These poisonous effects disappear once the dose is reduced.

Some degree of toxicity is acceptable if the expected benefit is great. For example, the toxicity expected for agents used for cancer chemotherapy is tolerable given the potential of these substances to eliminate fatal cancers. However, if the remedy is a tonic used by otherwise healthy patients, then toxicity is not acceptable.

The goal of this chapter is to discuss ways of evaluating safety, monitoring and cataloging of undesirable effects (adverse reactions and side effects), categorizing herbal products according to their degree of safety, the importance of product quality as a determinant of safety, situations in which certain products are contraindicated, and potential drug-herb interactions. Finally, we will suggest ways we can improve our knowledge of the safety of herbal preparations.

EVALUATION OF SAFETY

A well-established system is used to evaluate the safety of prescription (Rx) and over-the-counter (OTC) drugs. Studies exploring safety begin with in vitro (test tube) and animal laboratory procedures, and then progress to human clinical trials. Animal toxicity procedures determine the lethality of different doses of a drug when administered orally, intraperitoneally, or intravenously to different species of mammal. Clinical observations and laboratory examinations of the animals are performed after one dose (acute) or after many days (chronic) of administering the drug. If a drug appears reasonably safe, these findings are corroborated using human subjects in clinical trials which have been specifically designed to evaluate safety (and later in clinical trials designed to assess therapeutic efficacy).

In the United States, drug manufacturers sponsor the safety studies which the Food and Drug Administration (FDA) reviews before allowing a drug to be sold to the public. Once on the market, systems are in place to monitor possible adverse reactions to the drugs. If concerns arise regarding the safety of a product, then the product is removed from the market or the directions for use are modified.

This well-established procedure is followed for those few herbal products sold as Rx or OTC drugs. However, the bulk of herbal products in this country are not sold as drugs but as dietary supplements. According to the Dietary Supplement Health and Education Act (DSHEA) passed by the U.S. Congress in 1994, botanical ingredients on the market prior to 1994 are considered safe by definition (Blumenthal and Israelsen, 1998). Manufacturers are required to notify the FDA of their intention to market a new dietary ingredient (one brought on the market after the enactment of DSHEA) at least 75 days before the ingredients are introduced into the marketplace. When making the notification, manufacturers must provide documentation to the FDA that the new ingredient is safe. The level of evidence needed to demonstrate the safety of these new ingredients is much less rigidly defined and less rigorous than that required for new foods or drugs. Under DSHEA, manufacturers of dietary supplements are responsible for the safety of their products, but the burden of proving a product already on the market poses a significant or unreasonable risk of injury or illness lies with the FDA. In other words, the FDA reviews safety only after products are on the market (and generally only after adverse reactions are reported).

In spite of the lack of premarket safety review by the FDA for many botanical ingredients, the public generally assumes that herbal products will be nontoxic and free of side effects. Many botanicals marketed as dietary supplements have a long history of use. Therefore, one might expect that any potential adverse reaction would be well documented. This is generally true, but several caveats are worth consideration.

Traditional practitioners and their patients are likely to recognize immediate signs of toxicity, but they are less likely to detect effects due to long-term exposure. These subtle long-term effects may result in cancer or damage to internal organs, such as the liver and/or kidneys. The examples often used to support this viewpoint are the

length of time it took to recognize the link between tobacco smoking and lung cancer, or between alcohol and fetal alcohol syndrome.

Another consideration in evaluating safety is that many herbal products in the modern marketplace are not made in the traditional manner. In addition, they are freely available over the counter and are thus used by consumers without the advice of a practitioner. In an effort to establish a position in the market, many manufacturers of dietary supplements attempt to distinguish their products as being unique. Manufacturers may process the herb so that the products are more concentrated, selectively enhance certain constituents of the herb, or combine herbs and other ingredients in a unique (and nontraditional) manner. If products do not share the chemical composition or the dose level of the traditional preparation, or if they contain unique ingredients, they may not have the same safety profile. Furthermore, if the form (liquid, solid) or formulation (sole ingredient, one product in a mixture, capsule, tablet, delayed release, etc.) of the product is changed, the availability of the ingredient to the body's tissues (bioavailability) may also be changed. In all of these instances, the past experiences of traditional practitioners may not be relevant.

If a product has not been marketed previously, or if the formulation and composition have changed substantially, it is appropriate to conduct cell-based and/or animal toxicological procedures as mentioned previously. Once such a product is on the market, its safety record can be monitored using individual case reports, postmarket surveillance, and adverse-event reporting systems.

ADVERSE REACTIONS

According to the World Health Organization's (WHO) International Drug Monitoring Program, an adverse drug reaction (ADR) is defined as a response to a drug that is noxious and unintended, which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1972). Untoward reactions that result from ingesting excessive amounts of a substance can best be described as intoxications rather than adverse reactions. It should be noted, however, that the difference between a recommended or therapeutic dose and a toxic dose is very small in some cases.

In evaluating ADRs, it is important to determine whether the product in question actually caused the observed effect and if this effect was caused at the usual dose. The same criteria apply to this determination as those used in evaluating the efficacy of a product. The adverse reaction must first be linked with consumption of the product. The ingredients in the product should also be identified in some manner (chemically if at all possible), as it is not sufficient to rely on the ingredient declaration on the label. Several of the most well-known adverse reactions to botanical products have occurred because the wrong plant somehow ended up in the bottle. A clinician who reports an adverse reaction without performing, or directing, an independent check on the identity of the material can cause considerable confusion. In addition, the product must be examined for contaminants (pesticides, heavy metals, mycotoxins, pathogens) to rule them out as causes of the adverse reaction. Finally, a reaction may sometimes be product specific (linked to a particular product prepared in a specific manner) and may not be attributable to any particular individual botanical ingredient found in other preparations.

Even when a botanical or product is generally considered safe, it is possible for an adverse reaction to occur due to intolerance or an allergic reaction. Individual sensitivity can be responsible for a reaction of uncharacteristic or unpredictable nature and may not reflect any particular hazard to the general population. Although rare, individuals who are allergic to ragweed pollen may find themselves reacting when they consume Roman chamomile flower tea since both plants are members of the same family, the Asteraceae (Der Maderosian and Liberti, 1988).

ADVERSE-EVENT REPORTING SYSTEMS

Reporting systems have been designed to collect ADRs at the national level within the Food and Drug Administration and on the international level within the World Health Organization.

MedWatch is the reporting program for health professionals who wish to notify the FDA of serious reactions and problems with medical products such as drugs and medical devices. In 1993, the FDA Special Nutritionals Adverse Event Monitoring System (SN/AEMS) was established to monitor dietary supplements. This system, which received reports of adverse reactions from FDA's MedWatch pro-

gram, FDA field offices, other federal, state, and local public health agencies, as well as from letters and phone calls from consumers and health professionals, is now in the process of revision. A major limitation to the system was that many reports were not investigated to determine whether there was a causal link to the suspected substance. In addition, all ingredients in a multiple-ingredient product were listed as causal agents regardless of the quantity present in the formula and the likelihood of their being the actual causative agent.

The WHO maintains the international drug information system (INTDIS) database for ADRs, which is housed in the Uppsala Monitoring Centre in Sweden. Information is gathered from government agencies of countries that are members of the WHO International Drug Monitoring Program. Until recently this program lacked the structure to report ADRs for herbs and herbal ingredients, as they were not suspected of causing ADRs (Olsson and Edwards, 2000). To remedy this deficiency, the Uppsala Monitoring Centre created a special computerized herbal substance register within the INTDIS in the fall of 2001 (Fucik, Backlund, and Farah, 2002). This program is designed to analyze the reported ADR information for a possible causal relationship between the reaction and the botanical. Depending upon the seriousness of the reaction, the quality of the information, and the number of reports, an alert may be generated. Once this system is fully implemented, some of the old ADR reports for herbal products may be reevaluated and compared with other ADR profiles to identify differences and similarities between different herbal product categories, such as crude botanical drugs (infusions, decocotions, or herbal teas considered traditional preparations), refined herbal preparations including phytopharmaceuticals (OTC and prescription herbal drugs), and allopathic prescription drugs based on botanicals (such as digoxin).

It is clear that the pharmacovigilance programs for herbal medicines are in their nascent stage, still being developed both by the U.S. FDA and the WHO.

CATEGORIZATION ACCORDING TO THE DEGREE OF SAFETY

Botanical ingredients vary widely in their degree of safety. Some herbs are used as spices and are essentially food, others are only used

for their therapeutic value, and a few are toxic and their consumption should be avoided. Botanicals in commerce have been categorized by their degree of safety in a publication by the American Herbal Products Association titled *Botanical Safety Handbook.* In this book, the editors have divided botanicals into four categories. The first category (class 1) consists of those botanicals that can be safely consumed when used appropriately. The second category (class 2) contains herbs for which certain restrictions apply. Included in the third category (class 3) are botanicals for which warnings are appropriate, and in the fourth (class 4) are those botanicals for which insufficient data are available to classify them. As examples, valerian is listed as class 1, devil's claw is rated as class 2d (contraindicated for gastric and duodenal ulcers), and digitalis, which contains glycosides with potent stimulant action on the heart, is rated as class 3 (McGuffin et al., 1997). The *Botanical Safety Handbook* does not include culinary herbs, nor does it include poisonous herbs with restricted medicinal use because of their potential toxicity and small margin of safety. The categories are listed in the book as guidance for readers and are not found on product labels.

The U.S. Department of Agriculture (USDA) classification for plants uses three acronyms: GRAF (generally recognized as food); GRAP (generally recognized as poisonous or medicinal); and GRAS (generally recognized as safe). Some herbs can fall into all three categories depending on the plant part and the type of preparation (Duke, 1992).

In considering the safety of a botanical preparation, the mode of preparation of the botanical, the route of administration, the dose, and the duration of administration are very important. Even if a toxin is present in the plant, it may not necessarily be biologically available. Indigenous peoples have used this concept to their advantage, and many potentially poisonous, even deadly, plants have been used in folk medicine or as food (e.g., cassava). Extraction procedures that destroy or neutralize a toxin have been employed, and careful attention is paid to the dose. For example, in traditional Chinese medicine (TCM), the highly toxic roots of aconite, *Aconitum japonicum* Thunb., are processed at 120°C for 40 minutes before administration. This process hydrolyzes the poisonous aconite alkaloids (aconitine, etc.) into compounds that are less toxic (Croom, 1983).

Bioavailability is also affected by route of administration (topical, oral, or intravenous). For example, the pyrrolizidine alkaloids contained in comfrey, *Symphytum officinale* L., roots (and in the leaves in to a lesser extent) are known to be liver toxins. Therefore, the American Herbal Products Association does not recommend oral administration of comfrey preparations. However, topical administration is acceptable due to the minimal absorption following application of comfrey preparations to unbroken skin (McGuffin et al., 1997).

Many poisonous, even deadly, plants have been used in folk medicine. Examples are jimsonweed, *Datura stramonium* L., for asthma, American mistletoe, *Phoradendron serotinum* (Raf.) MC Johnson, for hypotension, and poke roots, *Phytolacca americana* L., for fever, arthritis, and dysentery. In order for these plants to be used safely, their administration must be carefully monitored by experienced practitioners (Croom, 1983).

PRODUCT QUALITY AS AN ASPECT OF SAFETY

As noted, when evaluating adverse events, it is important to examine the product to rule out adulteration or contamination as a source of the reaction. An ADR or even a toxicity observed only with high doses may result from either substitution or contamination of the declared ingredients with a toxic plant (De Smet, 1996).

As an example, a relatively young woman who had taken a product containing plantain and 13 other herbs was admitted to a hospital for treatment of nausea, vomiting, dizziness, and disorientation. Unexplained cardiac arrhythmias were discovered at the hospital, and a subsequent investigation revealed the substitution of the leaves of plantain, *Plantago major* L. with those of *Digitalis lanata* Ehrh. (Slifman et al., 1998). Whereas plantain leaves are considered safe, those of digitalis contain potent cardiac glycosides that can be fatal when consumed in sufficient quantity (Hardman et al., 1996).

Contamination of plant materials with biological pathogens (e.g., bacteria, viruses, parasites), pharmaceuticals, naturally occurring toxins (e.g., mycotoxins), pesticide residues (e.g., dioxins), toxic metals (e.g., lead, mercury), filth (e.g., insect fragments), and/or radioactivity may also be the cause of an ADR.

CONTRAINDICATIONS

Limited information on contraindications (restriction of use) for botanicals is available. Some information can be found in individual monographs that focus on the therapeutic aspects of botanicals. General consensus exists within the medical community that drugs should be given cautiously to patients with certain chronic medical conditions (e.g., diabetes and heart disease), as well as pregnant and lactating women. This same common sense approach should be applied to herbal products. Because some medicinal plants have also been used as foods, the contraindication is often a relative restriction based upon the size of the dose, the extent of its use, and the type of preparation (Brinker, 2001).

DRUG-HERB INTERACTIONS

Herbs may potentially affect the action of drugs or other herbs when the two are taken concurrently. An herbal product may act as an enhancer or inhibitor of another agent at the site of action. Or it may modify absorption, distribution, metabolism, and/or elimination of that agent.

Little reliable information is available on this topic. A few drug-herb interactions have been documented in human studies or case reports, while others have been observed only in animal studies. However, most proposed interactions are based on in vitro assays and speculation about the theoretical mode of action of the herb or its chemical constituents. Knowledge regarding the mode of interaction of the herb is often extrapolated from in vitro studies using individual chemical component(s) of the herb. This logic assumes that the purified, isolated chemical component or components is biologically available and that plasma concentrations reached following consumption by a human are commensurate with those used in the study.

Although assumptions about the mode of action of a botanical have provided useful leads in investigations of drug-drug interactions and some drug-herb interactions, they also lead to erroneous conclusions. Reports of drug-herb interactions often do not take into consideration product differentiation (i.e., garlic powder versus garlic oil). They often do not consider the dose of the herb or the drug, the dura-

tion of treatment, and other critical variables defined for drug-drug interactions, such as the age and genetic profile of the subject. Even so, lists of potential drug-herb interaction are useful as a basis for further study. Potential interactions have been reviewed in a number of publications (Ernst, 2000; Fugh-Berman, 2000; Brinker, 2001).

Key to many of the drug-herb interactions is the cytochrome P450 family of enzymes. These enzymes are particularly concentrated in the liver but are also present in other tissues, especially the gut. The P450 enzymes metabolize many drugs, essentially clearing them from the body. Many foods and drugs have been found to either stimulate or inhibit these enzymes. Stimulation or inhibition of these enzymes will cause the body to eliminate a drug too quickly or to prevent elimination of the drug, thus allowing the drug to build up in the body. These actions are especially a concern with pharmaceuticals whose plasma levels must be tightly controlled to ensure safety and/or efficacy.

One of the few herbs for which solid human clinical data on herb-drug interactions exist is St. John's wort. The issue was first raised by an HIV researcher who administered the protease inhibitor indinavir to healthy volunteers in conjuction with St. John's wort and found that the herb caused indinavir levels to drop to levels below those required for drug efficacy (Piscitelli et al., 2000). Other reports published around the same time indicated that the same phenomenon might be responsible for acute rejection in organ transplant patients who had used St. John's wort (Ruschitzka et al., 2000; Barone et al., 2000). Clinical experiments soon revealed that a St. John's wort product taken at 300 mg three times daily for 14 days stimulated the activity of a P450 isoenzyme called CYP3A4 (Roby et al., 2000). However, the story may be more complicated, as plasma levels of the anticonvulsant drug carbamazepine, which is also thought to be primarily metabolized via CYP3A4, were not affected by the addition of St. John's wort (Burstein et al., 2000).

Recent attention has also been paid to the effects of herbs on an inducible transport system that moves substrates out of cells. The pump, termed P-glycoprotein (Pgp), is a determinant of the oral bioavailability of many drugs. Here, too, it has been suggested that St. John's wort extract increases intestinal expression of Pgp, and, as a result, it is expected that 900 mg extract per day would decrease digoxin concentrations in heart patients after ten days of use (Durr et al., 2000;

Johne et al., 1999). Digoxin is a cardiac glycoside used in the treatment of a number of heart conditions including cardiac insufficiency. This drug is particularly problematic since it has a narrow therapeutic index, meaning that blood levels must be carefully controlled. As with the P450 enzymes, the story with St. John's wort is complex, as recent clinical experiments have revealed that a St. John's wort extract with a different chemical profile (low levels of hyperforin), but also clinically effective against depression, was demonstrated not to alter digoxin levels (Brattström, 2002).

The possibility that herbal preparations can affect the delicate balance of patients on anticoagulation agents is another concern. The discovery of the anticoagulant warfarin followed reports of cattle having hemorrhagic disorders following ingestion of sweet clover stored in silos (Vickery and Vickery, 1980; Bruneton, 1999). It was revealed that the hemorrhagic effect was due to the conversion of coumarins present in clover to the anticoagulant, bishydroxycoumarin (dicoumarol), by fungi growing on the clover. This background led numerous authors to pose an anticoagulant alert for any botanicals that contain coumarins. However, most natural coumarin derivatives found in plants do not ordinarily possess anticoagulant activity. Indeed, a few natural coumarins, such as esculetin and osthole, may affect platelet aggregation but do not have a similar mechanism of action as warfarin (Brinker, 2001). Therefore, the anticoagulant action of plants containing coumarins is not a certainty, as some reference books indicate (Miller and Murray, 1998; Barnes, Anderson, and Phillipson, 2002).

Until we know more about the modes of action of herbal products and their possible interactions with drugs, sensitive populations such as the elderly, chronically ill, and those with compromised immune systems would be well advised to be cautious when combining herbs and drugs.

IMPROVING OUR KNOWLEDGE OF SAFETY

Improvement in quality control for herbal products will help to assure the safety of herbal products. Conducting postmarketing surveillance studies and refining adverse-event reporting systems will certainly improve our knowledge of adverse reactions attributable to

herbs. More research into potential drug-herb interactions using animal models will help to separate fact from fiction and may yield an unexpected bonus use of herbs as pharmaceutical adjuncts that allow the doses of synthetic drugs to be lowered (i.e., a "good" herb-drug interaction). Pharmacokinetic studies can help us gain information as to the bioavailability of components of a preparation. Certainly our knowledge of the safe use of herbs will continue to expand as we extend to them the same level of scientific scrutiny given other health-related products.

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Chapter 9

Conducting Clinical Trials on Herbal Dietary Supplements in North America: Commercialization, Confidence, and Conflicts

Anthony L. Almada

Query most executives of dietary supplement marketing companies with, "Why don't you sponsor randomized controlled trials on one or more of your products?" and you're likely to receive volleys such as these:

> "They cost too much."
> "We do the pioneering work and then everyone benefits from it."
> "Why should we? We've been successful *without* them."
> "We have stacks of testimonials—we *already* know it's safe and effective."
> "What if the study shows our product *doesn't* work, or is *unsafe*?"

Despite the shortcomings and imperfections of randomized controlled trials (RCTs), they appear to be the best available tool to objectively assess the safety and especially the efficacy of prophylactic, therapeutic, and biological response-modifying agents, which effectively can describe botanical supplements. However, the primary incentives for undertaking research—namely, a rather exclusive position in the marketplace (by virtue of the competitor products almost categorically lacking independent validation of safety and effectiveness) and a consumer confidence-inspiring marketing message—do not appear to be attractive enough to many companies.

This chapter will explore and illustrate why a paucity of ingredient- and product-specific RCTs exist, the advantages and disadvantages of sponsoring RCTs, and both current and future thrusts to invite and recruit a greater commitment to specific, branded products that have been shown to be safe and effective.

THE SPIRIT TO SPONSOR: IS THERE AN ADEQUATE ECONOMIC INCENTIVE TO FUND RESEARCH?

Both short-term (tax incentives, marketing message, public relations campaign) and long-term (increased consumer confidence, market distinction, higher likelihood of being acknowledged by medical professionals, increased corporate value) economic incentives exist for the company that invests in clinical trials in the United States. However, if we examine the profiles of empowered dietary supplement company executives, i.e., CEOs, presidents, and COOs, we uncover a dearth of individuals who have biomedical research training and experience. The path to the pole position in the corporate structure of natural products companies is typically via scaling the sales and/or the marketing ladder. It is understandable to expect such a corporate leader to be challenged by the idea of embracing or even understanding the mechanics of *research and development* versus the norm of *search and duplicate*. Science and research is a wholly different language.

In contrast, if we focus the innovation telescope upon the biotechnology/life sciences communities, it is almost the norm for a leader to have a PhD, an MD, or even a combination of degrees. In the drug pathway, Food and Drug Administration (FDA) regulations mandate the performance of both "test tube" (in vitro) and animal studies (collectively known as preclinical studies), followed up by clinical (human) studies. The barrier to entry here is a compelling safety and efficacy evidence package.

However, unless a dietary supplement is a new botanical ingredient (either singly or in combination) being introduced to the market, *no* scientific evidence is required. The barrier to entry is at ground level. If a company seeks to introduce a new botanical ingredient, i.e., one that was not in commerce in the United States before passage of the 1994 Dietary Supplement Health and Education Act (DSHEA) (the FDA's rules governing dietary supplements) then one needs to

submit only adequate safety or human consumption data, *not* efficacy data. Although safety data are of critical importance, the consumer ultimately may purchase a product that is safe but innocuous—completely without efficacy (independent from the placebo effect).

Afforded the luxury of hyperbole, every company has the same product, makes the same soft efficacy and structure/function claims, and asserts their product(s) is the best, fastest acting, or most "synergistic." My colleagues and I have estimated that less than 0.01 percent of all the different products in commerce fly within the rarefied air accorded those with *product-specific science.*

Hard Costs: Softening the Reality

The challenge confronting botanical dietary supplements, from the perspective of both companies which market them and consumers who use them, is developing a cost-effective manner in which independent RCTs could be initiated. It is also to provide both a return on investment for the companies taking the risk and prescription drug-like confidence among individual consumer buyers. When I was directing research and development (R&D) for a medium-sized dietary supplement company in the early 1990s, I was told by one of the vice presidents that RCTs cost "six figures to half a million." Having previously been involved in a few clinical trials at the University of California, San Francisco, I knew that they *could* meet or exceed that figure, but they absolutely didn't *have to*. Yes, some studies have been done on botanical products to the tune of two million dollars plus. For example, Lichtwer Pharma sponsored a four-year study assessing the influence of its Kwai garlic upon atherosclerotic lesions in otherwise healthy adults (Koscielny et al., 1999).

Assuming one could design an RCT that was a fraction of this cost, do magnetic economic incentives exist to compel action? In other words, are there up front tax benefits for making the investment, back end advantages over the competition, and the promise of greater consumer demand if and when the product is introduced for sale and is marketed?

Manufacturers may not be aware that the execution of RCTs on botanical products is very much within the reach of most companies, even those in their first years of business. If one initially abandons the notion that an RCT must enroll 100 or more subjects, involve sup-

plementation for a year or longer, and employ a battery of expensive diagnostic and invasive measures, then one can envision the fiscal possibility of conducting a study. RCTs can be done for as low as $15,000, with incremental costs being mostly a function of the number of patients/subjects, the number of times the subjects are evaluated for changes, and the actual measures that are being performed. An RCT budgeted at $15,000 likely will not have more than 12 to 14 subjects and two low-cost measurements. Measurements of weight loss, blood total cholesterol, or knee pain, for example, could be made before supplementation and after supplementation ("pre-post"). A rule of thumb to apply is $1,200 to $1,500 per subject enrolled in a study in which simple measures of efficacy are performed and limited to pre-post frequency.

As a case in point, in 1994 my associates and I sponsored a collaborative study at an acknowledged and respected private research center. We collaborated with a cardiologist and a PhD student. We had an ample and motivated patient population (dyslipidemic men and women), a motivated and interested research team, and a willingness to engage in creative budgeting. We completed a 12-week RCT with 33 subjects, presented (Almada, Mitchell, and Earnest, 1996; Earnest, Almada, and Mitchell, 1996b; Mitchell, Almada, and Earnest, 1996) and published the data in a noted peer-reviewed journal (Earnest, Almada, and Mitchell, 1996a), and filed and prosecuted a patent (Almada and Byrd, 1997), all for less than $15,000 (including *all* of the legal fees). Although this was all conducted with a biochemical (creatine), one could apply the same template to a botanical product. Putting this in perspective, this amount is somewhat to far less than many companies' advertising budgets over a fiscal quarter, or sometimes even a month. This raises the question for companies marketing botanical dietary supplements as to how to allocate resources: exclusively for sales, marketing, advertising, and promotions, or accommodating a clinical research budget that grows with the company?

The exceptional RCT example cited is intended to serve as an impetus to readers to create both an awareness of the economic possibility and an earnest interest in pursuing research as a tool to create distinction and enhanced consumer desirability amid a sea of products that all claim to be "safe and effective." Similar collaborative research opportunities exist, in both the academic and the private sectors. One simply needs a skillful and experienced navigator (in-house or out-

sourced) to identify and harness them. The tacit dogma of a CEO's directives does not exclude identifying and constructing strategic research and development alliances and networks. The savvy CEO can inspire her or his management team with a mission of finding and developing cost-effective research alliances that serve the corporate goals and aim to provide consumers with safe and effective products.

Tax Tasking

Another salient message to communicate is that R&D expenditures enjoy special tax treatments. This includes expenditures associated with filing and prosecuting a patent (legal fees) related to a specific invention. Super allowances and tax credits exist for R&D expenditures, which are best identified by a tax professional with relevant experience. If a company is engaged in collaborative contract research, i.e., conducting research in alliance with another outside entity, they can enjoy a higher (75 percent) tax credit. Research qualifies if it simply is technological in nature and is expected to be useful in developing new or improved products for the company in question. Most important, the research can fail and one can *still* use the tax credit. Finding an individual or company who has expertise in this area—research tax credits and incentives—could instantly add to the bottom line. Such tax strategies can be applied both prospectively and retroactively, i.e., filings from previous years.

EXTRACTING VALUE FROM SCIENCE

If one can attach an umbilical cord from a specific branded ingredient or product to its complementary, well-designed and executed RCT data one now has assembled a multifaceted, bow-tied "package," boasting the following features:

- *Regulatory insulation:* Having one or more RCTs on a product, revealing safety and efficacy data, puts a manufacturer in good stead in the event either the FDA or the FTC (Federal Trade Commission) seeks to challenge label or off-label/advertising claims.

- *Off-label marketing communications:* Press releases and press conferences can lead to medium to big media pickup, resulting in free, credible advertising. This may be the most potent tactical tool to generate significant awareness about independent clinical research confirming safety and efficacy of a company's unique botanical product. If the data are first communicated through the forum of a national or international scientific research meeting, the chances of obtaining the interest of a prominent health journalist are augmented manyfold.
- *Competitive advantage:* Entering or existing in the market with product-specific clinical research, which is artfully communicated to the consumer and retailer, can generate immediate distinction for one's own product while creating doubt about other competitor products that claim to be safe and effective but lack any independent, specific evidence. In this era it is likely that the majority of the competition has *no* comparable studies on their actual ingredient or finished good.
- *Competitive insulation/intellectual property:* Even in the absence of a patent, data on a complex ingredient or entity is a form of intellectual property (IP) and provides specific rights to exclude competitors. In some ways branded product-specific science is superior to a patent in that it never expires, is instantly available for use (to exclude others), and is far more expensive for others to duplicate. In contrast, a company must wait for a patent to be issued before it can exclude competitors from practicing the same invention. Regrettably, the strength of a patent is often dependent upon the resources spent defending it.

COMPETITOR KEVLAR: PREVENTING PIRACY OF PRODUCT-SPECIFIC DATA

Perhaps the greatest challenge confronting the natural products industry today is the "borrowing of science," what I prefer to call *data piracy.* Not unlike unfettered *biopiracy*—the theft of natural products from lesser-developed/IP-unsophisticated countries by scientists and attorneys from other countries—these properties are taken and never returned, and no "use tax" is paid. These are *not* books checked out with a library card, destined to be returned. The best examples are illustrated by specific innovator botanical extracts, which were cre-

ated, developed, and ultimately researched by European phytopharmaceutical houses but rendered generic by a spate of other companies who have enjoyed a research-free balance sheet.

Although the transferability of data is not yet proven, companies use clinical research done on other companies' products to prove safety/efficacy of their own products. Do two botanical extracts manufactured by different companies show biological and pharmacological equivalence in humans? An element to the assumption is that the chemical marker compounds comprise most or *all* of the bioactive constituents in the plant. A striking illustration of this is St. John's wort, in which less than 4 percent of the extract composition is comprised of known marker compounds. No data exist to support the assumption that the remaining 96 percent have no bearing upon the biological activity of the extract in humans.

In the face of different chemical compositions between ostensibly identical botanical extracts (no two botanical handprints are identical, even if using the same biomass, unless they are processed identically), how can one logically argue that a generic *Ginkgo biloba* extract is pharmacoequivalent to the patented extract produced by Schwabe (EGb 761) until demonstrated as such? Indeed, one clinical investigation exploring the acute pharmacodynamic effects of three different standardized *Ginkgo* extracts found only one, the innovator product (EGb 761), to demonstrate "superior" central nervous system (CNS) bioactivity in humans (Itil and Martorano, 1995). Although this study used a specific research test to assess bioactivity (quantitative electroencephalography [EEG] readings) which may not be predictive of clinical efficacy, e.g., improved cognitive function, it does offer evidence to strongly suggest that different botanical products claiming to be chemically similar indeed are *not* identical and may differ in their biological activity. Whether this difference in biological activity is related to chemical composition or to bioavailability, metabolism, distribution in body fluids, or transformation by and entry into "target" tissues remains enigmatic.

What about protecting the value invested in an RCT on a proprietary product or ingredient? Let's see how intellectual property can be protected. Company X creates two product compositions, one consisting of (i.e., made solely of) and one containing (i.e., made of, in addition to one or more additional bioactive ingredients) a pine tree-derived extract containing 15 percent phytosterols by weight.

Company X sponsors one RCT on each product, presents the data at a few biomedical research conferences, and even gets one of the studies written up and published in a reviewed journal. After each RCT was completed, company X began to market, sell, promote, and advertise the respective product. Company Y notices one of X's products (and that it is enjoying strong sales growth) and creates its own pine tree-derived 15 percent phytosterol mixture. However, company Y never sponsors an RCT on its product. In its own marketing, promotional, or advertising materials, company Y cites the biomedical conference abstract (published in a supplement of a certain reviewed journal) and the full-length article that appeared in a different reviewed journal, both linked to one of company X's phytosterol products. Company X gets wind of these activities and consults their IP attorney. They then claim "Foul!" and file a lawsuit. Company Y retains its own attorneys, their day in court arrives, and the gavel strikes resoundingly. *Company Y is forever prevented from referring to company X's studies and attributing them to their (company Y's) product*. Is this a fantasy? This is anchored in federal law, but it is rarely invoked.

One such case was decided in Utah Federal District Court in April 1999. The parties were Pharmanex (Utah), then marketers of the proprietary (polymolecular) red yeast rice extract Cholestin, and HPF, LLC (Pennsylvania). The latter marketed a different red yeast rice product called Cholestene. Only Cholestin enjoyed product-specific preclinical and clinical research, but HPF attributed Pharmanex's studies to its own product. As a result, HPF was permanently prevented from making these false attributions, which were asserted by Pharmanex to be violations of the Lanham Act, a federal law in effect since 1947.

Undergoing numerous amendments since its introduction, the Lanham Act is the most potent weapon with which to seek redress for false advertising and attribution. It is an expensive undertaking, but if the measured or forecasted erosion of sales merits such an investment, the marketplace implications are very powerful.

In contrast, if a company sued one or more companies who were claimed to infringe on a patent, the costs would likely be even greater. Patent litigation costs, which proceed to trial, average around $500,000 per case. This enormous economic onus typically would overshadow, or dwarf, Lanham Act litigation.

A much less costly avenue to pursue is the National Advertising Division of the Council of Better Business Bureaus (NAD/CBBB). This independent body serves as a self-regulatory forum for the advertising industry and employs a variety of attorneys who assess complaints submitted by companies from a variety of business interests. The benefits of using this venue include greatly reduced costs (the filing fee is $1,000 to $2,000), a decision within 60 to 70 business days, and the exceptionally high degree of compliance among companies that are ultimately found to have unsubstantiated claims. Advertising in the eyes of the NAD includes labeling nationally advertised vehicles, which would include a Web site. If a product is simply offered for sale on the shelf and is *not* advertised the NAD does nothing. Advertising is subject to review if any person or entity submits a petition to the NAD. If a company fails to respond to a challenge submitted to the NAD, it will be the subject of a press release indicating such, with the possibility of the claim being referred to a federal agency, e.g., the FDA or the FTC. Numerous companies have used the NAD to settle disputes. The entity's Web site is <www.nadreview.org>.

The use of product- or ingredient-specific data to thwart and exclude others from making similar claims is akin to the Coca-Cola strategy, with the "experience" being systemic rather than gustatory. The secret recipe that makes this cola beverage "Coca-Cola" is known by less than a handful of individuals and enjoys more security than the FBI's most classified files. The "efficacy" of this polymolecular syrup is defined by the reproducible, high-fidelity taste experience enjoyed by global users of this product. All attempts to duplicate this recipe have failed. If one can extend the "efficacy" to a systemic process, e.g., deep venous circulation, or skin physiology, e.g., mitigation of inflammatory cell recruitment and cytokine expression in psoriatic lesions, then the user of such a product will enjoy reproducible efficacy. The ultimate objective of investing in clinical research on botanical products is to compel the consumer to try the proven brand and then, through the consumer's experience being positive (the product works), becoming a loyal, enduring customer. The bottom line is making consumers care enough to buy science-backed products versus the cheapest, "prettiest" things on the shelf.

HOW MUCH DATA IS ENOUGH?

How much data is enough to substantiate structure/function benefit claims for dietary supplements? The unwritten rule, voiced by both FDA and the FTC officials, is that two randomized, placebo-controlled clinical trials using state-of-the-art methods, the actual product in question, and statistical analysis yielding a statistically significant difference compared to placebo are required to show efficacy. For consumers, the amount of data required to show efficacy is a highly individualized question—some may say that one study is enough whereas more skeptical consumers would seek or require several studies, and perhaps even some long-term (one year or longer) studies before they would offer it to their children. For health professionals, again the quantity of data required to show efficacy would cover a broad range. A medical doctor may demand several hundred-person studies lasting up to two years (similar to that for prescription drugs) whereas a naturopath or chiropractor may be satisfied with one to two RCTs with a duration of only four to eight weeks.

My colleagues and I have found most prospective sponsors of clinical trials to be confronted with the *designing for dollars* conundrum: they want a great study, worthy of publication in a high-impact factor journal, with stunning statistics, and yet at a bargain-basement price. When asked about how many subjects they had in mind, for some obscure reason the reply most commonly is 60 subjects. For the first foray into sponsored clinical research, my colleagues and I recommend focusing upon the budget rather than the sample size.

Power calculations, which provide researchers with a ballpark estimate of how many persons would be needed in a study to measure a difference between two or more groups, are nice and desirable to perform. The calculated sample sizes depend upon (1) the study hypothesis or "what are we proposing to test"; (2) the amount of variability in measurement of what is expected to change, e.g., blood antioxidant activity or bone density; and (3) an estimate of a clinically meaningful and significant difference compared to presupplementation values and/or a placebo. However, if the sample size estimated via power calculations is prohibitively large, e.g., 84 subjects, does one close the research checkbook? As botanical product marketers do not have billions of dollars in revenue like drug companies, it is an economic impossibility for the majority of them to sponsor RCTs that enroll

hundreds (or even one hundred) subjects. In our experience, a study conducted with two groups of 12 to 15 or more subjects is noteworthy and provides a starting point, a foundation upon which other evidence can be based.

Strategy in product indication and clinical outcome parameter selection assume preeminent importance in designing a clinical study. Because the overwhelming majority of sponsored research is conducted with a return on investment in mind, if the results are not *consumer relevant* and *consumer compelling* why do the trial? For both ingredient and finished product marketing companies, the real selling target is the end user. Does a drop in interleukin-1ß or altered expression of uncoupling protein II mean anything, compared to a decrease in pain or a reduction in body fatness? Consumers and most health professionals will be compelled to read further and inquire into use of the product if the outcome measure(s) encompass at least one clinically meaningful measure, i.e., one that assesses a widely recognized and/or symptomatic or physical feature or attribute. Lowering of diastolic blood pressure, reduction of waist size or body weight, increased head hair growth, elevation of HDL cholesterol, or a reduction in fasting blood sugar, insulin, or hemoglobin A1C are examples of relevance and import to persons seeking to achieve these outcomes.

If the product or ingredient of interest requires a duration of use greater than 30 to 60 days the likelihood of extracting a robust return on investment is slim *or* it will require a string of studies, effectively and repetitively communicated through the media and through advertising, e.g., vitamin E, garlic, and echinacea.

It would appear prudent to choose investigators who have a demonstrated expertise in clinical research, especially in relation to the parameters intended to be assessed, i.e., a family practice physician would unlikely be skilled in assessing a population of osteoarthritic men and women being assessed for responses to a botanical formula purported to modify joint pain and disease progression (unless he or she had done similar research before). In addition, the use of investigators that lack material interests in the product or company marketing the product would be strongly encouraged. Given the policy of many journals and companies to not provide full disclosure of the interests of scientific investigators, many such relationships are opaque to consumers, clinicians, and regulators. Researchers and marketers

are earnestly encouraged to offer full disclosure of any interests, from consultancy fees and honoraria to travel and lodging to equity and stock options.

Mitigation of economic risk in research with innovative, "new to the world" compositions or those enjoying only preclinical (in vitro and animal studies) or anecdotal "validation" may involve taking a path that initially diverges from a phase II study approach. Phase II studies are small-scale RCTs done at a single research center where evaluating the efficacy of a product is the primary interest and the dose range is already established. Thus for a product where the dose response is unknown, it may be financially *imprudent* undertaking a phase II RCT. My associates and I often suggest that manufacturers do an open-label pilot study (six to ten participants) with applications that are much less prone to strong placebo responses, e.g., *not* chronic pain conditions, weight loss or appetite reduction, or mood disorders. Alternatively, employing a small sample size (three to five participants) with a conservative washout period and a crossover offers more statistical rigor, albeit at the expense of greater than doubling the time to completion of the study. These tactics can bolster confidence in going forward with phase II-type studies and still augment the "package" that encloses an ingredient or product invention.

Assuming one has an idea of a dose response or is willing to make the investment in a phase II study, we recommend the sponsored research investment to be dictated by both the budgetary restraints and reality—an RCT (adhering to the guidelines discussed) for $10,000 is unrealistic, as is one with 12 participants (that is, it will carry little weight). A safe number to start with is a sample size of at least 20 subjects, coupled with a power calculation done prior to the study. Although one may not be able to afford a properly powered study in the first round, one can obtain valuable preliminary evidence and, if the product outperforms expectations, achieve both a clinically and statistically significant result. Inevitably subjects drop out, for a myriad of reasons. One does not need to have a larger population to achieve *statistical* nirvana, as the magnitude of "effectiveness" dictates what is or is not statistically significant. For example, if a combination botanical product being tested for its ability to reduce the severity and size of psoriasis-related lesions (represented as a lesional sum score) shows a very large score reduction after four weeks of supplementation, compared to a very small score reduction in the placebo group,

the difference between the two groups (indicative of the effectiveness of the product) will be large. As long as there is not large variability between subjects in both groups, this result will manifest as both a statistically and clinically significant outcome. If the product in question has moderate to dramatic bioactivity or efficacy in vivo, this can likely override variability within and between groups and any psychogenic/placebo effects. Many preliminary drug studies have been published, with an RCT design, "favorable" statistics, and a sample size of only 20 to 30 subjects. This is a start, and a distinctive start indeed. If the results are promising and they are appropriately translated to the customer, incremental revenues can self-fund additional, larger studies, of even longer duration.

WE HAVE DATA—NOW WHAT?

There does not appear to be a need to present or publish the data emanating from sponsored studies, but one cannot underestimate the economic and brand-augmenting value from doing so. Product-specific clinical research that endures the scrutiny of the scientific peer review process and enters into the pages of a medium or high impact peer-reviewed journal brings instant clout to a product and also serves as independent third party evidence of safety and effectiveness. If the publication of such a study is coupled with a strategic media/public relations campaign, the possibility of this news entering a regional or national daily newspaper or even local or national network TV broadcast is imminently higher than if it never had been published. Moreover, the FTC shows favor upon studies that have been published in reviewed journals, viewing such data as having endured some independent scrutiny. Finally, omission of data that are contrary to what is being promoted can position a national marketing and advertising campaign within the central visual and auditory field of the regulatory agencies. The platform of two RCTs supporting the safety and efficacy of *Alpinia galanga* for rheumatoid arthritis will buckle if two or more other studies contravene these findings. Not unlike the blinded patron of justice, the overall weight of the evidence is what is assessed, not only the favorable evidence.

In the rush to begin extracting commercial value from the execution of a clinical research study on a botanical product, many compa-

nies are confronted with the challenge of patience. They can either wait for a scientific meeting (if they are even aware of such an opportunity and strategy) or seek an audience of peers who would likely buy the product on site, i.e., a trade show. One of the most distressing observations is witnessing a company who has sponsored research on a proprietary product or ingredient disseminating the results via presentation at a trade show, or via a press release with a dateline other than from a scientific conference or reviewed publication. The drive to disseminate the data and exploit it often engenders myopic activities such as these, in which the resulting impact is mired in the endemic bog of trade communications. Although this is a facet of data translation that should not be overlooked, what continues to be the onus of the natural products industry is the scrutiny and scoffing originating within the biomedical community. If one can get attention within this "esteemed" community, even without initial acceptance, such dialogue can foster interest and perhaps, with a continued commitment to research investigations, acknowledgement and adoption. Limiting the leverageability of data by avoiding the media-accepted audience of the academic and biomedical research communities diminishes the return on investment and attenuates the promise of greater consumer adoption. However, the allure of being able to both present to the trade (retailers, health professionals) and write orders afterward is hard for many to withstand and may prove irresistible. For some companies the instant gratification and reduced expenditures accompanying presentation of clinical research results at a trade convention may prove ideal.

The astute company plans a communication strategy in which they use the data to drive consumer demand via obtaining media coverage and reinforcing the brand message (not garlic extract but Allipin garlic—fictitious brand) with its own promotions, advertising, and marketing. My colleagues and I believe the best platform from which to obtain the loudest microphone is the national or international biomedical research conference/meeting. These range from the American Heart Association to Experimental Biology to Digestive Disease Week to the American Urological Association. If one such research story is picked up by even a regional newspaper or local TV network affiliate, the ensuing coverage in smaller consumer and trade media vehicles (magazines, local and regional newspapers, health and medi-

cine Web sites) is usually quite robust and the broad downstream cascade is invaluable.

WHO HAS SCIENCE AND HOW DID THEY ACQUIRE IT?

For consumers and health professionals, an appropriate question to ask of any botanical product marketer is simply for copies of any and all studies that support the *actual product being marketed.* If clinical research is provided, one needs to ascertain that indeed the entire product was the subject of the research, not just one ingredient. Last, ask if any of the researchers that conducted the clinical trial have received, are receiving, or will receive any financial or stock compensation for their involvement with the company, or if they happen to be an inventor of a patent related to the product.

CONCLUSION

Sponsoring and completing clinical research on botanical dietary supplements is an achievable reality for many product marketers, offering both direct (sales, marketshare, distinction) and indirect (tax benefits) economic incentives without the need to spend inordinately large amounts. For product consumers and "influencers," e.g., health professionals, the selection and recommendation of products that enjoy specific clinical research provides a degree of confidence in safety and efficacy largely absent from the majority of products on the market. Because proprietary botanical extracts are almost without exception unique recipes, the performance of clinical trials on a specific product confers upon it a form of intellectual property and competitive insulation that has valuable features distinctly different from that of a patent or untested trade secret. One hopes that both consumer purchase selection and corporate direction will steer the botanical dietary supplement industry into the realm of greater confidence and evidence circumscribed by the implementation of rigorous clinical research tools.

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Chapter 10

Motives for Conducting Clinical Trials on Botanicals in Europe: A Focus on Germany

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In the past two decades approximately 80 percent of the clinical research on botanical products has been conducted in Europe or on European products. Though other medicinal systems, such as the Ayurvedic medicine of India and traditional medicine of China, have extensive documentation of the use of botanicals, their use of classic Western preclinical and clinical research methods has been limited.

Several incentives exist for manufacturers in Europe to conduct clinical trials. One reason is to comply with regulatory requirements for product registration. For example, both Germany and France regulate botanical products mainly as drugs. Other incentives for conducting clinical studies include appeal to health care professionals, eligibility for reimbursement by medical insurance, product differentiation, and patent protection.

In order for a botanical product to be classified as a drug in Germany, it must be registered with the German Federal Institute for Drugs and Medical Devices (BfArM or Bundesinstitut für Arzneimittel und Medizinprodukte, <www.bfarm.de>). The product (and/or the ingredients) must comply with a monograph in the *European Pharmacopoeia,* or a pharmacopoeia from another European country—provided that such a monograph exists. Registration requirements are the same as those for synthetic drugs, including full chemical, pharmaceutical, preclinical (animal and in vitro testing), and clinical documentation, along with expert reports evaluating that documentation. Both the preclinical and clinical documentation can be

based on existing scientific literature or on recent research conducted on the product in question. Therapeutic claims for the prevention and cure of a disease that are supported by documentation are allowed. Botanical drugs are sold mostly in pharmacies, and their cost to the patient is often reimbursed by medical insurance. Insurance reimbursement of botanicals is common in Germany, France, Austria, and Switzerland, and, to a smaller extent, in the Netherlands, Belgium, and Greece.

Some botanicals are registered as "traditional" herbal medicines, a subcategory of the drug category. In Germany, a traditional herbal medicine must have been on the market in that country for at least 30 years. Proposed European guidelines would require traditional herbal medicines to be on the market for 30 years, with only 15 of those required to be in Europe. As traditional medicines are drugs, they require full pharmaceutical-quality documentation. In this category, products are allowed to make mild therapeutic claims (e.g., as tonics) that are defined in lists published by the government. Proof of efficacy is not required for these drugs. They often contain multiple ingredients and lower concentrations of botanicals than standard botanical drugs. Some products are combinations of botanicals and nonbotanicals such as vitamins, minerals, or amino acids. Traditional herbal medicines are not reimbursable by medical insurance and often are sold outside of pharmacies in supermarkets, drugstores (German "drugstores" do not contain pharmacies), health food stores, and via mail order.

Other regulatory categories for botanicals are dietary supplements and functional foods. The dietary supplement category in Europe is quite different from that in the United States, as it does not include the typical botanical medicines. The category includes vitamins and minerals as well as some herbal ingredients, such as lycopenes, flavonoids, and broccoli extracts. The dietary supplement category in Europe does not allow for any claims related to health or illnesses.

The system for registration of botanical drugs in Germany has a long history and is based mainly on existing clinical literature. These existing studies are the basis for general monographs of drug preparations in the *German* and *European Pharmacopoeias.* The pharmacopoeial monographs specify manufacturing details, such as the extraction parameters (plant to solvent ratios, solvent, etc.), as well as analytical methods for monitoring quality. Applicable therapeutic

claims and dosage information are not usually listed in the pharmacopoeial monographs. However, they are present in monographs produced by the German Commission E, the European Scientific Committee on Phytotherapy (ESCOP), and the World Health Organization (WHO) (Blumenthal et al., 1998; ESCOP, 1999; WHO, 1999).

Some European manufacturers produce their botanical drugs according to existing monographs. In doing so, they have to follow the quality guidelines listed in the monograph. Products in accordance with such monographs are regarded as complying with the standard and therefore do not need additional clinical studies for registration.

The incentive for many companies to perform clinical trials on their products is to differentiate them from the rest of the products on the market. They can do this by changing the dosage form or the extraction media. They can also develop a new indication (one that is not supported by established literature) or a new combination of ingredients. Changes of this sort require the company to conduct its own clinical studies before it can register its product as a drug. For example, in the Commission E monograph for St. John's wort, the upper dosage is four grams herb or one milligram total hypericin. This dose was usually delivered in a dose of 300 mg extract containing 0.3 percent hypericin. However, following clinical research, dosages of extract were increased to include up to 900 mg extract containing 2.7 mg total hypericin in three divided doses (Schulz, 2002). In addition, data from clinical studies that confirmed efficacy, and did not demonstrate additional side effects, allowed the usual three-times-a-day split dose to be converted to a once-a-day dose (Rychlik et al., 2001).

As mentioned previously, botanical products in some European countries are eligible for insurance reimbursement. Recently, the German system for insurance reimbursement changed so that only those products which have solid clinical documentation are eligible. Products produced under traditional guidelines whose efficacy is not established using clinical trials are mostly no longer eligible for reimbursement. This is a new interpretation of the existing law § 93 "Sozialgesetzbuch." This change provides yet another incentive for German manufacturers to conduct scientific studies on their products.

Another incentive to document the efficacy of a product with clinical studies is to appeal to health care professionals. Half of the products in the drug category are recommended by doctors either through

private prescription (not reimbursed by health insurance) or prescription with reimbursement. The other half of products in the drug category are purchased for self-medication, either directly requested by the patient or recommended by a pharmacist (Schwabe and Paffrath, 2001). In order for health care professionals to prescribe or recommend a product, it is essential for that product to have well-accepted scientific backing. For this reason, some manufacturers have chosen to document the efficacy of their products by performing double-blind, placebo-controlled trials. Examples of companies that perform these types of trials are Bionorica Arzneimittel, Dr. Willmar Schwabe Pharmaceuticals, Lichtwer Pharma AG, Madaus AG, Max Zeller Sohne AG, and Schaper & Brümmer GmbH.

Based on this approach, several herbal products that previously had only a small role in the market have become major players. This increase in popularity has occurred not only locally in Europe, but also internationally. In the past 20 years, completely new markets were created for botanicals based upon scientific support. Two good examples are garlic for reduction in cholesterol levels and St. John's wort for relieving depression. For both botanicals, there were already German Commission E approved monographs for these indications. However, several companies chose to develop these products by conducting additional good-quality clinical research. As a result, they have developed a worldwide market for garlic and St. John's wort in the range of approximately 300 and 500 million U.S. dollars in annual retail sales, respectively (Gruenwald, 2002). In a similar example, solid scientific data have enabled Indena S.p.A., an extraction company based in Italy, to become an internationally preferred source for numerous manufacturers.

Another incentive for the development of proprietary versions of botanicals and new combinations of botanicals is that of patent protection. However, patents for botanical preparations are often easier to circumvent than synthetic pharmaceuticals, as their specifications are often broad. In addition, obtaining the patent is only the first step, as the strength of a patent often depends upon the effort spent to support it. An example of a strong patent, with a combination of unique manufacturing specifications for upper and lower limits for several ingredients and broad clinical documentation, is that for Schwabe's ginkgo extract, EGb 761. As a result of this extensive documentation, the Commission E monograph for ginkgo is written according to

specifications for EGb 761 (Blumenthal et al., 1998), and Schwabe has established an almost exclusive market for its product in Germany.

Many clinical trials are not performed to receive a new registration or patent for a product; rather, they are conducted to promote and maintain existing registrations and for marketing purposes. For the majority of European manufacturers, clinical trials are used as additional marketing tools to improve their products' image in the eyes of the consumers. This concept of conducting trials for marketing purposes and to promote individual product recognition is developing internationally. Almost all of the successful botanical products in Europe have several well-controlled trials to support their use.

Top manufacturers follow the requirements for pharmaceutical drug clinical trials, i.e., they perform randomized, placebo-controlled or comparison trials with competitive products and follow good clinical practice (GCP) standards. However, a number of other forms of clinical trials are also common, including open (not blinded) trials, drug-monitoring trials, and small pilot studies. These trials can be used successfully for marketing and public relations purposes.

In addition, trials have been performed in order to expand population likely to use a product. As an example, manufacturers of some products with a record of safe use in adults are seeking to extend their products' use to children. In the past, administration to children was common, but only a few trials with children under 12 have been conducted. As a result of a review of existing data, the number of products allowed for use in children in Germany and in Europe has diminished tremendously (Gruenwald, 2002). For this reason, a political initiative has begun that urges manufacturers to perform trials on children in order to confirm the safety and efficacy of certain products for that population. For example, a multicenter, postmarketing surveillance study was carried out with 101 children aged one through twelve years assessing the use of St. John's wort (extract LI 160) for depression and psychovegetative disorders (Hubner and Kirste, 2001).

Conducting clinical trials also allows manufacturers to expand their worldwide distribution. For example, most European botanical products enter the U.S. market as dietary supplements. These products may be produced entirely by the European manufacturer. Alternatively, the raw materials or extracts from Europe can be reformu-

lated and/or packaged by American manufacturers. However, a number of European companies (along with American companies) are in the process of applying to the U.S. Food and Drug Administration (FDA) for drug status for their products in the United States. In order to comply with the FDA drug requirements, clinical trials need to be performed according to the scientific rigor of good clinical practice, i.e., placebo-controlled, double-blind studies.

A disincentive for the investment of companies into studies on botanical medicines is the financial risk involved in what may possibly be a negative clinical trial. Another disincentive is the limited exclusivity that manufacturers obtain with their clinical trial data. Even if a patent is obtained, it can require substantial investment to defend. In addition, if a clinical study is published, competitors may use that data to support their own products. This phenomenon, often called "borrowed science," is common in the United States.

In summary, the incentives for European manufacturers to conduct clinical studies include registration of a product as a new drug or registration for a new indication. Additional incentives include marketing advantages that come from differentiation from other products on the market, appeal to health care professionals, and patent protection. Further, experience indicates that conducting clinical trials can lead to expansion of the market and the population likely to take the product. Finally, conduction of clinical research and tight regulation of quality have allowed botanical products in Germany to be part of the mainstream health system.

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Chapter 11

Pharmacopoeias and Botanical Monographs

Marilyn Barrett
Roy Upton
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In order to ensure both the safety and efficacy of conventional and herbal drug products, quality control standards are required. Once the character, quality, and strength of the product are specified, then guidelines for therapeutic use can be established. These standards and guidelines are provided in texts known as pharmacopoeias (also spelled pharmacopeia, the spelling used by the United States Pharmacopeial Convention) or compendia. A pharmacopoeia is a collection of monographs that contain technical information on specific medicinal agents, including botanical and pharmaceutical drugs as well as inert additives used in the formulation of drugs. Some pharmacopoeias, and hence their monographs, are made official through governmental recognition. In this instance, compliance with the specifications in the monograph is enforced by governmental regulation. Monographs are of three basic formats. They contain information on quality, therapeutic use, or both.

Monographs that focus on quality contain information, assays, and specifications useful in assuring identity and purity. For botanical agents, these monographs include the plant names (common name and Latin binomial), plant part, and criteria or definition of the substance, as well as descriptions of the whole and ground plant material, along with chemical constituents. The *United States Pharmacopeia, European Pharmacopoeia, British Herbal Pharmacopoeia, Pharmacopoeia of Japan,* and *Ayurvedic Pharmacopoeia of India* contain monographs of this sort.

Therapeutic monographs vary greatly in scope and detail. They typically include information on therapeutic indication, dose, dosage forms, pharmacology, contraindications, drug interactions, side effects, and toxicology. Examples include the monographs of the *United States Pharmacopeia—Drug Information,* German Commission E, European Scientific Cooperative on Phytotherapy, and *British Herbal Compendium.*

The American Herbal Pharmacopoeia and the World Health Organization produce monographs that combine both quality control standards and therapeutic information.

UNITED STATES PHARMACOPEIA AND NATIONAL FORMULARY (USP-NF)

The *United States Pharmacopeia–National Formulary (USP-NF)* is the officially recognized standard for drugs in the United States. The first version of the pharmacopoeia was published in 1820 by the United States Pharmacopeial Convention, a private, nonprofit organization. The pharmacopeia was revised every ten years from 1820 to 1942, every five years until 2000, and, following the 2002 edition, it will be revised every year. In 1975, the USP acquired the National Formulary and started to publish both of them in a single volume, titled the *United States Pharmacopeia–National Formulary* (*USP-NF,* 2004). In a separate publication, the *United States Pharmacopeia—Dispensing Information (USP-DI)* provides a review of the clinical and pharmacological data, dosage recommendations, and safety assessments to assist health professionals and consumers in the appropriate use of drugs (USP-DI, 2003). In addition, the USP organization provides the reference standards to be used in the methods described in its monographs.

The *USP-NF* is recognized in several statutes and regulations, including the U.S. Federal Food, Drug, and Cosmetic Act and its amendments. These regulations stipulate that if a drug does not conform to *USP* standards for strength, quality, and purity, it is considered adulterated. The *USP* also has official governmental recognition outside the United States in over 40 countries, both developing and industrialized (*USP-NF,* 2004).

The *USP-NF* contains approximately 4,000 monographs containing tests and standards for assuring the strength, quality, and purity of drug substances and products (*USP-NF,* 2004). In general, monographs for active ingredients and preparations appear in the *USP* section of the book and the *NF* contains botanical dietary supplements and excipients (ingredients that aid in the formulation of drugs). With the publication of the 2004 edition, a new section was created in the *USP* for dietary supplements. Previously, monographs for botanicals marketed as dietary supplements were published in the *NF* as they are not subject to premarket approval by the FDA.

In the first edition of the *USP,* approximately 600 botanicals and botanical preparations were recognized. By the turn of the twentieth century, only 169 botanicals remained. Many of the original plant drugs were removed and supplanted by synthetic compounds and their preparations. By 1990 the USP was estimated to contain only 25 botanical drug preparations (Grady, 1994). At that time, the USP resolved to expand its scope to include monographs on nutritional supplements containing vitamins and minerals. In 1995, the USP adopted a resolution to once again develop monographs for botanicals currently being sold as dietary supplements. Since then the USP has proceeded with the development of a number of monographs for raw plant materials, extracts, and final formulations.

The primary goal of the USP regarding botanicals is to develop monographs for those widely used by the American public and constituting 90 percent of the monetary sales in the U.S. market (approximately 25 botanicals). Aside from market share, other criteria are applied in the identification and prioritization of botanicals for monograph development. These include evidence for historical use in traditional medicines; safety; availability of literature documenting pharmacological activity; identity and chemical constituents; and availability of reference standards used to document compliance with specifications for identity and quality.

Information monographs, containing therapeutic information, were prepared for inclusion in the *USP-DI* on ginger rhizome, valerian root, feverfew leaf, St. John's wort flowering plant, and saw palmetto berry. In addition, a negative monograph was published on comfrey, discouraging its use for safety reasons. In 2000 the USP established criteria for levels of evidence for judging the safety and efficacy of

botanical dosage forms and published these in the USP Web site (www.usp.org).

The USP continues to develop and establish monographs defining standards of quality for botanicals and their preparations. However, the development of information monographs on botanicals has been discontinued.

AMERICAN HERBAL PHARMACOPOEIA (AHP) AND THERAPEUTIC COMPENDIUM

The American Herbal Pharmacopoeia (AHP) is a private, nonprofit organization founded in 1995. The purpose of the AHP is to develop quality control standards and to critically review the therapeutic data for botanical supplements sold in the United States. Although lacking official government recognition, *AHP* monographs are considered authoritative and are accepted as compendial standards by many organizations.

AHP monographs cover botanicals with their origins in traditional Ayurvedic, Chinese, and Western herbal traditions. They provide a synthesis of traditional and scientific information.

The monographs are published individually, with the first *AHP* monograph published in 1997 on St. John's wort (Upton et al., 1997). As of the beginning of 2004, a total of 18 monographs had been finalized and another 30 were in development. The goal is to develop a total of 300 monographs.

The quality control section of each *AHP* monograph includes nomenclature standards, several methods of identification, purity standards, several methods of qualitative and quantitative chemical assessment, as well as guidelines for proper harvesting, storage, and processing of botanicals. Unlike all other pharmacopoeias, the *AHP* includes detailed graphics for use in raw material identification and detection of potential adulterants. The analytical methods are carefully chosen following an extensive review and are then subjected to trial and validation by a minimum of two independent laboratories.

The *Therapeutic Compendium,* another section of *AHP* monographs, provides a detailed and critical assessment of the currently available clinical and pharmacological literature. This enables the reader to determine the level of evidence available for specific thera-

peutic applications of each medicinal plant. Recommendations for dose are provided from both the traditional and scientific literature. Also included is a detailed review of safety aspects including side effects, contraindications, drug interactions, use in pregnancy and lactation, mutagenicity, and toxicology.

Each monograph contains many separate sections written by experts in those particular areas of botanical medicine. Once compiled, the monographs are subjected to an extensive peer review process. The reviewers are a multidisciplinary committee of medicinal plant experts worldwide, including botanists, chemists, herbalists, pharmacists, pharmacologists, and physicians.

EUROPEAN PHARMACOPOEIA (EP)

The *European Pharmacopoeia (EP)* was founded by eight states (Belgium, France, Germany, Italy, Luxembourg, Netherlands, Switzerland, United Kingdom) in 1964. It has since expanded to many other nations both within and outside the European Union. The pharmacopoeia is published by the Directorate for the Quality of Medicines of the Council of Europe (EDQM) in accordance with the Convention on the Elaboration of a European Pharmacopoeia (European Treaty Series No. 50). It is an official compendium for establishing the quality control standards, replacing the old national pharmacopoeias for member nations. It is currently in its fourth (2002) edition, and the fifth edition will be effective in January 2005. The pharmacopoeia contains specific monographs governing the quality of specific herbal products and it also contains general monographs that apply to all unspecified extracts, herbal drug preparations, herbal drugs, and herbal teas (Ph Eur, 2002).

BRITISH HERBAL PHARMACOPOEIA (BHP) *AND* BRITISH HERBAL COMPENDIUM (BHC)

The *British Herbal Pharmacopoeia (BHP)* is published by the British Herbal Medicine Association and written by the members of its Scientific Committee. The *BHP* monographs do not have official government recognition. *BHP* monographs establish standards of

quality control and purity for botanical raw materials but not for final product forms. The first monographs were published in 1971. A pharmacopoeia, with 232 monographs containing both quality and therapeutic information, was published in 1983. A subsequent edition with revised format emphasizing quality standards covering 84 botanicals was published in 1990 (*BHP,* 1996). Therapeutic and regulatory information were published separately in 1992 in a volume called the *British Herbal Compendium (BHC)* (Bradley, 1992). In 1996, an expanded version of the *BHP* incorporating an additional 85 monographs was published, thus providing quality standards for 169 botanicals (*BHP,* 1996).

GERMAN COMMISSION E

The German Commission E is an independent scientific committee of experts established in 1978 by the German Federal Health Agency for the evaluation of the therapeutic use of herbal remedies. The committee evaluated information on the safety and efficacy of crude herbal drug preparations and gave either a positive or negative assessment in a published monograph. In the case of a positive finding, the monograph was structured as a package insert, providing precise directions for use, including dosage, approved actions, side effects, drug interactions, contraindications, and chemical constituents. In the case of a negative decision, the monograph explains why the botanical was perceived to lack benefit. Monographs were first published as drafts for public comment, and then the final version appeared in the *Federal Gazette,* or *Bundesanzeiger.* Approximately 300 monographs were published before the Commission suspended monograph writing in August 1994. The Commission E monographs have been translated into English and published by the American Botanical Council (Blumenthal et al., 1998). When the Commission was actively writing monographs, those monographs formed the primary basis for approval of health or disease claims on botanical products in Germany. However, due to the availability of new scientific data, the Commission E monographs are no longer considered to be sufficient for governmental approval of therapeutic claims. The current focus of the Commission is to review the registration of botanical drugs in Germany.

EUROPEAN SCIENTIFIC COOPERATIVE ON PHYTOTHERAPY (ESCOP)

The European Scientific Cooperative on Phytotherapy (ESCOP) was formed in 1989 with the purpose of advancing the scientific status of phytomedicines and to assist in the harmonization of their regulatory status in Europe. ESCOP members include associations from the majority of countries within the European Union and from a number of non-European Union countries. ESCOP monographs are therapeutically oriented and do not include information on quality.

Monographs are initially written by individuals with professional backgrounds such as medical doctors, phytotherapists, pharmacognosists, and regulatory specialists. The drafts are then circulated to members of ESCOP's Scientific Subcommittees for review and discussion. The subcommittee prepares a second draft, which is reviewed by a board of supervising editors consisting of academic experts in phytotherapy and medicinal plant research. This process ensures that each monograph that is developed is reflective of many national viewpoints and the advice of many authorities on the subject. The final document is published and submitted to the Committee on Proprietary Medicinal Products of the Commission of the European Community (EEC). Between 1996 and 1999, six fascicles, each containing ten monographs, were published. More recently these original monographs were revised and twenty monographs added to produce a publication containing 80 monographs (ESCOP, 2003). The monographs are recognized by the European Medicines Evaluation Agency of the Council of Europe.

CHINESE PHARMACOPOEIA

The *Pharmacopoeia of the People's Republic of China* is now in its seventh edition, also known as the *Chinese Pharmacopoeia 2000* or *Ch.P.2000*. The People's Republic of China's Ministry of Public Health first published the *Chinese Pharmacopoeia* in 1953. The current pharmacopoeia is published in both English and Chinese and contains two volumes. Volume I includes 992 monographs of Chinese materia medica (botanicals and other crude drugs of natural sources) and traditional Chinese patent medicines (specified formu-

lations). As many as 602 botanical monographs in Volume I specify thin-layer chromatography for identification, and about 300 monographs specify quantitative analytical techniques (liquid or gas chromatography) for chemical constituents. Volume I also contains actions and indications of the botanicals and other crude drugs of natural sources. Volume II contains monographs on chemicals, antibiotics, biochemicals, radiopharmaceuticals, and biological agents (The Pharmacopoeia Commission of PRC, 2000).

AFRICAN PHARMACOPOEIA

The *African Pharmacopoeia* was published in English, French, and Arabic in a collaborative effort by the Council of Ministers of the Organization of African Unity (OAU) with the United Nations Industrial Development Organization, World Health Organization, and other donor agencies. This effort established the African Center for Traditional Medicines. Publication of the first edition of the *African Pharmacopoeia* was in two volumes. Volume I was published in 1985 and Volume II in 1986. Volume I includes 95 monographs containing names, botanical descriptions, uses, and geographical distributions of herbal drugs. Volume II is a companion to the first volume and contains general methods of quality control analysis (Inter African Committee, 1985-1986). Copies of the *African Pharmacopoeia* are difficult to locate and publication has not continued.

THE PHARMACOPOEIA OF JAPAN

The *Pharmacopoeia of Japan,* Fourteenth Edition, was published in 2001, in two parts. Included in the *Pharmacopoeia* are quality guidelines for crude drugs obtained from plants, animals, and minerals. The *Pharmacopoeia* contains guidelines for purity and identity for over 165 raw herbs used in traditional Kampo medicines. Kampo medicines, which are based mostly on decoctions of herbs, are indicated by prescription and reimbursed by Japan's national health insurance program (*The Pharmacopoeia of Japan,* 2001).

THE PHARMACOPOEIAS OF INDIA

The Ayurvedic Pharmacopoeia of India is the legal document of standards for the quality of single drugs of plant origin. The Ayurvedic Pharmacopoeia Committee was formed in 1963 to write monographs detailing identity, purity, and strength. Volume I, first published in 1986 by the Department of Health, Government of India, contains 80 monographs. Recently the Controller of Publications in Delhi has reprinted Volume I (2001), along with Volumes II (1999) and III (2001). Volume II contains 78 monographs, and Volume III contains 100, for a total of 258 single plant drugs in the three volumes. Volume IV is under preparation. A total of 636 combination formulas are described in *The Ayurvedic Formulary of India* (Volumes I and II contain 444 and 192 formulas, respectively), published by the Government of India (*The Ayurvedic Formulary of India,* 2001).

Another traditional form of medicine in India is Unani. The Unani Pharmacopoeial Committee in the Ministry of Health and Family Welfare, India, has recently prepared Part I of the *Unani Pharmacopoeia of India* containing 45 monographs on single drugs of plant origin. However, there is no official publication yet by the government of India.

WORLD HEALTH ORGANIZATION (WHO)

The World Health Organization (WHO) has had a long tradition of supporting the appropriate use of botanicals in the health care systems of both developed and developing nations (Akerele, 1993). The WHO is currently publishing model monographs in order to facilitate the proper use of high-quality herbal medicines in WHO member states (countries). The goal is to provide a model for assisting member states in developing their own monographs and to facilitate information exchange. The monographs are presented in two parts. Part 1 focuses on quality assurance, botanical features, geographic distribution, identity tests, purity requirements, and a listing of chemical constituents. Part 2 summarizes clinical applications, pharmacology, posology (dosage), contraindications, precautions, and potential adverse reactions. The monographs are prepared under the direction of

the WHO Collaborative Center at the University of Illinois–Chicago. Volume I, containing 28 monographs, was published in 1999, and Volume II containing an additional 30 monographs, was published in 2002 (WHO, 1999-2002). Volume III with 31 monographs is to be released soon, and IV is in development.

OTHER PHARMACOPOEIAS

In addition to the compendia described herein, the majority of nations have either official or unofficial pharmacopoeias. Although some are available in English, most are published only in their native languages. Numerous other books containing profiles of medicinal plants are considered to be authoritative and may be used by governmental agencies. The degree of accuracy and depth of information in these texts is variable.

SUMMARY AND PERSPECTIVE

The pharmacopoeias described offer a number of authoritative sources for information regarding the quality of botanicals. In addition, but not described in this chapter, both national and international standards for manufacturing of botanical products also exist. Together, the monographs and manufacturing standards have been developed to assure a level of quality and consistency for therapeutic products. Once the quality and consistency of products are assured, then guidelines may be established for therapeutic use.

In the United States, compliance with quality standards set by the USP for products sold as drugs is mandatory. Under current federal regulations, compliance for products sold as dietary supplements is voluntary. However, dietary supplements are not without regulation, as federal law dictates that botanical products sold as dietary supplements accurately disclose their ingredients, be free of pathogenic microbes and other contaminants, and be truthful regarding any claim regarding health benefits. Only if the USP name is put on the label of the product must the product conform to USP specifications. The AHP also provides guidelines for assurance of identity and quality, and the same rules apply. Seals of quality have begun to appear on dietary supplements, which vary in meaning depending upon their cer-

tification process. Both the USP and NSF International, a Michigan-based company, have begun to offer seals based on manufacturing site inspections as well as product quality testing. Until these and other mechanisms of assuring quality are more widespread, consumers and health professionals must take an active role in investigating the quality of botanical supplements they are contemplating consuming or prescribing.

SOURCES OF PHARMACOPOEIAS

American Herbal Pharmacopoeia and Therapeutic Compendium
P.O. Box 66809
Scotts Valley, CA 95067
Tel: 831-461-6318
FAX: 831-475-6219
Web site: www.herbal-ahp.org

American Botanical Council
P.O. Box 144345
Austin, TX 78714
Tel: 512-926-4900
FAX: 512-926-2345
Web site: www.herbalgram.org
(Source for *British Herbal Pharmacopoeia* and ESCOP monographs)

United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852
Tel: 301-881-0666
Fax: 301-816-8374
Web site: www.usp.org

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PART II: METHODS

Chapter 12

Methods of Product and Trial Inclusion and Evaluation

Marilyn Barrett

This chapter describes the methods used in generating the second half of this book. A description of how the information on products and clinical studies was collected is included. Also described are the selection criteria for both products and trials. The origin of the system used to evaluate clinical trial quality is also explained. Some of the main challenges encountered during the selection of products and the evaluation of the clinical studies are discussed. The criteria for evaluating the quality of the clinical trials are provided in Chapter 13, "Clinical Trial Reviewer's Guidance and Checklist."

GATHERING INFORMATION ON PRODUCTS AND TRIALS

We used two approaches to gathering products and clinical trial publications for inclusion in the book. The first approach was to contact manufacturers in the United States to ask if they had any products that had been evaluated in clinical studies. The second approach was to identify products from clinical studies published in the scientific literature. Once a product was identified from the literature, the manufacturer was contacted for further information.

In the first approach, manufacturers were contacted in letters sent out in July 1999. These letters were followed up with e-mails and telephone calls. The list of manufacturers was compiled from membership lists of American Herbal Products Association (AHPA), Council for Responsible Nutrition (CRN), and National Nutritional Foods

Association (NNFA). Approximately 200 manufacturers were contacted. Manufacturers were asked for copies of product labels and for reprints of the corresponding clinical literature.

In the second approach, clinical literature was identified through searches of Medline and Embase literature databases in the summer of 2000. Clinical trial reports were also identified through perusal of the author's personal files as well as from reference lists in books and review articles. Clinical trial literature was obtained from local libraries or requested from manufacturers. Translations of literature in Italian, German, and French were commissioned in a few instances. More often the manufacturer supplied the translation.

The list of botanicals to be included in the book was set in December 2000. At that time, we began to send the clinical literature to reviewers for evaluation of the quality of the trials. In the spring and summer of 2002, searches of Medline and Embase were repeated, and more recent trials were added to the original set. New trials were generally included if the botanical product used in the study was already included in the book.

Selection Criteria: Products and Trials

Selection Criteria for Products

- Products containing powdered plant material, teas, juices, oils, tincture, extracts (either simple or semipurified), etc., were evaluated for entry. Formulas containing multiple botanical ingredients were also evaluated for entry. Products containing only purified chemicals derived from plants were excluded.
- Products assessed in controlled clinical trials were evaluated for entry. Products assessed in studies without a control (placebo or other medication) were not included.
- Products sold in the United States were included as a first priority. However, products not for sale in the United States were also included. The purpose of including products sold outside the United States was to complete the profile of a botanical or formula that was already included and/or to supplement the understanding of the activity of that botanical. In a few instances, products that were for sale in the United States when originally included are no longer for sale in the United States. They are still included in the book.

- Products with raw material ingredients (i.e., extracts) that have been clinically tested, but whose final formulation has not, were included (see comments in the subsection regarding challenges in the selection process). If the final formulation included additional active ingredients, then that product was not included.
- Generic (unbranded) preparations tested clinically were included in many instances to help with the understanding of the activity of a botanical already included.

Selection Criteria for Clinical Trials

- Trials that included either a placebo or alternate medication as a comparative control were evaluated for entry. If a product or botanical was already selected for entry, then comparative dosage studies were allowed.
- Trials were generally not included if the test product was not described in sufficient detail as to allow for replication of the study. Leeway was granted for proprietary products, as it was assumed that more information could be obtained from other sources (see comments in the subsection regarding challenges in the selection process).
- Trials published after 1980 were given priority over those published earlier.
- Published and unpublished studies were accepted.
- Trials not easily translated or obtained in the English language were not profiled and were not reviewed as to their level of evidence.
- Full clinical papers were required for inclusion. Study abstracts were not sufficient to be included.
- Epidemiological studies, postmarketing surveillance studies, systematic reviews of clinical trials, and meta-analyses of clinical studies are mentioned in the botanical summary evaluations but are not profiled in detail and were not reviewed as to their level of evidence.

Challenges in the Selection Process

At the beginning of the book project, the product entry criteria were broader than they ended up being. I thought that if I included

only products directly tested in clinical studies, then I would necessarily be selecting for European products. I was therefore originally prepared to include products manufactured in the United States with specifications equivalent to those of products tested in clinical studies. In other words, I was ready to include products containing an extract or extracts made to the same specifications as a product tested in a trial. Specifications were to include the plant part, extraction method, extraction solvent, standardization parameters, and recommended dose. However, I found that this process of judging equivalency was not feasible. Even if products appeared to be chemically equivalent from the information available to me at the time, there was no guarantee of therapeutic equivalency (see Chapter 6 on borrowed science). In addition, I found in practice it was very difficult to obtain sufficient information to determine chemical equivalency. Also, manufacturers that had conducted clinical studies on their product(s) were, understandably, not eager to participate in a program that assisted their competition in "borrowing" their scientific studies. I therefore decided to include only products that had been directly tested clinically.

The only caveat to this rule is that I decided to include products containing extracts which had been tested clinically, even if the final product formulation had not been tested clinically. I made this decision for a number of reasons. First, some trials were conducted on extracts and did not name a final product. Second, I knew there was no way that I could determine if the final formulation had changed since the time of the trial. In addition, if a European extract was formulated in the United States, that formulation might be expected to be different from its European equivalent.

As an example, a few trials mentioned the ginkgo extract EGb 761 but gave no product name. Nevertheless, the book ties all the trials on EGb 761, whether a product was named or not, with two products in the United States that contain the EGb 761 extract: Ginkgold (Nature's Way Products, Inc.) and Ginkoba (Pharmaton Natural Health Products). These products differ in the excipients used in the final formulation. Another example is the St. John's wort extract Ze 117, manufactured by Zeller AG of Switzerland which is made available in two different final formulations by General Nutrition Corporation and Rexall Sundown.

Another consideration is the case of an Italian extract manufacturer, Indena S.p.A., who makes many extracts that have been tested

clinically. Indena sells extracts to manufacturers around the world, who then formulate them into their own products. Some of those manufacturers have conducted clinical trials on their final formulation, while others have not. For those who did not conduct their own trials, we relied on verification from Indena that the manufacturers' product(s) did indeed contain the Indena extract(s) that have been clinically tested. These products are listed separately from those that have been tested in their final form. As an example, listed separately are several products available in the United States that contain the Indena St. John's wort extract (St. John Select), namely, St. John's Wort Extract by Enzymatic Therapy, Hyper-Ex by Thorne Research, and Hypericum perforatum II by Hypericum Buyers Club. With the exception of the Hypericum Buyers Club product, which has been used in two drug interaction studies, these products have not been tested clinically in their final formulation. Listed in the main summary table are the U.S. product Kira and the European Union (EU) product Jarsin, both manufactured by Lichtwer Pharma AG, Germany. The clinical trials have been conducted either with the Lichtwer product final formulation or the Lichtwer extract LI 160. LI 160 is supplied by Indena and also known as St. John Select.

It is also difficult to determine whether the products on the market today are equivalent to the products tested in the clinical studies. Products with the same name may change in composition. For example, there have been changes in the extraction solvent used in the preparation of Remifemin (Schaper & Brümmer GmbH & Co. KG, Germany), a black cohosh product; however, these changes do not appear to have affected activity (see the black cohosh summary). Changes to the coating on Kwai (Lichtwer Pharma AG, Germany) garlic tablets, however, may have changed the bioavailability of the contents, resulting in a change in activity (see the garlic summary). An even more interesting example is the red yeast rice product, Cholestin. The U.S. version of the product no longer contains red yeast rice, due to a federal order. A formula with an alternate active ingredient is now marketed under the same name (see the red yeast rice summary). More problematic are complex formulas whose ingredients may have changed over time. In many cases, there is insufficient detail in the description in the study report to determine whether the product sold today is the same as the one used in the trial.

The lack of an adequate product description in the clinical study was often a problem. Ideally, the scientific name of the plant, the plant part, preparation details, as well as commercial name and manufacturer should be included. My assistants and I found many cases of inadequate descriptions of products, and the most egregious were not accepted into the book. If a product was described using a proprietary name, I decided to accept that description as adequate, the rationale being that the product details would be available from the manufacturer. However, I also realize that it is important to keep in mind the caveats listed previously.

Products that were provided by contract manufacturers under a private label were not included in the book. This is because the manufacturer and source of the raw material remain a secret and thus there is no assurance of continuity or uniformity of these products over time. As an example, a study conducted with a ginkgo product provided by Walgreens Co., Deerfield, Illinois, was not included. Walgreens is a retail pharmacy that does not manufacture botanicals. The product it offers is obtained via a private labeling contract that enables it to put its name on the contract manufacturer's product. The contract manufacturer is not named on the label and may change from time to time. Even if Walgreens continues to use the same contract manufacturer, the raw material supplier for that manufacturer may change.

In a few cases in which the trial was negative, the product was not described by brand name, instead being replaced by a seemingly generic description. Sometimes further research on our part would determine the true identity of the material. Sometimes, it would not.

A good deal of the information regarding the European products has come from the trials themselves. Not much detail regarding usage guidelines was easily available in English. Also, I do not know if they are still offered for sale or have changed names.

DATA ON PRODUCTS AND TRIALS

Product Information

Product information included in the book is almost entirely from the product labels. In some instances, the label information is supplemented with facts from clinical studies, product information supplied

by the manufacturer in promotional leaflets, company Web pages, and direct communication with the manufacturer.

When possible, the information on the botanical ingredients includes the name, the plant part, whether the material in the product was dried plant material or an extract, the quantity of that material, processing details, the name of the extract (if any), and standardization criteria.

In addition, information is included regarding the manufacturer of the product or extract, the distributor of the product in the United States, formulation (liquid, capsule, tablet), recommended dose, indications as to use (Dietary Supplement Health and Education Act [DSHEA] structure/function statements, unless otherwise noted), cautionary statements, other ingredients, miscellaneous comments, and the source(s) of the information.

Challenges in Product Information

The biggest challenge to the inclusion of the product information is keeping up with the changes in the market. While this book was being compiled some products were taken off the shelves. In a few instances the distribution of the product was transferred to another company. The end result is that some of the product information listed in the book may not be up to date.

Trial Information

Clinical trial information included in the book has been abstracted from the full clinical paper. The clinical study information includes the bibliographic reference, a summary of the product description (botanical name, product name, extract name, and manufacturer), and the therapeutic indication tested in the study. Information regarding the trial design includes a summary description, duration, dose, route of administration, randomization, blinding, and whether a placebo or another agent was present for comparison. Also included is information on the site of the study. The number of subjects enrolled and the number completing the study are presented. Details as to their age, sex, and inclusion and exclusion criteria are outlined. The end points of the study, measurements that were used to determine efficacy or clinical benefit, are also presented. The results of those end points,

along with any side effects, are noted. Also included are any comments that the author(s) of the study have made regarding the meaning of the study. Finally, the ratings and comments made by an independent reviewer regarding the quality of the study are presented. Further details on the review process and rating scales are provided in the following section, Evaluation of Clinical Trial Quality, and in the next chapter.

Botanical Summaries

Summaries of information on products and their trials were grouped by botanical or formula. Both common and Latin names are cited with reference to the American Herbal Products Association's *Herbs of Commerce* (McGuffin et al., 2000). The summaries were written by me, Marilyn Barrett, with reference to comments made by the trial reviewers. The summaries include an "at-a-glance" table of the products, manufacturers, U.S. distributors (if any), product characteristics, the dose used in the trials, indication, number of trials, and the ratings as to therapeutic benefit and evidence level (see the section Evaluation of Clinical Trial Quality for more information on rating of the studies).

The summary table is followed by a summary of the preparations used in the reviewed clinical studies. This is followed by a summary of the reviewed clinical studies. Following that is any additional information, when available, from meta-analyses, systematic reviews, or epidemiological studies. Next, obtainable information regarding adverse reactions, side effects, or clinical information concerning drug-herb interactions is presented. (*Author's note:* Many cautionary statements regarding drug-herb interactions are based on theoretical modes of action of the herb. I have not included that information in this book. I have included only drug-herb interactions that have been demonstrated clinically.)

Finally, information from published therapeutic monographs from select pharmacopoeias is included. Those sources include the *American Herbal Pharmacopoeia, United States Pharmacopeia, United States Pharmacopeia—Drug Information, British Herbal Compendium,* European Scientific Cooperative on Phytotherapy (ESCOP), German Commission E, and the World Health Organization.

EVALUATION OF CLINICAL TRIAL QUALITY

Development of the "Levels of Evidence" for the Clinical Studies

Tieraona Low Dog, MD, developed the "Levels of Evidence" used to rank the clinical studies included in this book (see the following chapter). The purpose of the ranking is to enable the reader to quickly and accurately assess the validity of the clinical trial. The levels of evidence imply a hierarchy of quality and/or strength of scientific evidence. Trials of the highest scientific quality are classed as Level I. Those trials of moderate quality are classed as Level II, and trials with insufficient strength in their methodology or write-up to support their conclusions are classed as Level III.

The levels of evidence are based on a score generated by the Reviewer's Checklist. The first half of the checklist includes criteria to minimize bias on the part of either the participants or the researchers. These criteria, established by Dr. Jadad and colleagues (1996), emphasize the importance of blinding the study participants and the investigators, random allocation of patients into study groups, and a complete accounting of all patients that discontinue the study.

The second half of the checklist is comprised of criteria provided by Dr. Low Dog. These include the quality of the data summary, statistical methods, and a clear definition of the outcome measures. In addition, descriptions of the botanical preparation, the inclusion and exclusion criteria for the participants, and the appropriateness of the number of participants are evaluated.

Dr. Low Dog compiled the second half of the levels of evidence used in this book following reference to the United States Pharmacopeia Botanical Information Experts Committee (USP, 2000), the World Health Organization, and the United States Agency for Health Care Policy and Research.

Selection of MD Reviewers

An effort was made to have physicians or PhDs with expertise in the clinical indication of the study determine the trial quality. For example, a physician with expertise in the area of immunology and infectious diseases reviewed clinical studies evaluating the efficacy of

echinacea to treat the common cold. In a few cases, the reviewer is also an author of a study he or she reviewed.

Review Process

Physician reviewers were sent packages that included the clinical studies and guidelines for ranking the quality of the studies. Points were given to each trial based upon an 11-point questionnaire (see the following chapter). A recommended level of evidence was given based upon the number of points. In addition, the reviewers assessed whether any therapeutic benefit was determined by the study and commented on the study in general.

Individual Trial Summaries

Included in each trial summary report is the level of evidence (I, II, or III) according to the reviewer's determination. Also included is a determination of therapeutic benefit (Yes, Trend, No, Undetermined). A designation of Yes meant the results were clearly in support of the therapeutic indication and the statistical analysis was strong. A Trend toward a positive benefit was designated when the results were generally positive but weak, in that they lacked sufficient statistical analysis or not all the analyses were positive. No therapeutic benefit was assigned when the results were clearly negative and the statistical analysis was strong. A designation of Undetermined was made if the results did not adequately address the therapeutic question.

A paragraph with the reviewer's comments is provided. At the end of this paragraph is the numerical score from the reviewer's checklist. This score is separated into two parts as described previously. The first score uses the Jadad criteria with a total of five points possible. The second score is derived from the second half of the checklist with a total of six points possible (see the reviewer's checklist in the following chapter for more detail).

Challenges in Clinical Trial Evaluation

The evaluation and ranking system that we used focuses more on the quality of the trial description than the true quality of the trial. The

trial may have been of good quality, but if the write-up or translation were inadequate, then the trial would not score well.

In addition, a trial may be ranked high in terms of its level of evidence, being well conducted and well described, without giving any direct indication of therapeutic benefit. Our level of evidence evaluation system does not take the therapeutic utility of the trial into account in its ranking system. For example, the trial end points may not be directly connected with a disease state. It is often more convenient to measure intermediate outcomes, and these outcomes can offer useful information if there is a good correlation with the therapeutic end point. As an example, hypertension and high cholesterol levels are the intermediate outcomes that correlate well with the therapeutic outcomes of heart attack and stroke. However, measured antioxidant activity does not necessarily indicate a benefit for those with heart disease or any other disease, as no direct connection is established.

If the purpose of the trial was to establish tolerance of the preparation, it was difficult, if not inappropriate, to evaluate a trial as to whether it established a therapeutic benefit. For example, studies with kava and valerian preparations studying reaction times or possible additive effects due to alcohol would end up as being rated as therapeutic benefit "Undetermined," as this is not their purpose. However, the numerical scoring system still gives valuable information about the quality of the trial, e.g., whether one should believe a trial claiming that a botanical is safe or unsafe.

If the purpose of the trial was to explore the mode of action of the preparation, it was also inappropriate to evaluate a trial as to whether it established a therapeutic benefit. In place of the therapeutic benefit assessment, these studies were designated MOA (mode of action).

Controlled studies include a group given a comparison treatment of placebo or another therapeutic agent, or both. If the comparison agent is an established therapeutic agent, recognized as effective by today's standards, then some reviewers felt that the study did not need a placebo arm. If, however, the comparison treatment is not established, then the benchmark is insufficient and a placebo arm is required. In the final analysis, this seems to be an issue addressed on an individual basis, depending upon the treatment and the opinion of the reviewer. In cases in which the reviewer thought a placebo arm was needed but not present, the trial was rated as therapeutic benefit "Undetermined." On the other hand, if the reviewer thought the compari-

son agent was adequate and the placebo arm was not needed, then the trial might be rated as therapeutic benefit "Trend," "Yes," or "No."

The trial evaluations were reviewed and checked for agreement with guidelines by the editors. In order to achieve consistency among reviewers, the level of evidence score was occasionally adjusted up or down by the editors to match the reviewer's guidelines. We found that according to their own personal experience, each reviewer focused on slightly different aspects of the trials, and some were more harsh than others in their judgment. Some reviewed the trials according to their previous experience, without strictly sticking to our guidelines. Some missed information in the trial reports, as several of the European trials include methods information in places other than the methods section of the paper. In addition, some reviewers commented on the "take home" message of the trial while others did not. We have included these comments if they are different from those included in the results section of the trial report.

REFERENCES

Jadad AR, Moore RA, Carroll D, Gavaghan DJ, McQuay HJ (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials* 17 (1): 1-12.

McGuffin M, Kartesz JT, Leung AY, Tucker AO (2000). *The American Herbal Products Association's Herbs of Commerce,* Second Edition. Silver Spring, MD: American Herbal Products Association.

United States Pharmacopeial Convention, Inc., The (USP) (2000). Saw Palmetto (sawpalmetto.pdf). <www.usp.org>. Accessed: December 3, 2002.

Chapter 13

Clinical Trial Reviewer's Guidance and Checklist

Tieraona Low Dog

LEVELS OF EVIDENCE

When reviewing individual trials it is important for the reader to be able to accurately assess the trials' validity. Levels of evidence describe an implied hierarchy of quality and/or strength of scientific evidence. In order to evaluate the probable effect of therapy, the reviewer must know if the allocation to treatment was random, if participants and investigators were blind to the allocation, and if all participants were accounted for. Statistical methods must be adequately stated and the data summarized in a fashion that permits alternative analyses and replication. The botanical preparation must be adequately described.

These levels of evidence used to rank the clinical trials were derived from the workings of the U.S. Pharmacopeia Botanical Experts Committee, the World Health Organization, and the U.S. Agency for Health Care Policy and Research.

Level I: Trials of the Highest Scientific Quality

A Level I study is a randomized, controlled trial that is adequately powered to show a treatment effect versus placebo, or an appropriate active or historical control. The study describes in detail the methods of blinding and randomization, accounts for all withdrawals and dropouts from the study, and describes the statistical methods employed. A study at this level does not have any methodological flaws sufficient to undermine the conclusions of the study.

Level II: Trials of Moderate Scientific Quality

A Level II study is also a randomized, controlled trial that is adequately powered to show a treatment effect versus placebo, or an appropriate active or historical control. However, a study at this level suffers from technical flaws or an inadequate description of the methods or analyses such that the study cannot meet the full criteria for Level I. The flaws in a Level II study are not serious enough to negate the results or conclusions of the study.

Level III: Nonexperimental Designs and Anecdotal Evidence of Uncertain Quality

This level includes studies not meeting the criteria for Levels I or II. It includes nonrandomized trials, efficacy studies lacking an appropriate control group, randomized studies with serious methodological flaws, or studies that are too small or of insufficient duration to be of value. There is insufficient strength in the methodology or write-up of a Level III study to support its conclusions; however, this does not mean that those conclusions are necessarily invalid.

GUIDELINES FOR REVIEWER CHECKLIST: PART I

Part I uses the Jadad scoring system whose purpose is to evaluate the potential for bias in the trial. It asks questions about randomization, blinding, and subject withdrawals or dropouts. For example, if one can predict which group an individual belongs to, bias can be introduced on the part of the investigator and/or the participant. If one group drinks tea and the other receives a tablet, it is apparent to the participant which group they belong to. If 200 participants begin the trial, but only 126 are included in the analysis without any discussion of the dropouts, there is a serious risk of bias in the trial. Did 74 people drop out of the trial because the intervention made them ill, didn't work, etc.?

The total possible score is five. A score of four or five indicates that the trial is relatively free of bias.

Question 1. Was the Study Randomized?

If the author describes the study in the article as randomized, random, or randomly give one point. If not, give zero.

Examine questions 1a and 1b together; only one of them applies.

Question 1a. Was the Randomization Process Adequately Described and Appropriate?

Add one point if the method of randomization is described and is appropriate (for instance: computer generated, table of random numbers, etc.). The trial should describe the methods used to generate the allocation schedule and concealment. Each study participant must have the same chance of receiving each intervention, and the investigators must not be able to predict which treatment will be next.

Question 1b. Was the Randomization Process Not Described or Inadequate?

Deduct one point, effectively making the score for question 1 zero, if the author fails to describe the method for randomization or the method described is inappropriate. Allocation should not be determined by hospital numbers, date of admission, date of birth, or alternating numbers.

Question 2. Was the Study Double-Blind?

If the author describes the trial as "double-blind" give one point. If not, give zero.

Examine questions 2a and 2b together; only one of them applies.

Question 2a. Was the Double-Blinding Described and Was It Appropriate?

Add one point if the double-blinding was described *and* appropriate. To be considered appropriate, neither the participants nor the investigators should be able to identify which intervention is being assessed (identical placebo, dummy, active placebo, etc.).

Question 2b. Was the Double-Blinding Not Described or Inappropriate?

Deduct one point, effectively making the score for question 2 zero, if the author fails to describe the double-blinding or if the description indicates the method was inappropriate (tablets differ in appearance, injection versus capsule, etc.).

Question 3. Was There a Description of All Withdrawals and Dropouts?

Participants who were included in the study but did not complete the trial and/or were not included in the analysis must be accounted for. The reasons for withdrawal must be clearly stated. Every participant must be accounted for. If there were no dropouts, this should be clearly stated. If the withdrawals/dropouts are not adequately described *or* if this item is not mentioned in the article, give zero points. If withdrawals are appropriately accounted for, give one point.

GUIDELINES FOR REVIEWER CHECKLIST: PART II

This part is designed to review the article for quality and is scored separately from the Jadad scoring system in Part I. A total of six points are possible. A score of five or six points indicates a likelihood of a good-quality study. Scores of three or less indicate that the quality of the study may be poor.

Question 4. Were the Data Summarized in Sufficient Detail to Permit Alternative Analyses and Replication?

Give one point if the data are summarized in a fashion that allows others to perform alternative analyses. This means error bars on plotted graphs, data presented in a complete and concise manner, clear description how the data were collected, etc. If the paper does not provide these, zero points are given.

Question 5. Were Statistical Methods Adequately Described and Applied?

Give one point if the paper states the estimated effect of the intervention on outcome measures including a point estimate and measure of precision. The paper should include an adequate description of the statistical methods used and how they were applied. If the paper does not provide these, zero points are given.

Question 6. Was the Botanical Preparation Adequately Described?

Due to the complex nature of botanicals, variation in the chemical composition between species, plant part, and preparation, it is essential that authors clearly provide an adequate description of the preparation used in the clinical trial. Descriptions should include identification (Latin binomial and authority), plant part (root, leaf, seed, etc.), and type of preparation (tea, tincture, extract, oil, etc.). Tincture and extract description should include the identity of the solvent and the ratio of solvent to plant material. If the preparation is standardized to a chemical constituent, then that information should also be included. If the trial substance is a proprietary product for which a detailed description is available from the manufacturer and/or product literature, then this is considered adequate. One point is given for an adequate description of the botanical, zero points if not.

Question 7. Were the Inclusion/Exclusion Criteria Adequate and Appropriate?

The inclusion and exclusion criteria should be clearly stated and relevant to the clinical condition being studied. For instance, a study for a cold treatment should clearly list appropriate exclusions for those with chronic illness and those taking antibiotics or over-the-counter cold/cough medications. One point is given for adequate description of inclusion/exclusion criteria, zero points if not.

Question 8. Was the Sample Size Appropriate?

Was a power calculation done? The study must be of appropriate size to generate meaningful results. If the trial included adequate numbers but did not describe a power calculation, one point should still be given. If the trial was very small (fewer than 40 subjects), zero points should be given.

Question 9. Were the Outcome Measures Clearly Defined?

Outcome measurements should be clearly stated using validated methods. If adequately described give one point, zero points if not.

SCORING

After reviewing the trials and answering the previous questions, the study must be ranked according to the levels of evidence as either a category I, II, or III. Studies given the rank of Level I must be of outstanding quality and have scored a total number of ten or eleven points. Studies of good quality with flaws that are unlikely to change the outcome of the study should be placed in Level II. Level III is reserved for those trials with severe risk of bias (three or less on the Jadad scale) and/or questionable quality (scoring three or less in Part II).

Please include a few sentences under "Reviewer's Comments" noting the major strengths or flaws observed in the trial. These comments are intended as rationale for the assigned level of evidence.

Checklist for Evaluation of Clinical Trial

Please fill out one sheet for every trial you review.

Reviewer: _____ Botanical: _____

Trial Number: _____ First Author: _____

Name of Trial: _____

Descriptor	**Points**
Part I	
Was the study randomized?	0 or 1
Was the randomization process adequately described and appropriate?	+1
Was the randomization process not described or inappropriate?	–1
Was the study double-blinded?	0 or 1
Was the double-blinding described and appropriate?	+1
Was the double-blinding not described and/or inappropriate?	–1
Was there a description of all withdrawals and dropouts?	0 or 1
Total	/5
Part II	
Were data summarized in sufficient detail to permit alternative analyses and replication?	0 or 1
Were statistical methods adequately described and applied?	0 or 1
Was the botanical preparation adequately described?	0 or 1
Were the inclusion/exclusion criteria adequate and appropriate?	0 or 1
Was the sample size appropriate?	0 or 1
Were the outcome measures clearly defined?	0 or 1
Total	/6

Reviewer's Comments:

_____

_____

_____

Recommended Level of Evidence: _____

Therapeutic Benefit? (circle one): Yes Trend No Undetermined

Comments on the Dose of Either the Botanical or Comparison Treatment (if any):

_____

_____

_____

Comments on the Length of Treatment:

_____

_____

_____

Adverse Effects Noted with Intervention:

_____

_____

_____

PART III: BOTANICAL PROFILES—PRODUCT AND CLINICAL TRIAL INFORMATION

(Artichoke–Ginseng)

Artichoke

Other common names: **Cynara, globe artichoke**
Latin name: ***Cynara scolymus* L.** [Asteraceae]
Plant part: **Leaf**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Artichokes were greatly valued by the ancient Greeks (fourth century B.C.) for treating digestive disorders. Clinical studies have been conducted on aqueous extracts of the leaves. The extracts characteristically contain caffeoylquinic acid derivatives, including caffeic acid, chlorogenic acid, and cynarin (1,5-dicaffeoylquinic acid) (Kraft, 1997).

Cynara-SL™ contains 320 mg per capsule of a dried aqueous extract called LI 120, with an herb-to-extract ratio of 3.8 to 5.5:1. It is manufactured in Germany by Lichtwer Pharma AG and distributed in the United States by Lichtwer Pharma U.S., Inc. This extract is marketed in Europe as Hepar-SL forte®.

Valverde Artischocke, which is manufactured by Novartis Consumer Health GmbH in Germany, is not provided in the United States. The tablets contain 450 mg of a dried aqueous extract called CY-450 with a ratio of 25 to 35:1.

ARTICHOKE SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Cynara-SL™ (US), Hepar-SL forte ® (EU)	Lichtwer Pharma AG, Germany/ Lichtwer Pharma U.S., Inc.	Aqueous extract (LI 120)	6 capsules, 1.92 g (intraduoden-ally)	Choleresis (bile secretion)	1	MOA (III-1)
Valverde Artischocke (EU)	Novartis Consumer Health GmbH, Germany/None	Aqueous extract (CY450)	2 tablets twice daily (1.8 g extract/day)	Hyper-lipo-proteinemia (elevated cholesterol levels)	1	Yes (I-1)

SUMMARY OF REVIEWED CLINICAL STUDIES

Artichoke preparations may relieve digestive complaints through increases in the formation and flow of bile. The increased flow of bile is called choleresis. Bile is excreted from the liver, stored in the gallbladder, and released into the intestine. Bile acids form a complex with dietary fats in the intestine and thereby assist in their digestion and absorption (Kraft, 1997).

In addition, stimulation of bile production results in reduced serum cholesterol, as cholesterol is pulled from the blood to be converted into bile acids. The increased flow of bile may also be beneficial for patients with irritable bowel syndrome (IBS) (Walker, Middleton, and Petrowicz, 2001).

Cynara-SL (LI 120)

Choleresis (Bile Secretion)

A mode of action study using the Lichtwer product Cynara-SL (Hepar-SL) demonstrated that artichoke extract increased the flow of bile. Administration of six capsules (1.92 g) intraduodenally caused a peak increase (100 to 150 percent compared to baseline) in bile one hour later (Kirchhoff et al., 1994). According to our reviewer, Dr. David Heber, this study inferred, but did not clearly demonstrate, therapeutic benefit for dyspepsia; the one-day study was too short, was not conducted on subjects with dyspepsia, and the product was not delivered orally.

Valverde Artischocke

Hyperlipoproteinemia (Elevated Cholesterol Levels)

A study with the Novartis product Valverde Artischocke on 131 patients with elevated cholesterol (total serum cholesterol greater than 280 mg/dl) reported a 20.2 percent decrease in cholesterol, compared to 7.2 percent in the placebo group. The product was given in a dose of 900 mg, twice daily, before meals, for six weeks (Englisch et al., 2000). This well-conducted trial indicates efficacy of Valverde Artischocke in the treatment of elevated cholesterol.

POSTMARKETING SURVEILLANCE STUDIES

A review of metabolic, pharmacological, and clinical studies described two postmarketing surveillance studies (Kraft, 1997). The first study, reported by Held (1991), included 417 patients with hepatic and biliary tract disease who were treated for four weeks with artichoke leaf extract (product not named). Prior to the study, the average duration of symptoms of abdominal pain, bloating, meteorism, constipation, lack of appetite, and nausea was four months. Elimination of these symptoms occurred in 65 to 77 percent of patients after one week, and in 52 to 82 percent of patients after four weeks.

The second postmarketing surveillance study was published by Fintelmann (1996) and Fintelmann and Menssen (1996). It included 553 subjects with dyspepsia who were administered the Lichtwer product Hepar-SL. The authors reported a clinically impressive and statistically significant improvement for 87 percent of patients within six weeks of treatment. In a subset of 302 patients for whom cholesterol values were routinely determined, serum cholesterol and serum triglyceride concentrations dropped significantly ($p < 0.001$). For this group of subjects, the average daily dose was approximately 1.5 g extract and treatment extended to an average of 43.5 days (six weeks) (Kraft, 1997).

Walker, Middleton, and Petrowicz (2001) reported an analysis of another patient subset with key symptoms of irritable bowel syndrome (279 in number). These patients experienced significant reductions in symptoms (71 percent) after six weeks of treatment with six capsules per day, with improvement noted within ten days. Although the initial survey by Fintelmann and Menssen (1996) did not include all the diagnostic criteria for IBS, patients were included if they had at least three of five key symptoms.

ADVERSE REACTIONS OR SIDE EFFECTS

No adverse reactions or side effects were reported in the clinical studies described. The Fintelmann (1996) postmarketing study reported that 1.3 percent of 553 subjects experienced mild reactions, such as flatulence, feeling of weakness, and hunger.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

German Commission E

Indications

The German Commission E approves the use of fresh or dried artichoke leaf for dyspeptic problems due to its choleretic action (Blumenthal et al., 1998).

Doses

Fresh or dried leaf: 6 g per day (Blumenthal et al., 1998)

Contraindications

The Commission E mentions the following contraindications: known allergies to artichokes and other composites and obstruction of bile ducts. It also suggests that in case of gallstones, use only after consulting with a physician (Blumenthal et al., 1998).

Adverse Reactions

The Commission E lists no known adverse reactions (Blumenthal et al., 1998).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998).

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DETAILS ON ARTICHOKE PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Artichoke Products

Product Profile: Cynara-SL™

Manufacturer	**Lichtwer Pharma AG, Germany**
U.S. distributor	Lichtwer Pharma U.S., Inc.
Botanical ingredient	**Artichoke leaf extract**
Extract name	**LI 120**
Quantity	320 mg
Processing	Plant to extract ratio 3.8-5:1, aqueous extract
Standardization	No information
Formulation	Capsule

Recommended dose: For regular longer-term use to help maintain a healthy liver and digestive system and to support the normal cleansing process of the liver take one to two capsules daily. For nutritional support, take one to two capsules shortly before or after eating or drinking too much. Up to six capsules may be taken per day. Effects can be noticed as soon as 30 to 60 minutes.

DSHEA structure/function: Clinically proven to help maintain a healthy liver and digestive system; clinically proven to provide fast and

effective herbal support for the digestive system when eating or drinking too much; supports the normal cleansing process of the liver.

Cautions: If taking prescription medicine, are pregnant, nursing a baby, or administering to children under the age of 12, consult a health care professional before using this product.

Other ingredients: Lactose, gelatin, magnesium stearate, silicon dioxide, talc, titanium dioxide, sodium lauryl sulphate, FD&C blue no. 1, yellow no. 5.

Comments: Sold in Europe as Hepar-SL forte®.

Source(s) of information: Kirchhoff et al., 1994; product packaging; information provided by distributor (11/2/99).

Clinical Study: Hepar-SL forte®

Extract name	LI 120
Manufacturer	Sertürner Arzneimittel GmbH, Germany (Lichtwer Pharma AG, Germany)
Indication	**Choleresis** (bile secretion)
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Kirchhoff R, Beckers CH, Kirchhoff GM, Trinczek-Gartner H, Petrowicz O, Reimann HJ (1994). Increase in choleresis by means of artichoke extract. *Phytomedicine* 1: 107-115. (Also published in *Arzneimittel-Forschung/Drug Research* 1993; 40 [1]: 1-12.)

Trial design
Crossover. Eight-day pretrial period to establish case histories and clinical and laboratory parameters. One-day treatment periods were separated by an eight-day washout period.

Study duration	1 day
Dose	Single dose of 6 capsules (1.92 g artichoke extract)
Route of administration	Intraduodenal
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind

Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	20
No. of subjects completed	18
Sex	Male
Age	Mean: 26 years

Inclusion criteria
Subjects with acute or chronic metabolic disorders with previous gastroenterological and chemical examination.

Exclusion criteria
Subjects with upper abdominal problems lasting more than four weeks, intolerance of fatty foods, irregular bowel movements with changes in feces color, heavy smokers (>10 cigarettes per day), or heavy coffee drinkers (>4 cups per day). Ingestion of metabolically active drugs not permitted two weeks prior to start of test.

End points
On days of the investigation, capsule contents were dissolved in 50 ml water and administered via an intraduodenal probe. Measurement of intraduodenal bile secretion began 30 minutes after substances were administered and continued for up to four hours using multichannel probes.

Results
Increases in bile secretion in the active group were 127.3 percent after 30 minutes, 151.5 percent after 60 minutes, and 94.3 percent after 90 minutes, each in relation to the initial value. These measurements were significantly different from placebo, $p < 0.01$. The most significant increase after administration of placebo was 39.5 percent after 30 minutes. At later times of 120 and 150 minutes the volume of bile secreted under the active treatment was still significantly higher than under placebo ($p < 0.05$).

Side effects
None reported.

Authors' comments
Results indicate that artichoke extract can be recommended for the treatment of dyspepsia, especially when the cause may be attributed to dyskinesia of the bile ducts or disorder in the assimilation of fat.

Reviewer's comments
This study was flawed by the small sample size and the short duration of treatment. (0, 5)

Product Profile: Valverde Artischocke

Manufacturer	**Novartis Consumer Health GmbH, Germany**
U.S. distributor	None
Botanical ingredient	**Artichoke leaf extract**
Extract name	**CY450**
Quantity	450 mg
Processing	Plant to extract ratio 25-35:1, aqueous extract of fresh leaves
Standardization	No information
Formulation	Tablet

Source(s) of information: Englisch et al., 2000.

Clinical Study: Valverde Artischocke

Extract name	CY450
Manufacturer	Novartis Consumer Health GmbH, Germany
Indication	**Hyperlipoproteinemia** (elevated blood lipid levels)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Englisch W, Beckers C, Unkauf M, Ruepp M, Zinserling V (2000). Efficacy of artichoke dry extract in patients with hyperlipoproteinemia. *Arzneimittel-Forschung/Drug Research* 50 (3): 260-265.

Trial design
Parallel.

Study duration	6 weeks
Dose	2 × 450 mg twice daily, before meals
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	3 hospitals
No. of subjects enrolled	143
No. of subjects completed	131
Sex	Male and female
Age	35-69 years

Inclusion criteria
Patients between 18 and 70 years old with total cholesterol of >7.3 mmol/l (>280 mg/dl) in plasma or serum. During participation in the study, patients were not allowed to take other cholesterol-lowering drugs or any antibiotic treatments.

Exclusion criteria
Patients who had taken lipid-lowering drugs within two weeks of enrollment.

End points
After enrollment, patients were seen on days 7, 14, 28, and 42. At each visit, blood samples were drawn and patient conditions noted. Blood samples were tested for total cholesterol, low-density lipoprotein (LDL cholesterol), high-density lipoprotein (HDL cholesterol), triglycerides, liver enzymes (gamma-glutamyl transferase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and glutamate dehydrogenase), and glucose.

Results
Artichoke extract was significantly superior to placebo in decreasing total cholesterol (18.5 percent versus 8.6 percent, $p = 0.001$), LDL cholesterol (22.9 percent versus 6.3 percent, $p = 0.001$), and LDL/HDL ratio (20.2 percent versus 7.2 percent). There was a slight decrease in gamma-GT levels in both groups from baseline to end of study, with no significant difference between groups. There were no changes to glucose levels in either group.

Side effects
No drug-related adverse events.

Authors' comments
This prospective study could contribute clear evidence to recommend artichoke extract CY450 for treating hyperlipoproteinemia and, thus, prevention of atherosclerosis and coronary heart disease.

Reviewer's comments
Well-conducted and well-designed study with positive and significant results. (5, 6)

Bilberry

Other common names: **European blueberry; huckleberry; whortleberry**
Latin name: ***Vaccinium myrtillus* L.** [Ericaceae]
Plant part: **Fruit**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Both the leaves and fruits of bilberry (European blueberry) have been used medicinally. Most commercial preparations are standardized to contain a percentage of flavonoids, specifically anthocyanidins or anthocyanins (anthocyanidins with sugars attached). These molecules are natural pigments responsible for the blue to purple color of the fruit. They also have strong antioxidant activity (Upton et al., 2001).

Most of the clinical studies on bilberry have been conducted with a product called Tegens® produced by Inverni della Beffa, Italy. Tegens contains an extract named Myrtocyan® (now called MirtoSelect™) that is manufactured by Indena S.p.A., Milan, Italy. It is characterized as containing 36 percent anthocyanins or 25 percent anthocyanidins. This extract is available in the United States in a product called Bilberry Extract produced by Enzymatic Therapy® and in a product named Vacimyr® produced by Thorne Research. The Indena extract is available in other products as well, but only single-ingredient products are included here. Products including other active ingredients are not included unless those ingredients have been studied in combination in a clinical trial.

FAR-1 is manufactured in Italy by Ditta Farmigea S.p.A.; it is not sold in the United States. FAR-1 is also characterized as containing 25 percent anthocyanidins.

BILBERRY SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Tegens® (EU)*	Inverni della Beffa, Indena S.p.A, Italy*	Contains the extract MirtoSelect™, formerly Myrtocyan®, with 25 % anthocyanidins	160 mg 2-3 times daily	Diabetic retinopathy	2	Trend (II-1) Undetermined (III-1)
				Varicose veins	1	Trend (III-1)
				Dysmenorrhea (painful menstruation)	1	Undetermined (III-1)
			80 mg 3 times daily	Pupillary reflex	1	MOA (III-1)
FAR-1 (EU)	Ditta Farmigea S.p.A., Italy/None	Extract contains 25% anthocyanidins	180 mg 2 times daily +Vit E	Senile cataracts	1	Trend (II-1)

*The following products, sold in the United States, contain the Indena extract (MirtoSelect) as a single ingredient; the extract in these products has been tested clinically but the final formulation has not.

Product Name	Manufacturer/Distributor
Bilberry Extract (U.S.)	Enzymatic Therapy®
Vacimyr® (U.S.)	Thorne Research

SUMMARY OF REVIEWED CLINICAL STUDIES

Bilberry products have been used to treat circulatory disorders, namely fragility and altered permeability of blood vessels that is either primary or secondary to arterial hypertension, arteriosclerosis, or diabetes. In vitro studies have shown that bilberry extracts have antioxidant activity, inhibit platelet aggregation, prevent degradation of collagen in the extravascular matrix surrounding blood vessels and joints, and have a relaxing effect on arterial smooth muscle. These actions have been described as vasoprotective, increasing capillary resistance and reducing capillary permeability (Morazzoni and Bombardelli, 1996). We report here a total of six studies with treatments for diabetic and hypertensive retinopathy, senile cataracts, pupillary reflex, varicose veins, and primary dysmenorrhea (painful menstruation).

Retinopathy is an eye disorder that results from changes to the blood vessels in the retina. It is characterized by an increase in vascular permeability and decrease in resistance of the vessels, resulting in microaneurisms, edema, and eventually hard exudates (Perossini et al., 1987). Varicose veins are blood vessels that have become twisted and swollen when their one-way valves begin to leak or when the vein wall weakens. The symptoms include edema in the legs and ankles, sensation of pressure, cramps, and tingling or "pins and needles" sensations (Gatta, 1988). Although the cause of primary dysmenorrhea is unknown (unlike secondary dysmenorrhea, it is not caused by an observable abnormality), it is characterized by pelvic pain, nausea and vomiting, diarrhea, headache, swollen breasts, and a sensation of heaviness in the legs and feet (Colombo and Vescovini, 1985).

Tegens (MirtoSelect)

Diabetic Retinopathy

Two studies on diabetic retinopathy, using a dose of 160 mg Tegens twice daily, demonstrated a trend toward improvement in mild cases of the disease. The first study was a one-month, placebo-controlled study that included 36 subjects, a few of which had hypertensive retinopathy. At the end of the month, 10 of 13 patients in the

Tegens group with opthalmoscopically detectable retinal abnormalities (microaneurisms, hemorrhagic foci, exudates) were improved, while all 15 patients with these abnormalities in the placebo group remained unchanged. A similar trend was observed among those patients with fluoroangiographic abnormalities (Perossini et al., 1987). The second study lasted one year and included 40 subjects who were given Tegens or placebo in addition to the usual therapy for retinopathy. As a result, in 50 percent of patients given bilberry, the retinal lesions and associated edema were improved, compared to 20 percent in the control group (Repossi, Malagola, and De Cadilhac, 1987). According to our reviewer, Dr. David Heber, the first study was relatively well designed and supported a trend toward efficacy. The second, although seemingly positive, was deemed undetermined due to the poorly described methodology. The evidence of both studies was limited by small sample sizes.

Varicose Veins

Symptoms of varicose veins were improved with 160 mg Tegens, three times daily for one month, in a placebo-controlled trial with 60 participants (Gatta, 1988). Determination of therapeutic benefit was hampered by the short length of the study and by poor methodology.

Dysmenorrhea (Painful Menstruation)

In a placebo-controlled trial with 30 females with primary dysmenorrhea, significant relief compared to placebo was reported for the symptoms of pelvic and lumbar-sacral pain, swollen breasts, and heaviness in the lower limbs following treatment with a dose of 160 mg Tegens, twice daily for two menstrual cycles (Colombo and Vescovini, 1985). The evaluation criteria in this trial were considered highly subjective, and the methodology was inadequately described. Thus, it was difficult to assess the potential benefit of this treatment.

Pupillary Reflex

A mechanistic study using Myrtocyan examined changes in pupillary reflexes to light following a single high dose of 240 mg anthocyanosides or placebo in 40 healthy volunteers. The study was conducted to explore the use of bilberry in work situations where exposure to

high light intensities dampens pupillary reflexes and leads to vision fatigue. The authors of the study suggested that the pigments in bilberry might increase sensitivity to light and improve blood flow in the capillaries of the eye. Improvement in pupillary reflexes was observed in both groups, with the improvement in the treatment group being only slightly better than that in the placebo group (Vannini et al., 1986). Dr. Heber judged the benefit to be undetermined.

Additional controlled clinical studies, which were not available to us for critical review, are summarized elsewhere (Morazzoni and Bombardelli, 1996; Upton et al., 2001).

FAR-1

Senile Cataracts

A mixture of vitamin E and bilberry (FAR-1) showed a trend toward prevention of senile cataracts after four months of 180 mg twice daily. When the placebo group was changed from placebo to the bilberry preparation, and the trial continued for an additional four months, there was no statistical difference between the two groups. The rationale for this study was previous indications that antioxidants might prevent the development of senile cataracts (Bravetti, Fraboni, and Maccolini, 1989).

ADVERSE REACTIONS OR SIDE EFFECTS

No side effects were reported in the clinical studies described. In a 1987 postmarketing surveillance study with 2,295 subjects, only 94 subjects (4.1 percent) complained of minor side effects, most of which involved the gastrointestinal tract. Most of the subjects took 160 mg Tegens twice daily for one to two months (Eandi, 1987). No details were given in the review that cited this study as to the efficacy of the treatment, which was given for lower limb venous insufficiency (24 percent), disorders due to fragile or permeable capillaries (21 percent), functional changes in retinal microcirculation (10 percent), hemorrhoids (7 percent), and other reasons (Morazzoni and Bombardelli, 1996).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

American Herbal Pharmacopoeia (AHP)
German Commission E

Indications

The dried, ripe fruit is approved by the German Commission E for treatment of nonspecific, acute diarrhea and mild inflammation of the mucous membranes of the mouth and throat (Blumenthal et al., 1998). The *American Herbal Pharmacopoeia* lists the following medical indications supported by clinical trials: vascular insufficiency and its associated symptoms (edema, varicosities, pain, paraesthesias, and cramping); capillary fragility and the associated tendency to bruising; pain, itching, and burning associated with hemorrhoidectomy and hemorrhoids; postoperative hemorrhagic complications (reducing the incidence and severity) when administered prior to ear, nose, and throat surgeries; and disorders of the eye (slows progression), including the early stage of diabetic and hypertensive retinopathy (Upton et al., 2001).

Doses

Dried, ripe fruit: 20 to 60 g per day (Blumenthal et al., 1998)
Decoction: 1 cup four to six times per day (Upton et al., 2001)
Extract: 160 to 960 mg powdered extract (standardized to 25 percent anthocyanin glycosides) per day in divided doses (Upton et al., 2001)
External: 10 percent decoction or equivalent preparations (Blumenthal et al., 1998)

Contraindications

The Commission E and the *AHP* list no known contraindications (Blumenthal et al., 1998; Upton et al., 2001).

Adverse Reactions

While the Commission E mentions no known adverse reactions, the *AHP* lists gastric pain, nausea, and pyrosis (Blumenthal et al., 1998; Upton et al., 2001).

Precautions

The *AHP* states no precautions, but the Commission E suggests if diarrhea persists for more than three to four days, a physician should be consulted (Upton et al., 2001; Blumenthal et al., 1998).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998).

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DETAILS ON BILBERRY PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Bilberry Products

Product Profile: Tegens®

Manufacturer	**Inverni della Beffa, Italy (Indena S.p.A., Italy**
U.S. distributor	None
Botanical ingredient	**Bilberry fruit extract**
Extract name	**Myrtocyan®** (now named Mirto Select)
Quantity	160 mg
Processing	Plant to extract ratio 100:1
Standardization	25% anthocyanidins
Formulation	Capsule

Source(s) of information: Perossini et al., 1987; Colombo and Vescovini, 1985; Indena USA, Inc., product information; and personal correspondence with Indena USA, Inc.

Product Profile: Bilberry Extract

Manufacturer	**Enzymatic Therapy® (Indena S.p.A., Italy)**
U.S. distributor	**Enzymatic Therapy®**
Botanical ingredient	**Bilberry fruit extract**
Extract name	**MirtoSelect™**
Quantity	80 mg
Processing	Plant to extract ratio 100:1
Standardization	25% anthocyanosides calculated as anthocyanidins
Formulation	Capsule

Recommended dose: Two capsules three times daily.

DSHEA structure/function: Dietary supplement to support healthy eye function.

Other ingredients: Cellulose, gelatin, magnesium stearate, titanium dioxide color.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Product Profile: Vacimyr®

Manufacturer	**Thorne Research (Indena S.p.A., Italy)**
U.S. distributor	**Thorne Research**
Botanical ingredient	**Bilberry fruit extract**
Extract name	**MirtoSelect™**
Quantity	80 mg
Processing	Plant to extract ratio 100:1
Standardization	25% anthocyanosides
Formulation	Capsule

Cautions: If pregnant, consult a health care practitioner before using this or any other product.

Other ingredients: Cellulose capsule. May contain one of the following hypoallergenic ingredients to fill space—magnesium citrate, silicon dioxide.

Source(s) of information: Product label; information from Indena USA, Inc.

Clinical Study: Tegens®

Extract name	Myrtocyan®
Manufacturer	Inverni della Beffa, Italy (Indena S.p.A., Italy)
Indication	**Diabetic and hypertensive retinopathy**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Perossini M, Chiellini S, Guidi G, Siravo D (1987). Diabetic and hypertensive retinopathy therapy with *Vaccinium myrtillus* anthocyanosides (Tegens) double-blind placebo-controlled clinical trial. *Annali di Ottalmologia e Clinica Oculistica* 113 (12): 1173-1190.

Trial design
Parallel. After the one-month placebo-controlled parallel study, placebo patients whose retinopathy was unchanged, worsened, or only slightly improved (all placebo patients) continued in the study for an additional month receiving bilberry extract; patients originally receiving bilberry did not continue the study.

Study duration	1 month
Dose	1 (160 mg) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	40
No. of subjects completed	36
Sex	Male and female
Age	19-78 years (mean: 59.5)

Inclusion criteria
Patients with diabetic or hypertensive vascular retinopathy.

Exclusion criteria
Patients with advanced or irreversible retinal lesions (stage IV); patients with

severe metabolic disorders, hyperproteinemia, decompensated diabetes, or severe liver deterioration; patients with severe systemic arterial hypertension or malignant hypertension; patients with glaucoma or opacification of the refractive media. Patients not permitted to take any therapeutic agents likely to exert an antiexudative, antiedemic, anti-inflammatory, vasoprotective, or hemorheological action.

End points

Before admission to the trial, and after 30 days (and 60 days for placebo patients continuing), patients underwent ophthalmoscopic examination and fluoroangiographic assessment. Blood pressure, heart rate, blood glucose, and glycosylated hemoglobin were recorded at the same time.

Results

Of the 36 subjects completing the trial, 33 had diabetes and three had arterial hypertension. At baseline, 28 subjects had opthalmoscopically detectable retinal abnormalities, 13 in the treatment group and 15 in the placebo group. After the placebo-controlled study, 10 of the patients taking bilberry were improved, whereas none showed any change in the placebo group. Also at baseline, after a fluoroangiographic exam, 17 patients taking bilberry and 18 taking placebo were found to have abnormalities. In the bilberry group, 13 showed improvement, whereas in the placebo group only one patient showed improvement, 14 had no change in their condition, and three showed deterioration. After the initial one-month study, patients originally taking placebo were given bilberry for an additional month. After this treatment, 12 of the 15 patients with opthalmoscopic abnormalities showed improvement, and 17 of the 18 with fluoroangiographic abnormalities showed improvement. There were no clinically relevant changes in blood pressure, blood glucose, or glycosylated hemoglobin values during the study.

Side effects

One mild epigastric complaint which cleared without discontinuing treatment.

Authors' comments

Tegens appears to be a safe and effective therapy for diabetic or hypertensive vascular retinopathy.

Reviewer's comments

Relatively well-designed and well-conducted trial. The study was limited by the small sample size. (5, 4)

Clinical Study: Tegens®

Extract name	Myrtocyan®
Manufacturer	Inverni della Beffa, Italy (Indena S.p.A., Italy)
Indication	**Diabetic retinopathy**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Repossi P, Malagola R, De Cadilhac C (1987). The role of anthocyanosides on vascular permeability in diabetic retinopathy. *Annali di Ottalmologia e Clinica Oculistica* 113 (4): 357-361.

Trial design
Parallel. Patients continued with their usual therapy for retinopathy (not described).

Study duration	1 year
Dose	1 (160 mg) capsule twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Not given
Age	Not given

Inclusion criteria
Diabetic patients with retinopathy in a relatively initial phase, showing at the back pole some hard exudates distributed or in circinate form, but not involving the macular region.

Exclusion criteria
Patients with hard exudates affecting the macular region of the eye were eliminated.

End points
All patients were examined by fluoroangiography before the trial and after 12

months. Opthalmoscopic evaluations were conducted every three months. Hard exudation was used as an index of alteration of capillary permeability to evaluate the integrity of the hematoretinal barrier.

Results
Of patients showing hard exudates in the back pole, 50 percent improved, 30 percent remained the same, and 20 percent worsened with treatment with anthocyanosides. In the placebo group, 20 percent improved, 45 percent remained the same, and 35 percent worsened.

Of patients showing circinate deposits of the hard exudates, 15 percent improved, 60 percent remained the same, and 25 percent worsened with treatment with anthocyanosides. In the placebo group, 10 percent improved, 50 percent remained the same, and 40 percent worsened.

Side effects
No short- or long-term side effects.

Authors' comments
The results obtained with the group of patients treated with anthocyanosides for a period of 12 months are significant. The results point out that the highest efficacy is gained with very early diagnosis and immediate therapy.

Reviewer's comments
This study was limited by several flaws: the sample was not randomized; there is no description of blinding; and there is no description of withdrawals or dropouts. (Translation reviewed) (0, 1)

Clinical Study: Tegens®

Extract name	Myrtocyan®
Manufacturer	Inverni della Beffa, Italy (Indena S.p.A., Italy)
Indication	**Varicosis** (varicose veins)
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Gatta L (1988). *Vaccinium myrtillus* anthocyanosides in the treatment of venous stasis: Controlled clinical study on sixty patients. *Fitoterapia* 59 (Suppl 1): 19-26.

Trial design
Parallel.

Study duration	30 days
Dose	3 (160 mg) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Outpatients
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Male and female
Age	19-66 years (mean: 44)

Inclusion criteria
Subjects with various forms of the varicose syndrome.

Exclusion criteria
None mentioned.

End points
Parameters chosen for the assessment of efficacy were the following symptoms: sensation of pressure in the legs, cramplike pains, paresthesias. Observations were also made of stasis edema and leg girth 2 cm above the medial malleolus and 12 cm below the patella. Blood flow graphs were also taken before and after 30 days of treatment in the patients treated with bilberry.

Results
Bilberry was superior to placebo in the reduction of symptoms: leg and ankle edema, sensation of pressure, and cramps ($p < 0.01$), as well as for paresthesias (tingling or "pins and needles" sensation) ($p = 0.05$). Reduction of leg and ankle circumference, although small, was statistically significant ($p < 0.001$). After treatment with placebo, the circumference values were practically unchanged. In the bilberry group, venous stasis, indicated in rheographic tracing, was significantly lower after treatment compared to baseline ($p = 0.05$).

Side effects
No undesirable effects attributable to the treatment.

Authors' comments
Based on this blind clinical trial, *Vaccinium myrtillus* anthocyanosides are of definite therapeutic value in the management of venous diseases.

Reviewer's comments
The study was limited by the inadequate length of treatment (too short), the inadequately described inclusion/exclusion criteria, and the small sample size. (Translation reviewed) (2, 3)

Clinical Study: Tegens®

Extract name	Myrtocyan®
Manufacturer	Inverni della Beffa, Italy (Indena S.p.A., Italy)
Indication	**Chronic primary dysmenorrhea** (painful menstruation)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Colombo D, Vescovini R (1985). Studio clinico controllato sull'efficacia degli antocianosidi del mirtillo nel trattamento della dismenorrea essenziale. *Giornale Italiano di Ostetricia e Ginecologia* 7 (12):1033-1038.

Trial design
Patients were treated over two consecutive menstrual cycles. Therapy began on the third day before the start of the cycle and continued for five days.

Study duration	2 menstrual cycles
Dose	1 (160 mg) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Female
Age	17-30 years

Inclusion criteria
Females suffering from chronic primary dysmenorrhea for at least one year (average 4.7 years).

Exclusion criteria
Females suffering from secondary dysmenorrhea (endomitriosis/adenomiosis, pelvic inflammatory diseases, vaginal/hymenal malfunctions, cervical stenosis, and ovarian cysts).

End points
The subjective symptoms of primary dysmenorrhea (pelvic and lumbar pain, mammary tension, headache, nausea and vomiting, heaviness of the lower limbs) were recorded before the study, on the first day of the cycle, and after treatment.

Results
Symptomatic relief occurred in patients taking bilberry, while the placebo was ineffective. After two menstrual cycles, the difference between the effects of bilberry and placebo were highly significant for pelvic and lumbar-sacral pain, swollen breasts, and heaviness in the lower limbs ($p < 0.002$). The benefit was less pronounced for nausea and vomiting ($p < 0.05$) and not significant for headache.

Side effects
None attributable to the therapy.

Authors' comments
Anthocyanosides, natural derivatives basically lacking any side effects, demonstrated results that were superior to expectations. Further studies are necessary to confirm these data and explore dosing requirements.

Reviewer's comments
The study was flawed by the highly subjective evaluation criteria for dysmenorrhea; therefore, it is difficult to assess the botanical's benefit. The treatment length was also inadequate, and there is no description of withdrawals or dropouts. (Translation reviewed) (4, 1)

Clinical Study: MirtoSelect™ (Myrtocyan®)

Extract name	Myrtocyan
Manufacturer	Indena S.p.A., Italy
Indication	**Pupillary reflex**
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Vannini L, Samuelly R, Coffano M, Tibaldi L (1986). Study of the pupillary reflex after anthocyanoside administration. *Bollettino d'Oculistica* 65 (Suppl. 6): 569-577.

Trial design
Parallel.

Study duration	1 day
Dose	3 (80 mg anthocyanosides w/25 percent anthocyanidins) capsules
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Male and female
Age	15-35 years (mean: 25.5)

Inclusion criteria
Volunteers who were internally and ophthalmologically normal.

Exclusion criteria
None mentioned.

End points
A computerized infrared videopupillograph was used to assess light reflex (amplitude of pupillary contraction, latency time, total contraction time, contraction velocity, dilation velocity, and acceleration of contraction). A baseline pupillographic recording was taken, then the drug or placebo was administered, and pupillographic tests were conducted after 1, 1.5, 2, and 4 hours.

Results
Fifteen of the 20 subjects who took bilberry extract showed an improvement in pupillary dynamics. With a constant latency time, the response of the pupil to light showed greater and faster movement, greater acceleration and in less time. The greatest improvement in pupillary dynamics occurred two hours after administration of bilberry. Thirteen of the 20 patients taking placebo showed improvement in pupillary dynamics. Contraction velocity and maximum acceleration improved and the total contraction time decreased, but the degree of contraction was unchanged.

Side effects
None mentioned in paper.

Authors' comments
Anthocyanosides may be used in healthy subjects who work in strong light, where the light reflex presumably wanes more easily, and who need a more efficient response to light due to fatigue.

Reviewer's comments
Mechanistic study. (Translation reviewed) (3, 5)

Product Profile: FAR-1

Manufacturer	**Ditta Farmigea S.p.A., Italy**
U.S. distributor	None
Botanical ingredient	**Bilberry fruit**
Extract name	None given
Quantity	180 mg
Processing	No information
Standardization	25% anthocyanidins
Formulation	Capsule

Other ingredients: DL-tocopherol (vitamin E, 100 mg).

Source(s) of information: Bravetti, Fraboni, and Maccolini, 1989.

Clinical Study: FAR-1

Extract name	None given
Manufacturer	Ditta Farmigea S.p.A., Italy
Indication	**Senile cataracts**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Bravetti GO, Fraboni E, Maccolini E (1989). Preventive medical treatment of senile cataract with vitamin E and *Vaccinium myrtillus* anthocyanosides: Clinical evaluation. *Annali di Ottalmologia e Clinica Oculistica* 115 (2): 109-116.

Trial design
Parallel, double-blind trial for four months. Then the trial was continued openly for another four months, with both groups receiving active treatment.

Study duration	4 months
Dose	2 (100 mg DL-tocopherol acetate, 180 mg anthocyanosides w/25 percent anthocyanidins)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	59
No. of subjects completed	50
Sex	Male and female
Age	48-81 years (mean: 67)

Inclusion criteria
Patients had central visual acuity for distant objects (with best correction) between 4/10 and 8/10.

Exclusion criteria
Patients could have no other ocular or systemic pathologies that might affect the purpose of the trial.

End points
Assessments of central visual acuity (measured with Snellen charts) both with and without correction, crystalline opacity, and subjective impression of patient of his or her vision were made prior to trial, as well as after four and eight months.

Results
After four months, 31 eyes remained unchanged and one worsened in the treated group. In placebo group, 23 eyes remained unchanged and seven worsened. There were no "improved" eyes. After eight months, the treatment group had 29 unchanged eyes and three worsened eyes, while the former-placebo group had 21 unchanged eyes and nine worsened eyes. At four months, there was a statistical significance between groups, $p < 0.05$. At eight months, when both groups had been receiving treatment, there was no statistical difference between the two.

Side effects
None found or reported.

Authors' comments
The validity of the trial is hindered by the lack of an objective, precise, and repeatable technique for detecting lenticular opacities in vivo. The observed data suggest, however, that the mixture of vitamin E and anthocyanosides can prevent the progression of senile cataracts.

Reviewer's comments
There was a 62 percent incidence of cataracts and no improved eyes after eight months. The study was limited by the outcome measures not being clearly defined. (Translation reviewed) (5,4)

Black Cohosh

Other common names: **Black bugbane, black snakeroot, rheumatism weed**
Latin name: ***Actaea racemosa* L.** [Ranunculaceae]
Latin synonyms: ***Cimifuga racemosa* (L.) Nutt.**
Plant parts: **Root, rhizome**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Black cohosh is native to North America. Native Americans used the rhizomes and roots as a gynecological remedy as well as for treatment of rheumatic conditions and hives. Black cohosh was also used for its sedative and pain-relieving properties. Dried plant material, hydroalcoholic liquid, and dried extracts are available commercially. The underground parts contain cycloartane-type triterpene glycosides, which are measured for quality control purposes (Flannery et al., 2002).

Clinical research has been conducted on a commercial preparation called Remifemin®, which is manufactured by Schaper & Brümmer in Germany and distributed in the United States by GlaxoSmithKline. Remifemin is available in tablet form, and each tablet contains black cohosh root extract equivalent to 20 mg root/rhizome. Over time, the formulation has changed from a solution to tablets, and the medium of extraction has changed from ethanolic alcohol (60 percent by volume) to isopropyl alcohol (40 percent by volume). The preparations are standardized to contain 1 mg total triterpene saponins (expressed as 27-deoxyactein) in each dose, equivalent to 20 mg root/rhizome. Recent analysis of the structure of 27-deoxyactein has determined that it is actually 26-deoxyactein (Chen et al., 2001).

BLACK COHOSH SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Remifemin®	Schaper & Brümmer GmbH & Co. KG, Germany/ GlaxoSmithKline	Isopropanolic extract	1 or 2 tablets twice daily (equivalent to 40 mg root/day)	Menopausal symptoms	6	Yes (II-I) No (II-I) Undetermined (III-3) MOA (III-I)

SUMMARY OF REVIEWED CLINICAL STUDIES

Black cohosh root extracts have been used for treating menopausal symptoms. Menopause is the cessation of menstruation, which generally occurs when women reach age 50. The physical symptoms of menopause include hot flashes, sweating, cardiovascular complaints, fatigue, vertigo, muscle and joint pain, urinary incontinence, vaginal dryness, and atrophy of the vaginal epithelium. Psychological symptoms include irritability, forgetfulness, anxiety, depression, sleep disturbances, and reduced libido. Menopause is thought to occur when no eggs are left in a woman's ovaries. The resulting decline in ovarian function causes a reduced production of estrogen and progesterone and a corresponding increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Murray and Pizzorno, 1999).

Remifemin

Menopausal Symptoms

We reviewed six clinical studies that examined the effects of Remifemin on menopause. The studies ranged in duration from two to six months. Measured end points included hormone levels, symptoms evaluated using the Kupperman Menopausal Index (an older scale that includes hot flashes, insomnia, and depression, but does not include vaginal dryness), and a battery of psychometric tests. Two tablets twice daily (8 mg extract, equivalent to 40 mg root/rhizome per day) was the common dose, although one trial used 40 drops twice daily of a liquid preparation (also equivalent to 40 mg root/rhizome).

In a comparison trial, 55 women with menopausal symptoms were randomly assigned to receive Remifemin (40 drops twice daily), conjugated estrogens (0.6 mg), or diazepam (2 mg) for three months. All treatments reduced symptoms according to the Kupperman index and the clinical global impression (CGI) scale. Treatment with Remifemin and estrogens caused changes in vaginal cytology from the forth to sixth week onward. As expected, the psychotropic drug (diazepam) had no effect on this end point (Warnecke, 1985). Our reviewer, Dr. Tieraona Low Dog, determined that the efficacy of Remifemin was not established in this trial due to poor methodology. Another study with 64 menopausal women compared Remifemin

(two tablets twice daily) with low-dose estrogen (0.6 mg) and placebo. After three months of treatment, all three groups improved. There was no improvement in the estrogen group compared to placebo, indicating that the dose was too low. However, the Kupperman index for the Remifemin group was significantly lower compared to the other two groups, indicating greater improvement for the black cohosh group. This group also uniquely exhibited positive changes in vaginal tissue, showing signs of increased proliferation of the vaginal epithelium (Stoll, 1987). The strength of the trial was reduced by the loss of 16 out of 80 women, including 12 of those in the estrogen group, during weeks five to eight due to perceived lack of efficacy.

In another study, also deemed poor quality, women who had undergone hysterectomy were given estriol (1 mg/day), conjugated estrogen (1.25 mg/day), combination therapy (estradiol 2 mg/day and norethisterone acetate 1 mg/day), or Remifemin. The authors reported similar reductions compared to baseline in all treatment groups in a modified Kupperman index at 4, 8, 12, and 24 weeks (Lehmann-Willenbrock and Riedal, 1988).

A dose-response study with 123 peri- and postmenopausal women compared the usual dose equivalent to 40 mg root to a tripling of the dose, equivalent to 127 mg root. Both doses caused a reduction in the Kupperman index and the self-depression scale over six months. Neither dose altered vaginal cytology or affected hormone levels (17-beta-estradiol, FSH, LH, prolactin, and sex hormone binding globulin) (Liske et al., 2002). This study did not include a placebo arm but was useful for safety data and indicated an absence of estrogenic effects even at the high dose.

A recent study with breast cancer survivors reported a comparable reduction in hot flashes and other menopausal symptoms following administration of Remifemin (two tablets per day) or placebo for two months. The only difference in favor of the treatment was a greater reduction in the amount of sweating. No effect on hormones FSH and LH was noted. It may be significant that approximately 70 percent of the women in this study were concurrently taking tamoxifen, an antiestrogenic agent (Jacobson et al., 2001).

Studies provide conflicting data regarding the potential estrogenic activity of this preparation of black cohosh root, as measured by suppression of LH and changes in vaginal cytology. A placebo-controlled study with 110 women with menopausal symptoms reported a

reduction in LH, but not FSH, following a dose of 8 mg extract (equivalent to 40 mg root) for two months (Duker et al., 1991). However, three other trials showed no significant effects on LH or FSH following treatment for two to six months with doses equivalent to 40 to 127 mg root (Lehmann-Willenbrock and Riedel, 1988; Liske et al., 2002; Jacobson et al., 2001). Two trials reported changes in vaginal cytology and increases in proliferation and maturation of vaginal epithelium following doses equivalent to 40 mg root for three months. These effects were comparable to those observed in the control groups given low-dose estrogens (0.6 mg per day) (Warnecke, 1985; Stoll, 1987). However, another study comparing doses of 40 mg root to 127 mg root found no such effect after the same three-month time period (Liske et al., 2002).

In general, the reviewed studies indicate that Remifemin may improve vasomotor symptoms and mood associated with menopause. However, Dr. Low Dog considered that the poor quality of the trials made it impossible to say with conviction that black cohosh extract given at the doses used in these trials is effective in alleviating menopausal symptoms and/or has any inherent estrogenic activity.

POSTMARKETING SURVEILLANCE STUDIES

A postmarketing surveillance study reported on 704 menopausal women who were treated with a dose of 40 drops Remifemin twice daily (equivalent to 40 mg root/rhizome) for six to eight weeks. Symptoms of hot flashes and profuse sweating improved, as did mood, in 75 percent of 629 women after four weeks (Stolze, 1982).

ADVERSE REACTIONS OR SIDE EFFECTS

No significant adverse reactions or side effects were reported in the clinical trials. Stolze's (1982) postmarketing surveillance study reported good tolerability for 93 percent of women with a dose of 40 drops twice daily. Mild and transitory symptoms, commonly gastrointestinal complaints, were reported in 7 percent.

Treatment of menopausal symptoms with estrogens is generally contraindicated for breast cancer survivors, due to a concern over in-

creased risk of cancer. A two-month study with 85 breast cancer survivors reported no evidence of harm from using black cohosh. The authors suggested that treatment with Remifemin for hot flashes might be more acceptable than conventional hormone replacement therapy (HRT) due to its lack of estrogenic effects (Jacobson et al., 2001).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

German Commission E
British Herbal Compendium (BHC)
American Herbal Pharmacopoeia (AHP)

Indications

Preparations of fresh or dried rhizome with attached roots are approved by the German Commission E for premenstrual discomfort, dysmenorrhea, or climacteric (menopausal) neurovegetative ailments; actions are listed as estrogen-like, binding to estrogen receptors, and suppression of luteinizing hormone (Blumenthal et al., 1998).

The *British Herbal Compendium* states that black cohosh is used to treat menopausal disorders, uterine spasm, muscular rheumatism, rheumatoid arthritis, and tinnitus; actions include endocrine (pituitary, oestrogen-mimetic) activity, emmenagogue, and antirheumatic (Bradley, 1992).

The *American Herbal Pharmacopoeia* lists the following indications supported by clinical trials of black cohosh extract: menopausal complaints, including outbreaks of sweating, anxiety, and hot flashes. The *AHP* also lists the following traditional indications for black cohosh: nervous disorders (chorea, nyalgia, epilepsy, hysteria, neuralgia, depression, anxiety and nervousness, and sciatica); cardiovascular disorders (hypertension and arrythmia due to vascular or nervous tension); various infectious diseases; and gynecological disorders (amenorrhea, leukorrhea, dysmenorrhea, atony of the uterus, premature labor, cramps during pregnancy, postpartum pain or hemorrhage, and pelvic pain). The traditional actions listed are anxiolytic; anti-

spasmodic; emmenagogue; nervine; uterine relaxant; partus preparatory; and uterine tonic (Flannery et al., 2002).

Doses

Dried rhizome and root: 40 to 200 mg or by decoction (Bradley, 1992); 1 g up to three times daily (Flannery et al., 2002)
Tincture: (1:10, 60 percent ethanol) 0.4 to 2 ml (Bradley, 1992); (1:10, 40 to 60 percent alcohol v/v) 0.4 ml daily (Flannery et al., 2002)
Extract: (alcohol 40 to 60 percent v/v) corresponding to 40 mg drug (Blumenthal et al., 1998; Flannery et al., 2002)

Treatment Period

The Commission E recommends that treatment should not last longer than six months (Blumenthal et al., 1998).

Contraindications

The Commission E lists no known contraindications, while the *BHC* lists pregnancy and lactation (Blumenthal et al., 1998; Bradley, 1992). The *AHP* states that a conclusive determination about contraindications cannot be made with the available data (Flannery et al., 2002).

Adverse Reactions

According to the Commission E, gastric discomfort occurs occasionally (Blumenthal et al., 1998). The *AHP* also lists mild gastrointestinal upset as the most frequent adverse event and lists several other minor adverse events (headache, vertigo, mastalgia, weight gain, heavy feeling in the legs, and a stimulant effect) (Flannery et al., 2002).

Precautions

The *AHP* warns that since the long-term use of black cohosh for menopausal symptoms is a new indication, women using black cohosh for menopausal symptoms, or those with a history of breast cancer,

should first consult a health care professional (Flannery et al., 2002). The *AHP* also suggests that black cohosh should not be used during pregnancy (except after consultation with a health care professional) or by children.

Drug Interactions

The Commission E and the *AHP* state there are no known drug interactions (Blumenthal et al., 1998; Flannery et al., 2002).

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DETAILS ON BLACK COHOSH PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Remifemin®

Manufacturer	**Schaper & Brümmer GmbH & Co. KG, Germany**
U.S. distributor	**GlaxoSmithKline**
Botanical ingredient	**Black cohosh root and rhizome extract**
Extract name	None given
Quantity	Equivalent to 20 mg root and rhizome
Processing	Isopropanol extract (40 percent v/v). Plant to extract ratio 0.78-1.14:1; 0.018-0.026 ml liquid extract in tablet
Standardization	Triterpene glycosides content (calculated as 27-deoxyactein)
Formulation	Tablet

Recommended dose: Take one tablet in the morning and one tablet in the evening, with water. Improvements can be expected within a few weeks with full benefits after using Remifemin twice a day for 4 to 12 weeks.

DSHEA structure/function: Clinically shown to reduce menopausal symptoms (including hot flashes, night sweats, mood swings, irritability, and related occasional sleeplessness).

Cautions: This product should not be used by women who are pregnant or considering becoming pregnant or are nursing. For a few consumers, gastric discomfort may occur but should not be persistent. If gastric discomfort persists, discontinue use and see a health care

practitioner. This product does not contain estrogen. Remifemin is not meant to replace any drug therapy.

Other ingredients: Lactose, cellulose, potato starch, magnesium stearate, and natural peppermint flavor.

Source(s) of information: Product packaging (©2000 SmithKline Beecham); Liske et al., 2002; information provided by Enzymatic Therapy; Remifemin® Scientific Brochure (Schaper & Brümmer GmbH & Co. KG, Germany, 1997).

Clinical Study: Remifemin®

Extract name	None given
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany
Indication	**Menopausal symptoms**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Warnecke G (1985). Influencing menopausal symptoms with a phytotherapeutic agent. *Die Medizinische Welt* 36: 871-874.

Trial design
Parallel. Three-arm study: 20 women received Remifemin, 20 were treated with 0.6 mg conjugated estrogens, and 20 were given 2 mg diazepam per day.

Study duration	3 months
Dose	40 drops twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Conjugated estrogens or diazepam
Site description	1 gynecology practice
No. of subjects enrolled	60
No. of subjects completed	55

Sex	Female
Age	45-60 years (mean: 54)

Inclusion criteria
Women between the ages of 45 and 60 with no or only irregular bleeding and menopausal symptoms that did not require high-dose hormone treatment or therapy with psychotropic drugs.

Exclusion criteria
Contraindications against one of the trial treatments, hormone treatment within the past four to six weeks, and surgery within the past six months.

End points
Patients were evaluated at the beginning of the study and after 2, 4, and 12 weeks of treatment. Neurovegetative symptoms were evaluated using the Kupperman index. Psychological symptoms were quantified using the Hamilton Anxiety Scale (HAMA) and the Self-Assessment Depression Scale (SDS). Vaginal epithelial calls were examined microscopically for changes. The clinical global impression scale assessed the outcome of therapy.

Results
All three forms of therapy had a comparably good effect on menopausal symptoms according to the Kupperman index and CGI. Remifemin and estrogens caused changes in vaginal cytology from the fourth to sixth week onward. The psychotropic drug, as expected, had no effect on these changes.

Side effects
None mentioned.

Author's comments
Long-term and consistent therapy with *Cimifuga* monoextract (Remifemin) yields at least equivalent rates of success against menopausal symptoms as low-dose conjugated estrogen and is better than therapy with psychotropic drugs.

Reviewer's comments
This study is limited by several flaws, including a lack of randomization and blinding, and an inadequate power calculation for the sample size. (1, 2)

Clinical Study: Remifemin®

Extract name	None given
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany

Indication	**Menopausal symptoms**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Stoll W (1987). Phytotherapy influences atrophic vaginal epithelium. *Therapeuticon* 1: 23-31.

Trial design
Parallel. Three-arm study: Remifemin (30 women), low-dose estrogen (30 women, 0.625 mg), and placebo (20 women).

Study duration	3 months
Dose	2 (2 mg extract) tablets twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Estrogen
Site description	Not described
No. of subjects enrolled	80
No. of subjects completed	64
Sex	Female
Age	46-58 years

Inclusion criteria
Women suffering from (1) neurovegetative complaints: hot flushes (at least three per day), sweating, and palpitation; (2) psychic complaints: anxiety, insomnia, and depression; and (3) somatic disorders such as vaginal dryness and menstrual disorders.

Exclusion criteria
Bilateral ovariectomy, castration, contraindication for hormone treatment, osteoporosis due to menopause, hormone therapy within the past four weeks, antihypertensive medications, menopausal complaints due to other causes.

End points
The Kupperman Menopausal Index (neurovegetative symptoms) and the Hamilton Anxiety Scale (HAMA) (psychological complaints) were assessed

every four weeks. The proliferative status of vaginal epithelium was measured at the beginning of the study and after 12 weeks.

Results
After three months of treatment, the Kupperman index showed a decrease for all three groups, but the Remifemin group was significantly lower than both estrogen and placebo groups, $p < 0.001$. The index for the Remifemin group fell from over 30 to under 15, an indication that treatment is no longer needed. The HAMA score also fell for all three groups, but again the Remifemin group was significantly lower, $p < 0.001$. The degree of proliferation of the vaginal epithelium improved in the Remifemin group, but there was no change for the other groups. The difference was significant, $p < 0.01$.

Side effects
Twelve of the Remifemin patients reported minor side effects.

Author's comments
Remifemin is suited as the drug of first choice to treat menopausal failure, particularly if a hormone therapy is only indicated on reflection or not wanted by the patient.

Reviewer's comments
The study is limited by several flaws: lack of randomization; risk of attrition bias due to the loss of 12 out of 30 women in the estrogen group between weeks five through eight because of perceived lack of efficacy; and FSH was not used as inclusion/exclusion criteria to determine menopausal status. (3, 4)

Clinical Study: Remifemin®

Extract name	None given
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany
Indication	**Menopausal symptoms** in hysterectomized patients
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Lehmann-Willenbrock E, Riedel HH (1988). Clinical and endocrinologic examinations concerning therapy of climacteric symptoms following hysterectomy with remaining ovaries. *Zentralblatt fur Gynakologie* 110: 611-618.

Trial design
Parallel. Patients were divided into four treatment groups: group 1 was given estriol (Ovestin) one tablet containing 1 mg; group 2 received conjugated estrogens (Presomen) one tablet containing 1.25 mg; group 3 received estrogen-gestagen (Trisequens) one tablet a day; and group 4 received Remifemin.

Study duration	6 months
Dose	2 (2 mg extract) tablets twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Estriol, conjugated estrogens, and estrogen-gestagen therapy
Site description	Not described
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Female
Age	Under 40 years

Inclusion criteria
Patients who had undergone hysterectomy between 1975 and 1984 and had at least one intact ovary. Patients also had climacteric symptoms, predominantly consisting of hot flushes and sweating.

Exclusion criteria
Women unable to undergo hormone therapy because of chronic hepatitis, deep vein thrombosis, postoperative state following mastocarcinoma, or uncontrollable diabetes mellitus were excluded. Patients refusing any hormone therapy at all were also excluded.

End points
Women assessed their severity of a list of symptoms on a modified Kupperman index at baseline and 4, 8, 12, and 24 weeks after starting the study. Blood was taken to measure concentrations of prostaglandin E2, progesterone, FSH, and LH.

Results
Compared to the initial severity of symptoms, results in patients taking

estriol or conjugated estrogens were significantly different after 8, 12, and 24 weeks. In patients taking Remifemin or estrogen-gestagen complex, symptom severity after 4, 8, 12, and 24 weeks also differed significantly from severity at the beginning of the trial. There were no significant differences in LH or FSH levels in any of the groups.

Side effects
None discussed in paper.

Authors' comments
Alleviation of menopausal symptoms due to ovarial deficiency following hysterectomy may be successfully treated by all four treatment schemes (estriol, conjugated estrogen, estrogen-gestagen complex, or Remifemin). If osteoporosis prevention is intended, conjugated estrogen or estrogen-gestagen is recommended.

Reviewer's comments
This trial was flawed by the lack of blinding and placebo control. There was also no power calculation to determine the appropriateness of the sample size. (1, 4)

Clinical Study: Remifemin®

Extract name	None given
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany
Indication	**Menopausal symptoms**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Liske E, Hänggi W, Henneicke-von Zeppelin HH, Boblitz N, Wüstenberg P, Rahlfs VW (2002). Physiological investigation of a unique extract of black cohosh (*Cimicifugae racemosae* rhizoma): A 6-month clinical study demonstrates no systemic estrogenic effect. *Journal of Women's Health and Gender-Based Medicine* 11 (2): 163-174. (Also published as Liske E, Boblitz N, Henneicke-von Zepelin H-H [2000]. Therapie Klmakterischer Beschwerden mit *Cimicifuga racemosa:* Daten zur Wirkung and Wirksamkeit aus einer randomisierten kontrollierten Doppelblindstudie. In *Phytopharmaka VI.* Eds. Rietbrock N, Donath MF, Loew D, Roots I, Schulz V. Darmstadt: Verlag Steinkopft, pp. 247-257.)

Trial design
Parallel. The trial had a 12-week treatment period with extension to 24 weeks.

Study duration	6 months
Dose	39 mg or 127.3 mg root daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	No
Site description	4 gynecological clinics
No. of subjects enrolled	152
No. of subjects completed	123
Sex	Female
Age	42-60 years (mean: 50)

Inclusion criteria
Peri- and postmenopausal volunteers aged 42 to 60 who had a Kupperman Menopausal Index of at least 20 were included in this study.

Exclusion criteria
Serious gynecological, internal, or psychiatric diseases were exclusion criteria, as well as all other circumstances that could interfere with the study.

End points
The primary assessment of the degree of menopausal symptoms and of possible therapeutic effects was the Kupperman Menopausal Index. The self-depression scale (SDS), as well as the clinical global impressions scale, were secondary parameters. Assessments were carried out at baseline and after 2, 4, 8, 12, 16, 20, and 24 weeks. Hormone tests (17 beta estradiol, lutenizing hormone, follicle-stimulating hormone, prolactin, and sex hormone-binding globulin) and studies of vaginal cytology were also conducted. Physiological parameters were evaluated at baseline and at weeks 4, 12, and 24.

Results
Both doses of black cohosh extract lowered the Kupperman index. Seventy percent of the standard-dose (39 mg) group were responders, as were 72 percent of the high-dose (127.3 mg) group. The median score on the SDS also decreased for both groups (from 44.5 to 37 and from 44 to 36, respec-

tively). A large majority of both groups rated the global assessment of efficacy after 12 weeks as "very good" or "good" (78.4 percent and 78.6 percent, respectively). Neither treatment was significantly better than the other for any of the efficacy criteria. Black cohosh did not alter the vaginal cytology measures in the 12-week study, and no significant differences were observed in hormone levels.

Side effects
The incidence of adverse events was statistically equal in both groups. Most of the adverse events were mild or moderate and included the following organ classes: gastrointestinal, CNS, breast/genitals, and other. Biochemical or hematological laboratory findings were not affected by either dose.

Authors' comments
The findings indicate that this *C. racemosa* formulation offers an alternative for menopausal complaints when HRT is either contraindicated or refused.

Reviewer's comments
The exclusion criteria is vague; no mention is made of medications, other botanicals, soy, etc. This study suffers from the lack of a placebo arm, but it provides useful safety data on endometrial effects, hormonal effects, and adverse events. (5, 5)

Clinical Study: Remifemin®

Extract name	None given
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany
Indication	**Menopausal symptoms;** hot flashes in women treated for breast cancer
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, Lo KMS, Moore A, Rosenman PJ, Kaufman EL, et al. (2001). Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *Journal of Clinical Oncology* 19 (10): 2739-2745.

Trial design
Parallel. Patients were either taking tamoxifen (59) or no tamoxifen (26), and these groups were then randomized to receive either placebo or black

cohosh. Subjects were allowed to use nonhormonal medications during the study but were instructed not to begin new therapy for hot flashes.

Study duration	2 months
Dose	1 tablet twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Medical center
No. of subjects enrolled	85
No. of subjects completed	69
Sex	Female
Age	>18 years

Inclusion criteria
Women over 18 years who were previously treated for breast cancer, completed primary therapy, including radiation therapy and chemotherapy, at least two months before the trial start, and experienced hot flashes daily

Exclusion criteria
The use of hormonal replacement therapy for hot flashes, pregnancy, major psychiatric illness, or known recurrent or metastatic breast cancer.

End points
Patients recorded the intensity and number of hot flashes for three days before beginning treatment, on days 27 to 30, and again on days 57 to 60. Subjects also completed a detailed menopausal symptom index and a visual analog scale rating overall health and well-being before starting treatment and at the end of the study. The first 41 subjects were asked to supply a blood sample at the first and last visits. Follicle-stimulating hormone and luteinizing hormone levels were examined for the first 37 and 18 women, respectively (of those who provided blood samples).

Results
Both groups reported a decline in the number of hot flashes; from baseline to the trial end this decline was about 27 percent. The differences between treatment groups at the trial end were not significant. Both groups also experienced a decline in hot flash intensity, but the difference between groups was not significant. Improvements in menopausal symptoms and the global

ratings of well-being and health were seen in both the treatment and placebo groups, but the treatment group reported only a significantly greater improvement for sweating ($p = 0.04$). For those samples tested, the changes in FSH and LH were small and not statistically significant in any group.

Side effects
Three serious adverse events were reported (one in placebo/tamoxifen group and two in treatment/tamoxifen group), including hysterectomy, breast cancer recurrence, and appendectomy. Ten minor adverse events were also reported (six in treatment/tamoxifen group, two in placebo/tamoxifen group, and two in placebo/no tamoxifen group). None of the adverse events appeared to be related to treatment with black cohosh.

Authors' comments
In short, for breast cancer survivors, these data provide little evidence of either harm or benefit from using black cohosh to control hot flashes, although a reduction in sweating may be important to patients.

Reviewer's comments
The dose of black cohosh extract was not given, and the identity of the product was obtained through credits to the manufacturer. Soy or other medications that may affect hot flashes (selective serotonin reuptake inhibitors, clonidine, etc.) were not excluded. The sample size was also too small for women not on tamoxifen. (5, 4)

Clinical Study: Remifemin®

Extract name	None given
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany
Indication	**Menopausal symptoms;** gonadotropins (LH and FSH release) in menopausal women
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Duker E, Kopanski L, Jarry H, Wuttke W (1991). Effects of extracts from *Cimicifuga racemosa* on gonadotropin release in menopausal women and ovariectomized rats. *Planta Medica* 57 (5): 420-424.

Trial design
Parallel.

Study duration	2 months
Dose	2 (2 mg extract) tablets twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	110
No. of subjects completed	Not given
Sex	Female
Age	Mean: 52 years

Inclusion criteria
Patients who had received no steroid replacement therapy for at least six months and complained about climacteric (menopausal) symptoms.

Exclusion criteria
None mentioned.

End points
After two months of treatment, blood samples were drawn. LH and FSH were measured in blood samples.

Results
LH, but not FSH, levels were significantly reduced in patients receiving the *Cimicifuga* extract compared with placebo ($p < 0.05$).

Side effects
None mentioned.

Authors' comments
Data demonstrate for the first time that a commercially available extract (Remifemin) selectively suppresses LH secretion in menopausal women, which points to an estrogenic effect of *Cimifuga racemosa* preparations.

Reviewer's comments
This trial is limited by several flaws: trial was not blinded or randomized; no exclusion criteria were provided; and no description of dropouts was given. (0, 3)

Boxwood

Latin name: ***Buxus sempervirens* L.** [Buxaceae]
Plant part: **Leaf**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

The leaves of the boxwood tree were formerly used as a botanical remedy in Europe for "purifying the blood" and for rheumatism (*PDR,* 1998). The preparation used in this clinical study is called SPV_{30}™ and contains boxwood leaf powder. It is manufactured by Arkopharma Laboratoires Pharmaceutiques in France and distributed by the U.S. division (Health from the Sun/Arkopharma) in Bedford, Massachusetts.

SUMMARY OF REVIEWED CLINICAL STUDIES

Human immunodeficiency virus (HIV) infection usually leads to AIDS (acquired immune deficiency syndrome) or AIDS-related symptoms. One indication of the progression of the disease is the number of CD4 T-lymphocytes (a type of white blood cell) in the blood. The idea for the use of boxwood in HIV disease came from an anecdotal report backed by laboratory data. It was noticed that an individual's intake of a boxwood product, $SPV_{30,}$ appeared to correlate with an increase in lymphocyte (CD4) cell count.

SPV_{30}

Human Immunodeficiency Virus

A well-designed, placebo-controlled study was designed to explore the use of SPV_{30} in 135 asymptomatic HIV patients who had

BOXWOOD SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
SPV_{30}™	Arkopharma Laboratoires Pharmaceutiques, France/Health from the Sun/ Arkopharma	Powdered leaves	2 (165 mg) capsules every 8 hours (990 mg per day)	HIV	1	Yes (I-1)

not previously taken any antiretroviral or immunomodulating medicines. There was a significant benefit compared with placebo in patients given a dose of two (165 mg each) capsules every eight hours. Benefit was seen as fewer decreases in CD4 cell counts, fewer increases in viral load, and a slower overall rate of disease progression. Less benefit was seen in the group given a higher dose of two (330 mg) capsules every eight hours (Durant et al., 1998). In spite of the positive outcome with the lower dose, our reviewer, Dr. Richard O'Connor, questioned the utility of the preparation due to the availability of highly effective modern antiretroviral therapy.

ADVERSE REACTIONS OR SIDE EFFECTS

No severe side effects were reported in the trial reviewed, and there was no significant difference in adverse reactions between the treatment and placebo groups.

No health hazards or side effects are reported with the proper administration of designated therapeutic dosages of boxwood leaf preparations in general. However, toxic effects, such as diarrhea, vomiting, severe clonic spasms, and ultimately signs of paralysis followed by fatal asphyxiation, can occur if taken in large doses (e.g., for dogs: 5 to 10 g/kg body weight) (*PDR,* 1998). This toxicity has been reported in cows, horses, and pigs that have eaten clippings left in the pasture (Bruneton, 1999).

REFERENCES

Bruneton J (1999). *Toxic Plants Dangerous to Humans and Animals.* Paris, France: Lavoisier Publishing.

Durant, J, Chantre Ph, Gonzales G, Vandermander J, Halfon Ph, Rousse B, Guedon D, Rahelinirina V, Chamaret S, Montagnier L, Dellamonica P (1998). Efficacy and safety of *Buxus sempervirens* L. preparations (SPV_{30}) in HIV-infected asymptomatic patients: A multicentre, randomized, double-blind, placebo-controlled trial. *Phytomedicine* 5 (1): 1-10.

PDR for Herbal Medicines (1998). Montvale, NJ: Medical Economics Co.

DETAILS ON BOXWOOD PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: SPV_{30}™

Manufacturer	**Arkopharma Laboratoires Pharmaceutiques, France**
U.S. distributor	**Health from the Sun/Arkopharma**
Botanical ingredient	**Boxwood leaf**
Extract name	**SPV_{30}**
Quantity	330 mg
Processing	Powdered plant material
Standardization	No information
Formulation	Capsule

Recommended dose: Take one capsule three times per day with a glass of water.

DSHEA structure/function: Nutritional support for the body's immune system. Strengthens immune function by maintaining a healthy immune cell count.

Cautions: If taking any medications or are pregnant or lactating, consult a physician before taking this product.

Other ingredients: Cellulose derivative (capsule shell).

Source(s) of information: Product package and leaflet.

Clinical Study: SPV_{30}™

Extract name	SPV_{30}
Manufacturer	Arkopharma Laboratoires Pharmaceutiques, France
Indication	**Human immunodeficiency virus**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Durant J, Chantre Ph, Gonzales G, Vandermander J, Halfon Ph, Rousse B, Guedon D, Rahelinirina V, Chamaret S, Montagnier L, Dellamonica P (1998). Efficacy and safety of *Buxus sempervirens* L. preparations (SPV_{30}) in HIV-infected asymptomatic patients: A multicentre, randomized, double-blind, placebo-controlled trial. *Phytomedicine* 5 (1): 1-10.

Trial design
Parallel. Two doses of SPV_{30} compared to placebo. The study was designed to last 18 months. However, it was stopped early due to the decision that it was unethical to carry on the trial with a placebo group. Therefore the median treatment duration for placebo was 37 weeks (range 8 to 64), for SPV_{30} 990 mg 37 weeks (range 4 to 64), and for SPV_{30} 1980 mg 38 weeks (range 4 to 64).

Study duration	4 to 64 weeks (median 37 weeks)
Dose	2 (165 mg or 330 mg) capsules every 8 hours (990 or 1980 mg/day)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	16 hospitals
No. of subjects enrolled	145
No. of subjects completed	135
Sex	Male and female
Age	Mean: 34 years

Inclusion criteria
Asymptomatic, seropositive HIV, CD4 lymphocyte counts from 250 to 500 ×

10^6/l, platelet count >75 × 10^9/l, hemoglobin >9.0 mg/dl, serum transaminases less than five times the upper limit of normal values, serum creatinine <200 µmol/l, Karnofsky performance score at least 90 percent, and age at least 18 years.

Exclusion criteria
Patients who had previously taken antiretroviral or immunomodulating medicines, and pregnant women. The following concomitant medication was not allowed during the study: anti-HIV therapy (AZT, DDI, D4T, 3TC, DDC); any drug under investigation; cancer chemotherapy; systemic corticosteroids (>7 days); and immunomodulator and immunosuppressive treatments.

End points
Patients were evaluated every four weeks for adverse events, signs, and symptoms of HIV disease. Body weight and Karnofsky performance scores were recorded and blood was taken. Therapeutic failures were defined by occurrence of AIDS, AIDS-related complex, or decrease of CD4 cell count below 200 × (10^6)/l twice.

Results
There was a statistically significant difference in therapeutic failures between groups in favor of the 990 mg group, including decreases of CD4 cell count and/or number of clinical aggravations. The treatment groups differed statistically in the rate of disease progression in favor of 990 mg/day. Fewer patients receiving 990 mg/day had an increase in viral load greater than 0.5 log at the end (p = 0.029). The higher-dose group did not experience an overall benefit.

Side effects
No severe side effects observed.

Authors' comments
From these results, SPV_{30} 990 mg per day has beneficial effects in HIV asymptomatic patients and appears to delay the progression of HIV disease.

Reviewer's comments
A well-designed, well-described study. Institutional review board (IRB) approval and informed consent from subjects were obtained. HIV seropositive patients were not receiving antiretroviral therapy in this study. The effectiveness seen in the low-dose group did not occur in the high-dose group, but the utility of SPV_{30} seems unlikely with the availability of highly active antiretroviral therapy (HAART) that is now used. (5, 6)

Butterbur, Purple

Other common names: **Petasites, sweet coltsfoot**
Latin name: ***Petasites hybridus* (L.) P. Gaertn. et al.** [Asteraceae]
Latin synonyms: ***Petasites officinalis* Moench**
Plant part: **Root**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Purple butterbur, or petasites, rhizomes (underground parts) have been traditionally used in Europe for their antispasmodic and analgesic activity. The active chemical constituents are thought to be a group of sesquiterpenes, the petasins (Grossmann and Schmidramsl, 2000).

Petadolex™ contains a liquid carbon dioxide extract of butterbur root (plant/extract ratio 30:1) standardized to contain at least 7.5 mg petasin and isopetasin. The commercial product contains 50 mg extract per capsule, and the recommended dose is one capsule twice daily. It is manufactured by Weber & Weber International GmbH & Co. KG in Germany and distributed by Weber & Weber USA in Manson, Washington.

ZE 339 is manufactured in Switzerland by Zeller AG. It is a carbon dioxide extract standardized to 8.0 mg total petasins per tablet. It is not sold in the United States.

BUTTERBUR SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Petadolex™	Weber & Weber Intl. GmbH & Co. KG, Germany/ Weber & Weber USA	Liquid carbon dioxide extraction	2 (25 mg) capsules twice daily	Migraine prevention	1	Yes (I-1)
ZE 339	Zeller AG	Liquid carbon dioxide extraction (ZE 339)	1 tablet four times daily	Allergic rhinitis (hay fever)	1	Yes (II-1)

SUMMARY OF REVIEWED CLINICAL STUDIES

Petadolex

Migraine Prevention

The cause of migraine headaches is largely unknown; however, the cause may be a combination of a constriction of blood vessels and an inflammation affecting the nerves in the brain. A well-designed and well-conducted study on the prevention (prophylaxis) of migraine headaches was conducted using 60 patients. A dose of 50 mg twice daily was given for three months. Patients taking Petadolex had significantly fewer migraine attacks and comparatively fewer migraine days per month compared to those given placebo (Grossmann and Schmidramsl, 2000).

ZE 339

Allergic Rhinitis (Hay Fever)

A trial was conducted comparing ZE 339 to cetirizine which included 124 adults with a history of seasonal allergic rhinitis (hay fever) with the symptoms of runny nose, nasal congestion, and itchy nose or eyes. Cetirizine reduces allergy symptoms through blocking histamine activity (Hardman et al., 1996). In a double-placebo design, subjects were given either ZE 339 (one tablet four times daily) or cetirizine (one 10 mg tablet daily) for two weeks. At the end of the treatment period, there was no difference in the two groups according to a questionnaire they filled out covering physical and emotional function, vitality, mental health, general health, physical activity, social functioning, and pain. There was also no difference in a clinical global impression scale (CGI) evaluated by attending physicians (Schapowal, 2002). Our reviewer, Dr. Richard O'Connor, commented that the study lacked a placebo group, which is essential in hay fever trials in which response rates of 40 to 50 percent have been reported. Also, it would have been preferable to examine hay fever symptoms as an end point and not just quality-of-life measures.

ADVERSE REACTIONS OR SIDE EFFECTS

No adverse effects were reported by patients taking Petadolex during the trial. In the trial with ZE 339, the incidence of side effects was similar to those with cetirizine (16 to 17 percent). In the butterbur group, the most commonly reported effects were fatigue and headache.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

German Commission E

Indications

The dried roots (underground parts) are approved by the German Commission E as supportive therapy for acute spastic pain in the urinary tract, particularly if stones exist. The action is antispasmodic. The leaf is not approved for use, as the effectiveness is not well documented, and the leaves may contain toxic pyrrolizidine alkaloids. However, the leaves are used for nervous cramplike states and associated pain, colic, headaches, as well as to stimulate the appetite (Blumenthal et al., 1998).

Doses

Root: preparations equivalent to 4.5 to 7 g per day (Blumenthal et al., 1998)

Treatment Period

The Commission E suggests that treatment periods not last longer than four to six weeks per year (Blumenthal et al., 1998).

Contraindications

Pregnancy and nursing are contraindicated while taking butterbur according to the Commission E (Blumenthal et al., 1998).

Adverse Reactions

The Commission E lists no known adverse reactions (Blumenthal et al., 1998).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998).

REFERENCES

Blumenthal M, Busse W, Hall T, Goldberg A, Gruenwald J, Riggins C, Rister S, eds. (1998). *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines.* Trans. S Klein. Austin, TX: American Botanical Council.

Grossmann M, Schmidramsl H (2000). An extract of *Petasites hybridus* is effective in the prophylaxis of migraine. *International Journal of Clinical Pharmacology and Therapeutics* 38 (10): 430-435. (Also published in Grossmann W [1996]. *Der Freie Arzt* 3 [May/June].)

Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG (1996). *Goodman and Gillman's The Pharmacological Basis of Therapeutics,* Ninth Edition. New York: McGraw-Hill.

Schapowal A (2002). Randomized controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. *British Medical Journal* 324 (7330): 144-146.

DETAILS ON BUTTERBUR PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Butterbur Products

Product Profile: Petadolex™

Manufacturer	**Weber & Weber International GmbH & Co. KG, Germany**
U.S. distributor	**Weber & Weber USA**
Botanical ingredient	**Butterbur root extract**
Extract name	None given
Quantity	50 mg
Processing	Plant to extract ratio 30:1, liquid carbon dioxide extraction
Standardization	At least 7.5 mg of petasin and isopetasin
Formulation	Capsule

Recommended dose: One capsule twice daily with meals. Discontinue Petadolex after the initial cycle of four to six months. It will maintain its benefits even after taking it. Resume supplementation for another four- to six-month cycle when the number of migraines experienced begins to increase.

DSHEA structure/function: Helps maintain proper muscle tone in cerebral blood vessels; 62 percent reduction of migraine days.

Cautions: If pregnant or nursing a baby, do not use this product.

Other ingredients: Natural coloring: carmine, glycerol, gelatin, titanium-oxide.

Source(s) of information: Product package; Petadolex Caregiver's Guide; Grossmann and Schmidramsl, 2000.

Clinical Study: Petadolex™

Extract name	None given
Manufacturer	Weber & Weber GmbH & Co. KG, Germany
Indication	**Migraine prophylaxis** (prevention)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Grossmann M, Schmidramsl H (2000). An extract of *Petasites hybridus* is effective in the prophylaxis of migraine. *International Journal of Clinical Pharmacology and Therapeutics* 38 (10): 430-435. (Also published in Grossmann W [1996]. *Der Freie Arzt* 3 [May/June].)

Trial design
Parallel. Four-week run-in phase without trial medication, followed by three-month treatment period.

Study duration	3 months
Dose	2 (25 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Hospital outpatient clinic
No. of subjects enrolled	60
No. of subjects completed	58
Sex	Male and female
Age	19-38 years (mean: 29)

Inclusion criteria
Outpatients with a minimum of three attacks per month within the past three months prior to the study, and a minimum of two attacks in the four-week run-in phase. Inclusion criteria were as defined by the International Headache Society in 1988.

Exclusion criteria
Exclusion criteria were as defined by the International Headache Society in 1988.

End points
Outcome variables were the frequency, intensity, and duration of migraine attacks as well as accompanying symptoms. Patients recorded migraine attacks and symptoms in a diary. They were seen every four weeks.

Results
Patients taking Petadolex had significantly fewer migraine attacks than the placebo group and comparatively fewer migraine days per month ($p < 0.05$). The difference was noted four weeks after treatment began and continued until the end of the study. Pain intensity of migraines and duration of migraine attacks were lower in Petadolex group, but significant only at the end of the second month (and not at the end of the study).

Side effects
None reported by patients.

Authors' comments
The results suggest that migraine patients can benefit from prophylactic treatment with this special extract. The combination of high efficacy and excellent tolerance emphasizes the particular value that *Petasites hybridus* has for the prophylactic treatment of migraine.

Reviewer's comments
Sixty patients is a relatively small trial. Otherwise, a well-designed study with clearly defined inclusion/exclusion criteria and definitive end points. However, values are provided as mean +/–, but we are not told if the standard error of the mean (SEM) or standard deviation (SD) is used. Length of treatment (12 weeks) was long enough for a clear separation between groups to occur. (5, 5)

Product Profile: ZE 339

Manufacturer	**Zeller AG, Switzerland**
U.S. distributor	None

Botanical ingredient	**Butterbur leaf extract**
Extract name	**ZE 339**
Quantity	20-54 mg extract; 8 mg petasins
Processing	Carbon dioxide extract
Standardization	8.0 mg total petasins per tablet
Formulation	Tablet

Recommended dose: Adults and children over 12 years old should take 1 tablet twice daily during the allergy season. Up to 4 tablets can be taken if exposure to allergen is increased.

DSHEA structure/function: Swiss drug indication is: treatment of all symptoms of allergic rhinitis (hay fever).

Source(s) of information: Schapowal, 2002; communication with Zeller AG.

Clinical Study: ZE 339

Extract name	ZE 339
Manufacturer	Zeller AG, Switzerland
Indication	**Allergic rhinitis** (hay fever)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Schapowal A (2002). Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. *British Medical Journal* 324 (7330): 144-146.

Trial design
Parallel. In a double-dummy design, subjects were given either butterbur extract or cetirizine (one 10 mg tablet daily).

Study duration	2 weeks
Dose	1 tablet 4 times daily (8 mg total petasine per tablet)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes

Placebo	No
Drug comparison	Yes
Drug name	Cetirizine
Site description	4 outpatient clinics
No. of subjects enrolled	131
No. of subjects completed	124
Sex	Male and female
Age	Mean: 37 years

Inclusion criteria
At least 18 years old with a history of seasonal allergic rhinitis (at least two consecutive years) with the presence of all the following symptoms: rhinorrhea, sneezing, nasal congestion, and itching (nose or eyes). Two or more of these symptoms must have been rated above 2 on a five-point scale (0 = none, 4 = very severe).

Exclusion criteria
Subjects were excluded if they had a history of alcohol or substance abuse; were pregnant or breast-feeding; had a parasitic disease causing an increase in IgE or eosinophil levels; had taken corticosteroids in the past two months, antihistamines in the past six weeks, or anti-inflammatories in the past two weeks; had nonseasonal rhinitis; had received an organ transplant; or had a serious concomitant disease.

End points
Participants were assessed at baseline and at the end of the two weeks of treatment. Assessment consisted of a full medical examination and laboratory tests (hematology and biochemistry). Participants also filled out a medical outcome health survey questionnaire (SF-36), and doctors rated the patients with a clinical global impressions score. The primary end point was the change from baseline to the treatment end of each score on the questionnaire, and the secondary outcome was the change in the clinical global impression score.

Results
Butterbur performed similarly to cetirizine on the primary outcome measure, the health survey questionnaire, which included questions regarding physical and emotional function, vitality, mental health, general health, physical activity, social functioning, and pain. There was also no difference in efficacy between the two treatments on the secondary outcome measure, the clinical global impression score, including the severity of the condition, global improvement, and the risk-to-benefit ratio.

Side effects
The incidence of adverse events was similar in both groups. None in the butterbur group could be specifically tied to the treatment, while two-thirds of the adverse events in the cetirizine group are typical of antihistamines (drowsiness and fatigue).

Author's comments
This randomized, double-blind study showed that the effects of butterbur (ZE 339 extract tablets) are similar to those of cetirizine in patients with seasonal allergic rhinitis. Butterbur did not produce the sedative effects associated with antihistamines and was well tolerated by patients.

Reviewer's comments
This study lacks a placebo group which is essential in trials of allergic rhinitis in which response rates of 40 to 50 percent have been reported. Also, it would have been better to examine clinical symptoms as a primary outcome, not just the quality-of-life measures. (5, 5)

Cat's Claw

Other common names: **Uña de gato**
Latin name: ***Uncaria tomentosa* (Willd.) DC.** [Rubiaceae]
Plant part: **Root**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Cat's claw, or uña de gato, is a South American vine that has been used widely as a folk remedy. Claims have been made for its effectiveness against viral infections, including human immunodeficiency virus (HIV), as well as cancer, arthritis, and a long list of largely incurable diseases. Following clues from the Asháninka Indians in the Central Peruvian rain forest, it was discovered that there are two chemotypes of *U. tomentosa.* One contains predominately pentacyclic oxindole alkaloids (pteropodine, isopteropodine, isomitraphylline, etc.), which are reported to have immunostimulatory activity. The other chemotype contains primarily tetracyclic oxindole alkaloids (rhynochophylline and isorynchophylline), which are thought to oppose the actions of the pentacyclic oxindole alkaloids. Because these two chemotypes are identical in appearance, commercial cat's claw is usually a mixture of the two. Thus, it is suggested that cat's claw products taken for their immunostimulatory action have no more than 0.02 percent tetracyclic oxindole alkaloids (Schulz, Hänsel, and Tyler, 2001; Reinhard, 1999).

Saventaro® (Krallendorn®) capsules contain 20 mg root extract, which is standardized to 1.3 percent pentacyclic oxindole alkaloids and free of tetracyclic oxindole alkaloids. Saventaro is manufactured by IMMODAL Pharmaka GmbH in Austria and under license in the United States by Enzymatic Therapy, Green Bay, Wisconsin.

CAT'S CLAW SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Saventaro® (US) Krallendorn® (EU)	IMMODAL Pharmaka GmbH, Austria/Enzymatic Therapy	Extract containing 1.3 percent pentacyclic oxindole alkaloids	3 (20 mg) capsules daily	Rheumatoid arthritis	1	Trend (III-1)

SUMMARY OF REVIEWED CLINICAL STUDIES

Saventaro

Rheumatoid Arthritis

Saventaro (three 20 mg capsules daily) was given to patients with rheumatoid arthritis stage II and III in a double-blind, placebo-controlled trial that included 40 subjects. After six months, there was a significant reduction in pain but no effect on joint swelling or laboratory indicators of inflammation compared to placebo (Clinical Examinations of Krallendorn Products, 1999). Our reviewer, Dr. John Trimmer Hicks, commented that although significant pain relief was documented, a much larger sample size is needed to prove significant differences in trials on disease-modifying agents for rheumatoid arthritis due to large placebo effects usually seen in these trials.

ADVERSE REACTIONS OR SIDE EFFECTS

The reviewed clinical trial reported no difference in adverse effects for the treatment and placebo groups.

REFERENCES

Clinical Examinations of Krallendorn Products: Double-blind placebo controlled trial in rheumatoid arthritis (1999). Confidential report by IMMODAL Pharmaka GmbH.

Reinhard KH (1999). *Uncaria tomentosa* (Willd.) DC: Cat's claw, *uña de gato,* or Savéntaro. *The Journal of Alternative and Complementary Medicine* 5 (2): 143-151.

Schulz V, Hänsel R, Tyler VE (2001). *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine,* Fourth Edition. Trans. TC Telgar. Berlin: Springer-Verlag.

DETAILS ON CAT'S CLAW PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Saventaro®

Manufacturer	**Enzymatic Therapy® (IMMODAL Pharmaka GmbH, Austria)**
U.S. distributor	**Enzymatic Therapy**
Botanical ingredient	**Cat's claw root extract**
Extract name	None given
Quantity	20 mg
Processing	No information
Standardization	A minimum of 1.3 percent pentacyclic oxindole alkaloids and no tetracyclic oxindole alkaloids
Formulation	Capsule

Recommended dose: One capsule three times daily for the first ten days and one capsule daily thereafter.

DSHEA structure/function: Enhances natural immunity and modifies the acquired immune system.

Other ingredients: Cellulose, calcium carbonate, magnesium stearate, silicon dioxide, and gelatin capsule.

Comments: Sold in Europe as Krallendorn®. Saventaro is a trademark of IMMODAL Pharmaka GmbH, Austria. Enzymatic Therapy is licensed by IMMODAL to manufacture the product in the United States.

Source(s) of information: Product package.

Clinical Study: Krallendorn®

Extract name	None given
Manufacturer	IMMODAL Pharmaka GmbH, Austria
Indication	**Rheumatoid arthritis**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Clinical Examinations of Krallendorn Products: Double-blind placebo controlled trial in rheumatoid arthritis (1999). Confidential report by IMMODAL Pharmaka GmbH.

Trial design
Parallel. Both treatment and placebo groups also received disease-modifying therapy (salazopyrine or plaquenil) and analgesic therapy (nonsteroidal and steroidal anti-inflammatory drugs) on demand.

Study duration	6 months
Dose	3 capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Hospital outpatient department
No. of subjects enrolled	40
No. of subjects completed	35
Sex	Male and female
Age	Not given

Inclusion criteria
Patients with rheumatoid arthritis stage II and III.

Exclusion criteria
None mentioned.

End points
Examination of patients was carried out at baseline and at weeks 4, 8, 16, and 24. Primary criteria of efficacy were the number of tender and swollen

joints (ARA Index), the number and severity of joint pain (Ritchie index), and the subjective assessment of the tenderness and swelling of the joints by the patient (visual analog scale). Secondary criteria of efficacy were the degree of physical impairment (Health Assessment Questionnaire), the rating of joint pain by the patient (visual analog scale), the duration of morning stiffness, and the changes in the surrogate markers, erythrocyte sedimentation rate (ESR), corticotropin releasing factor (CRF), and rheumatoid factor.

Results
After six months, the number of tender joints in the active treatment group was significantly lower than in the placebo group ($p = 0.035$). There was no difference in the number of swollen joints, as both groups showed a decrease. The number of painful joints and the severity of the pain was significantly reduced in the active treatment group, compared with the placebo group ($p = 0.004$). No significant differences were found between the two groups in the patients' assessment of the disease activity, physical impairment, or pain. The duration of morning stiffness was significantly shorter in the active group at the end of treatment than in the placebo group ($p = 0.021$). Rheumatoid factor was significantly lower in the active treatment group than in the placebo group ($p = 0.030$).

Side effects
Adverse events were reported for ten patients in both groups. A definite causal relationship with administration of Krallendorn was not established for any of them.

Authors' comments
This study could indicate a positive effect of Krallendorn on the pathological mechanisms underlying rheumatoid arthritis.

Reviewer's comments
A significant analgesic effect was documented, but no significant effect on joint swelling or lab indicators of inflammation were documented. The size of each study group was too small—a much larger sample size is usually needed to prove significant differences between disease-modifying antirheumatic drugs and placebo in rheumatoid arthritis trials because of the large placebo effect in these clinical trials. (1, 3)

Chaste Tree

Other common names: **Vitex, agnus-castus, chasteberry, monk's pepper**
Latin name: ***Vitex agnus-castus* L.** [Verbenaceae]
Plant part: **Fruit**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Chaste tree is a shrub native to the Mediterranean region. The hard, black, round berries are used medicinally. The dried, ripe fruits are characterized as containing approximately 0.5 percent volatile oil. Also characteristic of the fruits are the iridoid glycosides (agnuside and aucubin), flavonoids (aglycone, casticin), and diterpenes (Schulz, Hänsel, and Tyler, 2001). Although chaste tree preparations are sometimes standardized to the content of the water-soluble iridoid glycosides, lipid-soluble constituents, in particular the bicyclic diterpenes, have been reported in experimental studies to have dopaminergic activity (Stansbury et al., 2001).

Mastodynon® N, manufactured by Bionorica Arzneimittel GmbH in Germany, contains chaste tree tincture (53 percent alcohol) in combination with five homeopathic herbal extracts: *Caulophyllum thalictroides, Cyclamen purpurascens, Strychnos ignatia, Iris versicolor,* and *Lilium tigrinum.* The daily dose of 2 × 30 drops (1.8 ml solution) contains 32.4 mg chaste tree fruit tincture (2 g plant material in 10 g tincture). Mastodynon N is also sold in tablet form. Mastodynon is distributed in the United States by Mediceutix, Inc.

Agnolyt® capsules, produced by Madaus AG, Germany, contain 3.5 to 4.2 mg dry extract (plant/extract ratio 9.58 to 11.5:1, 60 percent ethanol). Agnolyt is also available in liquid form. Agnolyt was previously sold by Nature's Way Products, Inc., as Femaprin, but the formulation of this product has changed and an equivalent of Agnolyt capsules is not currently available in the United States.

CHASTE TREE SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Mastodynon® N (EU)	Bionorica Arzneimittel GmbH, Germany/Mediceutix, Inc.	Alcoholic tincture	30 drops twice daily	Mastalgia (cyclic breast pain)	3	Yes (II-1) Trend (II-1) Undetermined (III-1)
				Female infertility	1	Trend (II-1)
Agnolyt® (EU)	Madaus AG, Germany/None	Ethanolic extract	1 capsule (3.5-4.2 mg extract)	PMS	1	Yes (II-1)
Cycle Balance™ (US)	Zeller AG, Switzerland/General Nutrition Corporation (GNC)	Ethanolic extract (Ze 440)	1 tablet (20 mg extract)	PMS	1	Yes (II-1)

Ze 440, produced by Zeller AG, Switzerland, is a dried extract made with 60 percent ethanol (plant/extract ratio 6 to 12:1) and standardized to casticin levels. It is retailed in the United States by GNC under the name Cycle Balance™.

SUMMARY OF REVIEWED CLINICAL STUDIES

Clinical studies on chaste tree have explored its use for cyclical mastalgia (breast pain), female infertility, and premenstrual syndrome (PMS). Mild elevation of prolactin levels has been linked with breast tenderness, menstrual irregularities, infertility, and PMS. Chaste tree preparations are thought to reduce prolactin levels in the blood. Prolactin is secreted by the pituitary gland, and that secretion is mediated by dopamine through interaction with D_2 receptors. Chaste tree preparations are thought to act through stimulation of those receptors (Gorkow, Wuttke, and März, 1999).

Mastodynon

Mastalgia (Cyclic Breast Pain)

Three trials studied the use of Mastodynon for the treatment of cyclical mastalgia. The dose was 30 drops twice daily, or one tablet twice daily, taken for three to four menstrual cycles. In the first of two good-quality trials, Mastodynon solution and tablets were compared to placebo in a double-placebo designed trial with 104 women who had breast pain for at least three days in their most recent cycle. At the end of three menstrual cycles, the intensity of breast pain was significantly lower for both forms of Mastodynon compared to placebo. The onset of pain relief was earlier with the solution than with the tablet. The treatment had no effect on plasma levels of progesterone, follicle-stimulating hormone (FSH), or luteinizing hormone (LH). However, estradiol levels decreased and basal prolactin levels fell in comparison with placebo (Wuttke et al., 1997). The second study included 86 women who had breast pain for at least five days in the previous cycle. After the first and second cycles of treatment, pain intensity decreased significantly compared to placebo. After the third cycle, the pain scale level was so low for the Mastodynon group that only slight

reductions were possible, and as a result, there was only a borderline difference between the Mastodynon and the placebo group at this time. After three and four cycles, the total number of pain-free days was significantly greater for the Mastodynon group (Halaška et al., 1999).

A third trial compared Mastodynon (30 drops twice daily) and progestin (5 mg twice daily) to placebo in 121 women with severe breast pain. Both treatments were better than placebo. After four cycles, good relief from premenstrual symptoms was reported for 82 percent of those given progestin, 74.5 percent of those given Mastodynon, but only 36.8 percent of those given placebo (Kubista, Muller, and Spona, 1986). Due to several methodological inadequacies, the efficacy of treatments used in this trial was deemed undetermined.

Female Infertility

Another placebo-controlled study with 66 women indicated a possible role for Mastodynon in female infertility due to secondary amenorrhea (cessation of menstruation) and luteal insufficiency. As a result of three months of treatment with Mastodynon, pregnancy occurred more than twice as often as in the placebo group (Gerhard et al., 1998). The outcome was evaluated as a trend toward efficacy. A longer trial, especially for secondary amenorrhea, would be more conclusive.

Agnolyt

Premenstrual Syndrome

A study with 105 women examined the use of Agnolyt (one capsule daily) for PMS with positive results. The study compared Agnolyt, given daily for three menstrual cycles, to pyridoxine (vitamin B_6, 100 mg twice daily), given for only the last 19 days of each cycle. In the pyridoxine group, a placebo was given on days one through 15. The chaste tree preparation was superior to pyridoxine in relieving symptoms as assessed, using a PMS symptom scale, by both patients and doctors (Lauritzen et al., 1997). Our reviewer, Dr. Tieraona Low Dog, suggested that this trial, although basically good, could have been strengthened by the addition of a placebo arm.

Ze 440

Premenstrual Syndrome

An overall good study with 169 women with PMS, comparing Ze 440, one tablet daily for three cycles, to placebo, found a significant improvement in combined PMS symptoms using a self-assessment scale. A 50 percent reduction in symptoms was experienced by 52 percent of women taking Ze 440 and 24 percent given placebo (Schellenberg, 2001).

POSTMARKETING SURVEILLANCE STUDIES

Two drug monitoring surveys were conducted with 1,542 patients with PMS who had been treated with Agnolyt solution for periods of up to 16 years. The mean duration of treatment was approximately five and one-half months. The mean dose was 42 drops daily. Improvement in symptoms was generally seen after 25 days of treatment. The doctors assessed the efficacy of treatment as good to very good in 71 percent of cases and as satisfactory in 21 percent of cases. The patients judged their symptoms as relieved (33 percent), improved (57 percent), or not changed (4 percent), with no data on the remaining 5 percent of patients (Dittmar et al., 1992).

A review cited five postmarketing studies with chaste tree preparations for PMS. In addition to the Dittmar and colleagues (1992) study mentioned previously, there were two more studies on the Agnolyt solution, one on the Mastodynon solution, and another on Femicur capsules supplied by Schaper & Brümmer GmbH and Co. KG, Germany. In general, PMS symptoms were eliminated in about one-third of the women and improved for one-half of the women (Gorkow, Wuttke, and März, 1999).

Another postmarketing study evaluated the effectiveness of Mastodynon solution for treatment of menstrual cycle disorders. Following treatment with 60 drops per day, 31 of 50 women with secondary amenorrhea began menstruating. Cycle lengths were normalized in 187 of 287 women with oligomenorrhea (cycles longer than 35 days), and in 139 of 192 women with polymenorrhea (cycles shorter than 26 days) (Gorkow, Wuttke, and März, 1999).

ADVERSE REACTIONS OR SIDE EFFECTS

Adverse events reported in the trials reviewed were generally mild to moderate, consisting mostly of nausea and gastrointestinal complaints.

Two drug monitoring surveys reported that 32 of 1,542 (2.1 percent) patients treated with a mean dose of 42 drops daily of Angolyt solution for over five months experienced side effects. The most common complaints were nausea, gastric complaints, and acne (Dittmar et al., 1992).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

American Herbal Pharmacopoeia (AHP)
German Commission E

Indications

Preparations of the ripe, dried fruits of chaste tree are approved by the German Commission E for irregularities of the menstrual cycle, premenstrual complaints, and mastodynia (Blumenthal et al., 1998). The *American Herbal Pharmacopoeia* lists the following medical indications supported by clinical trials for chaste tree fruit: menstrual irregularities (secondary amenorrhea, oligomenorrhea, polymenorrhea); relief of PMS symptoms; mastalgia; latent hyperprolactinemia; and infertility due to luteal-phase dysfunction. The actions include menstrual cycle regulator; in vitro dopaminergic activity; prolactin release inhibition; and weak binding to opioid receptors in vitro (Stansbury et al., 2001).

Doses

Dried fruit: (powder) 30 to 40 mg once daily (Stansbury et al., 2001)

Tincture: (1:5) 20 drops two to three times daily (each dose equivalent to 36 mg/ml of dried chaste tree fruit (Stansbury et al., 2001)

Extracts: aqueous-alcoholic (50 to 70 percent v/v) from the crushed fruits taken as liquid or dry extract, amount corresponding to 30 to 40 mg fruit (Blumenthal et al., 1998)

Treatment Period

The *AHP* states that menstrual cycle disorders take three to six weeks of treatment to respond (Stansbury et al., 2001).

Contraindications

The Commission E lists no known contraindications, while the *AHP* claims that no authoritative data are available (Blumenthal et al., 1998; Stansbury et al., 2001).

Adverse Reactions

The Commission E states that there is an occasional occurrence of itching, urticarial exanthemas (Blumenthal et al., 1998). The *AHP* also lists the following adverse reactions for chaste tree: occasional minor skin irritations, nausea, acne, pruritis, rashes, headache, fatigue, tachycardia or palpitations, spotting, allergy, alopecia, circulatory problems, cycle changes, dizziness, ear pressure, edema, fibroid growth, hot flash, intraocular pressure, mastalgia, pelvic disease, polyurea, pyrosis, sweating, vaginitis, and weight gain (Stansbury et al., 2001).

Precautions

The Commission E lists no known precautions. However, the Commission E warns that chaste tree is not to be used during pregnancy, and in animal experiments, an influence on nursing (lactation) performance was observed (Blumenthal et al., 1998). The *AHP* also states that chaste tree is not to be used during pregnancy unless otherwise directed by an expert qualified in the use of the described substance. In addition, the *AHP* says that chaste tree should not be used

for PMS if the prevailing symptom is depression and that a qualified expert should be consulted before using chaste tree fruit extract for breast-related symptoms (Stansbury et al., 2001).

Drug Interactions

Both the Commission E and the *AHP* state that interactions are unknown. However, in animal experiments, there is evidence of a dopaminergic effect of the drug; thus, with administration of a dopamine-receptor agonist, a reciprocal decrease in effect may occur (Blumenthal et al., 1998; Stansbury et al., 2001).

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DETAILS ON CHASTE TREE PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Chaste Tree Products

Product Profile: Mastodynon® N

Manufacturer	**Bionorica Arzneimittel GmbH, Germany**
U.S. distributor	Mediceutix, Inc.
Botanical ingredient	**Chaste tree fruit extract**
Extract name	None given
Quantity	32.4 mg extract in 60 drops
Processing	10 g tincture (53 percent (v/v) alcohol) contains 2 g plant
Standardization	No information
Formulation	Solution

Recommended dose: Take 30 drops with some liquid in the morning and in the evening. Mastodynon N should be taken for at least three months, also during menstrual bleeding. Improvement is usually felt after six weeks.

DSHEA structure/function: German drug indications include menstrual disorders based on a temporary or permanent corpus luteum insufficiency; infertility due to corpus luteum insufficiency; complaints

which can appear shortly before the monthly bleeding (premenstrual syndrome), such as mastodynia, psychic lability swellings of feet and hands, constipation, as well as headache or migraine; benign painful affections of the breast (fibrocystic mastopathy).

Cautions: If complaints reappear upon discontinuation of intake, the therapy should be continued after consultation with the attending physician. Mastodynon N is not indicated for treatment of malignant affections of the breasts.

Other ingredients: *Caulophyllum thalictroides* (dil. D4), *Cyclamen purpurascens* (dil. D4), *Strychnos ignatii* (dil. D6), *Iris versicolor* (dil. D2), *Lilium tigrinum* (dil. D3).

Source(s) of information: Halaška et al., 1999; patient information leaflet (Bionorica GmbH).

Clinical Study: Mastodynon®

Extract name	None given
Manufacturer	Bionorica Arzneimittel GmbH, Germany
Indication	**Mastalgia** (cyclic breast pain)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Wuttke W, Splitt G, Gorkow C, Sieder C (1997). Treatment of a cyclical mastalgia with a medicinal product containing agnus castus: Results of a randomized, placebo-controlled, double-blind study. *Geburtshilfe und Frauenheilkunde* 57 (10): 569-574.

Trial design
Mastodynon solution and tablets were compared to placebo with a double-dummy technique, in three parallel groups, over three menstrual cycles. Treatment was preceded by an observation cycle during which the inclusion and exclusion criteria were evaluated.

Study duration	3 menstrual cycles
Dose	30 drops or 1 tablet Mastodynon twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	120
No. of subjects completed	104
Sex	Female
Age	Mean: 33 years

Inclusion criteria
Included were patients who had suffered from clinical mastodynia for at least three cycles with breast pain on at least three days in the last cycle prior to the study. During the course of treatment, the use of hormones or treatment with hormonelike medication was not permitted.

Exclusion criteria
Third-degree galactorrhea, purulent/bloody mammary discharge, severe endocrinopathy, malignoma, necessary breast surgery, simultaneous treatment with analgesics or nonsteroidal antiphlogistics, having undergone alcohol withdrawal treatment, pregnancy, and lactation.

End points
Checkups were conducted in the premenstrual week, in cycles 0, 1, 2, and 3. Patients kept a daily pain journal and indicated the intensity of breast pain on the visual, linear analog scale (VAS). Hormone levels were measured in the premenstrual week of cycles 0, 1, 2, and 3. Analysis of prolactin values after metoclopramide stimulation was carried out in cycles 0 and 3.

Results
At the end of the three-cycle treatment period, the VAS values for breast pain were significantly lower for the tablet and solution groups compared to placebo ($p = 0.0067$ and $p = 0.0076$, respectively). The onset of action for patients taking solution occurred after the first treatment cycle, which was faster than the tablet formulation. The treatment had no effect on progesterone, FSH, and LH. Under both active formulations, estradiol-17 beta values decreased. Basal prolactin levels fell significantly in comparison with placebo, $p = 0.039$ solution, $p = 0.015$ tablets. In comparison with placebo, stimulated prolactin levels at the end of treatment tended to be lower under both active formulations.

Side effects
In general, subjective tolerance was good. Adverse events were mostly mild to moderate, consisting of nausea and gastrointestinal complaints. Severe

adverse reactions in three subjects (nausea and punctual, severe breast pain) led to the discontinuation of treatment.

Authors' comments
The solution and the tablets of the preparation containing agnus castus are effective in mastalgia. Basal prolactin levels dropped significantly with both forms of the preparation. The subjective tolerance was good.

Reviewer's comments
Study was randomized and double-blind with the outcome measures clearly defined. However, subjects were not excluded for taking evening primrose oil, B_6, or other phytochemicals. No power calculation was performed, but sample size is likely sufficient. (5, 3)

Clinical Study: Mastodynon®

Extract name	None given
Manufacturer	Bionorica Arzneimittel GmbH, Germany
Indication	**Mastalgia** (cyclic breast pain)
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Halaška M, Beles P, Gorkow C, Sieder C (1999). Treatment of cyclical mastalgia with a solution containing a *Vitex agnus castus* extract: Results of a placebo-controlled double-blind study. *The Breast* 8 (4): 175-181. (Also published in Halaška M, Raus K, Beles P, Martan A, Paithner KG [1998]. *Ceskoslovenska Gynekologie* 63 [5]: 388-392.)

Trial design
Parallel. Trial was preceded by one menstrual cycle without treatment in which patients were examined for inclusion and exclusion criteria.

Study duration	4 menstrual cycles
Dose	2 × 30 drops (1.8 ml) daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes

Drug comparison	No
Site description	Single center
No. of subjects enrolled	97
No. of subjects completed	86
Sex	Female
Age	18-45 years

Inclusion criteria
Patients with mastalgia on at least five days in the cycle before treatment began. The minimum cycle duration within the last three cycles before treatment was 25 days; the maximum duration was 35 days. Signs of fibrocystic mastopathic tissue alterations were allowed. Hormonal contraceptives were admitted providing they had been taken for the past six months before treatment and were continued without alteration.

Exclusion criteria
Breast cancer, fibroadenoma, intraductal papilloma, galactorrhea, purulent or bloody nipple discharge, severe endocrinopathies, recent or impending breast surgery, concomitant therapy with analgesics or NSAIDs, and successful alcohol detoxication were exclusion criteria. Pregnancy and lactation were also reasons for exclusion from the study.

End points
Assessment was carried out on day 3 or 4 of cycles 1, 2, 3, and 4 using the visual analog scale score for the intensity of mastalgia. Patients also recorded pain in a daily diary.

Results
After the first and second cycles, there were significant differences in the mean decrease in pain intensity between the Mastodynon group and placebo ($p = 0.018$ and $p = 0.006$, respectively). After three cycles, there was only borderline significance between Mastodynon and placebo in the decrease in pain intensity ($p = 0.064$); in the treatment group after three cycles, the pain scale level was so low that only slight reductions were possible. After three and four cycles, the Mastodynon group had significantly more pain-free days compared with placebo ($p = 0.007$ and $p = 0.014$, respectively).

Side effects
Adverse events were slight; no difference in frequency in the two groups.

Authors' comments
The current study demonstrated that Mastodynon is an effective and well-tolerated treatment for breast pain. The favorable benefit-risk ratio justifies the use of *Vitex agnus-castus*–containing solution for at least three months

in women with severe breast pain, before alternative drugs with a higher rate of side effects are considered.

Reviewer's comments
Although the study was randomized, no description of the randomization process was provided. Subjects were not excluded for taking B_6, evening primrose oil, or other phytochemicals. Sample size was appropriate, and outcome measures were clearly defined. (3, 5)

Clinical Study: Mastodynon®

Extract name	None given
Manufacturer	Bionorica Arzneimittel GmbH, Germany
Indication	**Mastalgia** (cyclic breast pain)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Kubista E, Muller G, Spona J (1986). Treatment of mastopathy with cyclic mastodynia: Clinical results and hormone profile. *Gynakologische Rundschau* 26 (2): 65-79.

Trial design
Three parallel groups, Mastodynon compared with a progestin (Lynestrenol 2 × 5 mg from the sixteenth to twenty-fifth day of the cycle) and placebo.

Study duration	4 menstrual cycles
Dose	2 × 30 drops daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Lynestrenol (a progestin)
Site description	Gynecology and Obstetrics Division, University of Vienna
No. of subjects enrolled	160
No. of subjects completed	121

Sex	Female
Age	Not given

Inclusion criteria
Female patients with severe clinical manifestations of mastopathy with cyclic mastodynia, normal cycles, and nonsuspicious mammographic and thermographic results.

Exclusion criteria
Patients who had taken drugs with effects on prolactin levels.

End points
Before the study and after two and four cycles of treatment, prolactin and progesterone serum levels were measured. The clinical efficacy of treatment was evaluated on a basis of a self-evaluated pain scale. Thermographic and mammographic checks were conducted before and after three months of therapy.

Results
The best clinical result was obtained in the progestin group: 82.1 percent of patients reported a marked improvement of the premenstrual pain and premenstrual tension, compared to 74.5 percent of the Mastodynon group and 36.8 percent of placebo group. The efficacy of Mastodynon was significantly better than placebo ($p < 0.01$). After two cycles of treatment, prolactin levels increased and progesterone levels fell in the progestin group ($p < 0.01$) relative to the placebo and Mastodynon groups.

Side effects
Mild side effects, consisting mostly of nausea and weight gain, were reported by 7.2 percent of Mastodynon patients compared to 21.4 percent of the progestin group and 10.5 percent of the placebo group.

Authors' comments
Despite their efficacy, long-term therapy with progestins should be applied only after other possibilities of therapy have been exhausted. Therapy with the nonhormonal phytotherapeutic preparation Mastodynon constitutes a reliable alternative to progestins which is low in side effects.

Reviewer's comments
The study had no discussion of randomization. Only Mastodynon and placebo arms appear blinded, not the progestin arm. Although a description of withdrawals and dropouts was provided, adequate inclusion/exclusion details were not given. (1, 4)

Clinical Study: Mastodynon®

Extract name	None given
Manufacturer	Bionorica Arzneimittel GmbH, Germany
Indication	**Female infertility**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Gerhard I, Patek A, Monga B, Blank A, Gorkow C (1998). Mastodynon for female infertility: Randomized, placebo-controlled, clinical double-blind study. *Forschende Komplementarmedizin/Research in Complementary Medicine* 5 (6): 272-278.

Trial design
Parallel. After verification of inclusion and exclusion criteria, patients went through a treatment-free diagnostic cycle.

Study duration	3 months
Dose	2 × 30 drops daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	96
No. of subjects completed	66
Sex	Female
Age	Mean: 29 years

Inclusion criteria
Women suffering from secondary amenorrhea (spontaneous menstruation less than once every three months), corpus luteal insufficiency, or idiopathic infertility. Women trying unsuccessfully to become pregnant for about two years. Patency of at least one fallopian tube, positive or not more than restricted Sims-Huhner postcoital test eight to twelve hours after sexual intercourse on the ovulation date or after previous estrogen treatment, and good general health. Male partners were to present a current normal spermio-

gram. Women were to have used no medication at all, and the last hormone treatment was to have taken place at least three months previously.

Exclusion criteria
Anatomical anomalies causing infertility, previous alcohol withdrawal treatment, age under 18 years.

End points
Pregnancy or spontaneous menstruation in women with amenorrhea, pregnancy or improved concentrations of luteal hormones in women with luteal insufficiency or idiopathic infertility. Hormone levels were evaluated at baseline in all women and after three months in the women who did not become pregnant.

Results
The outcome measure was achieved in 31 of 66 women: 57.6 percent of the Mastodynon group compared to 36.0 percent of placebo group. A total of 15 pregnancies occurred, seven patients with amenorrhea, four with idiopathic infertility, and four with luteal insufficiency. Pregnancy occurred more than twice as often in women taking Mastodynon (21 percent) as with placebo (10 percent). There were no significant (5 percent level) hormonal changes due to therapy.

Side effects
One complaint (mastodynia) in the Mastodynon group and three complaints with placebo.

Authors' comments
In women with sterility due to secondary amenorrhea and luteal insufficiency, a treatment with Mastodynon can be recommended over a period of three to six months.

Reviewer's comments
Fairly well-designed and well-conducted study. However, study was of short duration, especially to assess secondary amenorrhea, and the outcome measure is questionable. A trend benefit was seen for women with infertility due to secondary amenorrhea or luteal insufficiency. (3, 5)

Product Profile: Agnolyt®

Manufacturer	**Madaus AG, Germany**
U.S. distributor	None
Botanical ingredient	**Chaste tree fruit extract**

Extract name	None given
Quantity	3.5 to 4.2 mg
Processing	Plant to extract ratio 9.58-11.5:1, ethanol 60 percent
Standardization	No information
Formulation	Capsule

Comments: Also available in liquid form.

Source(s) of information: Personal communication with Roy Upton, 1999; and Lauritzen et al., 1997.

Clinical Study: Agnolyt®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Premenstrual syndrome**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Lauritzen CH, Reuter HD, Repges R, Bohnert KJ, Schmidt U (1997). Treatment of premenstrual tension syndrome with *Vitex agnus castus:* Controlled, double-blind study versus pyridoxine. *Phytomedicine* 4 (3): 183-189.

Trial design
Parallel. Patients in the Agnolyt group received one capsule of Agnolyt and one capsule of placebo daily. Patients in the pyridoxine group received one capsule of placebo twice daily on days 1 to 15, then one capsule of pyridoxine HCL (100 mg) twice daily on days 16 to 35 of the menstrual cycle.

Study duration	3 menstrual cycles
Dose	1 capsule Agnolyt daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Pyridoxine (vitamin B_6)

Site description	15 study centers
No. of subjects enrolled	175
No. of subjects completed	105
Sex	Female
Age	18-45 years

Inclusion criteria
Premenstrual tension syndrome (PMTS) symptoms had to correlate with the luteal phase of the menstrual cycle, recur with every cycle, and be sufficiently severe to affect the patient's quality of life. For every menstrual cycle, the patient had to be able to indicate at least one week in which she was free from complaints. In addition, the patient should not have received any drug therapy for the syndrome during the three menstrual cycles preceding the start of the trial.

Exclusion criteria
Depression (not to exceed 10 point score on von Zerssen Depression Scale), premenopausal complaints or marked irregular cycle anomalies, women with idiopathic pregnancy icterus, severe pregnancy pruritus, or Morbus Parkinson were excluded by anamnesis. Women wishing to conceive, pregnant or nursing women, women with a known drug or alcohol abuse problem, psychiatric conditions, neurotic personality, and serious consuming illnesses. Disallowed concomitant medications included a list of drugs, botanical products, and vitamins.

End points
Therapeutic response was assessed using the premenstrual tension syndrome scale (PMTS scale), the recording of six characteristic complaints of the syndrome, and the clinical global impressions scale. After completion of the trial, efficacy was assessed subjectively by the patient and physician. Assessments were made at baseline and in the last seven days of the next three menstrual cycles.

Results
Absolute changes of the PMTS scores were 10.1 points in the Agnolyt group and 6.8 points in the pyridoxine group. This difference was significant, in favor of Agnolyt ($p = 0.037$). Improvement on the CGI scale was also more marked in the Agnolyt group. The benefit-to-risk ratio was more favorable for Agnolyt, as were the subjective ratings by doctors and patients.

Side effects
Mild adverse events (gastrointestinal and lower abdominal complaints, skin manifestations, and transitory headache) occurred in five patients taking pyridoxine and in 12 patients taking Agnolyt.

Authors' comments
At first glance, the effect of pyridoxine appears to be equivalent to that of Agnolyt in the present comparative trial. However, careful evaluation of all available data and scales permits the conclusion that Agnolyt was superior to pyridoxine in the present study.

Reviewer's comments
Although the outcome measures and inclusion/exclusion criteria were defined and appropriate, there was no description of randomization. Study rates Level II as there was no placebo arm, and pyridoxine is a questionable agent to use as a historical control. (3, 6)

Product Profile: Cycle Balance™

Manufacturer	**Zeller AG, Switzerland**
U.S. distributor	**General Nutrition Corporation**
Botanical ingredient	**Chaste tree fruit extract**
Extract name	**Ze 440**
Quantity	40 mg
Processing	Plant to extract ratio 6-12:1, 60 percent (m/m) ethanol
Standardization	0.6 percent casticin = 0.24 mg
Formulation	Tablet

Recommended dose: Take one tablet daily with eight ounces of water or juice.

DSHEA structure/function: May provide monthly support and hormonal balance in women.

Other ingredients: Cellulose, lactose.

Source(s) of information: Schellenberg, 2001; product package.

Clinical Study: Ze 440

Extract name	Ze 440
Manufacturer	Zeller AG, Switzerland
Indication	**Premenstrual syndrome**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Schellenberg R (2001). Treatment for the premenstrual syndrome with agnus castus fruit extract: Prospective, randomized, placebo controlled study. *British Medical Journal* 322 (7279): 134-137.

Trial design
Parallel.

Study duration	3 menstrual cycles
Dose	1 (20 mg extract) tablet daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	6 community clinics
No. of subjects enrolled	170
No. of subjects completed	169
Sex	Female
Age	Mean: 36 years

Inclusion criteria
Women 18 years or older, with premenstrual syndrome diagnosed according to the DSM-III-R.

Exclusion criteria
Exclusion criteria were participation in other trials, concomitant psychotherapy, pregnancy or breast-feeding, inadequate contraception, dementia, alcohol or drug dependence, concomitant serious medical condition, hypersensitivity to agnus castus, fever, pituitary disease, and concomitant use of sex hormones except oral contraceptives for which the doses were kept unchanged.

End points
Main efficacy variable: change from baseline to end point (end of third cycle) in women's self-assessment of irritability, mood alteration, anger, headache, breast fullness, and other menstrual symptoms including bloating. Secondary efficacy variables: changes in clinical global impressions (severity of condition, global improvement, and risk or benefit) and responder rate (50 percent reduction in symptoms). Assessment was carried out at baseline (start of the first menstrual cycle) and after the third cycle.

Results
Patients who received agnus castus had a significant improvement in combined symptoms compared with those on placebo according to self-assessment and each of the three global impression items ($p < 0.001$). Responder rates were 52 percent and 24 percent for active group and placebo, respectively.

Side effects
Four subjects in the active group and three in placebo reported adverse effects, but none caused discontinuation of treatment. Complaints included acne, intermenstrual bleeding or early period, and gastric upset.

Author's comments
Dry extract of agnus castus fruit is an effective and well-tolerated treatment for the relief of symptoms of premenstrual syndrome.

Reviewer's comments
A well-done study overall; however, the exclusion criteria did not include pyridoxine, evening primrose oil, or phytoestrogen substances. Women taking oral contraceptives were admitted to the study if the dose remained unchanged, but the author did not describe how long the participants had been on the hormonal therapy. (3, 5)

Cordyceps

Other common names: **Chinese caterpillar fungus, dong chong xia cao**
Latin name: ***Cordyceps sinensis* (Berk.) Sacc.** [Clavicipitaceae]
Plant part: **Fungal mycelium**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Cordyceps sinensis is a parasitic fungus that grows on several species of caterpillars found in the Tibetan highlands. The traditional remedy is a composite, consisting of the fungal body as well as the caterpillar larva. This natural material known as caterpillar fungus, dong chong xia cao, is rare. Therefore, Chinese scientists have developed a technique for isolating fermentable strains of the fungus. The result is a strain called Cs-4 that has been extensively characterized and its pharmacological actions researched. The active components of cordyceps have yet to be identified; however, cordycepin (3-deoxyadenosine) and cordycepic acid (actually *d*-mannitol) may play a role (Zhu, Halpern, and Jones, 1998a).

CordyMax® Cs-4 is a cordyceps product produced by Pharmanex, LLC, a wholly owned subsidiary of Nu Skin Enterprises, Inc. Each capsule contains 525 mg of fungal mycelium Cs-4. Cs-4 is available in China in a commercial product called JinShuiBao.

SUMMARY OF REVIEWED CLINICAL STUDIES

Cordyceps is reported to have a tonic effect in humans, reducing fatigue, intolerance to cold, dizziness, tinnitus, and memory loss, while increasing respiratory capacity. Treatments with cordyceps are associated with increased libido, lowered levels of blood lipid levels

CORDYCEPS SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
JinShuiBao (China), CordyMax® Cs-4 (US)	Pharmanex, LLC/ Pharmanex, LLC	Fermented mushroom mycelia (Cs-4)	330 mg 3 times daily	Hyperlipidemia (elevated blood lipid levels)	1	Yes (III-1)
				Asthenia syndrome (symptoms associated with aging)	1	Undetermined (III-1)

and blood sugar levels, as well as improved respiratory function, renal function, liver function, and kidney function (Zhu, Halpern, and Jones, 1998b).

CordyMax Cs-4

We reviewed two controlled studies on cordyceps (JinShuiBao), one exploring the blood lipid-lowering (hypolipidemic) effects and the other exploring the effects on fatigue associated with age.

Hyperlipidemia (Elevated Blood Lipid Levels)

The study on hypolipidemic effects was a large placebo-controlled study completed in China. The study included 273 patients with hyperlipidemia, including 215 with elevated cholesterol and 245 with elevated triglycerides. Patients were treated with three (330 mg mycelium) capsules three times daily for two months. Cordyceps lowered total cholesterol levels by 17.5 percent and trigylcerides by 9.2 percent. High-density lipoprotein levels were increased by 27.2 percent. All changes were statistically significant compared to the placebo group levels (Shao, 1995). Our reviewer, Dr. David Heber, concluded that this clinical effect could be significant and deserves repetition. The trial report was an internal Pharmanex document and did not include details such as the baseline lipid levels for the participants.

Asthenia Syndrome (Symptoms Associated with Aging)

The second trial included 59 men and women, 60 to 84 years old, and studied symptoms of aging known in traditional Chinese medicine as asthenia syndrome (Xu-Zheng). The symptoms included fatigue, intolerance to cold, dizziness, tinnitus, pain in loins, hyposexuality, urinary terminal dribbling, amnesia, alopecia (hair loss), and loosened teeth. After three months of treatment with a dose of three (330 mg mycelium) capsules three times daily, the symptom score was reduced compared with the placebo group. There was improvement in lassitude of loins and legs, intolerance to cold, cold in extremities, dizziness, tinnitus, and frequency of nocturia. There was no change in alopecia, loosened teeth, hyposexuality, or amnesia. Levels of the an-

tioxidant superoxide dismutase (SOD) in red blood cells was increased, and levels of malondialdehyde (MDA) in plasma were decreased, compared to baseline levels (Zhang et al., 1995). Dr. Heber concluded that the therapeutic benefit was undetermined due to the subjective outcome measures and other methodological inadequacies.

ADVERSE REACTIONS OR SIDE EFFECTS

Adverse effects reported in one of the clinical studies were gastrointestinal upset and thirst (Shao, 1995).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

Chinese Pharmacopoeia

Indications

The *Chinese Pharmacopoeia* states that Chinese caterpillar fungus composite, consisting of the stroma of the fungus parasitized on the larva along with the caterpillar, is indicated for chronic cough and asthma, hemoptysis in phthisis, impotence, and seminal emissions with aching of loins and knees. The action, according to traditional Chinese medicine, is to tonify the lung and kidney meridians, dispel phlegm, and arrest bleeding (Pharmacopoeia Commission of PRC, 1997).

Dose

Crude drug: 3 to 9 g (Pharmacopoeia Commission of PRC, 1997)

REFERENCES

Pharmacopoeia Commission of PRC, The (1997). *Pharmacopoeia of the People's Republic of China.* Beijing: Chemical Industry Press.

Shao G (1995). Clinical report of jinshuibao capsule in treating hyperlipidemia. *Journal of Administration of TCM.* Report# G 076 090 152. (Also published in *Chung hsi i chieh ho tsu chih* [China] 1985; 5 [11]: 652-654.)

Zhang Z, Huang W, Liao S, Li J, Lei L, Lui J, Leng F, Gong W, Zhang H, Wan L, et al. (1995). Clinical and laboratory studies of JinShuiBao capsules in eliminating oxygen free radicals in elderly senescent Xu-Zheng patients. *Journal of Management of Traditional Chinese Medicine* 5 (Suppl): 14-18. (Also published in part by Cao Z, Wen Y [1993], *Journal of Applied Traditional Chinese Medicine* 1: 32-33.)

Zhu JS, Halpern GM, Jones K (1998a). The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis.* Part I. *The Journal of Alternative and Complementary Medicine* 4 (3): 289-303.

Zhu JS, Halpern GM, Jones K (1998b). The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis.* Part II. *The Journal of Alternative and Complementary Medicine* 4 (4): 429-457.

DETAILS ON CORDYCEPS PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: CordyMax® Cs-4

Manufacturer	**Pharmanex, LLC**
U.S. distributor	**Pharmanex, LLC**
Botanical ingredient	**Cordyceps fermented mycelium**
Extract name	**Cs-4**
Quantity	525 mg
Processing	Fermentable mycelial strain isolated from the *Cordyceps sinensis* mushroom
Standardization	No information
Formulation	Capsule

Recommended dose: Take two capsules two to three times daily with food and drink.

DSHEA structure/function: Promotes vitality and stamina. Supports the body's natural ability to adapt to daily dietary, occupational, and environmental stresses. Clinical research supports its ability to promote healthy lung function.

Other ingredients: Gelatin.

Comments: Cs-4 is a specialized strain of cordyceps. It is sold in China as JinShuiBao.

Source(s) of information: Product package.

Clinical Study: JinShuiBao

Extract name	Cs-4
Manufacturer	Pharmanex, LLC
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Shao G (1995). Clinical report of jinshuibao capsule in treating hyperlipidemia. *Journal of Administration of TCM*. Report# G 076 090 152. (Also published in *Chung hsi i chieh ho tsu chih* [China] 1985; 5 [11]: 652-654.)

Trial design
Parallel. Seven days prior to study, other lipid-lowering drugs were stopped. All dietary habits, lifestyle, and activities were kept constant.

Study duration	2 months
Dose	3 (330 mg mycelium) capsules 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Several Chinese hospitals
No. of subjects enrolled	273
No. of subjects completed	Not given
Sex	Not given
Age	Not given

Inclusion criteria
Patients with primary hyperlipidemia or hypertriglyceremia with complaints of hypertension or ischemic heart disease and normal blood tests, as well as normal liver and kidney function.

Exclusion criteria
Patients with secondary hyperlipidemia due to diabetes, hypolipidemia, liver and bile disease, and syndromes of renal disease.

End points
Fasting blood specimens were collected to measure blood lipids, both before and after 30 and 60 days of treatment. Patients showing excellent or no response to the drugs were excluded from observation, and treatment continued on patients who showed effective response to cordyceps in the clinical tests. Blood levels of total cholesterol, triglycerides, and if possible high-density lipoproteins were determined. Percent of blood lipid variation was used to determine effectiveness of treatment to compensate for the different analytical methods at different sites.

Results
Cordyceps lowered total cholesterol by 17.5 percent after two months, statistically more than placebo ($p < 0.001$). Also, after two months, triglycerides were lowered by 9.2 percent and high-density lipoprotein levels were increased by 27.2 percent (both $p < 0.05$ compared to placebo). The report did not give baseline lipid levels.

Side effects
Study reported no serious side reactions (adverse effects included thirst, gastrointestinal upset, and nausea). Two patients in both control and test groups had increased serum glutamic pyruvic transaminase (SGPT), and two patients in control and one patient in test group had decreased platelets. Three patients stopped treatment due to somnolence, dizziness, and rash.

Author's comments
The study showed that the effects of JinShuiBao in lowering total cholesterol are trustworthy and can be used in treating hypercholesterolemia. A further study in observing its effects in reducing triglycerides is required.

Reviewer's comments
A significant decrease in cholesterol was documented; however, the study needs to be repeated. Treatment length and sample size were appropriate, and outcome measures were clearly defined. The sex and ages of patients were not mentioned. The numbers of subjects was also different for each variable and time frame. (0, 5)

Clinical Study: JinShuiBao

Extract name	Cs-4
Manufacturer	Jiangxi JinShuiBao Pharmaceutical L.L.C., China (Pharmanex, LLC)

Indication	**Asthenia syndrome** (symptoms associated with aging)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Zhang Z, Huang W, Liao S, Li J, Lei L, Lui J, Leng F, Gong W, Zhang H, Wan L, et al. (1995). Clinical and laboratory studies of JinShuiBao capsules in eliminating oxygen free radicals in elderly senescent Xu-Zheng patients. *Journal of Management of Traditional Chinese Medicine* 5 (Suppl): 14-18. (Also published in part by Cao Z, Wen Y [1993]. *Journal of Applied Traditional Chinese Medicine* 1: 32-33.)

Trial design

Parallel. Three-arm study. Elderly patients were treated with either cordyceps or placebo. In addition, 30 college students (age 17 to 20) formed a control group.

Study duration	3 months
Dose	3 capsules (containing 330 mg powder each) 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	59
No. of subjects completed	59
Sex	Male and female
Age	60-84 years

Inclusion criteria

Asthenia syndrome (Xu-Zheng) is a group of major disease conditions according to diagnostic classification of traditional Chinese medicine. Patients with the syndrome who had four or more of the following senescent symptoms: fatigue, intolerance to cold, dizziness, tinnitus (and/or deafness), pain in loins, hyposexuality, urinary terminal dribbling, amnesia, alopecia, and loosened teeth. Patients discontinued other medication for the duration of the study.

Exclusion criteria
Patients suffering from obvious heart, lung, liver, and renal disease, severe diabetes mellitus, stage III hypertension, and hyperthyroidism.

End points
Patients were examined every 15 days, and detailed recordings were made of all changes in symptoms, signs, blood pressure, and heart rate. A total accumulated score of senescent symptoms was obtained by inquiring, observation, and pulse reading. Superoxide dismutase activity in red blood cells as well as lipoperoxide (LPO) and malonaldehyde content in plasma were also measured.

Results
Cordyceps therapy decreased the symptom score by at least two-thirds in five patients, by one-third to two-thirds in 23 patients, and by less than one-third in five patients. In the control group, none of the 30 patients had a decrease in score greater than one-third. Over 80 percent improvement was seen in lassitude of loins and legs, intolerance to cold and cold in extremities, and dizziness. Also improved were tinnitus and frequency of nocturia. No improvement occurred in alopecia, loosened teeth, hyposexuality, or amnesia. JinShuiBao elevated SOD levels and reduced LPO compared with baseline measurement (both $p < 0.01$). SOD levels in the young adults was significantly higher than the pretreatment levels for the elderly, and MDA content was lower (both $p < 0.01$). However, after treatment with cordyceps, SOD levels in the elderly were higher than in young adults and MDA levels were comparable. Four months after completion of the study, SOD levels were back to prestudy levels but MDA levels were still somewhat reduced.

Side effects
None mentioned in paper.

Authors' comments
These data suggest that JinShuiBao (cordyceps) has the capability to increase SOD activity and to decrease MDA content, possibly delaying the senescence process of aging. It may be useful in treatment and/or prevention of elderly senescent Xu-Zhneg.

Reviewer's comments
This is a poorly described and designed study. No definite effect was reported with the cordyceps preparation. (Translation reviewed) (0, 0)

Cranberry

Other common names: **American cranberry, large cranberry**
Latin name: ***Vaccinium macrocarpon* Aiton** [Ericaceae]
Plant part: **Fruit**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Cranberry is native to eastern North America. The shrub produces small, dark-red fruits that are widely consumed as juice and sauce. Cranberries contain anthocyanidins (cyanidin, peonidin), proanthocyanins (condensed tannins), flavonols (predominately myricetin and quercetin), as well as organic acids (predominately quinic acid and citric acid) (Winston et al., 2002).

Cranberry juice concentrate and low-calorie cocktail products, which were studied clinically, are produced by Ocean Spray Cranberries, Inc., of Lakeville, Massachusetts.

A dry extract, Cranberry AF™, marketed by Solaray®, Inc., and manufactured by Nutraceutical Corporation, Park City, Utah, was also tested clinically. The extract is marketed in capsules containing 400 mg extract, under the trade name CranActin®.

SUMMARY OF REVIEWED CLINICAL STUDIES

The three double-blind, placebo-controlled studies on cranberry products we review here address prevention of urinary tract infection (UTI). In vitro studies indicate that cranberry products prevent adhesion of bacteria to the cell walls of the urinary tract, thus preventing infection (Winston et al., 2002). Although some of the study methods in the clinical studies cited could be improved, these studies also suggest a benefit in the prevention of bacteriuria (greater than or equal to

CRANBERRY SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Cranberry juice concentrate/ cocktail	Ocean Spray Cranberries, Inc.	Juice or juice concentrate	2 oz concentrate or 300 ml cocktail/day	Urinary tract infection (prevention)	2	Yes (I-1) No (II-1)
CranActin®	Nutraceutical Corp./Solaray®, Inc.	Contains the Cranberry AF™ dry extract	400 mg/day	Urinary tract infection (prevention)	1	Yes (II-1)

10,000 colony-forming units per ml) and symptomatic urinary tract infection.

Cranberry Juice Cocktail/Concentrate

Urinary Tract Infection (Prevention)

A well-conducted study with 153 elderly women demonstrated a reduced frequency of bacterial infections compared to placebo after four to eight weeks of administration of 300 ml cranberry juice cocktail per day. Those with bacterial infections, indicated by urine samples containing white blood cells and high concentrations of bacteria, and taking cranberry juice cocktail were only about one-quarter as likely as the placebo group to continue to have an infection the next month (Avorn et al., 1994).

A pilot study including 15 children with neurogenic bladder receiving intermittent catheterization four times a day investigated the effect of cranberry juice cocktail on the frequency of bacteriuria. Administration of 2 oz cranberry juice concentrate, the equivalent of 300 ml cranberry juice cocktail, for three months had no effect on bacterial counts in the urine of these children (Schlager et al., 1999).

CranActin

Urinary Tract Infection (Prevention)

A crossover trial studied ten sexually active women who had a history of urinary tract infections. They were given either 400 mg cranberry extract (CranActin) or placebo daily for three months before switching treatments. The women had significantly fewer infections while taking the cranberry product compared to when they took the placebo (Walker et al., 1997).

ADVERSE REACTIONS OR SIDE EFFECTS

No significant side effects were reported with the use of cranberry juice or extract.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

American Herbal Pharmacopoeia (AHP)

Indications

The *American Herbal Pharmacopoeia* lists the following indications supported by clinical trials for cranberry products: urinary tract infections and reduction of urinary odor. Actions include bacterial antiadhesion activity, possibly vitamin B_{12} absorption-enhancing effects, and cholesterol-lowering, anticancer, and vasorelaxant effects (Winston et al., 2002).

Doses

Juice: 30 to 300 ml daily (Winston et al., 2002)
Dry extract: 400 to 450 mg cranberry solids twice daily (Winston et al., 2002)

Contraindications

The *AHP* states that no contraindications are cited in the literature (Winston et al., 2002).

Adverse Reactions

The *AHP* lists no known adverse reactions (Winston et al., 2002).

Precautions

The *AHP* suggests that in the treatment of cystitis, conditions such as pyelonephritis must be ruled out before relying on only cranberry (Winston et al., 2002). Also, if urinary tract infection symptoms persist despite use of cranberry, a physician should be consulted.

Drug Interactions

The *AHP* lists no known drug interactions in the literature (Winston et al., 2002).

REFERENCES

Avorn J, Monane M, Gurwitz J, Glynn R, Choodnovskiy I, Lipsitz L (1994). Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *Journal of the American Medical Association* 271 (10): 751-754.

Schlager TA, Anderson S, Trudell J, Hendley JO (1999). Effects of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. *The Journal of Pediatrics* 135 (6): 698-702.

Walker EB, Barney DP, Mickelsen JN, Walton RJ, Mickelsen RA (1997). Cranberry concentrate: UTI prophylaxis. *The Journal of Family Practice* 45 (2): 167-168.

Winston D, Graff A, Brinckmann J, Länger R, Turner A, Reich E, Bieber A, Howell A, Romm AJ (2002). *Cranberry Fruit,* Vaccinium macrocarpon *Aiton.* American Herbal Pharmacopoeia and Therapeutic Compendium: Standards of Analysis, Quality Control, and Therapeutics. Eds. R Upton, A Graff. Santa Cruz, CA: American Herbal Pharmacopoeia.

DETAILS ON CRANBERRY PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Cranberry Products

Product Profile: Cranberry Juice Cocktail

Manufacturer	**Ocean Spray Cranberries, Inc.**
U.S. distributor	**Ocean Spray Cranberries, Inc.**
Botanical ingredient	**Cranberry fruit juice**
Extract name	N/A
Quantity	2 ounces cranberry concentrate equivalent to 300 ml cranberry juice cocktail
Processing	No information
Standardization	No information
Formulation	Liquid

Recommended dose: Serving size: 8 fl oz; for maintaining urinary tract health: 10 fl oz.

DSHEA structure/function: Food label: helps maintain immune system health; helps maintain healthy bones, teeth, and skin; and helps maintain urinary tract health

Other ingredients: Filtered water, high fructose corn syrup, ascorbic acid.

Source(s) of information: Schlager et al., 1999; product label.

Clinical Study: Cranberry Juice Cocktail

Extract name	N/A
Manufacturer	Ocean Spray Cranberries, Inc.
Indication	**Urinary tract infection; bacterial bladder infections** in elderly women (prevention)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Avorn J, Monane M, Gurwitz J, Glynn R, Choodnovskiy I, Lipsitz L (1994). Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *Journal of the American Medical Association* 271 (10): 751-754.

Trial design
Parallel. One-month run-in with placebo beverage.

Study duration	6 months
Dose	300 ml per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multisite
No. of subjects enrolled	192
No. of subjects completed	153
Sex	Female
Age	Mean: 78.5 years

Inclusion criteria
Subjects in long-term care facility and elderly housing complexes.

Exclusion criteria
Subjects with terminal diseases or severe dementia.

End points
Urine samples were collected at baseline and then monthly (total seven samples). Samples were tested for bacteria and white blood cells. If subjects

were taking antibiotics, collection of urine was cancelled for that month and then resumed the following month. The primary outcome was bacteriuria (greater than or equal to 100,000 organisms per ml urine) and pyuria (white blood cells in the urine).

Results
Effect of cranberries on reducing frequencies of bacteriuria with pyuria in elderly women was not seen until after four to eight weeks with daily cranberry juice intake. Bacteriuria with pyuria was found in 28.1 percent of urine samples in the placebo group, compared to only 15.0 percent in the cranberry group. Those with a bacteriuric-pyuric infected urine sample were only about one-quarter as likely as controls to continue to have an infected sample the next month (odds ratio 0.27, $p = 0.006$).

Side effects
None mentioned in study.

Authors' comments
These findings suggest that use of a cranberry beverage reduces the frequency of bacteriuria with pyuria in older women.

Reviewer's comments
A very good study demonstrating a decrease in bacteriuria and pyuria in older women. Length of treatment was adequate, sample size appropriate, and the outcome measures clearly defined. (4, 6)

Clinical Study: Cranberry Juice Concentrate

Extract name	N/A
Manufacturer	Ocean Spray Cranberries, Inc.
Indication	**Urinary tract infection; bacterial bladder infections** in children with neurogenic bladder (prevention)
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Schlager TA, Anderson S, Trudell J, Hendley JO (1999). Effects of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. *The Journal of Pediatrics* 135 (6): 698-702.

Trial design
Crossover after three months.

Study duration	3 months
Dose	2 ounces of cranberry concentrate per day (equal to 300 ml of cranberry juice cocktail)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Homes
No. of subjects enrolled	15
No. of subjects completed	15
Sex	Male and female
Age	2-18 years

Inclusion criteria
Children with neurogenic bladder receiving clean intermittent catheterization four times a day, living at home, with normal findings on renal ultrasonography and voiding cystourethrogram, and living within a one-hour drive of the hospital.

Exclusion criteria
None mentioned.

End points
Weekly home visits with sample urine from intermittent catherization. The urine was cultured and the frequency of bacteriuria (greater than or equal to 10,000 colony-forming units per mL urine) was determined.

Results
Frequency of bacteriuria in children drinking cranberry concentrate and placebo beverage were both 75 percent. No significant difference was observed in the acidification of urine in the two treatments.

Side effects
None observed.

Authors' comments
The frequency of bacteriuria in children with neurogenic bladder receiving intermittent catherization is 70 percent. Cranberry concentrate had no effect on bacteria counts in this population.

Reviewer's comments
This study demonstrated no beneficial effect of a cranberry concentrate on children with neurogenic bladder. The study is limited by small sample size; however, the treatment length was adequate. (3, 5)

Product Profile: CranActin®

Manufacturer	**Nutraceutical Corporation**
U.S. distributor	**Solaray, Inc.**
Botanical ingredient	**Cranberry fruit extract**
Extract name	**Cranberry AF™**
Quantity	400 mg
Processing	No information
Standardization	Tested for and guaranteed to contain bacterial antiadherence activity
Formulation	Capsule

Recommended dose: One capsule two to four times per day.

DSHEA structure/function: CranActin is intended to provide dietary support to help promote a normal, healthy urinary tract.

Other ingredients: Vitamin C (as ascorbic acid) 30 mg, gelatin (capsule), magnesium oxide, cellulose, magnesium stearate, vegetable juice, silica.

Comments: Also available as CranActin Chewables.

Source(s) of information: Product package.

Clinical Study: CranActin™

Extract name	Cranberry AF
Manufacturer	Solaray, Inc.
Indication	**Urinary tract infection** (prevention)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Walker EB, Barney DP, Mickelsen JN, Walton RJ, Mickelsen RA (1997). Cranberry concentrate: UTI prophylaxis. *The Journal of Family Practice* 45 (2): 167-168.

Trial design
Crossover after three months.

Study duration	3 months
Dose	1 (400 mg) capsule daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	1 hospital
No. of subjects enrolled	19
No. of subjects completed	10
Sex	Female
Age	28-44 years (median: 37)

Inclusion criteria
Sexually active women between the ages of 18 and 45 years who were generally healthy other than suffering from a demonstrated history of urinary tract infections (four UTIs during the previous year or at least one UTI within the previous 3 months).

Exclusion criteria
Pregnancy.

End points
Symptomatic urinary tract infection with diagnostic culture.

Results
Cranberry concentrate was found to be more effective than placebo in reducing the occurrence of UTI ($p < 0.005$). While taking cranberry, seven of the ten subjects exhibited fewer UTIs, two subjects exhibited the same number, and one subject experienced one more UTI. Of the total 21 incidents of UTIs recorded among the participants during the six months, six UTIs occurred during the time they were taking cranberry. The frequency was calculated to be an average of 2.4 infections per year. In contrast, a total of 15

UTIs occurred while on placebo. This frequency was calculated as an average of 6.0 infections per year.

Side effects
None mentioned.

Authors' comments
Data reveal that daily consumption of powdered cranberry extract as a dietary supplement can help reduce the number of urinary tract infections over a period of three months.

Reviewer's comments
This study demonstrates a reduction in the number of urinary tract infections experienced by women on a cranberry supplement. There are some flaws in the study, however, such as a small number of patients and no definition of a UTI. The study also lacks details regarding the cranberry supplement. (5, 3)

Devil's Claw

Latin name: ***Harpagophytum procumbens*** **(Burch.) DC. ex Meisn.** [Pedaliaceae]
Plant part: **Root**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Devil's claw is a native South African plant with large underground tubers. The chopped and dried tubers have been used traditionally for their tonic, antipyretic, and analgesic properties. Several iridoid glycosides, notably harpagoside, are used to characterize the plant (Schulz, Hänsel, and Tyler, 2001).

Harpadol® capsules, manufactured by Arkopharma Laboratoires Pharmaceutiques in France, contain powdered root. A dose of six (435 mg) capsules per day delivers 57 mg harpagoside. The capsules are sold in the United States as Arkojoint™ by Arkopharma/Health from the Sun in Newport, New Hampshire.

The extract WS 1531 is manufactured by Dr. Willmar Schwabe GmbH & Co. in Germany. The extract has a ratio of 6 to 9:1, and a dose of 600 or 1200 mg per day delivers 50 or 100 mg harpagoside, respectively. This extract is not sold in the United States.

Ardeypharm GmbH in Germany produces an extract with a ratio of 2.5:1. A dose of 800 mg three times daily delivers 50 mg harpagoside. This product is not available in the United States.

SUMMARY OF REVIEWED CLINICAL STUDIES

Devil's claw preparations have been examined for their analgesic (pain relieving) and anti-inflammatory properties (Schulz, Hänsel, and Tyler, 2001). We review three trials here, one for the treatment of osteoarthritis and two for lower back pain. Osteoarthritis is a com-

DEVIL'S CLAW SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Arkojoint™ (US), Harpadol® (EU)	Arkopharma Laboratoires Pharmaceutiques, France/Health from the Sun/ Arkopharma	Powdered root	6 (435 mg) capsules/day (57 mg harpagoside/ day)	Osteoarth-ritis	1	Trend (II-1)
(Not sold in US)	Dr. Wilmar Schwabe GmbH & Co., Germany/ None	Root extract (WS 1531)	600 or 1200 mg extract/day (50 or 100 mg harpagoside/ day)	Lower back pain	1	No (I-1)
(Not sold in US)	Ardeypharm GmbH, Ger-many/None	Root extract	800 mg 3 times daily (50 mg har-pagoside)/day	Lower back pain	1	No (I-1)

mon rheumatic disease, characterized by pain, inflammation, and reduced joint function. The cause of back pain is often unknown, but it has been attributed to several different causes, including weak back muscles and reduced flexibility of the spine (Chrubasik et al., 1996).

Arkojoint

Osteoarthritis

In a comparison study with 92 patients, Harpadol (Arkojoint) reduced pain due to osteoarthritis of the knee and hip. A dose of six capsules a day (2.6 g root powder) was compared with 100 mg of diacerhein (an anthraquinone derivative) in this four-month study. Diacerhein and Harpadol reduced pain to a similar extent, but by the end of the study, the Harpadol group used significantly fewer analgesics and NSAIDs (nonsteroidal anti-inflammatory drugs) (Chantre et al., 2000). This was a well-designed and well-conducted study. However, there was no placebo group, and diacerhein is a relatively unproven remedy. The choice of a well-documented agent to serve as the control would have strengthened the study.

WS 1531

Lower Back Pain

A study including 183 subjects with lower back pain compared two doses of devil's claw extract WS 1531 to placebo. Patients were given either 600 or 1200 mg extract WS 1531 or placebo for one month. As a result, there was a trend toward an increase in pain-free days for the two devil's claw groups during the last week of the study. However, there was no significant difference from placebo (Chrubasik et al., 1999).

Ardeypharm

Lower Back Pain

Another one-month study with 109 subjects with lower back pain again showed a trend toward reduction in pain with devil's claw that

was not significantly different from placebo. Reduction in pain was confined to a subgroup whose back pain did not radiate to one or both legs. The devil's claw treatment was 800 mg extract (Ardeypharm GmbH) three times daily (50 mg harpagoside daily) (Chrubasik et al., 1996).

ADVERSE REACTIONS OR SIDE EFFECTS

All three devil's claw products were well tolerated. The only side effects mentioned were diarrhea (Chantre et al., 2000) and mild and infrequent gastrointestinal symptoms (Chrubasik et al., 1999).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

British Herbal Compendium (BHC)
European Scientific Cooperative on Phytotherapy (ESCOP)
German Commission E

Indications

Devil's claw root, consisting of the dried, secondary tubers, is approved by the German Commission E and listed by the *BHC* and ESCOP as being used for the treatment of loss of appetite and dyspepsia. It is also indicated for supportive therapy of degenerative disorders of the locomotor system, including painful arthrosis and tendonitis (Blumenthal et al., 1998; Bradley, 1992; ESCOP, 1996). Actions include choleretic (digestive stimulant), antiphlogistic (anti-inflammatory), and mildly analgesic (Blumenthal et al., 1998; Bradley, 1992).

Doses

For Dyspepsia or Lack of Appetite

Tuber: 1.5 g daily (Blumenthal et al., 1998)

Decoction: 0.5 g tuber three times daily (Bradley, 1992; ESCOP, 1996)
Tincture: (1:5, 25 percent ethanol), 1 ml three times daily (Bradley, 1992) or (1:10, 25 percent ethanol) 2 ml three times daily (ESCOP, 1996)

For Painful Arthrosis or Tendonitis

Tuber: 1 to 3 g three times daily (ESCOP, 1996)
Decoction: 1.5 to 3 g tuber three times daily (ESCOP, 1996)
Extracts: hydroalcoholic, equivalent to 1 to 3 g tuber three times daily (ESCOP, 1996)

Other Indications

Tuber: 4.5 g daily (Blumenthal et al., 1998)
Decoction: 1.5 to 2.5 g dried tuber three times daily (Bradley, 1992)
Extract: (1:1, 25 percent ethanol), 1 to 2ml three times daily (Bradley, 1992)

Treatment Period

ESCOP recommends treatment for at least two to three months in the case of arthrosis; if symptoms persist, consult a doctor (ESCOP, 1996).

Contraindications

The Commission E, the *BHC,* and ESCOP list gastric and duodenal ulcers as contraindications (Blumenthal et al., 1998; Bradley, 1992; ESCOP, 1996).

Adverse Reactions

The Commission E lists no known adverse reactions, but ESCOP states that mild gastrointestinal disturbances may occur in sensitive individuals, especially at higher dosage levels (Blumenthal et al., 1998; ESCOP, 1996).

Precautions

The Commission E suggests that with gallstones, use only after consultation with a physician (Blumenthal et al., 1998).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998).

REFERENCES

Blumenthal M, Busse W, Hall T, Goldberg A, Gruenwald J, Riggins C, Rister S, eds. (1998). *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines.* Trans. S Klein. Austin, TX: American Botanical Council.

Bradley PR, ed. (1992). *British Herbal Compendium: A Handbook of Scientific Information on Widely Used Plant Drugs,* Volume 1. Dorset, UK: British Herbal Medicine Association.

Chantre P, Cappelaere A, Leblan D, Guedon D, Vandermander J, Fournie B (2000). Efficacy and tolerance of *Harpagophytum procumbens* versus diacerhein in treatment of osteoarthritis. *Phytomedicine* 7 (3): 177-183.

Chrubasik S, Junck H, Breitschwerdt H, Conradt Ch, Zappe H (1999). Effectiveness of *Harpagophytum* extract WS 1531 in the treatment of exacerbation of low back pain: A randomized, placebo-controlled, double-blind study. *European Journal of Anaesthesiology* 16 (2): 118-129.

Chrubasik S, Zimpfer Ch, Schütt U, Ziegler R (1996). Effectiveness of *Harpagophytum procumbens* in treatment of acute low back pain. *Phytomedicine* 3 (1): 1-10.

European Scientific Cooperative on Phytotherapy (ESCOP) (1996). *Harpagophyti radix:* Devil's claw. *Monographs on the Medicinal Uses of Plant Drugs.* Fascile 2. Exeter, UK: European Scientific Cooperative on Phytotherapy.

Schulz V, Hänsel R, Tyler VE (2001). *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine,* Fourth Edition. Trans. TC Telger. Berlin: Springer-Verlag.

DETAILS ON DEVIL'S CLAW PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Devil's Claw Products

Product Profile: Arkojoint™

Manufacturer	**Arkopharma Laboratoires Pharmaceutiques, France**
U.S. distributor	**Health from the Sun/Arkopharma**
Botanical ingredient	**Devil's claw secondary roots**
Extract name	None given
Quantity	435 mg
Processing	Powdered root
Standardization	Iridoid glycosides (14.5 mg)
Formulation	Capsules

Recommended dose: Take one to two capsules three times a day with food and a full glass of water. Best results are obtained after one month with continued use.

DSHEA structure/function: Helps maintain healthy, flexible joints.

Other ingredients: Cellulose derivative (capsule shell), vegetal magnesium stearate.

Comments: Sold as Harpadol in Europe.

Source(s) of information: Product package.

Clinical Study: Harpadol®

Extract name	N/A
Manufacturer	Arkopharma Laboratoires Pharmaceutiques, France
Indication	**Osteoarthritis**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference

Chantre P, Cappelaere A, Leblan D, Guedon D, Vandermander J, Fournie B (2000). Efficacy and tolerance of *Harpagophytum procumbens* versus diacerhein in treatment of osteoarthritis. *Phytomedicine* 7 (3): 177-183.

Trial design

Parallel. Patients in the comparison group took two (50 mg) capsules of diacerhein plus six capsules of placebo per day.

Study duration	4 months
Dose	6 (435 mg) capsules/day (plus 2 capsules placebo/day)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Diacerhein
Site description	Multicenter
No. of subjects enrolled	122
No. of subjects completed	92
Sex	Male and female
Age	30-79 years (mean: 62)

Inclusion criteria
Patients suffering from osteoarthritis of the knee and hip. Spontaneous pain intensity rated 50 mm on a 100 mm visual analog scale and a score of at least 4 in the Lequesne Algofunctional Index. Patients also had to show a grade 1, 2, or 3 in Kellgren's scale.

Exclusion criteria
Significant renal, hepatic, hematological, or cardiovascular disease. Inflammatory articular diseases, chondrocalcinosis. Very severe arthritis (unable to walk and/or requiring surgical intervention). Past or present malignancy. Oral, intra-articular, or parenteral corticosteroids within the previous four weeks. Chondroprotective drugs (e.g., glucosamine sulfate, hyaluronic acid, chondroitin sulfate, etc.) within the previous eight weeks. Gastritis and/or gastroduodenal ulcer in active phase. History of allergic reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). Pregnancy or lactation.

End points
Primary end point: visual analog scale was used to record the level of spontaneous pain. Secondary end point: functional disability of movement, Lequesne index score, and amount of diclofenac or paracetamol-caffeine taken as rescue drugs if pain relief was judged by the patient to be inadequate.

Results
Both treatments showed a marked reduction in spontaneous pain index (63.6 to 31.3 in Harpadol patients, 61.6 to 35.8 in diacerhein patients) without significant difference between the two. A similar result was true for the Lequesne functional index scores. At the completion of four months, patients on Harpadol were using significantly fewer NSAIDs and analgesics than patients on diacerhein. In a global assessment of efficacy, 65.3 percent of patients taking Harpadol and 60 percent taking diacerhein were judged as having a positive outcome.

Side effects
Frequency of adverse effects in Harpadol group was lower than in diacerhein group. Diarrhea (most frequently reported side effect) occurred in 8.1 percent of Harpadol patients and in 26.7 percent of diacerhein patients.

Authors' comments
One can argue that without a placebo arm it is difficult to judge effectiveness of the two drugs investigated in this study. However, the importance of placebo effect in osteoarthritis has been recently assessed. The results of the present study confirm the efficacy and the very good tolerance of Harpadol in the treatment of osteoarthritis. Harpadol is at least comparable with diacerhein and is an effective therapeutic agent in osteoarthritis and can be safely administrated to patients.

Reviewer's comments
This is a well-designed and well-conducted study. However, no placebo group was included. The trial is rated as Level II due to the use of diacerhein, an unproven remedy as a control and not a well-documented efficacious agent. (5, 6)

Product Profile: WS 1531

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	None
Botanical ingredient	**Devil's claw root extract**
Extract name	**WS 1531**
Quantity	200 mg
Processing	Plant to extract ratio 6-9:1
Standardization	17 mg harpagoside (8.3%)
Formulation	Tablet

Source(s) of information: Chrubasik et al., 1999.

Clinical Study: WS 1531

Extract name	WS 1531
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Lower back pain**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Chrubasik S, Junck H, Breitschwerdt H, Conradt Ch, Zappe H (1999). Effectiveness of *Harpagophytum* extract WS 1531 in the treatment of exacerbation of low back pain: A randomized, placebo-controlled, double-blind study. *European Journal of Anaesthesiology* 16 (2): 118-129.

Trial design
Parallel, three-group study.

Study duration	1 month
Dose	600 mg extract (50 mg harpagoside) or 1200 mg extract (100 mg harpagoside) daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	197
No. of subjects completed	183
Sex	Male and female
Age	18-75 years

Inclusion criteria
Subjects suffering from low back pain with or without radiation to the legs, at least six months susceptibility to low back pain, a current exacerbation of their complaint affecting both rest and movement, pain greater than a 5 on a 1 to 10 visual analog scale, and expected to require at least four weeks of symptomatic treatment.

Exclusion criteria
Low back pain attributable to identifiable causes such as disc prolapse, hip disease, spondylolisthesis, osteomalacia, or inflammatory arthritis. Participation within 30 days in any other clinical study. Serious organic illness affecting any organ system. A history of drug or alcohol abuse or requirement for psychotherapeutic agents. Pregnancy, actual or possible, or lactation. Known allergy to any of the proposed trial medications. Difficulties with language or anticipated cooperation.

End points
Patient condition was monitored using the Arhus Low Back Pain Index. The primary outcome measure was the number of patients who were pain-free without the permitted rescue medication for five days out of the last week of the study. Subsidiary outcome measures were the change in Arhus Low Back Pain Index relative to baseline and the consumption of rescue medication, tramadol (tramadol was allowed to patients in doses from 50 to 400 mg per day if necessary).

Results
The number of patients who were pain-free without using tramadol for at least five days of last week was three in placebo group, six in H600 group,

and ten in H1200 group. The median overall change in Arhus index was about 20 percent in all three groups. These changes in the three groups were significantly different from baseline, but not significantly different from one another.

Side effects
No evidence for side effects except possibly for mild and infrequent gastrointestinal symptoms.

Authors' comments
Harpagophytum can probably help many of those suffering from low back pain who might also be helped by bed rest, paracetamol, NSAIDs, or manipulation, and back school. Of a wide range of treatments for low back pain, none is convincingly effective in patients suffering from back pain for more than three months. Overall, 10 percent of the patients in this study responded to the primary outcome measures (no pain for five days of last week of study), but most of these responders had had back pain for less than six weeks. One could argue that at least half of the patients who would have responded to anything responded to the treatment (including placebo). The daily contact and interest of the investigators probably provided its own distinct psychotherapeutic benefits in an ailment which is heavily influenced by psychological and social factors.

Reviewer's comments
This is a well-designed study with adequate sample size and inclusion/exclusion criteria. There was a trend toward less need for tramodal in the two devil's claw groups, but no significant differences from the placebo group were seen. (5, 6)

Product Profile: Devil's Claw

Manufacturer	**Ardeypharm GmbH, Germany**
U.S. distributor	None
Botanical ingredient	**Devil's claw secondary roots extract**
Extract name	None given
Quantity	400 mg
Processing	Plant to extract ratio 2.5:1
Standardization	2% harpagoside
Formulation	Tablet

Source(s) of information: Chrubasik et al., 1996.

Clinical Study: Devil's Claw

Extract name	None given
Manufacturer	Ardeypharm GmbH, Germany
Indication	**Lower back pain**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Chrubasik S, Zimpfer Ch, Schütt U, Ziegler R (1996). Effectiveness of *Harpagophytum procumbens* in treatment of acute low back pain. *Phytomedicine* 3 (1): 1-10.

Trial design
Parallel.

Study duration	1 month
Dose	2 (400 mg) tablets 3 times daily (50 mg harpagoside/day)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	118
No. of subjects completed	109
Sex	Male and female
Age	18-75 years

Inclusion criteria
Patients with at least six months of low back pain not attributable to identifiable causes (e.g., disc prolapse, hip disease, spondylolisthesis, osteomalacia, or inflammatory arthritis). Those suffering from acute increases of pain that affected both rest and movement, who were expected to require at least four weeks of symptomatic treatment.

Exclusion criteria
Participation in other clinical studies within the past 30 days, pregnancy, lactation, or insufficient contraceptive methods, difficulties with language or co-

operation, known allergy to any of the proposed trial medications, a history of drug or alcohol abuse, requirement for psychotherapeutic agents, or serious organic illness affecting any of the organ systems.

End points
Patients given either placebo or devil's claw were allowed to take a rescue medication, tramadol, if pain relief not adequate. Primary measure of effectiveness was amount of tramadol patients took to alleviate back pain in the last three weeks of study. Secondary measures were numbers of totally pain-free patients at the end of treatment and change in Arhus Low Back Pain Index relative to baseline.

Results
Tramadol (rescue drug) consumption during the last three weeks of treatment was 95 mg in the drug group and 102 mg in the placebo group. Average pain score on the Arhus index did not correlate with average tramadol consumption. After four weeks, nine patients in the drug group and one patient in the placebo group were pain-free. Arhus index in both groups improved significantly after four weeks of treatment (20 percent improvement in drug group, 8 percent in placebo group; difference between the groups: $p = 0.059$). Reduction in pain in the drug group was confined to the subgroup of patients whose pain did not radiate to one or both legs.

Side effects
No identifiable clinical, hematological, or biochemical side effects.

Authors' comments
Change in tramadol consumption was chosen as the principal outcome measure on the simplistic assumption that greater pain would lead to greater consumption. That was probably confounded by the fact that most patients prefer a degree of pain to some of the side effects that can accompany most conventional analgesic treatments. Although the design of this study prevents conclusions to be drawn, treatment with devil's claw for four weeks appears to have caused a greater number of patients to become pain-free than did placebo and a greater percentage of pain reduction in the Arhus index.

Reviewer's comments
This study was well designed, but there was really no proven benefit of test drug over placebo. (5, 6)

Dragon's Blood Croton

Other common names: **Sangre de drago**
Latin name: ***Croton lechleri* Müll. Arg.** [Euphorbiaceae]
Plant part: **Sap**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Sangre de drago, meaning dragon's blood, is a common name for closely related species of *Croton* growing in South America. The English term, dragon's blood, is a common name used to describe different genera from Malaya, the Canary Islands, Guyana in the West Indies, and South America. Dragon's blood croton, or *C. lechleri,* is a South American tree whose blood-red latex or sap is a traditional remedy. It is used internally for coughs, flu, "lung problems," diarrhea, and stomach ulcers, and externally for wound healing. The major constituents of the sap are proanthocyanidins, which are also called condensed tannins. The sap also contains taspine (a phenanthrene alkaloid) as well as lignans (Jones, in press; Ubillas et al., 1994).

SP-303™ is an extract from the sap of dragon's blood croton that is high in proanthocyanidin content. The SP-303 extract is manufactured by Shaman Pharmaceuticals, Inc., and is found in two different products: SB-Normal Stool Formula™, distributed by ShamanBotanicals.com; and Bowel Support Formula, distributed by General Nutrition Corporation. Tablets of both products contain 250 mg SP-303 each. SP-303 was studied experimentally under the name Provir.™

DRAGON'S BLOOD CROTON SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
SB-Normal Stool Formula™; Bowel Support Formula	Shaman Pharmaceuticals, Inc./ ShamanBotanicals.com; General Nutrition Corporation	Extract (SP-303™)	500 mg every 6 hours	Diarrhea in AIDS patients	2	Yes (I-1, III-1)

SUMMARY OF REVIEWED CLINICAL STUDIES

The two trials reviewed here study the use of SP-303 for AIDS-related diarrhea. These studies are relevant, as chronic diarrhea is often a problem for those affected with HIV (human immunodeficiency virus). The incidence of diarrhea caused by infectious organisms has been reduced with the advent of new treatments for HIV. However, many patients continue to have chronic diarrhea even though extensive evaluation has not revealed any pathogenic cause (Holodniy et al., 1999).

SP-303

Diarrhea in AIDS Patients

A well-conducted, placebo-controlled, double-blind study included 45 AIDS patients (HIV-1 infection) with chronic diarrhea. After four days of administration of two (250 mg) capsules every six hours, there was a significant reduction in stool weight and stool frequency compared to placebo (Holodniy et al., 1999).

A subsequent study with 393 AIDS patients with diarrhea compared 250 mg delayed-release tablets, 500 mg delayed-release tablets, and 500 mg delayed-release beads to placebo. The final dose levels were 500 mg or 1000 mg four times daily. A significant reduction in stool weight was observed for the group given 500 mg delayed-release tablets (a total of 4 g per day) compared with placebo. There was also a significant reduction compared to baseline measurements. No other treatment group showed significant changes (Koch, 2000). Unfortunately, this study was not written up in full, and many details of the study methodology were not included in the report we reviewed.

ADVERSE REACTIONS OR SIDE EFFECTS

No serious adverse effects or laboratory abnormalities were observed in either study cited.

REFERENCES

Holodniy M, Koch J, Mistal M, Schmidt JM, Khandwala A, Pennington JE, Porter SB (1999). A double blind, randomized, placebo-controlled phase II study to assess the safety and efficacy of orally administered SP-303 for the symptomatic treatment of diarrhea in patients with AIDS. *The American Journal of Gastroenterology* 94 (11): 3267-3273.

Jones K (In press). "Sangre de drago" *(Croton lechleri):* Clinical and preclinical studies of a South American medical tree sap. *Journal of Alternative and Complementary Medicine*.

Koch J (2000). A phase III, double-blind, randomized, placebo-controlled multicenter study of SP-303 (Provir) in symptomatic treatment of diarrhea in patients with acquired immunodeficiency syndrome (AIDS). Unpublished paper.

Ubillas R, Jolad SD, Bruening RC, Kernan MR, King SR, Sesin DF, Barrett M, Stoddart CA, Flaster T, Kuo J, et al. (1994). SP-303, an antiviral oligomeric proanthocyanidin from the latex of *Croton lechleri* (sangre de drago). *Phytomedicine* 1: 77-106.

DETAILS ON DRAGON'S BLOOD PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Dragon's Blood Products

Product Profile: SB-Normal Stool Formula™

Manufacturer	**Shaman Pharmaceuticals, Inc.**
U.S. distributor	**ShamanBotanicals.com**
Botanical ingredient	**Dragon's blood croton sap from bark extract**
Extract name	**SP-303**
Quantity	350 mg
Processing	No information
Standardization	250 mg SP-303
Formulation	Tablet (enteric coated)

Recommended dose: Take one to two tablets, two to four times per day as needed or as directed by a physician. Take with water. Do not break or crush tablets.

DSHEA structure/function: Normalizes excess water flow in the bowel (intestinal tract) and promotes normal stool formation, without causing constipation.

Cautions: This product should not be used for people with bloody diarrhea and high fever. If experiencing these symptoms, consult a physician.

Other ingredients: Microcrystalline cellulose, coating (methacrylic acid copolymer, magnesium silicate, triethyl citrate), glyceryl monostearate, sodium starch glycolate, silicon dioxide.

Comments: Also called Provir.

Source(s) of information: Product label; Holodniy et al., 1999.

Product Profile: Bowel Support Formula

Manufacturer	**Shaman Pharmaceuticals, Inc.**
U.S. distributor	**General Nutrition Corporation**
Botanical ingredient	**Dragon's blood croton sap extract**
Extract name	**SP-303™**
Quantity	350 mg
Processing	No information
Standardization	250 mg of SP-303
Formulation	Tablet

Recommended dose: Take one to two tablets, two to four times a day with water, as needed or as directed by a physician. Do not break or crush tablets.

DSHEA structure/function: Helps manage occasional diarrhea. Normalizes water and chloride secretion in the bowel. Promotes normal stool formation.

Cautions: For occasional diarrhea only. Consult a physician if experiencing persistent diarrhea. Do not use this product if experiencing bloody diarrhea or a fever.

Other ingredients: Microcrystalline cellulose, coating (methacrylic acid copolymer, magnesium silicate, triethyl citrate), glyceryl monostearate, sodium starch glycolate, silicon dioxide.

Comments: Also called Provir.

Source(s) of information: Product package; Holodniy et al., 1999.

Clinical Study: Provir™

Extract name	SP-303
Manufacturer	Shaman Pharmaceuticals, Inc.
Indication	**Diarrhea in AIDS patients**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Holodniy M, Koch J, Mistal M, Schmidt JM, Khandwala A, Pennington JE, Porter SB (1999). A double blind, randomized, placebo-controlled phase II study to assess the safety and efficacy of orally administered SP-303 for the symptomatic treatment of diarrhea in patients with AIDS. *The American Journal of Gastroenterology* 94 (11) 3267-3273.

Trial design
Parallel. Subjects remained in the study unit throughout the 24-hour screening period and treatment period (a total of 96 hours after the first dose).

Study duration	4 days
Dose	2 (250 mg) capsules every 6 hours
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	2 academic medical centers
No. of subjects enrolled	51
No. of subjects completed	45
Sex	Male and female
Age	21-60 years

Inclusion criteria
AIDS patients with chronic diarrhea between 18 and 60 years of age; HIV-1 infection confirmed by serological screening; a diagnosis of AIDS based on CDC criteria; on a stable medical regimen for treatment of HIV disease and associated conditions for at least two weeks before and during the trial; a history of three or more abnormal stools per day. Subjects were required to discontinue all antidiarrheal medications at least 24 hours before entry into the trial.

Exclusion criteria
Subjects pregnant or nursing; with neutrophil count less than 500 cells/μl; decompensated liver disease; a creatinine clearance of <25 percent of predicted; or if they were previously enrolled in a study within 30 days.

End points
Study personnel recorded the frequency, weight, and consistency of all bowel movements during the treatment period.

Results
The SP-303 treatment group demonstrated a mean reduction from baseline stool weight of 451 g/24 h, compared with 150 g/24 h in the placebo group on day 4 of treatment. A mean reduction in abnormal stool frequency of three abnormal stools in 24 h for the SP-303 group occurred, compared with a reduction of two in 24 h in the placebo group. Daily measures analysis over four days of treatment demonstrated that SP-303 subjects had a significant reduction in stool weight ($p = 0.008$) and an abnormal stool frequency ($p = 0.04$) when compared to placebo-treated subjects.

Side effects
No serious adverse events or laboratory abnormalities.

Authors' comments
SP-303 is safe and well tolerated. These results suggest that SP-303 may be effective in reducing stool weight and frequency in patients with AIDS and diarrhea.

Reviewer's comments
This is a thorough and relevant study, adequate for a phase II trial. The dosage choice was not discussed in the paper or substantiated by reference(s). Given that no adverse effects were noted, a higher dose may have demonstrated greater efficacy. The trial was brief in length, considering that SP-303 is intended for the treatment of chronic, noninfectious, iatrogenic diarrhea. Significant differences from placebo were not present until day 4 in measurements of stool number and chloride, and not until day 3 in measurements of stool weight. Dietary changes made while in the inpatient study unit are a potential confounder. Both placebo and SP-303 showed significant changes in stool weight and number from day 1 onward, suggesting a common underlying factor (e.g., controlled diet) played a role in the observed outcomes. A longer study duration could have allowed for clear resolution of data profile differences between the SP-303 and placebo. (5, 6)

Clinical Study: Provir™

Extract name	SP-303
Manufacturer	Shaman Pharmaceuticals, Inc.
Indication	**Diarrhea in AIDS patients**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Koch J (2000). A phase III, double-blind, randomized, placebo-controlled multicenter study of SP-303 (Provir) in symptomatic treatment of diarrhea in patients with acquired immunodeficiency syndrome (AIDS). Unpublished paper.

Trial design
Parallel. Four groups: two capsules of one of the following four times daily for six days: 250 mg SP-303 delayed-release tablet; 500 mg SP-303 delayed-release beads; 500 mg SP-303 delayed-release tablet; or placebo. Pretrial monitored washout period of 24 hours. After seven-day inpatient study, subjects who had a decrease in stool weight of 50 percent or more compared to baseline were allowed to continue taking the same SP-303 regimen for another 21 days. Nonresponders were discontinued from treatment.

Study duration	6 days
Dose	2 (250 mg) tablets, 2 (500 mg) beads, or 2 (500 mg) tablets, taken 4 times a day
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	25 academic centers
No. of subjects enrolled	400
No. of subjects completed	393
Sex	Male and female
Age	Mean: 39.5 years

Inclusion criteria
Subjects over 18 years with HIV-1 infection and AIDS diagnosis based on

CDC criteria; stable medical regimen for treatment of HIV disease for at least two weeks; abnormal stool samples (soft or watery) of 300 g or more within the inpatient 24-hour screening period; history of at least one abnormal stool or use of antidiarrheal medication each day for at least 14 days prior to the 24-hour inpatient screening period; cessation of antidiarrheal medication 24 hours prior to admission to the research center.

Exclusion criteria
Subjects who were pregnant or breast-feeding; with neutrophil count less than 500 cells/microliter; decompensated renal or liver disease; frank blood in stool two weeks prior to or during study; enteric infection requiring antimicrobial medication; previously enrolled in a study within 30 days prior to entrance into the study.

End points
The primary efficacy end point was the reduction in the total daily stool weight over the six-day inpatient treatment period. Daily stool weight, frequency, and consistency were measured during the 24-hour screening and 144-hour study period. The daily gastrointestinal index score was assessed by rating and summing seven gastrointestinal complaint measures.

Results
For the 500 mg tablet group, intent-to-treat random regression analysis of the rate of reduction with treatment was significant compared to placebo ($p = 0.033$). An analysis of the reduction rate from baseline to the end of treatment yielded $p = 0.078$. No other treatment group showed significant changes in reduction rate. In subjects with stools weighing 1000 g or more, there was a statistically significant mean change in stool weight between subjects in the placebo and 500 mg groups ($p = 0.008$). In the outpatient phase of the study (continued treatment for patients who had responded to treatment in the first seven days), the 500 mg tablet group saw a sustained effect, and the drug was well tolerated throughout the study.

Side effects
No adverse events or laboratory abnormalities were found among treatment groups.

Author's comments
SP-303 is a safe and effective treatment for diarrhea in subjects with AIDS. Subjects with 1000 g or more in stool weight had statistically significant improvements in diarrhea.

Reviewer's comments
The sample size may have been appropriate; however, no power calculation was presented. Dietary changes made while in the inpatient study unit are a potential confounder, and a pretrial washout period of 24 hours is likely in-

sufficient for certain antidiarrheal agents (e.g., Imodium® or Lomotil®). Safety was mentioned as a primary focus of the study, but it was not described in detail in the results section. Dropouts/withdrawals were also not discussed. The trial period was adequate when the follow-up period is included. Unfortunately, this paper was not written up in full, so methodological details were missing. (0, 3)

Echinacea

Species-specific common names:
E. angustifolia: **Narrow-leaf echinacea, Kansas snakeroot, narrow-leaf purple coneflower**
E. pallida: **Pale-flower echinacea, pale purple coneflower**
E. purpurea: **Purple coneflower**
Latin names:
Echinacea angustifolia **DC. [Asteraceae]**
Echinacea pallida **(Nutt.) Nutt. [Asteraceae]**
Echinacea purpurea **(L.) Moench [Asteraceae]**
Latin synonyms: ***E. purpurea* = *Rudbeckia purpurea*** **L.**
Plant parts: **Aerial parts, root**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Echinacea species are plants in the daisy family that have pale (occasionally white) to deep purple flowers and are native to the central plains of North America. Although nine species of echinacea have been identified, only three are commonly used commercially. They are *Echinacea angustifolia, E. pallida,* and *E. purpurea.* Historically, there has been confusion over the identity of the plant material used both commercially and in scientific studies. *Echinacea angustifolia* root has been sold interchangeably with *E. pallida* roots. In addition, *E. purpurea* has been adulterated or substituted with *Parthenium integrifolium* L., a plant also known by the common name snakeroot. Fortunately, modern techniques of botany and chemistry now allow for better determination of identity (Awang and Kindack, 1991).

Many types of echinacea products are available on the market. They differ in species, plant part, and method of preparation. The most common products are the expressed juice of *E. purpurea* and aqueous alcoholic extracts of the roots and/or tops of all three species. Little scientific work has been done on possible differences in the ac-

ECHINACEA SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Single Ingredient Products						
Echinagard®, Echinacin® (EU); EchinaGuard® (US)	Madaus AG, Germany/Nature's Way Products, Inc.	Juice of *E. purpurea* tops preserved with ethanol (EC31)	24-40 drops three times daily or 4-5 ml twice daily	Cold (treatment)	2	Yes (I-1, II-1)
				Cold (prevention)	1	No (I-1)
				Exercise-induced immuno-suppression (prevention)	1	No (II-1)
				Vaginal candidiasis (prevention)	1	Undetermined (III-1)
Echinaforce®	Bioforce AG, Switzerland/Bioforce USA	Ethanolic extract of *E. purpurea* tops and roots	2 tablets 3 times daily	Cold (treatment)	1	Undetermined (II-1)
				Genital herpes	1	No (II-1)
Generic	None/None	Ethanolic extract of *E. purpurea* roots	180 drops daily (equiv. to 900 mg root)	Flu-type infections (treatment)	1	Undetermined (III-1)

Generic	None/None	Aqueous alcoholic extract of *E. pallida* roots	90 drops daily	Cold (treatment)	1	Yes (II-1)
Generic	None/None	Alcoholic extracts of *E. angustifolia* and *E. purpurea* roots	50 drops (1 ml) twice daily	Cold (prevention)	1	No (I-1)
			Combination Products			
Esberitox™	Schaper & Brümmer GmbH & Co. KG, Germany/ Enzymatic Therapy	Ethanolic extracts of *E. purpurea* roots, *E. pallida* roots, white cedar, and wild indigo	2-3 tablets 3 times daily	Cold (treatment)	2	Yes (I-1) Undetermined (III-1)
Echinacea Plus®	Traditional Medicinals, Inc./ Traditional Medicinals, Inc.	*E. purpurea* tops, *E. angustifolia* tops, and dry extract of *E. purpurea* root with lemongrass and spearmint	5-6 cups tea down to 1 per day over 5 days	Cold (treatment)	1	Yes (II-1)

tion of these different preparations, although we know them to differ chemically. Further, there is little scientific agreement as to which of the numerous chemical constituents identified in echinacea are responsible for the purported immunostimulatory action. Indeed, the only consensus may be that numerous constituents have activity (Bauer and Wagner, 1991).

The most clinically studied echinacea preparation is made from the expressed juice of *E. purpurea* flowering plants harvested without the roots. The expressed juice preparation contains 22 percent ethanol as a preservative. It is manufactured and sold in Germany by Madaus AG as Echinacin® or Echinagard® and distributed in the United States by Nature's Way Products, Inc. as EchinaGuard®. EchinaGuard is supplied in liquid, capsules, and chewable tablet forms, although only trials on the liquid preparation were reviewed.

Echinaforce® contains an extract of *E. purpurea* made with 65 percent ethanol. It is made from fresh plant material in the ratio of 95 percent herb and 5 percent root. Produced in Switzerland by Bioforce AG, it is distributed in the United States by Bioforce USA, Hudson, New York. It is also marketed in liquid and tablet forms.

One trial was performed with a generic *E. purpurea* root liquid extract made with 55 percent alcohol in a plant to extract ratio of 1:5. Another was performed with a generic extract of the roots of both *E. angustifolia* and *E. purpurea* made with 30 percent alcohol with a plant-to-extract ratio of 1:11. A third was performed with a generic *E. pallida* root liquid extract.

Many products on the market contain echinacea plus other ingredients. Two such products have been tested in clinical studies. The first is Esberitox™, which is manufactured in Germany by Schaper & Brümmer GmbH & Co. KG, and distributed in the United States by Enzymatic Therapy in Green Bay, Wisconsin. It contains root extracts of *E. purpurea* and *E. pallida* made with ethanol in a ratio of 1:1. Esberitox also contains extracts of wild indigo [*Baptisia tinctoria* (L.) R. Br.] root and white cedar (*Thuja occidentalis* L.) leaf.

The second product is a tea formula called Echinacea Plus®, which is manufactured and distributed by Traditional Medicinals in Sebastopol, California. The tea formula contains a blend of *E. purpurea* herb, *E. angustifolia* herb, and a dry extract of *E. purpurea* root (plant-to-extract ratio 6:1), in addition to lemongrass [*Cymbopogon*

citratus (DC. ex Nees) Stapf.] leaf and spearmint (*Mentha spicata* L.) leaf. Each tea bag delivers 20 mg of phenolic compounds.

SUMMARY OF REVIEWED CLINICAL STUDIES

Thirteen trials using echinacea products were reviewed, with the majority being focused on the common cold or upper respiratory tract infections. Various organisms cause the cold, the most common being the rhinovirus. An inflammatory response that follows the viral infection is responsible for the characteristic symptoms of sore throat, nasal discharge, cough, headache, and fever (Giles et al., 2000). The clinical studies indicate that echinacea products tend to reduce the severity of the symptoms and length of a cold, if taken when symptoms first appear. However, the studies also indicate that echinacea does not appear to prevent catching a cold when taken on a long-term basis.

EchinaGuard

EchinaGuard (Echinacin) was found to be efficacious in the treatment, but not in the prevention, of colds in three well-conducted studies. Two other trials studied the prevention of exercise-induced immunosuppression and the prevention of recurrence of vaginal candidiasis. Neither trial yielded strongly positive results.

Cold (Prevention and Treatment)

In the first well-conducted, placebo-controlled study, 118 employees of a factory were enrolled at the initial signs of a cold. They were treated for up to ten days with either EchinaGuard (20 drops every two hours for the first day and subsequently three times daily) or placebo. In the EchinaGuard group, only 40 percent experienced a "real" cold with full symptoms, compared to 60 percent of the placebo group. For those who developed a real cold, the time taken to improve was four days compared to eight days for the placebo group (Hoheisel et al., 1997).

Another placebo-controlled trial included 80 subjects with the first signs of a cold and used a dose of 5 ml twice daily for ten days. In this

study, the patients evaluated their illness with a scoring system (Jackson score). There was no significant reduction in subjects obtaining a full cold. However, the length of illness was shorter, six days compared to nine days, and the symptom score was reduced in comparison to the placebo group (Schulten et al., 2001).

In the third study, 108 subjects with a history of colds, but otherwise healthy, were given either Echinacin (4 ml twice daily) or placebo for two months. As a result there was no statistically significant difference in the incidence, duration, or severity of colds between the two groups (Grimm and Muller, 1999).

Exercise-Induced Immunosuppression

A trial with EchinaGuard (Echinacin) studying the prevention of exercise-induced immunosuppression included 40 triathletes who were training for a competition. They were given 40 drops three times daily, or a total of 8 ml per day. Small changes in immune parameters were reported in comparison with the placebo group. None of the treatment group developed colds, which were reported in a quarter of the control groups (Berg et al., 1998). In the opinion of our reviewer, Dr. Richard O'Connor, the trial would have benefited from a larger sample size and more clearly described randomization process and outcome measures.

Vaginal Candidiasis

In a study examining the possible benefit of echinacea on recurrent vaginal candidiasis, all patients were given econazole nitrate cream topically, in addition to oral or injectable Echinacin or placebo. The rate of reoccurrence was 60.5 percent for those treated only topically with econazole and 16.7 percent following oral administration of Echinacin, 30 drops three times daily. The reoccurrence rate was even smaller when Echinacin was given subcutaneously (15 percent), intramuscularly (5 percent), or intravenously (15 percent) (Coeugniet and Kuhnast, 1986). However, according to Dr. O'Connor, the trial was so badly designed and described that the benefit was deemed undetermined.

Echinaforce

Echinaforce reduced cold symptoms in a trial in which the quality was insufficient to evaluate benefit and failed to prevent recurrence of genital herpes in another study.

Cold (Treatment)

The effectiveness of Echinaforce in treatment of the common cold was assessed in a controlled, four-arm trial including Echinaforce (extract of 95 percent *E. purpurea* herb and 5 percent root), Echinaforce seven times concentrate, *E. purpurea* root extract (manufacturer and preparation details not given), and placebo. The doses were two tablets three times daily (Echinaforce 40.7 mg extract, Echinaforce concentrate 289.8 mg extract, *E. purpurea* root extract 177.6 mg) for up to seven days. Both Echinaforce and its concentrate significantly reduced cold symptoms compared to placebo, according to the complaint index compiled by the attending doctor. The effect of the *E. purpurea* root extract was not significantly different from placebo (Brinkeborn, Shah, and Degenring, 1999). Although the trial was well designed in many aspects, the analysis of the data was not optimal, and therefore, the extent of benefit could not be determined.

Genital Herpes

A placebo-controlled trial with 30 participants with herpes type II examined the influence of Echinaforce on the recurrence of genital herpes. Participants were given 800 mg extract twice daily or placebo for six months. As a result, there was no difference in the frequency, severity, or duration of recurrences and pain scores in the two groups (Vonau et al., 2001).

Generic Echinacea

Three generic echinacea root extracts were tested in trials. Two trials addressed the treatment of colds, and the other addressed the prevention of colds.

Flu-Type Infections (Treatment)

Patients treated with an *E. purpurea* root extract equivalent to 900 mg dried root per day had a shorter length of illness and reduced symptom score. The study included 180 subjects with flu-like symptoms who were given extract equivalent to 450 mg root, 900 mg root, or placebo. Those given the lower dose of extract did not differ from placebo in symptom scores (Braunig et al., 1992). Dr. O'Connor concluded that the benefit was undetermined as the study was poorly designed and poorly described.

Cold (Treatment and Prevention)

Another study including 160 subjects with symptoms of an upper respiratory tract infection compared an extract of *E. pallida* root (equivalent to 900 mg root) to placebo. When taken for eight to ten days, the extract significantly reduced the length of illness (cold) and symptom scores in comparison with placebo (Dorn, Knick, and Lewith, 1997).

A good-quality study included 289 healthy subjects who took 1 ml root extracts of either *E. angustifolia* or *E. purpurea* or placebo twice daily, Monday through Friday, for 12 weeks. As a result there was no significant difference between the three groups in the time until the first upper respiratory infection. There was also no difference between the groups in the number, severity, or duration of cold symptoms (Melchart et al., 1998).

Esberitox

Cold (Treatment)

The ability of Esberitox to treat colds was studied in two trials. A well-designed, placebo-controlled study included 238 subjects who visited their family doctor for treatment for a cold. The participants were given Esberitox, three tablets three times daily, or placebo for seven to nine days. Compared to placebo, Esberitox was more effective at reducing cold symptoms (rhinitis score, bronchitis score, clinical global impression score, and general well-being), especially for those who started therapy at an early stage of their cold (Henneicke-von Zepelin et al., 1999).

An earlier study, which was limited by design flaws and poorly reported, included 90 subjects with cold symptoms. The subjects were given either Esberitox, two tablets three times daily, or vitamin C for ten days. After three days, the Esberitox group had a significant reduction in symptoms compared to the control group (Vorberg, 1984).

Echinacea Plus

Cold (Treatment)

Another study, which included 95 participants reporting the earliest symptoms of a cold or flu, compared the effects of a tea formula, Echinacea Plus, to the effects of another tea formula on cold symptoms. The dose was five to six cups of tea on the first day of symptoms, tapered down to one cup per day over the next five days. As a result, there was a significant decrease in intensity and duration of symptoms, as measured through a subjective questionnaire, in the Echinacea Plus group compared with the control group (Lindenmuth and Lindenmuth, 2000).

REVIEWS AND META-ANALYSES OF CLINICAL STUDIES

In a clinical review of 13 blinded, placebo-controlled, randomized studies published between 1981 and 1999, the authors concluded that echinacea may be beneficial as early treatment of upper respiratory infections. They also found that very little evidence supports the prolonged use of echinacea for the prevention of such infections. Eight of nine treatment trials reported generally positive results, and three of the four prevention trials reported a marginal benefit. The methodological quality of the trials was modest. A true meta-analysis was not possible due to differences in products, trial methods, and outcome measurements. Due to the variety of products, specific dose recommendations were also problematic. The authors warned of the possibility of publication bias, as the one unpublished report they reviewed had negative results (Barrett, Vohmann, and Calabrese, 1999).

Another systematic review of 17 trials published between 1961 and 1999, which included some of the same studies reviewed previously, also concluded that the studies supported the use of echinacea to treat, but not prevent, upper respiratory tract infections (Giles et al., 2000). An earlier review examined 26 controlled trials conducted on echinacea alone or in combination with other ingredients. Nineteen trials studied the prevention or treatment of infection, four trials studied the reduction of side effects caused by anticancer therapies, and three trials studied the modulation of various laboratory immune parameters. The authors found the quality of most of the studies to be low, with only eight trials of moderate to good quality. The authors concluded that the available published literature provides evidence that products containing echinacea are efficacious immunomodulators, but insufficient evidence existed to make clear therapeutic recommendations as to which preparation to use and at what dose (Melchart et al., 1994).

ADVERSE REACTIONS OR SIDE EFFECTS

Adverse events reported in the trials were mild and transitory and included tiredness, dizziness, headache, and gastrointestinal symptoms. According to a review of clinical studies, echinacea is considered to be relatively safe for short-term use (Barrett, Vohmann, and Calabrese, 1999).

A benefit/risk assessment of Echinacin included clinical reports of therapy for respiratory and gynecological infections. The authors concluded that for all ages of subjects, ranging from infants to adults, oral administration for up to 12 weeks caused few complaints, the most common being an unpleasant taste. The paper cited an unpublished general practice study including 1,231 patients with respiratory or urinary infections who were treated for four to six weeks with Echinacin lozenges, one lozenge three times daily. The incidence of adverse effects was 5.04 percent, and of those complaints, the only one that can be clearly distinguished from symptoms of the infection was that of unpleasant taste (1.7 percent of the total population) (Parnham, 1996).

A prospective, controlled study was conducted on 206 women who had used echinacea during their pregnancy. This group was matched with a control group of women who did not use echinacea. There

were no statistical differences between the study and control groups in pregnancy outcome or rates of major or minor malformations. Doses of capsules or tablets ranged from 250 to 1000 mg per day, and doses of tinctures ranged from 5 to 30 drops per day. Duration of use was normally five to seven days continuously. The products included preparations of *E. purpurea* and *E. angustifolia,* with only one patient taking *E. pallida.* Although relatively small in size, this study had an 80 percent chance of detecting a 3.5-fold difference in rate of malformations, and thus the overall conclusion is the use of echinacea by pregnant women is not associated with birth defects (Gallo et al., 2000).

An Australian paper explored hypersensitivity reactions to echinacea by subjects known to be atopic (have an inborn tendency to develop immediate allergic reactions, such as asthma, allergic skin reactions, or hay fever). From 1979 to 2000, there were 26 Australian adverse drug reports suggestive of possible immunoglobulin E-mediated hypersensitivity due to exposure to echinacea. In addition, 20 percent of 100 atopic subjects never previously exposed to echinacea had positive skin prick reactions when tested. The authors also examined five cases of patients with allergic reactions possibly due to echinacea. Three of them had positive skin prick reactions and reported symptoms after repeated exposure to echinacea products. The authors speculated that since echinacea is in the daisy family along with known allergens such as ragweed, there may be some cross reactivity. They suggest, therefore, that atopic patients should use echinacea cautiously (Mullins and Heddle, 2002). It must be noted that the details of the echinacea preparation used in the skin prick test, i.e., species, plant part, extract details, concentration, etc., were not given. Thus, the information from this paper is useful only as a vague cautionary note.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

British Herbal Compendium (BHC)
European Scientific Cooperative on Phytotherapy (ESCOP)
German Commission E
World Health Organization (WHO)

Indications

Echinacea angustifolia

The *British Herbal Compendium* lists the uses of *E. angustifolia* root as treating chronic viral and bacterial infections, mild septicaemia, furunculosis, and skin complaints, and it states the following actions: immunostimulant, anti-inflammatory, antibacterial, antiviral, and vulnerary (Bradley, 1992). The German Commission E monograph states that *E. angustifolia* fresh and dried roots as well as aboveground parts, collected at the time of flowering are used to support and promote the body's natural resistant powers, especially in infectious conditions (cold/flu) in the nose and throat, as an alterative in influenza, inflammatory and purulent wounds, abscesses, furuncles, indolent leg ulcers, herpes simplex, inflammation of connective tissue, wounds, headaches, metabolic disturbances, diaphoretic, and as an antiseptic. However, the Commission states that those therapeutic uses cannot be recommended, as they have not been substantiated. The Commission acknowledges that *E. angustifolia* preparations on the market may be incorrectly labeled as *E. pallida,* and it does recommend the use of *E. pallida* root (Blumenthal et al., 1998). The WHO lists the use of *E. angustifolia* root preparations in supportive therapy for colds and infections of the respiratory and urinary tract. The WHO does not distinguish the use of *E. angustifolia* root from that of *E. pallida* root (WHO, 1999). ESCOP has not published a monograph for *E. angustifolia* root but does have one for *E. pallida* root (ESCOP, 1999a).

Echinacea pallida

Echinacea pallida herb (fresh or dried aboveground parts collected at the time of flowering) is used to support and promote the body's natural resistant powers, especially in infectious conditions (cold/flu) in the nose and throat, as an alterative in influenza, inflammatory and purulent wounds, abscesses, furuncles, indolent leg ulcers, herpes simplex, inflammation of connective tissue, wounds, headaches, metabolic disturbances, diaphoretic, and as an antiseptic. The German Commission E monograph states that since the activity of the herb for the conditions listed has not been substantiated, its therapeutic use cannot be recommended (Blumenthal et al., 1998).

The Commission E approves the use of *E. pallida* root, fresh or dried, as supportive therapy for influenza-like infections (Blumenthal et al., 1998). The WHO indicates *E. pallida* root for use as supportive therapy for colds and infections of the respiratory and urinary tract (WHO, 1999). ESCOP indicates the use of *E. pallida* roots as adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract (common cold) (ESCOP, 1999a).

Echinacea purpurea

Echinacea purpurea fresh aboveground parts collected at flowering time are approved for internal use in supportive therapy for colds and chronic infections of the respiratory tract and lower urinary tract. They are also approved for external use for poorly healing wounds and chronic ulcerations (Blumenthal et al., 1998; ESCOP, 1999b; WHO, 1999).

ESCOP states that *E. purpurea* fresh or dried roots are indicated for internal use for adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract (common cold) (ESCOP, 1999c). The Commission E does not approve *E. purpurea* root for use, as its effectiveness is not documented (Blumenthal et al., 1998). The WHO does not mention *E. purpurea* root (WHO, 1999).

Doses

Echinacea angustifolia *Root*

Dried root: 1 g three times daily (Bradley, 1992)
Decoction: 1 g three times daily (Bradley, 1992; WHO, 1999)
Liquid extract: (1:5, 45 percent ethanol), 0.5 to 1 ml three times daily (Bradley, 1992; WHO, 1999)
Tincture: (1:5, 45 percent ethanol), 2 to 5 ml three times daily (Bradley, 1992; WHO, 1999)

Echinacea pallida *Root*

Tincture: (1:5) with 50 percent (v/v) ethanol from native dry extract (50 percent ethanol, 7 to 11:1), corresponding to 900 mg herb (Blumenthal et al., 1998; WHO, 1999; ESCOP, 1999a)

Echinacea purpurea *Herb*

Expressed juice: 6 to 9 ml daily (Blumenthal et al., 1998; ESCOP, 1999b; WHO, 1999)
External: semisolid preparations containing at least 15 percent pressed juice (Blumenthal et al., 1998; ESCOP, 1999b; WHO, 1999)

Echinacea purpurea *Root*

Tincture: (1:5, ethanol 55 percent v/v), 3 × 60 drops equivalent to 3 × 300 mg of crude drug (ESCOP, 1999c)

Treatment Period

The Commission E, ESCOP, and WHO recommend use not to exceed eight successive weeks (Blumenthal et al., 1998; ESCOP, 1999a,b,c; WHO, 1999).

Contraindications

Echinacea angustifolia *Herb and Root*

The Commission E and WHO state that *E. angustifolia* herb and root should not to be used when progressive systemic diseases such as the following exist: tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS, HIV infection, and other autoimmune diseases (Blumenthal et al., 1998; WHO, 1999). The *BHC* lists no known contraindications (Bradley, 1992). The WHO also lists allergy to plants in the daisy family as a contraindication for the external use of the root (WHO, 1999).

Echinacea pallida *Herb and Root*

The Commission E, ESCOP, and WHO list the following contraindications: not to be used when progressive systemic diseases such as the following exist: tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS, HIV infection, and other autoimmune diseases (Blumenthal et al., 1998; ESCOP, 1999a; WHO, 1999). The WHO also lists

allergy to plants in the daisy family as a contraindication for the external use of the root (WHO, 1999).

Echinacea purpurea *Herb*

The Commission E lists the following contraindications for internal consumption: progressive systemic diseases, such as tuberculosis, leukosis, collagenosis, and multiple sclerosis (Blumenthal et al., 1998). ESCOP lists known hypersensitivity to plants of the daisy family (Compositae) as a contraindication. As with all immunostimulants, echinacea is not recommended in progressive systemic disorders or autoimmune diseases such as tuberculosis, leucosis, collagenoses, multiple sclerosis, AIDS, or HIV infection (ESCOP, 1999b).

The Commission E lists no known contraindications for the external use, but both ESCOP and WHO list allergy to plants in the daisy family (Blumenthal et al., 1998; ESCOP, 1999b; WHO, 1999).

Echinacea purpurea *Root*

ESCOP lists known hypersensitivity to plants of the daisy family (Compositae). As with all immunostimulants, echinacea is not recommended in progressive systemic disorders or autoimmune diseases such as tuberculosis, leukosis, collagenoses, multiple sclerosis, AIDS, or HIV infection (ESCOP, 1999c).

Adverse Reactions

ESCOP and the WHO state that in rare cases hypersensitivity reactions, e.g., skin reactions, may occur (ESCOP, 1999a,b,c; WHO, 1999).

Precautions

The WHO suggests that oral administration is not recommended for children, except on the advice of a physician, and states that no reliable studies have been conducted on use during pregnancy or for nursing mothers (WHO, 1999). The Commission E and ESCOP,

however, list no precautions (Blumenthal et al., 1998; ESCOP, 1999a,b,c).

Drug Interactions

The Commission E states that there are no drug interactions (Blumenthal et al., 1998).

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DETAILS ON ECHINACEA PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Echinacea Products

Product Profile: EchinaGuard®

Manufacturer	**Madaus AG, Germany**
U.S. distributor	**Nature's Way Products, Inc.**
Botanical ingredient	**Echinacea aerial parts juice**
Extract name	**EC31J0**
Quantity	No information
Processing	Fresh expressed juice of the stem, leaf, and flower of *Echinacea purpurea.* Raw material is pressed, and then the juice is preserved with ethanol
Standardization	At least 10 µg/ml *p*-coumaric acid
Formulation	Liquid

Recommended dose: Maintenance—take 2.5 ml, three times daily for six to eight weeks followed by a two-week break; children under 12 take one-half adult dosage. Intensive—take 2.5 ml, every two hours for the first 48 hours; then 2.5 ml, three times daily for the next eight to nine days. Best if added to water or juice.

DSHEA structure/function: Clinically proven to support the immune system.

Cautions: Not recommended for individuals with autoimmune conditions or allergic to flowers of the daisy family.

Other ingredients: Alcohol, water.

Comments: EchinaGuard is also available in chewable tablets and capsules. Sold as Echinacin® and Echinagard® in Europe.

Source(s) of information: Product label (© Nature's Way Products, Inc., 1999); Grimm and Muller, 1999.

Clinical Study: Echinagard®

Extract name	EC31J0
Manufacturer	Madaus AG, Germany
Indication	**Common cold; upper respiratory tract infection** (treatment)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Hoheisel O, Sandber M, Bertram S, Bulitta M, Schafer M (1997). Echinagard treatment shortens the course of the common cold: A double-blind placebo-controlled clinical trial. *European Journal of Clinical Research* 9: 261-268.

Trial design
Parallel. Subjects were recruited at first sign of a cold.

Study duration	Up to 10 days
Dose	20 drops every 2 hours for the first day and thereafter 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind

Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	120
No. of subjects completed	118
Sex	Male and female
Age	Mean: 36 years

Inclusion criteria
Employees of a furniture-making factory with a history of recurrent upper respiratory infection. Patients had suffered from at least three respiratory infections within the previous six months and presented with justifiable initial signs of acute respiratory infection.

Exclusion criteria
Subjects who reported acute respiratory infections the week before the start of the study, pregnant or breast-feeding women, subjects with systemic immunological diseases and those on immunotherapy, or with a history of hypersensitivity to plants of the Asteraceae [Compositae] family.

End points
Patients recorded subjective symptoms daily on a diary card and answered a questionnaire at the end of the treatment period. The primary variables were the number of patients who reported that they had had a "real" cold and the time to improvement.

Results
An intention-to-treat analysis revealed that 24/60 patients (40.0 percent) in the Echinagard group, and 36/60 (60.0 percent) in the placebo group, experienced a "real" cold (fully expressed disease). The mean treatment effect was 20 percent (95 percent CI 2.5-37.5 percent, $p = 0.044$). The time taken to improvement was significantly shorter ($p < 0.0001$) in the Echinagard group (median: zero days) than in the placebo group (median: five days). In the subgroup of patients with a "real" cold, the median time taken to improvement was four days (Echinagard, $n = 24$) and eight days (placebo, $n = 36$), respectively. More patients taking Echinagard (31.7 percent) than placebo (18.3 percent) stopped treatment because of improvement. The time taken to stop treatment as a result of improvement in the subgroup of patients with a "real" cold was shorter with Echinagard (median: six days) than with placebo (median: ten days).

Side effects
None were reported.

Authors' comments
The findings of this study show that daily treatment with Echinagard, from the first signs of an upper respiratory infection, on the one hand inhibits the full expression of the disease and on the other, when symptoms have developed fully, leads to more rapid recovery than in patients treated with placebo.

Reviewer's comments
Well-designed and well-conducted study except for failure to obtain informed consent and no mention of institutional review board (IRB) approval. Results suggest that the duration of symptoms was shorter in the patients receiving echinacea versus placebo but that symptom severity was not different. However, 20 drops of Echinagard every two hours in the first day is cumbersome, and patient adherence to such a regimen is doubtful. (5, 6)

Clinical Study: Echinacin®

Extract name	EC31J0
Manufacturer	Madaus AG, Germany
Indication	**Common cold; upper respiratory tract infection** (treatment)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Schulten B, Bulitta M, Ballering-Brühl B, Köster U, Schäfer M (2001). Efficacy of *Echinacea purpurea* in patients with a common cold. *Arzneimittel-Forschung/Drug Research* 51 (7): 563-568.

Trial design
Parallel. Subjects were recruited at first signs of a cold.

Study duration	10 days
Dose	5 ml 2 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No

Site description	Single center
No. of subjects enrolled	80
No. of subjects completed	77
Sex	Male and female
Age	Mean: 38.8 years

Inclusion criteria
Employees of Madaus AG with first signs of an infection of the upper respiratory tract with the subjective sensation of the following symptoms: sneezing, rhinorrhea, congestion of the nose, sore throat, cough, headache, malaise, and chilliness during the previous 24 hours.

Exclusion criteria
Acute respiratory tract infection during the week preceding the trial, allergy to composites, progressive systemic diseases (e.g., tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS, HIV infections, or other autoimmune diseases), or pregnancy and lactation. Therapy with immunosuppressants in the week prior to the trial and during participation in the trial, and therapy with immunostimulants (herbal immunostimulants, cytokines, thymus fractions), zinc, or antibiotics during two weeks before the commencement of the trial.

End points
Efficacy was measured by the number of days of illness and the number of patients who had developed a complete picture of a common cold, the duration of the illness, and the area under the curve (AUC) standardized to baseline with regard to the modified Jackson score (the cumulative unweighted sum of eight subjective symptom ratings—documented daily by the patients). A "complete picture of a cold" was a cumulative Jackson score of at least 5, rhinorrhea for three consecutive days, and subjective sensation of a cold. The secondary end points included the patients' subjective assessment of efficacy at the final examination; the AUC of each individual symptom; and the proportion of patients who developed a complete picture of the disease during days one to five.

Results
The median length of illness for the group taking echinacea was 6.0 days compared to 9.0 days for the placebo group; this difference was statistically significant ($p = 0.0112$). Fewer patients taking echinacea (85.4 percent) than placebo (97.4 percent) had a complete picture of the common cold, but this difference was not significant. More patients taking echinacea (61.0 percent) subjectively assessed that their cold was "shorter than usual" than placebo (28.2 percent) ($p = 0.007$). The echinacea group had a smaller AUC for symptom severity than the placebo patients ($p = 0.008$). There were also

statistical differences (favoring the echinacea group) for the following AUCs of single symptoms: sore throat; rhinorrhea; and congestion of the nose.

Side effects
No serious adverse events (AEs) occurred. Six patients in each group (echinacea and placebo) experienced similar AEs. The most frequent AEs were gastrointestinal disorders and respiratory system disorders (may be reactions related to the basic illness).

Authors' comments
In the study of Hoheisel and colleagues (1997) the patients assessed subjectively the presence or a "real" cold, whereas in the current study, the more objective measurement of the Jackson score was used. This study did not evaluate more diagnostic, possibly objectifiable, measures of cold severity, such as tissue counts or nasal mucus weight, because of the impracticability of obtaining these measures in the population of co-workers. The results of this study showed that the time to resolution of all symptoms and the duration of the disease were significantly shorter and less severe in the active treatment group.

Reviewer's comments
Other than the small sample sizes (40 subjects in each group, this is a well-designed, -conducted, and -reported trial. (5, 5)

Clinical Study: Echinacin®

Extract name	EC31J0
Manufacturer	Madaus AG, Germany
Indication	**Common cold; upper respiratory tract infection** (prevention/treatment)
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Grimm W, Muller HH (1999). A randomized controlled trial of the effect of fluid extract of *Echinacea purpurea* on the incidence and severity of colds and respiratory infections. *The American Journal of Medicine* 106 (2): 138-143. (Also published in Schoneberger D [1992]. *Forum Immunologie* 8: 2-12.)

Trial design
Parallel. Subjects with a history of colds received either echinacea or placebo.

Study duration	2 months
Dose	4 ml extract twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	109
No. of subjects completed	108
Sex	Male and female
Age	23-59 years

Inclusion criteria
Reported more than three common colds or respiratory infections in the preceding year and at least 12 years old.

Exclusion criteria
Acute infections of any kind within one week of recruitment; pregnancy or nursing; use of immunostimulating drugs within four weeks before study entry; known allergy against coneflowers; severe underlying disease of immunosuppression; inability to give informed consent; or unreliability for follow-up as judged by the investigator.

End points
Routine assessments were at baseline and after four and eight weeks. The primary efficacy parameters were incidence and severity of colds and respiratory infections. Patients were asked to come in for unscheduled visits if they experienced symptoms. The severity of each incidence was graded by investigators.

Results
There were no significant differences in the incidence, duration, or severity of colds and respiratory infection in the two groups. During the eight weeks, 35 of the 54 patients in the echinacea group and 40 of 54 patients in the placebo group had at least one cold or respiratory infection [RR = 0.88; 95 percent CI (0.60, 1.22)]. The mean number of colds and respiratory infections per patient was 0.78 in the echinacea group, and 0.93 in the placebo group [difference = 0.15; 95 percent CI (–0.12, 0.41), $p = 0.33$]. Median duration of colds and respiratory infections was 4.5 days in the echinacea group and 6.5 days in the placebo group (95 percent CI –1, +3 days; $p = 0.45$). There were

no significant differences between treatment groups in the number of infections in each category of severity ($p = 0.15$).

Side effects
The adverse events were transient and mild, and included tiredness, dizziness, headache, and gastrointestinal symptoms. They were observed in 11 patients (20 percent) of the echinacea group and in seven patients (13 percent) of the placebo group ($p = 0.44$).

Authors' comments
Eight weeks of follow-up treatment with fluid extract of *Echinacea purpurea* did not decrease the incidence or severity of colds and respiratory infections as compared to placebo. (Study was reevaluated by Grimm and Muller. Previous publication by Schoneberger reported positive results.)

Reviewer's comments
This well-designed trial assessed the prevention of upper respiratory infections and symptom severity. Active treatment was no different than placebo. The sample size was relatively small. (5, 5)

Clinical Study: Echinacin®

Extract name	EC31
Manufacturer	Madaus AG, Germany
Indication	**Exercise-induced immunosuppression**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Berg A, Northoff H, Konig D, Weinstock C, Grathwohl D, Parnham MJ, Stuhlfauth I, Keul J (1998). Influence of Echinacin (EC31) treatment on the exercise-induced immune response in athletes. *Journal of Clinical Research* 1: 367-380.

Trial design
Parallel. Three-arm double-dummy: Echinacin, Biomagnesin (12 tablets each containing the equivalent of 43 mg Mg^{++}), or placebo.

Study duration	1 month
Dose	40 drops 3 times daily (8 ml total)
Route of administration	Oral
Randomized	Yes

Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Biomagnesin
Site description	Not described
No. of subjects enrolled	42
No. of subjects completed	40
Sex	Male
Age	18-47 years (mean: 27.5)

Inclusion criteria
Triathletes who were undergoing regular training for triathlon sprint competition.

Exclusion criteria
Infection during the two weeks before the start of the study.

End points
Fluorescence activated flow cytometry analysis of blood cell populations, serum and urine levels of interleukin 6 (IL-6), and soluble interleukin 2 receptor (sIL-2R) together with clinical chemical and hematological variables were determined at baseline, after 28 days of treatment, and both 1 and 20 hr after the competition (days 29 and 30).

Results
Pretreatment with Echinacin produced slight changes in total peripheral (CD3+) T-lymphocytes, natural killer cells, and CD8+ lymphocyte counts which remained within the range of baseline variation. In comparison to the placebo group, Echinacin markedly decreased sIL-2R in urine before the competition and enhanced the exercise-induced decrease in serum sIL-2R. It further enhanced the exercise-induced increases in urine IL-6 and serum cortisol. None of the Echinacin-treated athletes developed upper respiratory tract infections, which were reported by 3/13 and 4/13 subjects treated with magnesium and placebo, respectively.

Side effects
None reported for the Echinacin group.

Authors' comments
On the basis of these results, it is likely that prophylactic treatment with Echinacin counteracts the immunosuppressive effects of exhaustive exercise and reduces the risk of upper respiratory infections in athletes.

Reviewer's comments
This study is a classic example of overanalysis and overinterpretation of small numbers. However, the study was IRB approved and the inclusion/exclusion criteria appropriate. (3, 3)

Clinical Study: Echinacin®

Extract name	EC31J0
Manufacturer	Madaus AG, Germany
Indication	**Recurrent vaginal candidiasis** (prevention)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Coeugniet E, Kuhnast R (1986). Recurrent candidiasis: Adjuvant immunotherapy with different formulations of Echinacin. *Therapiewoche* 36: 3352-3358.

Trial design
Parallel. All patients were given econazole nitrate cream, a topical treatment, for six days. After this, patients were allocated to groups for additional treatment with one of four forms of Echinacin or placebo. The forms of Echinacin were intravenous (IV), subcutaneous (SC) or intramuscular (IM) injection, or oral. Milder cases were put into the oral group.

Study duration	10 weeks
Dose	Ampoules (SC, IM, IV) 0.5 ml increased to 2 ml twice weekly or liquid 30 drops 3 times daily
Route of administration	Oral, injection, intravenous
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	203
No. of subjects completed	203
Sex	Female
Age	16-65 years

Inclusion criteria
Patients with recurrent candidal colpitis and/or vulvitis confirmed through culturing. The infection was considered recurrent if the inflammation reappeared at least three times after the use of not less than two different antifungal agents or if symptoms recurred within four weeks of the withdrawal of topical treatment.

Exclusion criteria
Not mentioned.

End points
Cell-mediated immunity was assessed in a cutaneous antigen reaction test (Merieux multitest) before the start of treatment and repeated in the second and tenth weeks after initiation of Echinacin treatment. Recurrences of infection within six months of topical treatment were noted.

Results
The incidence of recurrences in patients treated only locally with econazole nitrate (control group) was very high (60.5 percent). This rate was markedly reduced, however, in patients receiving additional nonspecific immunostimulant therapy with Echinacin according to the form of treatment (SC 15 percent, IM 5 percent, IV 15 percent, and oral 16.7 percent). The baseline Merieux skin reactions were small and increased significantly following two weeks of injections or ten weeks of oral treatment ($p < 0.05$).

Side effects
None for oral treatment, both local and systemic with injections.

Authors' comments
The current trial showed that the basic therapeutic principle of immunostimulation with Echinacin represents an important addition to the therapeutic measures available, especially for problem patients whose immunocompetence is likely to be impaired.

Reviewer's comments
This study was not well designed or described. The study was neither randomized nor blinded, and the authors gave no description of statistical methods used. Replication or reanalysis might not be possible due to poor description. IRB review was not obtained. (Translation reviewed) (0, 3)

Product Profile: Echinaforce®

Manufacturer	**Bioforce AG, Switzerland**
U.S. distributor	**Bioforce USA**

Botanical ingredient	**Echinacea aerial parts and root extract**
Extract name	None given
Quantity	6 mg herb and 0.3 mg root (equivalent to 269 mg of fresh material)
Processing	*Echinacea purpurea* aerial parts (95%) and root (5%); plant to extract ratio 9:1, 65% ethanol
Standardization	At least 3 mg cichoric acid and 8 mg alkylamides per 100 g Echinaforce®
Formulation	Tablet

Recommended dose: Adults take one to two tablets three to five times per day. Allow to dissolve slowly in the mouth.

DSHEA structure/function: Supports healthy immune system, natural winter resistance during winter season.

Other ingredients: Lactose, potato starch, magnesium stearate.

Comments: Also available as a liquid.

Source(s) of information: Product label; information supplied by distributor.

Clinical Study: Echinaforce®

Extract name	None given
Manufacturer	Bioforce AG, Switzerland
Indication	**Common cold** (treatment)
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Brinkeborn RM, Shah DV, Degenring FH (1999). Echinaforce preparations and other echinacea fresh plant preparations in the treatment of the common cold. *Phytomedicine* 6 (1): 1-5.

Trial design
Parallel. Patients received one of four treatments to be taken immediately after the onset of the first symptoms of the common cold. The treatments were Echinaforce (6.78 mg *E. purpurea* extract 95 percent herb and 5 percent root), Echinaforce 7 times concentrate (48.3 mg), *E. purpurea* root extract (29.6 mg), or placebo. Patients were directed to take their treatment until they felt healthy but not longer than seven days.

Study duration	Up to 7 days
Dose	2 tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Other echinacea preparation
Site description	Single center
No. of subjects enrolled	559
No. of subjects completed	246
Sex	Male and female
Age	26-58 years

Inclusion criteria
Older than 18 years and prone to common cold, otherwise healthy.

Exclusion criteria
Participation in another clinical trial during the past four weeks, suffering from chronic diseases which influence the test variables (diabetes mellitus, bronchial asthma, allergy, or autoimmune deficiency), suffering from serious non-related illnesses, especially progressive systemic diseases, and/or taking other medicines which may affect the immune system, such as immunostimulants and antibiotics, or may influence the symptoms, such as nose-drops or anticoughs.

End points
Subjects reported to investigators when they experienced the first symptoms of the common cold. They recorded the progress of their cold daily in a diary and reported to investigators either when they felt healthy or not longer than seven days after beginning treatment. Symptoms were assessed by the investigator at these visits. The primary end point was the relative reduction of the complaint index according to the doctor's record. Secondary end points were the relative reduction of the complaint index according to the patient's diary and assessment of tolerance.

Results
According to the doctor's records, the relative reduction in the complaint index for the Echinaforce concentrate and Echinaforce groups were significantly higher than for the placebo group ($p = 0.003$ and $p = 0.020$, respectively). Results with the *E. purpurea* root extract were not significantly different

from placebo. Similar results were obtained from analysis of the patient's diary. According to the doctors' as well as the patients' judgment, Echinaforce concentrate was more effective than placebo ($p = 0.001$ doctors and $p = 0.002$ patients). The same was true for Echinaforce ($p = 0.035$ doctors and $p = 0.022$ patients). The efficacy of the root extract was not judged as significantly different from placebo by either doctors or patients.

Side effects
The frequency of adverse events was not significantly higher in the echinacea groups than in the placebo group. They were reported in 33 of 246 cases (13 percent), and the majority involved the gastrointestinal tract.

Authors' comments
In summary, Echinaforce and its concentrated preparation represent low-risk and effective alternatives to standard medicine for symptomatic treatment of the common cold.

Reviewer's comments
Overall a well-designed study. However, the use of per-protocol results is not valid since it includes only patients completing the trial and in essence results in "cherry picking" the data. The authors also include the intent-to-treat analysis. They used a one-tailed U test but should have used a repeated measure analysis since the sum score was a composite of 12 different symptoms. (4, 6)

Clinical Study: Echinaforce®

Extract name	None given
Manufacturer	Bioforce AG, Switzerland
Indication	**Genital herpes**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Vonau B, Chard S, Mandalia S, Wilkinson D, Barton SE (2001). Does the extract of the plant *Echinacea purpurea* influence the clinical course of recurrent genital herpes? *International Journal of STD and AIDS* 12 (3): 154-158.

Trial design
Crossover. Patients received six months each of placebo and echinacea extract.

Study duration	6 months
Dose	800 mg extract twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	49
No. of subjects completed	30
Sex	Male and female
Age	22-72 years (mean: 36.5)

Inclusion criteria

Subjects with culture-proven genital herpes or serology-proven HSV type 2 antibody positivity, no suppressive acyclovir or similar drugs within 14 days of study entry, a minimum of four recurrences in the previous 12 months or prior to suppressive acyclovir.

Exclusion criteria

Subjects who were pregnant or not using effective contraception during the study period, immunosuppression or severe cardiovascular disease, liver disease, renal disease, inability to communicate sufficiently or comply with the study protocol, or a known lactose intolerance.

End points

At baseline, patients had a physical examination and the following assessments and measurements were taken: visual analog scales (VAS) recorded the average pain, impairment of the quality of life, and the impairment of sex life experience during a recurrence; psychological assessment included a Hospital Anxiety and Depression (HAD) scale and an Eysenck Personality Questionnaire (EPQ); and laboratory parameters were taken, including blood count, urea and electrolytes, liver function tests, and HSV serology. During study, patients were evaluated monthly and within 72 hours of the start of a recurrence. The main end point was the frequency, severity, and duration of each recurrence and a pain score using a VAS. Patients also kept a daily diary of symptoms, compliance, and adverse events. At the crossover and at the final visit, biochemistry measurements and the HAD scale were repeated.

Results
There were no statistically significant differences between the echinacea treatment and the placebo for any of the outcomes measured.

Side effects
One patient withdrew due to severe diarrhea while taking the active therapy (may be due to lactose intolerance). Four patients taking echinacea and two on placebo experienced nausea.

Authors' comments
In conclusion, no statistically significant benefit of the plant and root extract of *Echinacea purpurea* (Echinaforce) was shown in the treatment of frequently recurrent genital herpes. Given that there are safe and efficacious alternatives, the value of further studies into its benefits for this indication seems unjustified.

Reviewer's comments
This is a well-designed trial in culture-proven patients. My only criticism is the relatively small sample size. (5, 5)

Product Profile: *Echinacea purpurea* (Generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Echinacea purpurea root extract**
Extract name	None given
Quantity	450 mg per 90 drops
Processing	Plant to extract ratio 1:5, 55% ethanol
Standardization	No information
Formulation	Liquid

Source(s) of information: Braunig, Dorn, and Knick, 1992.

Clinical Study: *Echinacea purpurea* (Generic)

Extract name	None given
Manufacturer	None

Indication	**Flu-type upper respiratory tract infection** (treatment)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Braunig B, Dorn M, Knick E (1992). *Echinacea purpurea* radix for strengthening the immune response in flu-like infections. *Zeitschrift fur Phytotherapie* 13 (1): 7-13.

Trial design
Parallel. Three treatment groups: two doses *E. purpurea* root extract and placebo.

Study duration	8-10 days
Dose	90 drops extract (2 droppersful, 450 mg root) or 180 drops extract (4 droppersful, 900 mg root) daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	General practice
No. of subjects enrolled	180
No. of subjects completed	180
Sex	Male and female
Age	18-60 years

Inclusion criteria
Patients between 18 and 60 years old with flu-type infections.

Exclusion criteria
Patients who had been ill for more than three days from a flu-like infection; not readily cooperative; with additional infections, for instance, of the urological tract; those under treatment with antihistamines, antibiotics, and other relevant medications that influenced the disease profile; those who suffered other autoimmune diseases or immunologically relevant chronic diseases; patients who showed secondary infections such as bronchitis, pneumonia, pleuritis, and septic infections; bacterial illnesses such as pneumoconiosis and fungal infections; pussy angina tonsilleris; a sublingually measured fever of more than 40.5°C; or other serious illnesses.

End points
Subjects were assessed at the beginning of treatment, after three to four days, and after eight to ten days. The target parameter was length of illness and symptom score. The control parameters were clinically objective reports (inflamed nose, swelling of the lymph glands, coated tongue, rhoncus) and flu symptoms reported by the patients (sense of weakness/exhaustion, chills/perspiration, burning eyes, nasal congestion or secretions, sore throat, ear pain, limb or muscle pain, headaches, and cough). Secondary parameters were occurrence of new symptoms, severity of illness (score), comparison of blood workups, and red blood cell sedimentation rate.

Results
Patients treated with 450 mg echinacea extract did not differ significantly from patients treated with placebo in clinically objective scores. However, patients treated with the higher dose of echinacea extract (900 mg) differed significantly from the placebo group for clinically objective scores, and for the patient-reported symptoms, after three to four days. In addition, there was a significant difference in clinical report score between days 3 and 4 and days 8 and 10.

Side effects
None mentioned.

Authors' comments
The therapeutic effectiveness of 900 mg echinacea for patients with flu-type symptoms was good to very good. The therapeutic effect of taking 450 mg of echinacea extract was satisfactory to poor, as was the placebo.

Reviewer's comments
This study was poorly designed and described. The primary end points were duration of illness, symptoms, and results of physical exam; the data regarding duration of illness could not be found in the report. Also, the study title is misleading. No tests of immune function were conducted. There may be improvement at the higher dose, but the SDs overlap and statistics are not adequately described. No adverse events were described, so it is difficult to know if data about adverse events were recorded. (Translation reviewed) (0, 3)

Product Profile: *Echinacea pallida* (Generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Echinacea root extract**
Extract name	None given

Quantity	No information
Processing	Aqueous alcoholic extract
Standardization	No information
Formulation	Liquid

Source(s) of information: Dorn, Knick, and Lewith, 1997.

Clinical Study: *Echinacea pallida* (Generic)

Extract name	None given
Manufacturer	None
Indication	**Cold; upper respiratory tract infection** (treatment)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference

Dorn M, Knick E, Lewith G (1997). Placebo-controlled, double-blind study of *Echinacea pallidae* radix in upper respiratory tract infections. *Complementary Therapies in Medicine* 3 (1): 40-42.

Trial design

Parallel.

Study duration	8 to 10 days
Dose	90 drops extract (900 mg root per day)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	160
No. of subjects completed	Not given
Sex	Male and female
Age	Not given

Inclusion criteria
Subjects over 18 years old with an upper respiratory tract infection (infection could be either viral, indicated by a raised differential lymphocyte count, or bacterial, indicated by a raised differential neutrophil count), and with a symptom score of >15 at entry. Patients should not have been sick for more than three days prior to the start of the study. A record of the frequency of infection over the past three years was noted at trial entry.

Exclusion criteria
Subjects with infections involving other organs, being treated with other drugs that might interact with a herbal preparation, suffering from fungal infections or pneumonia, or had other significant diseases such as multiple sclerosis.

End points
Symptoms were recorded at entry into the trial, after day three or four, and again on day eight or ten of the trial. The main end points were the length of the illness and the resolution of cold and cough symptoms.

Results
Compared to placebo, the length of the illness was reduced from 13 days to 9.8 days in putative bacterial infections or 9.1 in putative viral infections ($p < 0.0001$). The lymphocytosis and differentia neutrophil counts also fell at a far faster rate in the treatment group compared to the placebo group. Overall symptom scores and whole clinical scores were significantly improved for the treatment group compared to placebo ($p < 0.0004$ and $p < 0.001$, respectively).

Side effects
None mentioned.

Authors' comments
From these results it is quite clear that *Echinacea pallidae* radix shortens the course in URTI as compared with placebo. The specific clinical signs and symptoms improved and in fact disappeared far more swiftly with real treatment than with placebo treatment. This was correlated with appropriate changes in the lymphocyte and neutrophil count, but past history of recurrent infections had no influence on outcome.

Reviewer's comments
The authors use a lymphocyte versus neutrophil count to allocate causation of the URI as viral or bacterial. I am not sure of the use of this technique or its validity. The authors state that counts declined at a faster rate in the treatment group but do not show data. Also, the symptoms of a URI listed as "weakness" and "pain in arms and legs" are not the usual symptoms of a URI. (4, 2)

Product Profile: *Echinacea angustifolia/E. purpurea* (Generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Echinacea root extract**
Extract name	None given
Quantity	No information
Processing	Plant to extract ratio 1:11, 30% alcohol. Extracts of either *Echinacea angustifolia* or *Echinacea purpurea*
Standardization	No information
Formulation	Liquid

Source(s) of information: Melchart et al., 1998.

Clinical Study: *Echinacea angustifolia/E. purpurea* (Generic)

Extract name	None given
Manufacturer	None
Indication	**Cold; Upper respiratory tract infection (prevention)**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Melchart D, Walther E, Linde K, Brandmaier R, Lersch C (1998). Echinacea root extracts for the prevention of upper respiratory tract infections: A double-blind, placebo-controlled randomized trial. *Archives of Family Medicine* 7 (6): 541-545.

Trial design
Parallel. Three-arm study: ethanolic extracts of *Echinacea purpurea* roots, *E. angustifolia* roots, or placebo. Healthy participants took trial preparations from Monday to Friday for 12 weeks.

Study duration	3 months
Dose	50 drops (1ml) twice daily (of either preparation)

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	4 military institutions and 1 industrial plant
No. of subjects enrolled	302
No. of subjects completed	289
Sex	Male and female
Age	18-65 years

Inclusion criteria
Persons free of acute illness at time of enrollment.

Exclusion criteria
Acute respiratory tract infection or other infections within the past seven days; serious progressive disease such as tuberculosis, multiple sclerosis, or AIDS; systemic intake of corticosteroids, antibiotics, or immunostimulants in the previous two weeks; allergy to the Asteracea [Compositae] family; and pregnancy.

End points
Main outcome measure was time until first upper respiratory tract infection. Secondary outcome measures were the number of participants with at least one infection, global assessment, and adverse effects.

Results
There was no significant difference between the three groups in the time until first upper respiratory infection. In the *E. angustifolia* group 32 percent had at least one upper respiratory infection, compared with 29 percent in *E. purpurea* group and 37 percent in placebo group. No significant difference between groups in number, severity, or duration of upper respiratory tract infections and quality of life. More subjects in the treatment groups believed they had benefited from taking the medication than those in the placebo group ($p = 0.04$).

Side effects
No adverse effects that were serious or required therapeutic action.

Authors' comments
In this study a prophylactic effect of the investigated echinacea extracts could not be seen. However, based upon the results of this and two other studies, one could speculate that there might be an effect of echinacea products in the order of magnitude of 10 to 20 percent relative risk. Future studies with much larger sample sizes would be needed to prove this effect.

Reviewer's comments
A well-designed, well-described study with clear primary end points. (5, 6)

Product Profile: Esberitox®

Manufacturer	**Schaper & Brümmer GmbH & Co. KG, Germany**
U.S. distributor	**Enzymatic Therapy®**
Botanical ingredient	**White cedar leaf extract**
Extract name	None given
Quantity	2 mg
Processing	Aqueous ethanolic extract
Standardization	No information
Botanical ingredient	**Echinacea root extract**
Extract name	None given
Quantity	7.5 mg
Processing	*Echinacea purpurea* and *Echinacea pallida* plant to extract ratio 1:1, aqueous ethanolic extract
Standardization	No information
Botanical ingredient	**Wild indigo root extract**
Extract name	None given
Quantity	10 mg
Processing	Aqueous ethanolic extract
Standardization	No information
Formulation	Tablet (chewable)

Recommended dose: Adults and children over 12 years, three tablets three times per day; ages 8 to 12, two tablets three times per day; age seven and under, one tablet three times per day.

DSHEA structure/function: Dietary supplement to nutritionally support and stimulate the immune system; unique combination of herbs to promote the body's resistive functions.

Cautions: Not recommended for individuals with autoimmune diseases, HIV infection, or who are allergic to echinacea.

Other ingredients: Lactose, sugar, macrogol, ascorbic acid, magnesium stearate.

Source(s) of information: Product package (Enzymatic Therapy ©1999); information supplied by distributor; Henneicke-von Zepelin et al., 1999.

Clinical Study: Esberitox® N

Extract name	None given
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany
Indication	**Common cold** (treatment)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference:
Henneicke-von Zepelin HH, Hentschel C, Schnitker J, Kohnen R, Kohler G, Wustenberg P (1999). Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (acute viral respiratory tract infection): Results of a randomized, double blind, placebo controlled multicentre study. *Current Medical Research and Opinion* 15 (3): 214-227.

Trial design
Parallel.

Study duration	7 to 9 days
Dose	3 tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	15 doctors' practices
No. of subjects enrolled	263
No. of subjects completed	238

Sex	Male and female
Age	18-70 years

Inclusion criteria
Patients were included who were attending their family doctor for an acute common cold.

Exclusion criteria
Acute influenza, the actual cold lasting longer than three days; chronic diseases of the respiratory tract; a fever resulting in a temperature greater than 38.5°C; more than one respiratory tract infection lasting longer than three weeks during the previous year; bacterial respiratory tract infection; progressive systemic diseases; organ transplantation; known impairment of resorption; intake of antibiotics during the study; immunosuppressing, immunostimulating, or immunomodulating medication during four weeks before baseline; allergy tests or vaccination during the study; cytostatic therapy during six months before baseline; severe internal diseases; known clinically relevant abnormalities in laboratory values; pregnancy or lactation; inability to understand the consequences of participation in the study; participation in any other study during this clinical trial of 12 weeks before baseline; and previous participation in this study.

End points
Patients daily documented the intensity of 18 cold symptoms, as well as the cold overall, using a ten-point scale, and estimated their general well-being using the Welzel-Kohnen color scale. In addition, the severity of illness was assessed by the physician using the clinical global impression item 1 (CGI-1) on days 4 and 8. The main outcome measure was a total efficacy measure gauged from the primary end points (rhinitis score, bronchitis score, CGI-1, and general well-being).

Results
Esberitox was effective compared to placebo according to the primary efficacy score ($p < 0.05$). Effect size was 20.6 percent for the "intention to treat" population (ITT) and 23.1 percent for subjects who followed protocol (VC). For general well-being, the effect size was 33.9 percent (VC). The patients who suffered from at least moderate symptoms at baseline showed response rates of 55.3 percent in the Esberitox group and 27.3 percent in the placebo group ($p = 0.017$). In the subgroup of patients who started therapy at an early phase of their cold, the efficacy of the herbal remedy was most prominent ($p = 0.014$ primary efficacy parameter). The therapeutic benefit of Esberitox was observed on day 2, reached significance ($p < 0.05$) on day 4, and continued until the end of the treatment. Improvement was observed three days earlier in the Esberitox group than in the placebo group.

Side effects
Serious adverse events did not occur.

Authors' comments
This study shows that the remedy is effective and safe and that therapeutic benefits consist of a rapid onset of improvement of cold symptoms, particularly if patients are able to start the remedy at the onset of initial symptoms.

Reviewer's comments
Well-designed study. Using the intent-to-treat analysis, the active compound was better than placebo, but only marginally so ($p = 0.0497$). Informed consent was obtained. This is one of the few echinacea studies that actually collected adverse event data and reported them (no significant adverse events occurred). (5, 6)

Clinical Study: Esberitox™

Extract name	None given
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany
Indication	**Cold; upper respiratory tract infection** (treatment)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Vorberg G (1984). For colds, stimulate the nonspecific immune system; a double-blind study shows: The proven phytotherapeutic Esberitox shortens the duration of symptoms. *Arztliche Praxis* 36 (6): 97-98.

Trial design
Parallel. The control was vitamin C which was called a placebo in the write-up. There was no mention of the quantity of vitamin C.

Study duration	10 days
Dose	2 tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No

Placebo	No
Drug comparison	Yes
Drug name	Vitamin C
Site description	Not described
No. of subjects enrolled	100
No. of subjects completed	90
Sex	Male and female
Age	18-60 years

Inclusion criteria
Subjects with acute infections of the upper respiratory tract.

Exclusion criteria
Patients needing primary antibiotic treatment and patients with true viral flu (influenza).

End points
Subjects were assessed prior to the study and after days 3 and 10 of treatment. The parameters used for assessing therapy were subjective and objective pathological symptoms of the cold infection.

Results
After three days, patients taking Esberitox had a significant reduction in fatigue, tiredness, reduced performance, runny nose, sore throat, headache, and subfebrile temperatures compared to placebo ($p < 0.001$). Several symptoms such as purulent secretion, furring, and lymph node swelling remained unaffected by both forms of therapy.

Side effects
None occurred.

Author's comments
The results show a significant superiority of Esberitox over vitamin C in colds. The immunostimulating action of Esberitox leads to an improvement in the endogenous immune response which is relevant to combating an infection in its early phase. The therapeutic use of the drug considerably shortens the duration of illness in most cases and simultaneously contributes to prophylaxis against recurrence.

Reviewer's comments
This study was limited by many flaws. Blinding was inappropriate, as the placebo and active were distinguishable. The statistical analysis is poorly reported: no numbers are supplied; and there are just graphs without standard deviation data. No IRB review was obtained. The study probably would not

allow for replication. Repeated measures would demand a different statistical approach. (1, 0)

Product Profile: Echinacea Plus®

Manufacturer	**Traditional Medicinals, Inc.**
U.S. distributor	**Traditional Medicinals, Inc.**
Formula botanicals	***Echinacea purpurea* (herb)** ***E. angustifolia* (herb)** **Water-soluble dry extract of *E. purpurea* (root; ratio 6:1),** **lemongrass (leaf), spearmint (leaf)**
Quantity	Equivalent
Processing	See Formula botanicals
Standardization	Minimum 20 mg phenolic compounds (cichoric acid, chlorogenic acid, echinacoside) per one tea bag, as determined by HPLC
Formulation	Tea bag

Recommended dose: Three cups or more daily as needed. Pour 8 oz of boiling water over one tea bag and steep, covered, for 10 to 15 minutes.

DSHEA structure/function: Supports the immune system. Induces interferon production if needed by the body.

Cautions: The product should not be used during pregnancy and lactation without medical advice from a practitioner trained in medical herbalism.

Source(s) of information: Product package (Traditional Medicinals ©1999); Echinacea Plus® Herbal Dietary Supplement Technical Paper (©1998).

Clinical Study: Echinacea Plus®

Extract name	None given
Manufacturer	Traditional Medicinals, Inc.
Indication	**Common cold/flu** (treatment)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Lindenmuth GF, Lindenmuth EB (2000). The efficacy of echinacea compound herbal tea preparation on the severity and duration of upper respiratory and flu symptoms: A randomized double-blind placebo-controlled study. *The Journal of Alternative and Complementary Medicine* 6 (4): 327-334.

Trial design
Parallel. The control for Echinacea Plus tea was another tea called Eater's Digest.

Study duration	6 days
Dose	5-6 cups tea the first day of symptoms, titrating down by 1 cup per day over the next 5 days
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	95
No. of subjects completed	95
Sex	Male (7 percent) and female (93 percent)
Age	24-62 years (mean: 39.7)

Inclusion criteria
Employees of a nursing center who reported the earliest symptoms of cold or flu: runny nose, scratchy throat, fever, etc.

Exclusion criteria
Pregnant or nursing mothers; persons who had known allergies to coneflowers, or those who claimed to be allergic to many different flowering plants and pollens; and those who had acute infections and were already placed on antibiotics.

End points
Symptoms were assessed through a questionnaire which asked about the effectiveness of relieving cold or flu symptoms, duration of the cold, and how long it took to notice a change in symptoms.

Results
There was a significant difference between the Echinacea Plus group versus the control group in effectiveness of symptom relief, in number of days of symptoms, and in days of noticeable symptom change (all three $p < 0.001$).

Side effects
No negative effects reported by any subjects.

Authors' comments
Treatment with Echinacea Plus tea at early onset of cold or flu symptoms was effective for relieving these symptoms in a shorter period of time than a placebo.

Reviewer's comments
This study had clearly defined outcome measures and adequate inclusion/exclusion criteria; however, there were several flaws. Alternating assignment was used which does not truly randomize subjects; sample size was relatively small, and no IRB review obtained. Results do suggest shorter duration of symptoms and decrease in severity of symptoms with active treatment. (2, 5)

Elderberry

Other common names**: European elder, black elder**
Latin name: ***Sambucus nigra* L.** [Caprifoliaceae]
Plant part: **Fruit**

Note: Sambucus nigra L. ssp. *canadensis* (L.) R Bolli or *Sambucus canadensis* L. is American elder or sweet elder

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

European elder or black elder is a common shrub in Europe with sweet-smelling flowers and shiny black berries. Historically, the flowers, berries, leaves, and bark have all been used medicinally. However, the most commonly used plant part is the flower. Preparations of the flowers have been used for their diaphoretic and diuretic effect in the treatment of colds. In addition, the flowers and berries are used to make wine, which has been heated until hot and taken for colds (Wren, Williamson, and Evans, 1988).

The use of an elderberry fruit extract in treatment for flu was borne out of laboratory testing which found activity against several strains of influenza virus (Mumcuoglu, 1998). That testing resulted in a product, Sambucol®, a syrup containing elderberry juice and raspberry extract. Sambucol is manufactured by Razei Bar Industries Ltd., Israel, and distributed in the United States by Nature's Way Products Inc.

ELDERBERRY SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Sambucol®	Razei Bar Industries Ltd., Israel/Nature's Way Products Inc.	Syrup containing elderberry juice and raspberry extract	Children: 2 tbsp daily, Adults: 4 tbsp daily	Flu	1	Trend (III-1)

SUMMARY OF REVIEWED CLINICAL STUDIES

Sambucol

Flu

Sambucol was tested for the treatment of flu in a small trial with members of a kibbutz. Early symptoms of flu, caused by the influenza virus, are sudden fever, chills, body aches, and eventually a runny nose, headache, and cough. The trial initially included 40 children and adults who had developed flu symptoms within 24 hours before the start of the trial. Participants were given either placebo or Sambucol (two tablespoons per day were given to children, and four tablespoons per day were given to adults) for three days. Only 27 subjects were included in the study evaluation, which reported a significant improvement in symptoms of the flu, including fever, in 93 percent of the treatment group within two days. The placebo group showed such an improvement within six days. The treatment group had a greater increase in antibody titers to influenza B/Panama compared to the control group, but this difference was not significant (Zakay-Rones et al., 1995). According to our reviewer, Dr. Richard O'Connor, evaluation of the clinical effectiveness of Sambucol was limited by the small number of subjects included in the final analysis.

ADVERSE REACTIONS OR SIDE EFFECTS

No side effects were observed in the trial that included 15 subjects in the treatment group, ages 5 to 50 years.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

German Commission E
British Herbal Compendium (BHC)

Note: Both the German Commission E and the *British Herbal Compendium* have published monographs on the flower. There is no mention of the fruit in these monographs.

Indications

The German Commission E approves the use of dried, sifted flowers for colds and feverish conditions. The *British Herbal Compendium* also lists these indications. Actions include diaphoretic, diuretic, and increased bronchial secretion (Blumenthal et al., 1998; Bradley, 1992).

Doses

Flower: 10 to 15 g daily (Blumenthal et al., 1998); dried, 3 to 5 g in infusion three times daily (preferably taken hot) (Bradley, 1992).
Fluid extract: 1.5 to 3 g daily (Blumenthal et al., 1998).
Liquid extract: (1:1, 25 percent ethanol), 3 to 5 ml three times daily (Bradley, 1992).
Tincture: 2.5 to 7.5 g daily (Blumenthal et al., 1998); (1:5, 25 percent ethanol), 10 to 25 ml three times daily (Bradley, 1992).

Contraindications

The Commission E and the *BHC* list no known contraindications (Blumenthal et al., 1998; Bradley, 1992).

Adverse Reactions

The Commission E lists no known adverse reactions (Blumenthal et al., 1998).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998).

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Bradley PR, ed. (1992). *British Herbal Compendium: A Handbook of Scientific Information on Widely Used Plant Drugs,* Volume 1. Dorset, UK: British Herbal Medicine Association.

Mumcuoglu M (1998). *Wonderful Sambucus: The Black Elderberry. How a Tiny Berry Can Defeat Influenza and Protect You.* Jerusalem, Israel: Shmuel Tal Printing Service.

Wren RC, Williamson EM, Evans FJ (1988). *Potter's New Encyclopaedia of Botanical Drugs and Preparations.* Saffron Walden, UK: The SW Daniel Company, Ltd.

Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M (1995). Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambuscus nigra* L.) during an outbreak of influenza B Panama. *Journal of Alternative and Complementary Medicine* 1 (4): 361-369.

DETAILS ON ELDERBERRY PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Sambucol®

Manufacturer	**Razei Bar Industries, Ltd.**
U.S. distributor	**Nature's Way Products, Inc.**
Botanical ingredient	**Raspberry fruit extract**
Extract name	None given
Quantity	No information
Processing	No information
Standardization	No information
Botanical ingredient	**Elderberry fruit extract**
Extract name	None given
Quantity	3.8 g extract in 2 teaspoons
Processing	No information
Standardization	No information
Formulation	Liquid

Recommended dose: Suggested daily usage: adults take 2 teaspoons daily; children take 1 teaspoon daily. Suggested intensive usage: adults take 2 teaspoons four times daily; children take 1 teaspoon four times daily.

DSHEA structure/function: Popular supplement during the winter season for its health-promoting benefits.

Other ingredients: Glucose syrup, honey, citric acid, natural flavor.

Source(s) of information: Product label.

Clinical Study: Sambucol®

Extract name	None given
Manufacturer	Razei Bar Industries, Ltd.
Indication	**Flu**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M (1995). Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama. *Journal of Alternative and Complementary Medicine* 1 (4): 361-369.

Trial design
Parallel. Patients received trial medication for three days.

Study duration	6 days
Dose	2 tbsp (children), 4 tbsp (adults) daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Dispensary
No. of subjects enrolled	40
No. of subjects completed	27
Sex	Male and female
Age	5-56 years (mean: 22)

Inclusion criteria
Members of a kibbutz with at least three of the following symptoms of less than 24 hours in duration: fever >38°C, myalgia (muscle pain), nasal discharge, and cough.

Exclusion criteria
Patients vaccinated against influenza and those with a sore throat caused by streptococcus A.

End points
Patients were assessed for six days for the following symptoms: fever, rhinitis with flow, headache, pharyngitis, cough, malaise, fatigue, and myalgia. Feelings of improvement or complete cure were also noted. Samples of sera were obtained from patients on their first visit and in the convalescent phase. Sera was tested for antibodies to influenza A and B using the complementation fixation test (CFT) and the hemagglutination inhibition test (HI).

Results
A significant improvement of the symptoms, including fever, was seen in 93.3 percent of the cases in the Sambucol-treated group within two days, whereas in the control group 91.7 percent of the patients showed improvement within six days ($p < 0.001$). A complete cure was achieved within two to three days in nearly 90 percent of the Sambucol group and within at least six days in the placebo group ($p < 0.001$). Differences in antibody titers to influenza B/Panama were higher in the group treated with Sambucol, but these differences were not significant.

Side effects
No side effects observed.

Authors' comments
Considering the efficacy of the extract in vitro on all strains of influenza virus tested, the clinical results, its low cost, and absence of side effects, this preparation could offer a possibility for safe treatment for influenza A and B.

Reviewer's comments
This study is hampered by its small sample size (12 placebo and 15 active treatment patients). The statistics used to calculate odds ratios are not described and are unlikely to have involved regression analysis and log transformed data. The study is not adequately powered. This study needs to be replicated with a larger sample size that is adequately powered and subjected to much more rigorous statistical analysis. Informed consent was obtained, but there was no mention of institutional review board (IRB) approval. (5, 1)

Evening Primrose

Latin name: ***Oenothera biennis* L.** [Onagraceae]
Plant part: **Seed**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Evening primrose seeds contain up to 25 percent oil. Evening primrose oil (EPO) contains two types of omega-6 fatty acids: linoleic acid (LA) (60 to 80 percent) and gamma-linolenic acid (GLA) (8 to 14 percent) (Schulz, Hänsel, and Tyler, 2001). These acids are considered essential fatty acids (EFAs) because they are required for health and are not synthesized by the body. Linolenic acid deficiency produces visible signs in the skin, including eczema, impetigo, and erythema. Evening primrose oil is used in the formulation of cosmetic products and also as a dietary supplement (Chen, 1999).

Editor's note: Most of the product and manufacturer information supplied as follows comes from the clinical trials themselves, some of which were published as many as twenty years ago. We were unable, after extensive research, to contact any of the companies listed. We suspect that the companies may no longer exist or have been bought out by other companies. Thus the following paragraphs provide information about products that were used in clinical studies but may not exist today.

Efamol® is manufactured in the United Kingdom by Efamol Ltd. Each 500 mg capsule contains 360 mg LA, 50 mg oleic acid, and 45 mg GLA. Efamol is no longer available in the United States.

Epogam® is manufactured by Scotia Pharmaceuticals Ltd. in the United Kingdom. Each 500 mg capsule contains 321 mg LA and 40 mg GLA. One trial used Epogam topically in the form of an emulsion that contained 32 mg GLA/ml. Epogam is not sold in the United States.

EVENING PRIMROSE SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Single Ingredient Products						
Efamol®	Efamol Ltd., UK/ None	500 mg EPO capsules including 360 mg LA, 50 mg oleic acid, 45 mg GLA	adults: 2-6 capsules 2 times daily; children: 1-2 capsules 2 times daily	Atopic dermatitis (eczema)	2	Yes (I-1) Undetermined (II-1)
				Uremic skin symptoms in dialysis patients	1	Yes (II-1)
			3 or 4 capsules 2 times daily	Attention deficit/ hyperactivity problems in children	2	No (I-2)
			6 capsules 2 times daily	Rheumatoid arthritis	2*	No (I-2)
			3 capsules 2 times daily	PMS	1	Undetermined (II-1)
Epogam®	Scotia Pharmaceuticals Ltd., UK/ None	500 mg EPO capsules including 321 mg LA, 40 mg GLA	6 capsules 2 times daily	Atopic dermatitis (eczema)	1**	No (I-1)
				Chronic hand dermatitis	1	No (I-1)
				Diabetic neuropathy (nerve degeneration)	1	Yes (I-1)

		Emulsion containing 32 mg GLA/ml	10 ml topical twice daily	Uremic pruritus (itch) in dialysis patients	1	Trend (III-1)
Efamast	Searle, UK/None	500 mg capsules	4 capsules 2 times daily	Fibroadenomas (benign breast lumps)	1	Undetermined (III-1)
Generic	None/None	0.6 ml capsules	4 capsules 2 times daily	Obesity	1	Undetermined (III-1)
Combination Product						
Efamol Marine	Scotia Pharmaceuticals Ltd., UK/None	430 mg EPO plus 107 mg marine fish oil (17 mg eicosapentaenoic acid, 11 mg docosahexaenoic acid)	6 capsules 2 times daily	Rheumatoid arthritis	2*	No (I-2)
				Psoriatic arthritis	1	No (II-1)
				Atopic dermatitis (eczema)	1**	No (I-1)

*One of these studies compared Efamol with Efamol Marine and is listed twice in the table, once with each product.
**This study that compared Epogam with Efamol Marine is listed twice in the table, once with each product.

Efamol Marine is supplied in capsules containing 430 mg EPO plus 107 mg marine fish oil (17 mg eicosapentaenoic acid [EPA], 11 mg docosahexaenoic acid [DHA]). Efamol Marine is manufactured in the United Kingdom by Scotia Pharmaceuticals Ltd. and is not available in the United States.

Efamast capsules, which contain 500 mg EPO, are manufactured by Searle in the United Kingdom. Efamast is not sold in the United States.

One trial used a generic product containing 0.6 ml EPO per capsule.

SUMMARY OF REVIEWED CLINICAL STUDIES

Essential fatty acids, including linoleic acid found in evening primrose oil, cannot be manufactured in the human body, and their supply is dependent on adequate dietary intake. Inadequate intake or compromised conversion to active metabolites can result in symptoms such as hair loss, eczema, disorders in connective tissue, poor wound healing, poor immune and reproductive function, and degeneration of organs, including the liver and kidney (Chen, 1999).

Trials using evening primrose oil preparations have been conducted on subjects with eczema, arthritis, attention-deficit hyperactivity disorder (ADHD, in children), diabetic neuropathy, premenstrual syndrome (PMS), benign fibroadenomas in the breast, and obesity. The majority of trials have focused upon atopic eczema, in which there appears to be a trend toward efficacy. EPO may also help ameliorate the uremic skin symptoms of those undergoing dialysis. In addition, EPO may improve mild diabetic neuropathy. No evidence indicates that it has any effect on ADHD in children, improves symptoms of arthritis or PMS, reduces benign fibroadenomas in the breasts, or helps obese women lose weight.

Atopic eczema or atopic dermatitis is a type of dermatitis in which an inflammation of the skin develops in persons subject to allergic reactions. It is associated with itching, redness, swelling, and blisters that may be weeping and progress to crusted, scaly, and thickened skin. The skin rash can be widespread or limited to a few areas. In teens and young adults, the patches typically occur on the hands and feet (American Academy of Dermatology, 1995).

Efamol and Efamol Marine

Atopic Dermatitis (Eczema)

Two studies explored the use of Efamol in the treatment of atopic eczema. The first study was of good quality, with a crossover design including 80 subjects with moderate to severe atopic eczema, from eight months to 58 years old. The children were given one or two (500 mg) capsules twice daily, and the adults were given two, four, or six (500 mg) capsules twice daily. Each subject was given 12 weeks of EPO and 12 weeks of placebo in random order. An analysis of symptom scores indicated that EPO produced a 30 percent improvement overall in severity of the eczema, while those receiving the higher doses had a 43 percent improvement. At the higher doses for children and adults, EPO was significantly superior to placebo in reducing symptoms of itch, scaling, and patients' general impression of severity. At the lower doses, only itch was significantly reduced compared to placebo (Wright and Burton, 1982).

The second study included 24 adults, with moderate to severe atopic eczema, who were given either placebo or four (500 mg) capsules twice daily for three months. Compared to baseline, patients in the EPO group consumed significantly less topical steroids and had significant improvement in the severity and grade of inflammation, including a reduction in surface area involved. The degree of improvement in clinical parameters in the EPO group was significantly greater compared to the placebo group (Schalin-Karrila et al., 1987). Our reviewer, Dr. John Trimmer Hicks, deemed the study inconclusive due to the small sample size.

Uremic Skin Symptoms in Dialysis Patients

A small study with 16 hemodialysis patients compared the results of Efamol and LA in the treatment of uremic skin symptoms. This good-quality six-week trial compared two capsules twice daily of Efamol (each 500 mg capsule containing 360 mg LA, 50 mg oleic acid, and 45 mg GLA) with pure LA (500 mg capsules). Compared to LA, there was a significant improvement in the combined symptom score (including itch, redness, and dryness) following treatment with

Efamol. There was a trend toward improvement in itch when it was measured independently (Yoshimoto-Furuie et al., 1999).

Attention-Deficit/Hyperactivity Problems in Children

The effect of Efamol on attention-deficit problems or attention-deficit hyperactivity disorder in children was studied in two well-conducted crossover trials. No statistical improvement in overall behavior compared to placebo occurred in either study. The children, with a mean age of nine years, received three or four (500 mg) capsules twice daily for one month. The trials were of good quality but of moderate size; a total of 48 children were included in the two studies (Aman, Mitchell, and Turbott, 1987; Arnold et al., 1989). One study included 10 to 15 mg D-amphetamine as a positive control, and this substance did have a significant effect compared to placebo (Arnold et al., 1989).

Rheumatoid Arthritis

Efamol was tested for efficacy in improving symptoms of rheumatoid arthritis in two good-quality, double-blind, placebo-controlled studies. In both studies the dose was 6 g (12 capsules) per day. Neither study showed an impressive benefit. In the first study, which ran for six months and included 30 subjects, there was no clear benefit in comparison with the placebo (olive oil) (Brzeski, Madhok, and Capell, 1991). The second study compared Efamol with Efamol Marine and placebo. In this study, treatment was given for one year followed by a three-month observation period. Compared to placebo, significantly more patients taking Efamol and Efamol Marine experienced a subjective improvement and were able to reduce their NSAID (nonsteroidal anti-inflammatory drug) therapy. There was no objective improvement in clinical measures, including duration of morning stiffness, grip strength, Ritchie articular index, and pain scale (Belch et al., 1988).

Psoriatic Arthritis

The effect of Efamol Marine on inflammatory arthritis associated with psoriasis (negative for rheumatoid factor) was tested in a well-designed, double-blind, placebo-controlled study involving 32 subjects. The treatment group received 12 capsules per day for nine

months. No improvement was seen in either the skin disease or the arthritis. In addition, therapy with Efamol Marine did not decrease the use of NSAIDs to alleviate joint symptoms (Veale et al., 1994).

Premenstrual Syndrome

The effect of Efamol on premenstrual tension was compared to placebo in 30 women over the length of four menstrual cycles. The treatment group was given three (500 mg) capsules twice daily. The PMS symptom scores substantially improved in both the Efamol and placebo groups, and the improvement was slightly greater for the Efamol group. The authors of the study suggested that larger doses and longer treatment length might have shown greater benefit (Puolakka et al., 1985).

Epogam and Efamol Marine

Atopic Dermatitis (Eczema) and Chronic Hand Dermatitis

Two good-quality studies found no benefit from Epogam for dermatitis. The first study was a double-blind, placebo-controlled study including 123 adults and children with atopic dermatitis (eczema), Epogam was compared with Efamol Marine and placebo (paraffin). Subjects were given six capsules twice daily of each treatment. Epogam capsules contained 500 mg EPO, while Efamol Marine capsules contained 430 mg EPO and 107 mg marine fish oil. After 16 weeks, there was no difference in dermatitis symptom scores between either Epogam or Efamol Marine and placebo (Berth-Jones and Graham-Brown, 1993). The second study was a double-blind, placebo-controlled study including 34 subjects with chronic hand dermatitis. In this study, chronic hand dermatitis was defined as dermatitis limited to the hands, excluding eczema. The study ran for four months with continued observation for an additional two months. Improvement was reported in symptoms of dryness, redness, and cracking with Epogam, 12 (500 mg) capsules per day, and placebo (sunflower oil), with no statistical difference between the two (Whitaker, Cilliers, and de Beer, 1996).

Uremic Pruritus (Itch) in Dialysis Patients

A poorly described, double-blind, placebo-controlled study of six months examined the effect of a topical Epogam emulsion on itch (uremic pruritus) experienced by patients undergoing either continuous ambulatory peritoneal dialysis or hemodialysis. Only 16 of the original 33 patients completed the six-month study (five in the placebo group and 11 in the Epogam group). There was no statistically significant difference in the score for itch between the placebo and treatment cream; however, some individuals experienced relief with the Epogam cream, which vanished upon cessation of treatment and was relieved again with use of the cream (Tamimi, Mikhail, and Stevens, 1999).

Diabetic Neuropathy

Epogam was determined to have a positive effect on mild diabetic neuropathy in a well-conducted, double-blind, placebo-controlled study with 84 patients. Treatment with six capsules twice daily, or 6 g per day, for one year improved neurophysiological parameters (motor nerve conduction velocity [MNCV], compound muscle action potential, sensory nerve action potential [SNAP], and warm and cold thresholds) and neurologic parameters (isometric muscle strength and tendon reflexes) compared to baseline, most of them significantly. These parameters mostly deteriorated with placebo (Keen et al., 1993).

Efamast

Fibroadenomas (Benign Breast Lumps)

In a nonrandomized trial including 23 women with benign breast lumps, six months of treatment with four (500 mg) Efamast capsules twice daily was compared to controls who received no treatment. As a result, there was no significant reduction in the size of the lump for women in the treatment group, compared to controls (Kollias et al., 2000).

Generic

Obesity

In a double-blind, placebo-controlled study with 74 obese women (at least 20 percent in excess of ideal body weight), generic EPO was given in a dose of four (0.6 ml) capsules twice daily. Both EPO and placebo groups were given ascorbic acid (250 mg three times daily) and put on a restricted diet. After three months of treatment both the EPO and placebo groups lost some weight, but no indication was found that EPO assisted in weight loss (Haslett et al., 1983)

SYSTEMATIC REVIEWS AND META-ANALYSES

A meta-analysis of nine double-blind, randomized, placebo-controlled studies found Epogam to have highly significant effects on atopic eczema. It appears that the trials, four of parallel design and five of crossover design, were previously unpublished. A total of 311 patients, both children and adults, were included. The majority of adults were given eight (500 mg) capsules per day, but the dose ranged from 4 to 12 capsules. Six trials had a duration of three months, two lasted for two months, and another lasted for one month. Both doctors and patients assessed the severity of the eczema by scoring symptoms at baseline and at several intervals, with an initial assessment after three to four weeks in all studies. Improvements in the Epogam groups in comparison to the placebo groups were often highly significant (two-tail tests, $p < 0.01$), particularly in the case of itch, whereas no improvement, or even a slight deterioration, was seen with placebo. Those treated with Epogam saw progressive improvement, with the effects consistently better at the final assessment point. Higher doses of Epogam produced a greater response, indicating a significant dose-response relationship. In the crossover studies, there was a carryover effect; patients receiving placebo in the second round had little to no deterioration following the earlier benefit from Epogam. When plasma essential fatty acid levels were measured, an improvement in the clinical score for atopic eczema positively correlated with a rise in EFA levels (particularly increased dihomogammalinolenic acid [DGLA] and arachidonic acid). Finally, improvement

with Epogam was in addition to benefits from conventional eczema therapy (Morse et al., 1989).

ADVERSE REACTIONS OR SIDE EFFECTS

Occasional side effects noted in the trials included nausea, diarrhea, and headache.

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Yoshimoto-Furuie K, Yoshimoto K, Tanaka T, Saima S, Kikuchi Y, Shay J, Horrobin D, Echizen H (1999). Effects of oral supplementation with evening primrose oil for six weeks on plasma essential fatty acids and uremic skin symptoms in hemodialysis patients. *Nephron* 81 (2): 151-159.

DETAILS ON EVENING PRIMROSE PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Evening Primrose

Product Profile: Efamol®

Manufacturer	**Efamol Ltd., UK**
U.S. distributor	None
Botanical ingredient	**Evening primrose seed oil**
Extract name	N/A
Quantity	500 mg
Processing	No information
Standardization	360 mg linoleic acid, 50 mg oleic acid, and 45 mg gamma-linolenic acid in each capsule
Formulation	Capsule

Source(s) of information: Schalin-Karrila et al., 1987; Wright and Burton, 1982.

Clinical Study: Efamol®

Extract name	N/A
Manufacturer	Efamol Ltd., UK
Indication	**Atopic eczema**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Wright S, Burton JL (1982). Oral evening-primrose-seed oil improves atopic eczema. *The Lancet* 2 (8308): 1120-1122.

Trial design
Crossover study: 12 weeks of evening primrose oil and 12 weeks of placebo in random order. Patients allowed to continue their normal treatment (mild topical steroid, an emollient, and systemic antihistamines). Adult patients (age 15 to 58) randomly allocated to three dosage groups: A, B, and C received two, four, or six capsules twice daily, respectively. Children (ages 8 months to 14 years) divided into two treatment groups, D and E, and given one or two capsules twice daily. Groups A and D were analyzed separately as low-dose groups.

Study duration	3 months
Dose	Adults: 2 to 6 (500 mg) capsules twice daily; children: 1 to 2 (500 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	99
No. of subjects completed	80
Sex	Male and female
Age	8 months to 58 years

Inclusion criteria
Clinical diagnosis of moderate or severe atopic eczema, in addition to either a family history of atopy or a personal history of other atopic symptoms.

Exclusion criteria
Patients receiving potent topical steroids or systemic steroid therapy.

End points
Eczema was assessed before the trial and every three weeks during the trial. Degree of scaling, redness, and overall severity were separately assessed on a 10 cm linear scale. Each patient (or parent) also assessed the severity of itching. In the adult patients blood was also taken at 0, 12, and 24 weeks for blood count, urea, electrolytes, and liver-function tests.

Results
In the analysis of the mean symptom scores for all 99 patients, and the impressions of doctors and patients, evening primrose oil produced an improvement of about 30 percent in overall severity of the eczema, and the adults responded better than the children. For patients in the high-dose groups, the overall improvement in severity was about 43 percent, and the patient's self-assessment showed that the EPO was significantly superior to the placebo with regard to itch ($p < .003$), scaling ($p < .002$), and general impression of severity ($p < .01$). In the low-dose groups, itching was the only symptom which responded better to evening primrose oil than placebo ($p < .05$). The doctors' assessments also showed a beneficial effect of EPO on overall severity of the condition ($p < .002$). The other symptom scores showed the same trend but failed to reach statistical significance. No significant effect resulted from the order of the treatment.

Side effects
None mentioned in paper.

Authors' comments
This study has shown that larger doses of linoleic and gamma-linolenic acid in the form of evening primrose seed oil significantly improves the symptoms of atopic eczema, particularly in adults. The relatively poor results with evening primrose seed oil in children may be due to the greater placebo effect in children, or it may be that the doses of evening primrose seed oil used were not adequate.

Reviewer's comments
A good study with pretty convincing efficacy. (5, 6)

Clinical Study: Efamol®

Extract name	N/A
Manufacturer	Efamol Ltd., UK

Indication	**Atopic eczema**
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Schalin-Karrila M, Mattila L, Jansen CT, Uotila P (1987). Evening primrose oil in the treatment of atopic eczema: Effect on clinical status, plasma phospholipid fatty acids and circulating blood prostaglandins. *British Journal of Dermatology* 117 (1): 11-19.

Trial design
Parallel. Two-week pretrial washout for dermatitis medication.

Study duration	3 months
Dose	4 (500 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	25
No. of subjects completed	24
Sex	Male and female
Age	19-31 years

Inclusion criteria
Moderate to severe atopic eczema, in addition to either a family history of atopy or atopic respiratory symptoms.

Exclusion criteria
None mentioned.

End points
Patients were monitored for extent and severity of eczema. Blood samples were also taken to monitor effect of treatment on plasma phospholipids. Extent and severity of the eczema was estimated on a linear scale from 0 (no symptoms) to 100 (worst possible). Percentage of body surface involved was estimated, and the degree of inflammation, dryness, and itch graded on a scale of 0: none, 1: mild, 2: moderate, 3: severe. The amount of emollient

cream and topical steroids used by patients during the study (as rescue medication) was also recorded.

Results
Patients in the evening primrose oil group consumed significantly less topical steroids over the course of 12 weeks (60 g versus 200 g, $p < .05$). A statistically significant improvement was observed in overall severity and grade of inflammation ($p <. 001$), a significant reduction in surface area involved, as well as in dryness and itching ($p < .01$). Patients in the placebo group also showed a significant reduction in inflammation ($p < .05$). However, in every clinical parameter, the degree of improvement was significantly greater in the EPO group than in the placebo group. The level of DGLA increased significantly in the EPO group.

Side effects
No side effects were observed in the study.

Authors' comments
Although the patients were allocated to the two groups at random, the mean initial status of the eczema was somewhat worse in the EPO group than in the placebo group, which made it difficult to estimate the real effect of EPO. However, significantly greater improvement in every parameter in the EPO group, and the fact that the patients in the placebo group needed about three times as much topical steroids as did those in the EPO group, suggest that EPO was superior to placebo.

Reviewer's comments
The study was well designed and conducted, but the results were weakened by the small sample size. (5, 4)

Clinical Study: Efamol®

Extract name	N/A
Manufacturer	Efamol Ltd., UK
Indication	**Uremic skin symptoms** in hemodialysis patients
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Yoshimoto-Furuie K, Yoshimoto K, Tanaka T, Saima S, Kikuchi Y, Shay J, Horrobin D, Echizen H (1999). Effects of oral supplementation with evening

primrose oil for six weeks on plasma essential fatty acids and uremic skin symptoms in hemodialysis patients. *Nephron* 81 (2): 151-159.

Trial design
Parallel. Evening primrose oil compared with linoleic acid. Group receiving LA took two (500 mg) capsules twice daily. After six weeks, the group receiving evening primrose oil continued treatment for another six weeks to study the biochemical effects of EPO.

Study duration	6 weeks
Dose	2 (500 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Linoleic acid
Site description	Not described
No. of subjects enrolled	16
No. of subjects completed	16
Sex	Male and female
Age	23-79 years

Inclusion criteria
Patients undergoing hemodialysis who suffered from pruritus and other uremic skin symptoms (i.e., dryness or erythema). Severe dryness of the skin and erythrematous lesions were a prerequisite for participation in the study.

Exclusion criteria
None mentioned.

End points
Assessments of skin symptoms were performed at the beginning of the study and weekly thereafter. Plasma composition of essential fatty acids was analyzed from predialysis blood samples taken at weeks 0 and 6, and for patients on EPO, week 12. Severity of uremic skin symptoms (i.e., pruritus, erythema, and dryness) were measured by a grading-scale system. Dryness of the skin and erythrematous lesions were assessed separately by visual inspection by a single investigator and assessed in severity. The intensity of pruritus was assessed with a self-administered questionnaire.

Results
Statistically significant ($p < 0.05$) overall improvement in the EPO group with regard to the three categories of uremic dermatosis, whereas no significant changes observed in skin symptoms of the LA group. At 6 and 12 weeks, patients given EPO showed significant ($p < 0.01$) increases in the mean plasma concentration of dihomogamma-linolenic acid and gamma-linolenic acid. Patients given LA for six weeks showed a significant increase in the mean plasma concentration of LA, a reduction in docosahexaenoic acid, but no significant changes in DGLA concentrations throughout the study. No significant differences were observed in gross lipid profiles for either group over the duration of the study.

Side effects
EPO was very well tolerated with no adverse clinical symptoms.

Authors' comments
Oral supplementation with EPO significantly improved skin scores during the six-week intervention period, while LA did not. EPO (containing 0.18 g/day of GLA) produced significant elevations in the plasma concentrations of DGLA; supplementation with LA did not. This finding is in good agreement with previous data obtained from healthy subjects and suggests that conversion of LA into GLA is the rate-limiting step in humans. Thus, supplementation with EPO (rich in GLA) rather than LA is an effective means for accelerating the synthesis of DGLA in patients on dialysis.

Reviewer's comments
This is a very detailed and internally consistent set of data, even though the study group was small. The trial is rated Level II due to the small sample size. (5, 5)

Clinical Study: Efamol®

Extract name	N/A
Manufacturer	Efamol Ltd., UK
Indication	**Attention-deficit problems** in children
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Aman MG, Mitchell EA, Turbott SH (1987). The effect of essential fatty acid supplementation by Efamol in hyperactive children. *Journal of Abnormal Child Psychology* 15 (1): 75-90.

Trial design
Crossover. Subjects received either Efamol or placebo for four weeks in randomized order with a one-week washout period between the two phases.

Study duration	1 month
Dose	3 (500 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	31
No. of subjects completed	30
Sex	Male and female
Age	Mean: 8.86 years

Inclusion criteria
Children were admitted to the study if their scores on both the Attention Problem subscale of the Revised Behavior Problem Checklist and the Inattention scale of the Conners Teacher Rating Scale exceeded the 90th percentile. Most children (26/31) qualified for the study through this criteria. Several children (5/31) had been seen by a child psychiatrist as part of another study and were given a diagnosis of attention deficit disorder (either with or without hyperactivity). Children were perceived to have attention deficits in both the home and the classroom.

Exclusion criteria
Neurological disorders; mental retardedness; less than a year's duration of inattention, impulsivity, or overactivity; children receiving medication at the time of study.

End points
Subjects were assessed prior to the study and twice during each four-week treatment phase on a variety of cognitive, motor, and standardized rating scale measures. Parents rated the children on the Revised Behavior Problem Checklist, and teachers rated the children on the Conners Teacher Rating Scale. Teachers also completed the ADD-H: Comprehensive Teacher's Rating Scale to assess hyperactivity. Subjects were assessed at each visit for side effects using the Dosage Record and Treatment Emergent Symptom Scale (DOTES). At the pretest and after each treatment phase, a blood sample was taken to determine levels of essential fatty acids.

Results
There were some suggestions of therapeutic changes following administration of Efamol, but the large majority of measures failed to show an effect when the rigorous criterion of significance of $p < 0.0012$ was applied. Only two behavioral measures, response time on the distraction task and parent ratings of attention problems, showed significant change. During treatment with Efamol, palmitoleic acids levels decreased significantly and dihomo-gamma-linolenic acid levels increased (14 percent over placebo). The remaining essential fatty acids showed no significant changes, although there was a tendency for alpha-linolenic acid to decrease.

Side effects
No significant side effects in the Efamol group.

Authors' comments
It must be concluded that essential fatty acid supplementation, employed with hyperactive children unselected for baseline EFA concentrations and treated at the present dosage, had relatively few clinical or cognitive effects. However, the rationale for employing essential fatty acid supplementation with hyperactive children appears reasonable on the basis of clinical characteristics and previous work suggesting EFA deficiencies in these children.

Reviewer's comments
Well-designed and well-conducted study. Evening primrose oil does not appear to have any efficacy in hyperactive children. (5, 6)

Clinical Study: Efamol®

Extract name	N/A
Manufacturer	Efamol Ltd., UK
Indication	**Attention-deficit hyperactivity disorder** in children
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB, Tobin K (1989). Gamma-linolenic acid for attention-deficit hyperactivity disorder: Placebo-controlled comparison to D-amphetamine. *Biological Psychiatry* 25 (2): 222-228.

Trial design
Latin-square, double-crossover study. The three groups were D-amphetamine group (one capsule [10 or 15 mg based on body weight] D-amphetamine + eight capsules placebo); Efamol group (one capsule placebo + eight capsules Efamol); and placebo (nine capsules placebo).

Study duration	1 month
Dose	4 (500 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	D-amphetamine
Site description	Not described
No. of subjects enrolled	18
No. of subjects completed	18
Sex	Male
Age	6-12 years (mean: 9)

Inclusion criteria
Aged between 6 and 12 years; normal intelligence; diagnosis of attention deficit disorder wth hyperactivity by DSM-III criteria; score of 18 or more on Conners Hyperactivity Index; and a sum of 24 or more on the first six items of the Davids Hyperkinetic Rating Scale.

Exclusion criteria
Use of psychoactive drugs in the week preceding the study; history of seizures.

End points
At screening, at baseline, and every two weeks during the 12 treatment weeks, each subject had blind behavioral ratings by parents and teachers. The teachers used the Conners' Teacher Rating Scale (CTRS).

Results
Behavorial ratings following Efamol treatment were not significantly different from either placebo or D-amphetamine on most measures. Parents' ratings generally showed no difference between Efamol and placebo but a moderate response to D-amphetamine. Teachers' ratings found significant response to D-amphetamine only on the hyperactivity factor of the CTRS, with Efamol response between placebo and D-amphetamine. Post hoc

sample subdivision showed that the six subjects who had D-amphetamine immediately preceding Efamol showed no benefit from Efamol administration, whereas the other 12 subjects showed a response to Efamol closer to D-amphetamine than to placebo.

Side effects
None mentioned in paper.

Authors' comments
Gamma-linolenic acid should be considered to be an experimental treatment for ADHD. The data reported here do not establish its effectiveness. Further studies should use designs that control for a possible sequence interaction and should probably use ten EPO capsules per day.

Reviewer's comments
In this well-conducted study, D-amphetamine was statistically significantly better than placebo, but Efamol (containing GLA) was not. (5, 5)

Clinical Study: Efamol®

Extract name	N/A
Manufacturer	Efamol Ltd., UK
Indication	**Rheumatoid arthritis**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Brzeski M, Madhok R, Capell HA (1991). Evening primrose oil in patients with rheumatoid arthritis and side-effects of non-steroidal anti-inflammatory drugs. *British Journal of Rheumatology* 30 (5): 370-372.

Trial design
Parallel. Patients were given either evening primrose oil (Efamol) or olive oil (placebo).

Study duration	6 months
Dose	6 g/day (540 mg GLA per day)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	40
No. of subjects completed	30
Sex	Male and female
Age	16-75 years

Inclusion criteria
Patients with rheumatoid arthritis and upper gastrointestinal lesions due to nonsteroidal anti-inflammatory drugs (i.e., peptic ulcer or gastritis at endoscopy or on barium meal, or symptoms strongly suggestive of these diagnoses).

Exclusion criteria
Patients taking systemic corticosteroids were excluded.

End points
Patients were allowed to continue routine medication (NSAIDs, H2 blockers, analgesics). After three months, patients were asked every week to attempt reduction of their NSAIDs and analgesics. At zero, three, and six months, the following assessments were performed: daily use of NSAIDs and analgesia; morning stiffness; 100 mm horizontal visual analog scales for pain and well-being; Ritchie articular index and health assessment questionnaire (HAQ); and Hb, platelets, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), globulins, and plasma fatty acid analysis.

Results
The evening primrose oil group had significantly reduced morning stiffness at three months with a trend to reduction at six months. In the placebo group, there was a significant reduction in articular index and pain at six months, and a trend to reduced morning stiffness at six months. There was no change in well-being, HAQ scores, or laboratory parameters of inflammation in either group. Of the 13 patients completing treatment in the EPO group, ten showed a significant rise in plasma dihomogamma-linolenic acid (a metabolite of gamma-linolenic acid), suggesting good compliance with the study. No patients stopped NSAIDs, but three in each group reduced the dose of NSAID by one tablet (e.g., t.d.s. to b.i.d.). One patient in the evening primrose group increased NSAID dosage. Four patients taking placebo and one patient taking EPO reduced analgesia dosage, and two in each group increased dosage.

Side effects
No major effects reported in paper. Several patients dropped out of the study due to nausea, which occurred equally in both groups.

Authors' comments
The study found that only 23 percent (3 out of 13) of patients completing treatment with EPO could reduce their NSAID dose and none could stop, similar to placebo. This contrasts with a previous study in which the same dose of EPO enabled 25 percent to stop and an additional 38 percent to reduce NSAID dose after six months without clinical deterioration. In that study, patients had less severe rheumatoid arthritis and none was on second-line therapy. EPO may thus be beneficial only in mild rheumatoid arthritis. We are unable to recommend EPO for severe rheumatoid arthritis. It is disappointing that we have been unable to confirm the possibility of substituting EPO for NSAIDs in patients with NSAID-induced gastrointestinal side effects. It is interesting that olive oil enabled as many patients to reduce NSAIDS as did EPO and produced improvement in more clinical parameters than EPO.

Reviewer's comments
In this well-designed and well-described study, there was no clear benefit of EPO for patients with rheumatoid arthritis. (5, 6)

Clinical Study: Efamol®

Extract name	N/A
Manufacturer	Efamol Ltd., UK
Indication	**Premenstrual syndrome**
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Puolakka J, Makarainen L, Viinikka L, Ylikorkala O (1985). Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors. *The Journal of Reproductive Medicine* 30 (3): 149-153.

Trial design
Crossover.

Study duration	4 menstrual cycles
Dose	3 (500 mg) capsules twice a day, 15th day of the menstrual cycle until the 1st day of the next cycle
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	30
No. of subjects completed	Not given
Sex	Female
Age	25-47 years (mean: 38.5)

Inclusion criteria
Severe and incapacitating premenstrual syndrome, with symptoms starting between the fourteenth and nineteenth day of the cycle (mean: fifteenth day).

Exclusion criteria
None mentioned.

End points
Women recorded their premenstrual symptoms at the end of each cycle, before and during the trial. Numerous symptoms were scored, forming the PMS score. Blood samples were obtained from 22 patients during both the Efamol and placebo phases of the trial, as well as from 25 healthy control women. Blood samples were collected between the twelfth to fourteenth days and twentieth to twenty-sixth days and, with the exception of the controls, on the second to fifth days of the next cycle. Blood samples were measured for the stable metabolites of PGI2 (6-keto-PGF1alpha) and TxA2 (TxB2).

Results
The PMS score significantly ($p < 0.001$) decreased following treatment with Efamol and placebo. However, the decrease was greater with Efamol treatment, 62 percent compared to 40 percent with placebo ($p < 0.05$). Depression was alleviated significantly ($p < 0.01$) more frequently by Efamol than by placebo. Irritability was not improved by either. No differences arose in plasma 6-keto-PGF1alpha and serum TxB2 levels in women with or without PMS before the trial. Efamol treatment decreased the formation of TxB2 dur-

ing the luteal phase of the cycle but had no effect on plasma 6-keto-PGF1alpha or on various pituitary or ovarian hormones.

Side effects
None reported in paper.

Authors' comments
Findings are consistent with the idea that essential fatty acids may modulate responses to hormones in PMS. Clinically, both the active and placebo groups improved substantially, but at the dose regime used, the additional effect of Efamol was only small. Larger dosages and longer treatment could improve the therapeutic effect of Efamol in PMS, as has been suggested by an open study on patients who failed to respond to other treatment.

Reviewer's comments
Both Efamol and placebo worked equally well for PMS, but Efamol's efficacy cannot be determined from this trial. (4, 5)

Product Profile: Epogam®

Manufacturer	**Scotia Pharmaceuticals Ltd., UK**
U.S. distributor	None
Botanical ingredient	**Evening primrose seed oil**
Extract name	N/A
Quantity	500 mg
Processing	No information
Standardization	321 mg linoleic acid, 40 mg gamma-linolenic acid in each capsule
Formulation	Capsule

Source(s) of information: Berth-Jones and Graham-Brown, 1993; Whitaker, Cilliers, and de Beer, 1996.

Clinical Study: Epogam®

Extract name	N/A
Manufacturer	Scotia Pharmaceuticals Ltd., UK
Indication	**Atopic dermatitis**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Berth-Jones J, Graham-Brown RAC (1993). Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *The Lancet* 341 (8860): 1557-1560.

Trial design
Parallel. Three-arm study: patients received six capsules twice daily of Epogam, Efamol Marine (one capsule contained 430 mg EPO and 107 mg marine fish oil), or placebo (liquid paraffin). Subjects participating in this study were divided according to age into two groups: adults and children up to 12 years of age. These two groups were randomized separately to achieve age balance in the three treatment groups. Treatment with sedative antihistamines continued throughout the study if used by patients at entry into the study.

Study duration	4 months
Dose	6 capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Efamol Marine
Site description	Dermatology department outpatients
No. of subjects enrolled	123
No. of subjects completed	102
Sex	Male and female
Age	2-60 years

Inclusion criteria
Outpatients with atopic dermatitis; equal numbers of adults and children (aged up to 12 years).

Exclusion criteria
None mentioned in paper.

End points
Subjects were examined at 0, 4, 8, and 16 weeks, and again after an eight-week washout phase. Patients were allowed to use topical steroids and emollients as required. Disease activity was monitored by clinical severity scores recorded by the investigator, topical steroid requirements, and symptom scores recorded by subjects. The primary response criterion was mean

change from baseline in Leicester score at 16 weeks. The body was divided into ten zones. Each zone was scored for erythema, excoriation, dryness, cracking, and lichenification. Usage of topical steroids was assessed by weighing the tubes of unused medication. Each week, patients recorded itch, dryness, scaling, redness, and overall impression on separate 10 cm visual analog scales.

Results
At 16 weeks, there was no significant difference in mean Leicester scores between either active treatment or placebo (improvements: 8.48 in Epogam group, 2.45 in Efamol Marine group, and 7.15 in placebo group). The only significant differences for individual components were in favor of placebo over Efamol Marine for erythema ($p = 0.04$) and cracking ($p = 0.05$). Mean percentage of skin affected at 16 weeks fell 3.26 percent in the Epogam group, fell 0.11 percent in the Efamol Marine group, and rose 3.26 percent in the placebo group, with no significant differences between either treatment or placebo. Reduction in topical steroid use occurred in all groups; however, the greatest reduction was recorded for the placebo group. In the patient response diaries, the greatest mean overall reduction in visual analog scales was seen in the placebo group. However, there were no significant differences from placebo at 16 weeks in total score or in any component. In particular, there was no significant difference in pruritus (itch) score.

Side effects
None mentioned in paper.

Authors' comments
This study has demonstrated no response of atopic dermatitis to essential fatty acid supplementation nor any evidence of an additional effect when n3 series EFAs were used in combination with EFAs of the n6 series.

Reviewer's comments
In this well-designed and well-executed study, the authors argue that all prior studies were flawed and that their study is not! They were unable to document any efficacy of evening primrose oil with atopic dermatitis. (5, 6)

Clinical Study: Epogam®

Extract name	N/A
Manufacturer	Scotia Pharmaceuticals Ltd., UK
Indication	**Chronic hand dermatitis**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Whitaker DK, Cilliers J, de Beer C (1996). Evening primrose oil (Epogam) in the treatment of chronic hand dermatitis: Disappointing therapeutic results. *Dermatology* 193 (2): 115-120.

Trial design
Parallel. Medication or placebo (sunflower oil) was given for 16 weeks and observation continued for another eight weeks. A group of ten healthy age- and sex-matched subjects acted as controls.

Study duration	6 months
Dose	12 (500 mg) capsules per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Dermatology department outpatients
No. of subjects enrolled	39
No. of subjects completed	34
Sex	Male and female
Age	19-75 years

Inclusion criteria
Chronic stable hand dermatitis lasting over a year.

Exclusion criteria
Patients with an inflammatory skin disorder other than eczema; allergic contact dermatitis with eczema reactions that resolved after allergen avoidance; patients with severe intercurrent illnesses; or patients currently receiving oral steroids, PUVA therapy (a combination of psoralen and ultraviolet radiation), immune suppressants, phenothiazines, or antidepressants.

End points
Patients were evaluated clinically at baseline and at four-week intervals throughout the twenty-four weeks. Unlimited quantities of standard emollient and a limited amount of a semipotent group III topical steroid cream could be used during the trial. Topical steroid use was monitored by weighing the unused cream at each visit. A 100 mm visual analog scale was used to evaluate dryness, redness, itch, cracking, vesiculation, edema, and overall impression of hand dermatitis. Standard patch test using European standard

of allergens, hematogram, and serum IgE values were determined. Skin biopsies for epidermal lipograms and histology as 5 mm punchbiopsies were taken from the lateral palmar quadrant in the area of greatest activity at 0, 16, and 24 weeks. Plasma, red cells, and separated epidermal lipograms were performed at weeks 0, 16, and 24. Histologically, skin was evaluated for signs of acute, subacute, or chronic hand dermatitis.

Results
After 16 weeks of therapy, both the Epogam and placebo groups had statistical clinical improvement in dryness, redness, and cracking with no statistical difference between the two. After 24 weeks (washout period weeks 16 to 24), the Epogam group additionally had statistically significant improvement in itch, vesiculation, and edema. At baseline, four patients in the Epogam group, three in the placebo group, and all of the control group showed normal histology. During the first 16 weeks of the trial, seven Epogam patients and 15 placebo patients showed histological improvement. During the washout phase of the trial, the histological parameters of both groups were comparable to week 16. No significant difference was found in the change in Odland bodies or intracellular multilamellar lipid sheets or epidermal GLA content. No statistically significant decrease in topical steroid use was found.

Side effects
None mentioned in paper.

Authors' comments
The similarity of favorable results between the two patient groups underlines that hand dermatitis is often characterized by a chronic relapsing course. It is possible that the trial period fell into the natural improvement phase of the disease. Regular follow-up visits made the patients more aware of their condition, and clinical guidance could have enhanced the use of emollients and avoidance of allergens. This study therefore indicates that orally administered GLA for chronic hand dermatitis has no superior therapeutic value to that of placebo. The significant improvement of all clinical parameters at the end of the trial for both study groups emphasizes the necessity of long-term randomized and controlled double-blind studies.

Reviewer's comments
This was a well-designed study showing evening primrose oil is not efficacious in this type of dermatitis. (5, 5)

Clinical Study: EF4 (Epogam)®

Extract name	N/A
Manufacturer	Scotia Pharmaceuticals Ltd., UK

Indication	**Diabetic neuropathy** (nerve degeneration)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Keen H, Payan J, Allawi J, Walker J, Jamal GA, Weir AI, Henderson LM, Bissessar EA, Watkins PJ, Sampson M, et al. (1993). Treatment of diabetic neuropathy with gamma-linolenic acid. *Diabetes Care* 16 (1): 8-15.

Trial design
Parallel.

Study duration	1 year
Dose	6 capsules twice daily (480 mg/day GLA)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	7 centers
No. of subjects enrolled	111
No. of subjects completed	84
Sex	Male and female
Age	18-70 years (mean: 53)

Inclusion criteria
Mild diabetic neuropathy with clinical evidence such as parasthesia, numbness, weakness, impaired reflexes, or pain; idiopathic diabetes mellitus of either main clinical type; no major changes in diabetes management for at least six months; at least two of the following neurophysiological criteria in the same limb: peroneal MNCV <40 m/s at 34°C, sural MNCV <40 m/s at 34°C, sural SNAP <5μV, and heat threshold or cold threshold outside the 99 percent confidence limit for normal individuals.

Exclusion criteria
Other forms of neuropathy, including carpal tunnel syndrome; or severe neuropathy (immeasurable conduction in common peroneal nerve and/or absent sural sensory potential).

End points
Patients were evaluated at baseline and at 3, 6, and 12 months. The following neurophysiological measurements were performed on limbs: motor nerve conduction velocity (m/s), compound muscle action potential (CMAP) amplitudes (mV), sensory nerve action potential amplitudes (μV), and warm and cold threshold measurements. Neurological examination consisted of isometric muscle strength measurements in wrists, fingers, and toes, and tendon reflexes in upper and lower limbs. Sensation was also assessed for upper and lower limbs. Blood taken at each visit was tested for glucose, hemoglobin A1 (HbA, a measure of blood glucose control), routine hematology, urea, electrolytes, total protein, albumin, fructosamine, alkaline phosphatase, gamma-glutamyl transferase, and aspartate aminotransferase.

Results
All ten neurophysiological parameters improved with evening primrose oil, eight significantly. All ten parameters modestly deteriorated with placebo, four significantly. All six neurological assessments improved with EPO, two significantly. Five of the six assessments deteriorated with placebo, three significantly so. Hemoglobin A1 levels significantly influenced a patient's response to EPO. When the starting level of HbA was less than or equal to 10 percent, improvement with treatment was considerably greater for all 16 parameters than if the HbA starting level was greater than 10 percent.

Side effects
The treatment was well tolerated. No major biochemical or clinical adverse effects were attributable to the treatment.

Authors' comments
Gamma-linolenic acid was found to be superior to placebo. This supports the view that an important factor contributing to the neuropathy of diabetes may be a reduced formation of linoleic acid metabolites. Administration of GLA to patients with mild diabetic polyneuropathy may prevent deterioration and, in some cases, reverse the condition. The treatment is not associated with any important adverse events and may offer an advance in the management of diabetic neuropathy.

Reviewer's comments
The results seem indisputable. EPO has a clear effect on diabetic neuropathy. (5, 6)

Clinical Study: Epogam®

Extract name	N/A
Manufacturer	Scotia Pharmaceuticals Ltd., UK

Indication	**Uremic pruritus** (itch) in dialysis patients
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Tamimi N, Mikhail A, Stevens P (1999). Role of gamma-linolenic acid in uraemic pruritus. *Nephron* 83 (2): 170-171.

Trial design
Parallel.

Study duration	6 months
Dose	Epogam emulsion (10 ml) (32 mg/ml) twice daily
Route of administration	Topical
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	33
No. of subjects completed	16
Sex	Not given
Age	Not given

Inclusion criteria
Dialysis patients on continuous ambulatory peritoneal dialysis (CAPD) or hemodialysis (HD) with intractable itching (pruritus).

Exclusion criteria
None mentioned.

End points
Severity of pruritus and response to treatment assessed by a questionnaire based on severity, frequency, and distribution of pruritus; scratching; number of sleeping hours; and frequency of waking up during the night for scratching. Renal and liver function tests, full blood count, cholesterol, triglycerides, uric acid levels, ferritin, magnesium, zinc, and parathormone levels were measured at the beginning and end of the study.

Results
Epogam had no effect on hematological and biochemical parameters measured.The difference in itching score between groups failed to reach statistical significance ($p < 0.08$). However, some patients derived marked relief from itching. In two cases, itching recurred after cessation of EPO and was relieved again after EPO was reissued.

Side effects
None mentioned in paper.

Authors' comments
Treatment effects are not instantaneous, as time is needed to reconstitute the normal fatty acid balance in the cutaneous cells. The optimal dose and duration of treatment seems not to be known. This study suggests that evening primrose oil may be beneficial in alleviating the symptoms of dialysis itch, and the mechanism may be through reversal or modulation of the pathological changes alluded to previously, but further studies are needed to confirm this.

Reviewer's comments
This study was briefly described in a letter to the editor. The issue of randomization was not addressed, the sex and age of subjects were not described, the data were summarized in insufficient detail to permit analysis, and there was a large number of dropouts. The placebo was also not described. (1, 2)

Product Profile: Efamast

Manufacturer	**Searle, UK**
U.S. distributor	None
Botanical ingredient	**Evening primrose seed oil**
Extract name	N/A
Quantity	500 mg
Processing	No information
Standardization	No information
Formulation	Capsule

Source(s) of information: Kollias et al., 2000.

Clinical Study: Efamast

Extract name	N/A
Manufacturer	Searle, UK
Indication	**Fibroadenomas** (benign breast lumps)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Kollias J, Macmillan RD, Sibbering DM, Burrell H, Robertson JFR (2000). Effect of evening primrose oil on clinically diagnosed fibroadenomas. *The Breast* 9 (1): 35-36.

Trial design
Parallel. Twenty-three women were given the treatment, and 19 women served as controls and received no treatment.

Study duration	6 months
Dose	4 (500 mg) capsules twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	1 hospital breast unit
No. of subjects enrolled	23
No. of subjects completed	20
Sex	Female
Age	22-49 years (median: 29)

Inclusion criteria
Female patients with breast lumps classified as benign (less than 3 cm and having benign characteristics) who did not wish to have lumps removed surgically.

Exclusion criteria
None mentioned.

End points
Clinical size of breast lumps measured in two dimensions using calipers and

ultrasound measurements taken in 3D prior to initial fine needle aspiration. Measurements were repeated at six months.

Results
After six months, change in mean ultrasound size of fibroadenomas in treatment and control groups was not statistically significant (p = 0.6). In the Efamast group, 11 out of 21 fibroadenomas reduced in size (52 percent), while in the control group, 8 out of 19 fibroadenomas reduced in size (42 percent), a non-statistically significant comparison between the two groups. No fibroadenomas in either group became impalpable.

Side effects
None mentioned in paper.

Authors' comments
The present study failed to demonstrate that the administration of oil of evening primrose was followed by any appreciable size reduction in women with fibroadenomas compared with a control group. The small number of patients used in this study made statistical evaluation between groups difficult.

Reviewer's comments
This study is flawed by its lack of randomization, blinding, placebo control, and small sample size. (1, 3)

Product Profile: Evening Primrose Oil (generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Evening primrose seed oil**
Extract name	N/A
Quantity	No information
Processing	No information
Standardization	No information
Formulation	Capsule

Source(s) of information: Haslett et al., 1983.

Clinical Study: Generic

Extract name	N/A
Manufacturer	None

Indication	**Obesity**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Haslett C, Douglas JG, Chalmers SR, Weighhill A, Munro JF (1983). A double-blind evaluation of evening primrose oil as an antiobesity agent. *International Journal of Obesity* 7 (6): 549-553.

Trial design
Patients were divided into two groups: (A) 40 subjects suffering from refractory obesity. These subjects had attended the obesity clinic for one year or more and had failed to lose weight in the previous three months (during which they had not received an antiobesity agent). (B) 60 subjects referred to the clinic for the first time. In each group, the subjects were divided into two groups—placebo and active treatment. Subjects were given carbohydrate-restricted dietary advice designed to provide 1,000 calories per day. They were also given a supply of ascorbic acid tablets (250 mg/tablet) and told to take them three times per day.

Study duration	3 months
Dose	4 (0.6 ml) capsules twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Hospital obesity clinic
No. of subjects enrolled	100
No. of subjects completed	74
Sex	Female
Age	19-61 years (mean: 42)

Inclusion criteria
Women at least 20 percent in excess of ideal body weight.

Exclusion criteria
Subjects outside the age range of 16 to 69; cardiac failure; dependent edema; nonstable endocrine disease such as poorly controlled diabetes or untreated hypothyroidism; subjects taking salicylates or other medications known to interfere with prostaglandin synthesis or action.

End points
Subjects assessed hunger rating on a linear analog scale from 0 to 100. They were weighed and blood was obtained for hematological and biochemical analysis every two weeks.

Results
In group A, mean weight loss achieved after two weeks was 1.1 kg in the placebo group and 0.9 kg in the evening primrose oil group. In group B, mean weight loss after two weeks was 4.1 kg in the placebo group and 3.2 kg in the EPO group. There was no statistical difference with either group. Eighteen reported a reduction in appetite, nine of whom were receiving placebo.

Side effects
Two subjects complained of hair loss (one active, one placebo), and three subjects taking EPO complained of skin changes.

Authors' comments
In this double-blind study, EPO was given in a high-dose regime and ascorbic acid was administered concurrently in order to facilitate the conversion of gamma-linolenic acid to prostaglandin. Overall weight losses achieved in those subjects treated at time of referral to the clinic are comparable to previous experience. Neither in these subjects nor in those with refractory obesity did EPO exert a clinically relevant antiobesity effect. Findings show that EPO is of no practical value in the treatment of the obese female subject.

Reviewer's comments
Despite the methodological flaws, one might have expected some trends if there was any efficacy here. The trial was not randomized, and the statistical methods were not adequately described. (1, 3)

Product Profile: Efamol Marine

Manufacturer	**Scotia Pharmaceuticals Ltd., UK**
U.S. distributor	None
Botanical ingredient	**Evening primrose seed oil**
Extract name	N/A
Quantity	430 mg
Processing	No information
Standardization	No information
Formulation	Capsule

Other ingredients: Marine fish oil (107 mg, contains 17 mg eicosapentaenoic acid and 11 mg docosahexaenoic acid).

Source(s) of information: Veale et al., 1994; Berth-Jones and Graham-Brown, 1993.

Clinical Study: Efamol Marine

Extract name	N/A
Manufacturer	Efamol Ltd., UK
Indication	**Rheumatoid arthritis**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Belch JJF, Ansell D, Madhok R, O'Dowd A, Sturrock RD (1988). Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: A double-blind placebo-controlled study. *Annals of the Rheumatic Diseases* 47 (2): 96-104.

Trial design
Parallel. Three-arm study: Efamol; Efamol Marine; and placebo. Patients taking Efamol were given 12 capsules (540 mg GLA) per day. Each group's capsules also contained 120 mg/day of vitamin E as an antioxidant. During the first three months of treatment, patients were instructed to take the treatment along with their usual NSAIDs. From 3 to 12 months, patients were instructed to decrease or stop taking their NSAIDs if possible without exacerbation of rheumatoid arthritis symptoms. From 12 to 15 months, patients were instructed to maintain, if possible, their current dose of NSAIDs. At 12 months, all patients received placebo capsules without vitamin E in order to assess whether any improvement in condition was due to vitamin E and to monitor relapse. The last phase of the trial was single-blinded.

Study duration	1 year 3 months
Dose	12 capsules (450 mg GLA, 240 mg EPA) per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Efamol

Site description	Not described
No. of subjects enrolled	49
No. of subjects completed	34
Sex	Male and female
Age	28-74 years (mean: 49)

Inclusion criteria
Classical or definite rheumatoid arthritis as defined by the American Rheumatism Association. Patients with mild rheumatoid arthritis requiring first-line NSAID therapy for control of symptoms.

Exclusion criteria
Patients with severe rheumatoid arthritis requiring second-line therapy.

End points
Patients were monitored monthly for the first six months, then every three months thereafter. Full metrological assessment was carried out at 0, 3, 6, 12, and 15 months, including duration of morning stiffness in minutes, grip strength of each hand, Ritchie articular index, and a 10 cm visual analog pain scale completed by patients. Side effects were noted. Patients were asked to assess whether they had received any benefit from treatment. Blood was drawn and assessed for erythrocyte sedimentation rate (ESR), C reactive protein levels, and hemoglobin and rheumatoid factor.

Results
The amount of NSAIDs after 12 months was reduced for 11 of 15 patients taking Efamol ($p < 0.003$), 12 of 15 taking Efamol Marine ($p < 0.002$), and 5 of 15 taking placebo ($p < 0.05$). At that time, improvement was reported by 94 percent on Efamol, 93 percent on Efamol Marine, and 30 percent on placebo. However, there were no significant changes in clinical or lab measurements in any of the groups throughout the study. After the three-month run-out placebo phase at the end of the trial, 100 percent of Efamol patients and 80 percent of Efamol Marine patients, compared with only 14 percent of placebo patients, had returned to baseline or become worse. Overall, the only difference between the Efamol and Efamol Marine groups was that the Efamol Marine group had an earlier response to treatment.

Side effects
Two patients in the Efamol group experienced nausea and diarrhea (respectively) and subsequently withdrew from the study. Two patients in the Efamol Marine group experienced nausea and headache (respectively), but neither withdrew from the study.

Authors' comments
It is possible to decrease or stop NSAID treatment in some patients with

rheumatoid arthritis by introducing Efamol or Efamol Marine treatment. It should be noted, however, that although patients claimed a subjective improvement, no change was recorded in any of the measures conventionally used to measure disease activity. It would seem that these oils may be best used in clinical situations in which NSAID therapy should be avoided.

Reviewer's comments
This was a well-designed study, but there was no clear benefit of evening primrose oil for rheumatoid arthritis. These results are in contrast to trials in which eicosapentanoic acid in fish oil has shown a consistent trend toward efficacy in rheumatoid arthritis. (5, 6)

Clinical Study: Efamol Marine

Extract name	N/A
Manufacturer	Scotia Pharmaceuticals Ltd., UK
Indication	**Psoriatic arthritis**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Veale DJ, Torley HI, Richards IM, O'Dowd A, Fitsimons C, Belch JJF, Sturrock RD (1994). A double-blind placebo controlled trial of Efamol Marine on skin and joint symptoms of psoriatic arthritis. *British Journal of Rheumatology* 33 (10): 954-958.

Trial design
Parallel. For nine months, patients took either Efamol Marine (evening primrose oil plus fish oil) or placebo, followed by three months run-out phase in which all took placebo. For the first three months, patients maintained their normal intake of NSAIDs. After that, patients were asked to reduce their intake and maintain that decrease providing that they experienced no worsening of joint symptoms.

Study duration	9 months
Dose	12 capsules (480 mg GLA, 240 mg EPA, 132 mg DHA) per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	38
No. of subjects completed	32
Sex	Male and female
Age	18-76 years (mean: 40)

Inclusion criteria
Chronic stable plaque psoriasis and inflammatory arthritis; negative for rheumatoid factor (RF) (latex); involvement of at least one peripheral joint with or without sacroiliitis; stable dose of paracetamol and/or NSAID for at least one month prior to study.

Exclusion criteria
Patients suffering from epilepsy, undergoing treatment with systemic steroids, beta-blocking drugs, or phenothiazines.

End points
Clinical assessments of inflammatory joint disease, grip strength, number of active joints, Ritchie articular index, duration of morning stiffness, and NSAID intake were performed at 0, 1, 3, 6, 9, and 12 months. Prostatic skin disease severity was assessed using a 100 mm visual analog scale. The patient recorded changes in skin itch. At each visit, blood tests for hemoglobin, white cell count, platelet count, ESR, CRP, immunoglobulins, urea, electrolytes, and liver enzymes were performed. The effect on arachidonic acid metabolism was determined by measuring levels of TXB2 in serum and LTB4 in supernatants following stimulation of polymorphonuclear (PMN) cells.

Results
No significant differences were found between the two groups in clinical or laboratory indices of arthritis disease activity at 6, 9, or 12 months. Three patients in the Efamol group and four patients in the placebo group were able to discontinue use of NSAIDs without worsening their condition. No significant difference was observed in skin disease severity or activity between the two groups. The level of LTB4 decreased over the study period in the Efamol group and was significantly different at nine months in comparison to baseline ($p < 0.03$). No significant change occurred in the placebo group. TXB2 levels consistently were lower in the Efamol group than in the placebo group. During the last three months (the placebo phase) of the trial, significant increases in TXB2 levels in the Efamol group suggested a rebound increase in production. This increase did not occur in the placebo group.

Side effects
Two patients in the active treatment group withdrew due to diarrhea.

Authors' comments
This trial failed to demonstrate that fish oil could substitute for NSAID therapy in psoriatic arthritis. However, it did demonstrate metabolic effects on prostanoid and leukotriene metabolism suggesting that larger doses of fish oil might produce a clinical response.

Reviewer's comments
A well-designed study with appropriate inclusion/exclusion criteria and outcome measures. However, the study was too small to document differences in response rates. (5, 4)

Garlic

Latin name: ***Allium sativum* L.** [Liliaceae]
Plant part: **Bulb**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Garlic has been used as a medicine for more time and by more cultures than perhaps any other plant. Garlic is unique in its high sulfur content, which is four times greater than that of the other high sulfur-containing vegetables and fruits, such as onion, broccoli, cauliflower, or apricots. The most abundant sulfur compound in garlic is alliin, which is typically present at 10 mg per gram fresh weight. When garlic cloves are cut, crushed, or chewed there is a conversion, within seconds, of alliin to allicin by the enzyme allinase. Allicin is thought to be important to the beneficial effects of garlic and is also responsible for its characteristic odor. Therapeutic effects are also attributed to other sulfur compounds (Lawson, 1996).

Garlic powder is the product most similar to fresh cloves in chemical composition, as it is dehydrated at a low oven temperature and then pulverized. When carefully prepared, the allinase activity is preserved. A very important aspect of the effective quality of garlic powder products is that allicin can be formed after consumption. Therefore, many garlic supplements are standardized to their "allicin potential." Because the enzyme allinase, necessary to produce allicin, is destroyed by the acidic pH of the stomach, many garlic preparations are enteric coated. This coating delays dissolution of the capsule or tablet until it reaches the intestine (Lawson, 1996).

Powdered garlic preparations tested in clinical studies include Kwai®, Pure-Gar®, as well as unbranded or generic dried garlic. Kwai is manufactured by Lichtwer Pharma AG in Germany and distributed in the United States by Lichtwer Pharma US, Inc. The tablets contain a preparation known as LI 111 that is standardized to contain

GARLIC SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Kwai®	Lichtwer Pharma AG, Germany/ Lichtwer Pharma U.S., Inc.	Dried garlic, standardized to 1.3 % alliin, 0.6% allicin	300 mg 3 times daily, total 900 mg	Hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia (elevated blood lipid levels)	15	Yes (I-2, II-1, III-3) Trend (II-2, III-1) No (I-3, II-2) Undetermined (III-1)
				Lipids and lipoproteins in normal volunteers	1	Undetermined (III-1)
				Atherosclerosis	1	Trend (II-1)
				Postmeal lipid levels	1	Undetermined (II-1)
				Increased spontaneous platelet aggregation	1	Trend (II-1)

Pure-Gar®	Essentially Pure Ingredients™/ Essentially Pure Ingredients™	Dried garlic, 0.3% allicin	680 mg twice daily, total 1,360 mg	Hypercholesterolemia (elevated cholesterol levels)	1	Yes (II-1)
Generic	None	Dried garlic	594 to 1,350 mg daily	Hyperlipoproteinemia	1	No (III-1)
Generic	Government Pharmaceutical Organization, Thailand/ None	Spray-dried garlic	700 mg daily	Hyperlipoproteinemia	1	Undetermined (III-1)
				Diabetes (NIDDM)	1	Undetermined (III-1)
Kyolic® Aged Garlic Extract™, HIPO™ Formula 100	Wakunaga of America Co., Ltd./ Wakunaga of America Co., Ltd.	Aged garlic (ethanolic extract)	2.4 to 7.2 g daily	Hypercholesterolemia	2	Yes (I-1) Undetermined (III-1)
				Blood clotting factors	1	MOA (I-1)
				Lipid oxidation	1	MOA (III-1)
Kyolic® Liquid Aged Garlic Extract™	Wakunaga of America Co., Ltd./ Wakunaga of America Co., Ltd.	Aged garlic (ethanolic extract)	4 (1 ml) capsules daily	Hypercholesterolemia	1	Undetermined (III-1)

GARLIC SUMMARY TABLE (continued)

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Garlic oil	None	Oil, ethyl acetate extracted	Equivalent of 2 g raw garlic daily/0.25 mg oil per kg body weight	Heart disease	2	Yes (II-1, III-1)
Garlic oil	General Nutrition Research Laboratories/None	Oil, cold pressed	18 mg daily	Cardiovascular risk factors	1	Yes (II-1)
Tegra	Hermes Arzneimittel GmbH, Germany/None	Oil, steam distilled, bound to cyclodextrin	10 mg daily	Hypercholesterolemia	1	No (II-1)
Garlic (raw)	None	Raw	10 g daily	Hypercholesterolemia	1	Trend (III-1)
				Cardiovascular risk factors	1	Trend (III-1)

600 mcg allicin in 100 mg garlic powder. Kwai is also sold as Sapec®. Pure-Gar is a brand of garlic powder supplied as raw material to manufacturers that incorporate it into numerous branded products. It is manufactured by Essentially Pure Ingredients™, which is owned by Natrol, Inc.

Aged garlic extract (AGE) is prepared by storing sliced garlic in 15 to 20 percent aqueous ethanol for 18 to 20 months. After this time, the liquid is filtered and concentrated. Most of the sulfur compounds responsible for the characteristic garlic odor are removed during processing. There are few allicin or alliin-derived compounds. The sulfur compound measured for quality purposes is *S*-allylcysteine. Aged garlic extract is available in both liquid and dry forms. The liquid form contains 10 percent ethanol (Lawson, 1996). Kyolic® Aged Garlic Extract™ is provided by Wakunaga of America Co., Ltd. The trials reviewed used both dry and liquid forms; however, the doses used in the trials were much higher than those suggested in the available product literature.

Garlic contains only a very small amount of oil-soluble compounds. Commercial garlic oil is produced by steam distillation of chopped garlic, a process that converts allicin and other thiosulfinates to oil-soluble allyl sulfides. Garlic oils are also prepared by maceration with organic solvents or common plant oils such as soybean oil. Garlic oils contain mostly alliin-derived compounds. In addition, vinyldithiins and ajoene are present. Garlic oils are not usually characterized by their sulfide content, but tend rather to be promoted as containing a specific amount of "pure garlic oil" (Lawson, 1996).

Three garlic oil preparations have been tested in clinical studies, including ethyl acetate extracted, cold pressed, and steam distilled. The ethyl acetate preparation was made by extracting peeled, crushed garlic cloves with ethyl acetate, evaporating the solvent, and finally dissolving the resultant oil in soy oil. No details were provided for the manufacturer of the "cold-pressed garlic oil" used in the reviewed clinical trial, except that the oil was provided by General Nutrition Research Laboratories. Steamed distilled garlic oil is commonly referred to as the "essential oil of garlic." It is produced by steam distillation of crushed garlic cloves, but, as garlic itself contains very little essential oil, the term is a misnomer. Commercial-grade products are often diluted with a vegetable oil. We list one trial that used a proprietary product called Tegra, which contains garlic oil bound to cyclo-

dextrin. Tegra is manufactured by Hermes Arzneimittel GmbH in Germany and is not sold in the United States.

Finally, two trials used fresh garlic that was consumed raw.

SUMMARY OF REVIEWED CLINICAL STUDIES

Clinical trials using garlic preparations have mostly focused on the possible reduction in risk for atherosclerotic heart disease. Elevated plasma (blood) lipids (cholesterol and triglycerides) are considered risk factors for heart disease, and much of preventative treatment has focused on lowering these levels to within parameters considered normal.

Sources for cholesterol are dietary intake of animal fats and production by the liver. Cholesterol is transported in the blood by lipoproteins, and the major categories of lipoproteins are very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). VLDL and LDL transport fats, primarily triglycerides (TG) and cholesterol, from the liver to cells throughout the body. Elevations of either VLDL or LDL are associated with an increase in risk for developing atherosclerosis, a primary cause of heart attack and stroke. The role of HDL is to return fats to the liver. Hence the ratios of total cholesterol (TC) to HDL cholesterol and LDL to HDL indicate whether cholesterol is being deposited into tissues or broken down and excreted. It is recommended that total serum cholesterol be less than 200 mg/dl, LDL be less than 130 mg/dl, HDL cholesterol be greater than 35 mg/dl, and triglyceride levels be less than 150 mg/dl (Pizzorno and Murray, 1999).

Cholesterol levels above 240 mg/dL are generally treated with statin drugs, such as lovastatin (Mevacor) and simvastatin (Zocor). Statins inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in the biosynthesis of cholesterol. A reduction in serum cholesterol levels of 25 to 45 percent can be expected with statins (Hardman et al., 1996).

Two other classes of drugs used to reduce cholesterol levels are bile acid sequestrants and nicotinic acid (niacin). Bile acid sequestrants are anion exchange resins that prevent the normal reabsorption of bile salts from the intestine. The reduction in bile reabsorption causes an increase in demand for bile salts to replenish the supply. As bile contains cholesterol, this results in a decrease in plasma levels

and a restoration of bile acid production. Treatment often results in reductions in plasma cholesterols levels of 15 to 30 percent. Nicotinic acid (niacin) has diverse actions affecting lipoprotein metabolism. It appears to reduce VLDL levels through transient inhibition of liposis, delivery of free fatty acids to the liver, triglyceride synthesis, and VLDL-triglyceride transport. A reduction of 10 to 20 percent in plasma cholesterol levels is common with this treatment (Hardman et al., 1996).

The garlic preparations studied clinically for reduction in risk for atherosclerotic heart disease include dried garlic, aged garlic, garlic oil, and raw garlic. The end points of those trials include elevated serum cholesterol, hypertension, blood clotting factors, and lipid oxidation. By far, the most extensive number of studies has been conducted on the ability of dried garlic, essentially Kwai, to reduce elevated levels of plasma lipids, especially cholesterol.

Kwai Garlic

A total of 19 controlled studies on Kwai garlic were reviewed. All but two of these studies investigated the potential role of Kwai garlic on serum lipid levels. Six of these studies also reported results on blood pressure testing, and three also examined lipid oxidation. In all but five studies, 900 mg of dried garlic powder was used daily and administered in 300 mg doses three times per day. Most of the trials were conducted for a period of three months or longer.

Hyperlipidemia, Hypercholesterolemia, Hyperlipoproteinemia (Elevated Blood Lipid Levels)

Of the trials which examined the possible beneficial effect of Kwai on plasma lipid profiles, nine studies were positive and eight studies were negative. In the positive trials, statistically significant reductions in serum total cholesterol were reported after one to three months of treatment.

Three studies of good quality reported significant reductions in total cholesterol. A study with 219 subjects reported a reduction in mean serum total cholesterol from 266 to 235 mg/dl after four months of treatment, a reduction of 12 percent. The author stated that the greatest benefit was seen with the subgroup of patients with initial

cholesterol levels between 250 and 300 mg/dl, compared to the subgroup with initial levels between 200 and 250 mg/dl (Mader, 1990). Another high-quality trial with 94 subjects with total serum cholesterol levels above 250 mg/dl compared Kwai (900 mg/day) to bezafibrate (600 mg/day). Bezafibrate belongs to a class of drugs that lowers the levels of triglyceride-rich lipoproteins, such as VLDL, and modestly raises HDL levels (Hardman et al., 1996). In this study, garlic reduced mean serum cholesterol from 282 mg/dl to 210 mg/dl after 12 weeks of treatment, a reduction of 25 percent. Bezafibrate reduced total cholesterol to a similar extent, with no significant difference between the two groups. Over the 12 weeks of the study, both groups also had significant decreases in LDL and triglyceride levels as well as a significant increase in HDL levels (Holzgartner, Schmidt, and Kuhn, 1992). In the third good-quality, placebo-controlled trial with 47 subjects with mild hypertension, the total cholesterol in the treatment group fell from 268 mg/dl to 239 mg/dl after eight weeks, and to 230 mg/dl after 12 weeks (Auer et al., 1990). A modest (6 percent) reduction in elevated total cholesterol, from 262 to 247 mg/dl after three months, was reported in a good-quality, placebo-controlled study with 42 subjects. In this study, LDL was also significantly reduced in comparison to placebo (Jain et al., 1993).

Four other placebo-controlled studies, deemed poor quality, reported significant reductions, in the range of 9 to 21 percent, of elevated total cholesterol. The first study included 52 subjects and reported a significant reduction in total cholesterol compared to baseline and placebo after six months. LDL levels also decreased significantly compared to baseline in the treatment group. There was no significant change to triglyceride or HDL levels (De A Santos and Grunwald, 1993). In a small crossover trial with 19 subjects, treated for four months, there was a significant reduction in total cholesterol compared to baseline, an insignificant increase in HDL, and no change in triglyceride levels (Melvin and Chappell, 1996). A parallel study with 40 subjects reported a significant drop in total cholesterol and triglyceride levels compared to placebo after four months (Vorberg and Schneider, 1990). The fourth study included 46 subjects with elevated cholesterol and used a combination of single- and double-blinding to compare the effects of garlic, fish oil (12 g/day), both garlic and fish oil, and placebo on lipid levels following three months of treatment. As a result, those receiving garlic and garlic plus fish oil

had a reduction in both total cholesterol and LDL. Fish oil alone did not lower cholesterol and slightly elevated LDL. By contrast, triglycerides were reduced by fish oil as well as the combination of fish oil and garlic, but not by garlic alone (Adler and Holub, 1997).

Seven good-quality, placebo-controlled studies including participants with elevated lipid levels reported no significant effects on cholesterol levels. The most remarkable was a six-month study that included 106 subjects with an initial mean total cholesterol of roughly 270 mg/dl. This very well conducted and designed study showed no significant differences in serum lipids, lipoproteins, apolipoprotein A1 or B, or resistance of LDL to oxidation (Neil et al., 1996). The second trial with 30 children aged eight to 18 with a baseline level of total cholesterol of 265 mg/dl reported no effect on lipid levels after two months (McCrindle, Helden, and Conner, 1998). A third study with 42 subjects with initial cholesterol levels of 262 mg/dl also reported no change in lipid levels after three months (Isaacsohn et al., 1998). A crossover study with 29 subjects with mildly elevated cholesterol (254 mg/dl) found no significant differences in plasma cholesterol or other lipids after three months of treatment. There was also no effect on experimental ex vivo oxidation of LDL (Simons et al., 1995). A placebo-controlled trial with 50 subjects with moderately elevated cholesterol (245 mg/dl) found no effect from three months of treatment with Kwai on levels of triglycerides, total cholesterol, LDL, or HDL (Superko and Krauss, 2000). Another good-quality study with 68 healthy volunteers with slightly elevated cholesterol (223 mg/dl) found no significant reductions in total cholesterol or triglyceride levels at the end of 15 weeks of treatment (Saradeth et al., 1994). A study including 120 subjects with mildly elevated cholesterol levels of 228 mg/dl reported no change after one month of treatment (Kiesewetter et al., 1991).

A poor-quality study, including 60 non-insulin-dependent diabetics (NIDDM) with elevated cholesterol (254 mg/dl), showed a trend toward reduction of serum total cholesterol and LDL that was not significant at the end of three months of treatment. However, HDL cholesterols rose in comparison to the placebo group (Mansell et al., 1996).

There are several possible explanations for the mixed results of Kwai in regard to serum cholesterol levels. One suggestion is that studies must be designed carefully to optimize outcome. In only a few

studies was diet carefully controlled, and this aspect may be important in evaluating the potential benefit of garlic. Another consideration is the formulation of the Kwai product. If the release of contents is not timed properly, the full allicin potential may not be reached, rendering the product inactive. A recent paper explored the release of allicin under simulated gastrointestinal conditions (USP method for dissolution testing). The authors were able to test the lots of Kwai used in clinical studies in the dissolution test. They found that the amount of allicin released from garlic powder tablets under simulated gastrointestinal conditions correlated well with the success or failure of such tablets to lower serum cholesterol values in controlled clinical trials. Of interest was a highly significant difference in the effect on serum cholesterol found between trials conducted on Kwai garlic tablets before 1993 and those conducted in 1993 and later. The sharp decline in the effectiveness of the tablets is paralleled by sharp declines in both the acid resistance and the allicin release from the tablets, apparently caused by a change in the coating of the tablet (Lawson, Wang, and Papadimitriou, 2001).

Elevated Blood Pressure

Two of the previously described studies that included patients with hypertension (blood pressure ≥140/90 mmHg, systolic/diastolic) reported decreases in blood pressure, both systolic and diastolic, of 11 to 17 percent (Auer et al., 1990; De A Santos and Grunwald, 1993). Four other studies that measured blood pressure and included subjects without hypertension reported little to no effect (Adler and Holub, 1997; Kiesewetter et al., 1991; McCrindle, Helden, and Conner, 1998; Simons et al., 1995). It appears that garlic may have a normalizing effect, reducing only blood pressure that is already elevated.

Lipids and Lipoproteins in Normal Volunteers

A crossover study included ten subjects with initial normal lipid levels who were given 600 mg LI 111 or placebo for two-week treatment periods with a one-week washout period in between. Kwai garlic did not alter levels of total cholesterol, LDL, or HDL. The authors of the study commented that two weeks was probably too short a time to see any significant changes in lipid levels. However, there was a

significant reduction in ex vivo oxidation of apoB-containing lipoproteins after two weeks compared to baseline (Phelps and Harris, 1993).

Antioxidant Activity

Two studies reviewed previously examined the role of Kwai in reducing oxidation of lipoproteins and did not find any benefit. These studies, which included hyperlipidemic subjects, also did not report any cholesterol-lowering activity (Neil et al., 1996; Simons et al., 1995). These results contrast the results of the study reviewed which reported a reduction in ex vivo oxidation of apoB-containing lipoproteins in subjects with normal lipid levels (Phelps and Harris, 1993). It is possible that the discrepancy between these findings is due to the variability in the bioavailability of allicin in Kwai products, as previously discussed.

Atherosclerosis

A well-conducted study included 152 subjects with advanced atherosclerotic plaques as measured by ultrasound. The subjects were given 900 mg LI 111 or placebo for four years. As a result, the plaque volume in the treatment group decreased by 2.6 percent. The plaque volume in the placebo group increased by 16 percent, and there was a significant difference between the two groups. An analysis of subgroups found that those subjects aged 50 to 80 years had a larger reduction in plaque size (6 to 13 percent) compared to placebo. Further subgroup analysis reported that the reductions compared to placebo were 4.4 percent for men and 58 percent for women. The significance of the result with women was questioned, as the predominately younger women in the placebo group (age range 40 to 55 years) had a drastic increase in plaque volume (53 percent), while the mainly older women (aged over 55 years) in the garlic group had a plaque reduction of 4.6 percent (Koscielny et al., 1999).

Postmeal Lipid Levels

In a novel approach, lipid levels were measured before and after a high-fat meal in groups of healthy volunteers taking placebo or Kwai

garlic (900 mg daily), at baseline, and after three and six weeks. The increase in triglycerides after the meal was less in the garlic group than in the placebo group, but it was not significant due to the small number of participants (24) and the large variation in individual lipid levels. However, after six weeks, the garlic group had a significant decrease in fasting triglyceride levels compared to the placebo group (Rotzsch et al., 1992).

Platelet Aggregation

Authors of a good-quality study, with 120 subjects given 800 mg Kwai garlic for one month, reported a reduction in spontaneous platelet aggregation, from 10 to 56 percent depending upon the test method (Kiesewetter et al., 1991). This study indicated a possible use for Kwai garlic in the inhibition of thrombocyte aggregation in patients unable to tolerate aspirin.

Pure-Gar

Hypercholesterolemia (Elevated Cholesterol Levels)

A fairly well-designed study included 35 renal failure patients with hypercholesterolemia. The subjects were given placebo or Pure-Gar, a preparation standardized to deliver 4 mg allicin per day for three months. Baseline levels of total cholesterol were significantly reduced from 290 to 275 mg/dl and levels of LDL from 193 to 182 mg/dl, while there was no such effect from placebo (Lash et al., 1998).

Generic Dried Garlic Preparations

Hyperlipoproteinemia (Elevated Blood Lipid Levels)

There was no benefit to cardiovascular risk parameters in two poorly described, placebo-controlled, crossover studies including subjects with hyperlipoproteinemia that were reported together. The first study included 34 subjects and used an unnamed commercial dried garlic preparation at a dose of 594 mg per day. The second study included 51 subjects and used a specially prepared supplement at 1350 mg per day. Following six weeks of treatment, there was no effect on

total cholesterol, HDL, LDL, or triglycerides in either study. In addition, the second study found no effect on whole blood coagulation time, prothrombin time, or fibrinogen levels (Luley et al., 1986).

Another poorly described study was conducted with a garlic preparation supplied by the Thai government. In the trial of crossover design, 30 subjects with hyperlipoproteinemia did not experience any significant effects on plasma lipid levels. Baseline lipid levels for total cholesterol (280 mg/dl), triglycerides (355 mg/dl), and HDL (38 mg/dl) did not change significantly following a dose of 700 mg dried garlic per day for two months (Plengvidlya et al., 1998).

Diabetes (NIDDM)

Another poorly described study was conducted with the garlic preparation supplied by the Thai government. This was a placebo-controlled study conducted with 33 diabetic patients with mildly elevated serum cholesterol (228 mg/dl). Treatment for one month, with 700 mg dried garlic per day, had no effect on blood glucose, serum insulin, or lipid levels compared to baseline. This study included a highly heterogeneous sample of non-insulin-dependent diabetics, and the sample size may have been too small to show any changes (Sitprija et al., 1987).

Kyolic Aged Garlic Extract

We reviewed five studies with Kyolic Aged Garlic Extract, one using the liquid formulation. Three studies indicated a reduction in lipid levels for those with hyperlipidemia. One study indicated a reduction in platelet aggregation, and two studies indicated reductions in platelet adhesion. Another study demonstrated weak, inconsistent antioxidant activity that was not as powerful as supplementation with vitamin E.

Hypercholesterolemia (Elevated Cholesterol Levels) and Platelet Function

A three-part, six-month pilot study included 51 volunteers, some of whom had elevated cholesterol. The participants were treated with liquid AGE, four (1 ml) capsules daily, or placebo for six months.

Lowering of cholesterol, triglycerides, LDL, and VLDL was reported in the majority of those with elevated baseline levels. The garlic preparation did not affect those whose lipids levels were normal to begin with. In a subgroup with initial cholesterol levels between 220 and 440 mg/dl, 11 of 15 subjects on AGE had a greater than 10 percent lowering of cholesterol (Lau, Lam, and Wang-Cheng, 1987). Our reviewer, Dr. David Heber, concluded that the results of the study were undetermined due to the poor methodology and small sample size.

A study with 34 subjects, with serum cholesterol levels from 220 to 285 mg/dl, reported a 7 percent reduction in serum total cholesterol and a 10 percent reduction in LDL cholesterol compared to baseline after five months of treatment with 7.2 g AGE daily. No change was seen in the placebo group (Yeh et al., 1997). This study was rated as being poor quality.

A good-quality, double-blind, crossover study included 41 moderately hypercholesterolemic men (serum cholesterol levels from 220 to 290 mg/dl). Treatment with a dose of nine (800 mg) capsules (a total of 7.2 g) daily over four to six months led to a 6 to 7 percent reduction in total serum cholesterol compared to placebo. In addition, LDL decreased by 4 percent, blood pressure decreased by 5.5 percent, and there was a 30 percent reduction in platelet adhesion to fibrinogen (Steiner et al., 1996).

Another double-blind, crossover study, with 28 normal healthy adults, studied the effect of 2.4 to 7.2 g AGE per day for six weeks on the function of platelets taken from the subjects' blood. Significant reductions in platelet aggregation with several agonists (epinephrine, adenosine diphosphate [ADP], collagen) were reported, although no consistent increase in response followed an increase in dose. Platelet adhesion to collagen- and fibrinogen-coated surfaces was also reduced by intake of AGE (Steiner and Li, 2001).

Lipid Oxidation

A poor-quality study compared the effects of seven days of administration of either 2.4 g of AGE, 6 g raw garlic, or 0.8 g vitamin E on LDL oxidation in a total of nine subjects. The authors found that AGE provided an inconsistent protection of LDL oxidation which was less than what was observed with vitamin E supplementation (Munday et al., 1999).

Garlic Oil

Four studies on garlic oil are described. Two of these studies used an ethyl acetate extract of crushed garlic, another study used a cold-pressed garlic oil, and the remaining study used a steam-distilled garlic oil preparation bound to cyclodextrin.

Heart Disease

The two studies using the ethyl acetate preparation were double-blind, placebo-controlled studies showing a clear cholesterol-lowering effect in patients with heart disease. The first study, with a dose equivalent to 4 g raw garlic per day for three months, reported a 13 percent decrease in cholesterol (from 253 to 220 mg/dl) and a 15 percent decrease in triglycerides (from 130 to 110 mg/dl) in patients taking garlic oil. High-density lipoprotein cholesterol was increased by 22 percent, and platelet aggregation was also reduced (Bordia, Verma, and Srivastava, 1998). The strength of the evidence in this trial was reduced, as neither the randomization process nor the placebo were described in any detail. The second study, an overall good placebo-controlled study, enrolled subjects with high cholesterol levels (250 to 350 mg/dl). The garlic oil was administered in a dose of 0.25 mg oil per kg body weight (15 g oil, corresponding to 30 g raw garlic, for a 132 lb person) for ten months. After eight months, serum cholesterol was reduced by 18 percent (from a mean of 298 to 244 mg/dl), and this trend continued over the next two months after treatment stopped (dropping to 228 mg/dl) (Bordia, 1981).

Cardiovascular Risk Factors

A study with cold-pressed oil showed a beneficial effect on serum lipid levels in a small, placebo-controlled pilot trial including 20 healthy volunteers. Cholesterol levels dropped from 195 to 180 mg/dl and HDL levels rose from 56 to 69 mg/dl compared to baseline. There was also a reduction in platelet aggregation following a dose of 18 mg of oil, equivalent to 9 g fresh garlic, for four weeks (Barrie, Wright, and Pizzorno, 1987).

Hypercholesterolemia (Elevated Cholesterol Levels)

A study using steam-distilled garlic oil bound to cyclodextrin (Tegra) was widely publicized following publication in the *Journal of the American Medical Association.* This crossover study used a dose of 5 mg twice daily, equivalent to four or five fresh cloves, administered for three months to a total of 25 subjects with moderate hypercholesterolemia. The authors reported no effect on cholesterol metabolism (Berthold, Sudhop, and von Bergmann, 1998a). However, the study was criticized because of the use of steam distillation, which converts allicin to other sulfur compounds, the small dose, and the "prolonged release" formulation that bound the oil to cyclodextrin. In an accompanying letter to the editor, Dr. Lawson reported that the bioavailability of garlic sulfur compounds in this formulation appears to have been limited. Under simulated gastrointestinal conditions (USP methods) only 1.8 mg of the 5 mg present in each tablet was released. In addition, an experiment with two volunteers found only 25 to 40 percent of the expected sulfur on the breath, and whole tablets and large pieces were found in the stool 21 to 24 hours later (Lawson, 1998). The authors of the study replied that the product was specially formulated for slow release, and analysis of 400 stool samples for the trial did not reveal undigested tablets (Berthold, Sudhop, and von Bergmann, 1998b).

Raw Garlic

Hypercholesterolemia (Elevated Cholesterol Levels) and Cardiovascular Risk Factors

Two studies on raw garlic show changes that can be interpreted as beneficial for cardiovascular risk. In both trials, the garlic groups consumed 10 g raw garlic after breakfast for two months, and the control groups were not given anything. The first study included 25 healthy subjects who had never ingested garlic before, with initial cholesterol levels of 160 to 250 mg/dl. This study reported a 15 percent reduction in cholesterol levels from baseline (Bhushan et al., 1979). The second study included 50 healthy volunteers with a mean initial serum cholesterol level of 213 mg/dl. Significant changes were reported in the garlic group, in cholesterol (16 percent decrease), clotting time (17 percent increase), and fibrinolysis (22 percent de-

crease). No significant change in these parameters occurred in the placebo group (Gadkari and Joshi, 1991). The main problems with these studies are that they were not blinded, and eating raw garlic after breakfast could have other effects on the diet that were not accounted for in the control groups.

META-ANALYSES AND SYSTEMATIC CLINICAL REVIEWS

The Agency for Healthcare Research and Quality, an agency in the U.S. Department of Health and Human Services, sponsored a systematic review of garlic through one of its evidence-based practice centers (EPC). The evidence report summarized the effects of garlic on cardiovascular-related factors and disease, associations between garlic and cancer, as well as possible adverse effects. Preparations ranging from dehydrated garlic, aged garlic extracts, and garlic oil macerates to distillates, raw garlic, and combination tablets were pooled together.

The review of cardiovascular-related effects was limited to randomized, controlled trials in humans lasting at least four weeks. The report examined 37 randomized, controlled trials, all but one in adults. Compared with placebo, various garlic preparations led to small, statistically significant reductions in total cholesterol after one month (range of average pooled reduction: 1.2 to 17.3 mg/dl) and even greater reductions after three months (range of average pooled reduction: 12.4 to 25.4 mg/dl). However, eight trials with outcomes at six months showed no significant reduction in total cholesterol compared with placebo. The reason for this disparity was not apparent. Changes in LDL levels and triglycerides mirrored total cholesterol results following three months of treatment. No significant changes to HDL levels were seen after three months.

Potential cardiovascular benefits, other than lipid lowering, that were evaluated in the report are summarized as follows. Effects on blood pressure in 27 small, randomized, placebo-controlled studies were mixed, with some studies reporting a small significant decrease in blood pressure and others reporting no effect. There was no effect on blood glucose in subjects with or without diabetes in 12 small, randomized trials. Two small short trials reported no effect on serum in-

sulin or C peptide levels compared with placebo. Ten small trials, all but one in adults, showed positive effects on platelet aggregation and both positive and negative effects on plasma viscosity and fibrinolytic activity. The report stated that insufficient data were available to confirm or refute garlic's effect on clinical outcomes such as heart attack, peripheral vascular occlusive disease, and atherosclerosis.

Reviews of associations between garlic and cancer were limited to controlled studies that reported precancerous or cancerous lesions in humans consuming varying amounts of garlic. Scant data, primarily from case-control studies, suggest that garlic is associated with decreased odds of certain cancers (laryngeal, gastric, colorectal, and endometrial cancer, and adenomatous colorectal polyps) (Mulrow et al., 2000).

Another meta-analysis of randomized, double-blind, placebo-controlled clinical trials for treating hypercholesterolemia (mean total cholesterol of at least 200 mg/dl or 5.17 mM) was published in the same year as the EPC report. In the 13 trials included in the analysis (a total of 796 persons), treatment with garlic reduced total cholesterol significantly more than placebo ($p < 0.01$); the weighted mean difference was 0.41 mmol/l, equivalent to a 5.8 percent reduction in total cholesterol. An analysis of only six diet-controlled studies with the highest scores for methodological quality found no significant difference in comparison with placebo. The authors concluded that although the data suggest garlic is superior to placebo in reducing total cholesterol, the size of the effect is modest and the reliability of the effect is debatable. Therefore, the implication for clinical use is that garlic supplements may not be an effective way to decrease serum total cholesterol (Stevinson, Pittler, and Ernst, 2000). As in the previous analysis, all forms of garlic preparations were evaluated together.

A meta-analysis examining the effect of garlic on blood pressure concluded that a dose of 600 to 900 mg/day of dried garlic (Kwai) appears to lower systolic and diastolic blood pressure over a period from one to three months. However, the authors concluded that insufficient evidence existed at that time to recommend garlic as an effective antihypertensive agent for routine clinical use. Eight randomized controlled trials, which included 415 subjects, were reviewed. Only three of the trials were specifically conducted with hypertensive subjects (Silagy and Neil, 1994).

EPIDEMIOLOGICAL STUDIES

A critical review of the epidemiologic literature on garlic and cancer found that the evidence from available studies suggests a preventive effect of garlic consumption in stomach and colorectal cancers. Site-specific case-controlled studies, for which multiple reports were available, suggest a protective effect of a high intake of raw and/or cooked garlic. Cohort studies confirm this inverse association for colorectal cancer. However, no link was found with garlic supplements as analyzed in four cohort studies and one case-controlled report (Fleischauer and Arab, 2001).

A case-controlled epidemiological study with 202 adults, from 50 to 80 years old, was included in a study evaluating the possible protective effects of garlic on elasticity of the aorta. The garlic group took at least 300 mg/day of Kwai powdered garlic for at least two years. The elastic properties of the artery were measured using pulse-wave velocity and pressure-standardized elastic vascular resistance. Both measurements were statistically lower in the garlic group ($p < 0.0001$). Aortic elastic properties decreased with increasing age and increased blood pressure in both groups. However, the decrease was significantly lower for the garlic group ($p < 0.0001$). The authors concluded that chronic garlic powder intake reduces age-related increases in aortic stiffness (Breithaupt-Grögler et al., 1997).

ADVERSE REACTIONS OR SIDE EFFECTS

Adverse reactions in the 19 controlled studies on Kwai garlic were mild and not observed in all subjects. Bad breath was the most frequently noted side effect, followed by body odor and mild gastrointestinal distress. The adverse reaction noted in some of the studies of other dried garlic preparations and aged garlic was garlic body odor. The studies on garlic oil preparations noted garlic odor. Abdominal distension was also noted in the study using the steam-distilled preparation bound to cyclodextrin.

A meta-analysis of 13 trials reported that adverse events most commonly included gastrointestinal symptoms and garlic breath (Stevinson, Pittler, and Ernst, 2000). According to the EPC report, adverse effects of oral ingestion of garlic include “smelly” breath and

body odor. In addition, the EPC report cited possible, but unproven, adverse effects of flatulence, esophageal and abdominal pain, small intestinal obstruction, dermatitis, rhinitis, asthma, and bleeding (Mulrow et al., 2000).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

British Herbal Compendium (BHC)
European Scientific Cooperative on Phytotherapy (ESCOP)
German Commission E
World Health Organization (WHO)

Indications

The German Commission E, along with the European Scientific Cooperative on Phytotherapy, the World Health Organization, and the *British Herbal Compendium,* state that garlic bulbs are supportive to dietary measures taken when blood lipid levels are elevated and that they can be used as preventative measures for age-dependent vascular changes (atherosclerosis) (Blumenthal et al., 1998; ESCOP, 1997; WHO, 1999; Bradley, 1992). The *BHC* and WHO maintain that garlic can be used to treat hypertension, and these two monographs, in addition to ESCOP, also suggest garlic for respiratory infections (WHO, 1999; Bradley, 1992; ESCOP, 1997). The *BHC* and ESCOP also suggest garlic for catarrhal conditions. Other indications listed include atheroma (Bradley, 1992), urinary tract infections, ringworm and rheumatic conditions, dyspepsia (WHO, 1999), and circulation improvement in peripheral arterial vascular disease (ESCOP, 1997). The actions of garlic listed by the Commission E include antibacterial, antimycotic, lipid-lowering, inhibition of platelet aggregation, prolongation of bleeding and clotting time, and enhancement of fibrinolytic activity (Blumenthal et al., 1998). The *BHC* lists the following actions: lowers blood cholesterol and triglycerides, hypotensive, lowers blood viscosity, activates fibrinolysis, inhibits platelet aggregation, antimicrobial, anti-inflammatory, and anthelmintic (Bradley, 1992).

Doses

Preparations equivalent to: 4 to 12 mg of alliin (approx. 2 to 5 mg of allicin) daily (Bradley, 1992); 6 to 10 mg of alliin (approx. 3 to 5 mg of allicin) daily (ESCOP, 1997)
Fresh: 4 g fresh garlic daily (Blumenthal et al., 1998); 2 to 5 g fresh (air-dried) bulb (Bradley, 1992)
Dried powder: 0.4 to 1.2 g daily (Bradley, 1992); 0.5 to 1 g daily (ESCOP, 1997)
Oil: 2 to 5 mg (Bradley, 1992)
Extract: 300 to 1,000 mg (as solid material) (WHO, 1999)
Tincture: (1:5, 45 percent ethanol) 2 to 4 ml 3 times daily (ESCOP, 1997)
Note: ESCOP suggests specific dosages for certain indications:

- For prophylaxis of atherosclerosis: the equivalent of 6 to 10 mg of alliin (approx. 3 to 5 mg of allicin) daily, typically contained in one clove of garlic or in 0.5 to 1 g of dried garlic powder (ESCOP, 1997)
- For upper respiratory tract infections: 2 to 4 g of dried bulb or 2 to 4 ml of tincture (1:5, 45 percent ethanol), 3 times daily (ESCOP, 1997)

Treatment Period

ESCOP advises long-term treatment in the prevention of atherosclerosis and prophylaxis or treatment of peripheral arterial vascular diseases (ESCOP, 1997).

Contraindications

The Commission E, *BHC,* and ESCOP list no known contraindications (Blumenthal et al., 1998; Bradley, 1992; ESCOP, 1997).

Adverse Reactions

The Commission E, *BHC,* and ESCOP note that gastrointestinal symptoms, changes to the intestinal flora, or allergic reactions rarely occur (Blumenthal et al., 1998; Bradley, 1992; ESCOP, 1997). The WHO lists one reported case of spontaneous spinal epidural hema-

toma, which was associated with excessive ingestion of fresh garlic cloves (WHO, 1999).

Precautions

The WHO states that consumption of large amounts of garlic may increase the risk of postoperative bleeding and that garlic should be taken with food to prevent gastrointestinal upset (WHO, 1999). ESCOP also advises caution when taking garlic after surgical operations (ESCOP, 1997).

Drug Interactions

ESCOP and the Commission E list no known drug interactions (Blumenthal et al., 1998; ESCOP, 1997). However, the WHO states that patients on warfarin therapy should be warned that garlic supplements may increase bleeding time. Blood clotting times have been reported to double in patients taking warfarin and garlic supplements (WHO, 1999).

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DETAILS ON GARLIC PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Garlic Products

Product Profile: Kwai®

Manufacturer	**Lichtwer Pharma AG, Germany**
U.S. distributor	**Lichtwer Pharma U.S., Inc.**
Botanical ingredient	**Garlic clove powder**
Extract name	**LI III**
Quantity	100 mg concentrated dry garlic, equivalent to 300 mg fresh garlic

Processing	Garlic cloves are cut into slices and carefully dried in 50-60°C air for several hours. The dried slices are ground into powder and sieved
Standardization	600 mcg allicin per tablet
Formulation	Tablet

Recommended dose: Take two tablets three times daily with liquid, ideally with meals. Cholesterol-lowering results observed after 12 weeks of usage.

DSHEA structure/function: Clinically proven to lower cholesterol.

Cautions: If a disease or health-related condition requires the lowering of cholesterol, consult a doctor.

Other ingredients: Lactose, powdered cellulose, silicon dioxide, magnesium stearate, sucrose, magnesium silicate (mineral source), hydroxypropyl methylcellulose, gelatin, beeswax.

Comments: There are two other Kwai products: Kwai® 150 mg and Kwai® Heart Fit™. They have 150 mg and 300 mg garlic powder, respectively. Kwai® Heart Fit™ also contains vitamins A, C, and E. Kwai® is also sold as Sapec®.

Source(s) of information: Product package; Kwai® LI 111: Product Information, Lichtwer Pharma AG, 1999; Auer et al., 1990.

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Mader FH (1990). Treatment of hyperlipidaemia with garlic powder tablets. *Arzneimittel-Forschung/Drug Research* 40 (10): 1111-1116.

Trial design
Parallel.

Study duration	4 months
Dose	4 tablets daily (800 mg garlic powder)

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	30 general practices
No. of subjects enrolled	261
No. of subjects completed	219
Sex	Male and female
Age	47-71 years (mean: 59)

Inclusion criteria
Total serum cholesterol values of 200 to 300 mg/dl and/or triglyceride values of 200 to 300 mg/dl.

Exclusion criteria
None mentioned.

End points
Total cholesterol and triglyceride levels, as well as supine and diastolic blood pressure, were measured.

Results
After four months, mean cholesterol levels dropped in the garlic group by 12 percent (266 to 235 mg/dl) and triglyceride levels by 17 percent (226 to 188 mg/dl). The difference between the garlic and placebo groups was highly significant ($p < 0.001$). Subgroup analysis showed that patients with initial total cholesterol levels between 250 to 300 mg/dl showed the most improvement compared with placebo. Effects, if any, on blood pressure were not mentioned.

Side effects
Mild garlic smell in 21 percent of garlic and 9 percent of placebo groups. Also minor gastrointestinal upset.

Author's comments
Standardized garlic tablets at a sufficiently high dose can be considered as an alternative for general practitioners in the treatment of mild and medium forms of hyperlipidemia.

Reviewer's comments
This is a good study showing a statistically significant reduction in serum cholesterol and triglycerides with 800 mg garlic powder daily. The length of treatment was appropriate for observing lipid-lowering effects. (5, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hyperlipoproteinemia** (elevated blood lipid levels)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Holzgartner H, Schmidt U, Kuhn U (1992). Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. *Arzneimittel-Forschung/ Drug Research* 42 (12): 1473-1477.

Trial design
Parallel. Pretrial period with placebo (six weeks) proceeded drug comparison trial with 600 mg/day bezafibrate. All patients advised to observe a low-fat "step I" diet for the duration of the study.

Study duration	3 months
Dose	1 (300 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Bezafibrate
Site description	5 general practices
No. of subjects enrolled	98
No. of subjects completed	94
Sex	Male and female
Age	44-69 years

Inclusion criteria
Primary type IIa, IIb, or IV hyperlipoproteinemia according to Fredrickson. Cholesterol and/or triglycerides higher than 250 mg/dl at the end of the pretrial phase.

Exclusion criteria
Pregnancy, nursing, drug or alcohol abuse, severe renal and hepatic insufficiency, diabetes mellitus, and any therapy with other lipid-lowering agents or with anticoagulants.

End points
Patients were evaluated before the treatment period and after 28, 56, and 84 days. Levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and blood pressure and heart rate were determined.

Results
Both medications caused a statistically significant reduction in total cholesterol, LDL cholesterol, and triglycerides, and an increase in HDL cholesterol. Following 12 weeks of treatment, mean cholesterol levels in the garlic group decreased from 282 to 210 mg/dl and in the bezafibrate group from 287 to 208 mg/dl ($p < 0.001$ for both). There was no significant difference between the groups.

Side effects
Side effects were mentioned by five patients in both treatment groups (lack of appetite, fatigue, and myalgia), none of which led to withdrawal of the patients.

Authors' comments
It can be concluded that garlic tablets standardized to 1.3 percent alliin at a sufficient dose are equivalent to other lipid-lowering agents in therapeutic administration.

Reviewer's comments
This was a well-run and well-designed study showing garlic to have effects equivalent to those of bezafibrate. The treatment length was appropriate. (5, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany

Indication	**Hyperlipidemia and hypertension** (elevated blood lipids and blood pressure)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Auer W, Eiber A, Hertkorn E, Hoehfeld E, Koehrle U, Lorenz A, Mader F, Merx W, Otto G, Schmid-Otto B, et al. (1990). Hypertension and hyperlipidaemia: Garlic helps in mild cases. *The British Journal of Clinical Practice* S69: 3-6.

Trial design
Parallel. Pretrial run-in period of two weeks.

Study duration	3 months
Dose	2 (100 mg) capsules 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	11 general practices
No. of subjects enrolled	47
No. of subjects completed	Not given
Sex	Male and female
Age	51-65 years

Inclusion criteria
Patients with mild hypertension (WHO stages I and II) and diastolic blood pressure between 95 and 104 mmHg on two measurements two weeks apart.

Exclusion criteria
Patients being treated with other antihypertensive agents or lipid-lowering agents, cases with severe forms of hypertension and hyperlipidemia, and patients who were seriously ill and might be expected to deteriorate or suffer complications suddenly during the period of the trial.

End points
Supine and standing blood pressure, pulse rates, serum cholesterol, and triglycerides were measured before admission to the trial, after the two-week

pretrial period, and 4, 8, and 12 weeks after start of treatment. At the start and the end of the trial, serum glutamate-pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), gamma-glutamyl transferase (GT), and blood sugar were measured.

Results
Supine diastolic blood pressure in the garlic group fell from 102 to 91 mmHg after eight weeks ($p < 0.05$) and to 89 mmHg after 12 weeks ($p < 0.01$). Supine systolic blood pressure fell after 12 weeks from 171 to 152 mmHg ($p < 0.05$). There was no significant change in blood pressure in the placebo group. The serum cholesterol and triglycerides were also significantly reduced after 8 and 12 weeks of treatment. Total serum cholesterol fell from 268 mg/dl after eight weeks ($p < 0.05$) and to 230 mg/dl after 12 weeks ($p < 0.05$), a decrease of 14 percent. In the placebo group, on the other hand, no significant differences occurred. No significant changes were found in pulse rate, SGPT, SGOT, gamma GT, or blood sugar levels.

Side effects
No serious side effects were reported. In three cases a slight smell of garlic was noted.

Authors' comments
This trial demonstrated that a preparation of garlic powder, which was free of side effects, significantly reduced blood pressure, total cholesterol, and triglycerides. Doctors now have a medication at their disposal which can be used adjunctively with diet and behavior alterations to reduce raised blood pressure and raised lipid levels, and thus contribute to a reduction in cardiovascular risk.

Reviewer's comments
This was a well-run and well-designed study with an appropriate length. The randomization process and the withdrawals were not described. (2, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference

Jain AK, Vargas R, Gotzkowsky S, McMahon FG (1993). Can garlic reduce levels of serum lipids? A controlled clinical study. *The American Journal of Medicine* 94 (6): 632-635.

Trial design

Parallel. Pretrial two-week washout period.

Study duration	3 months
Dose	1 (300 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	42
No. of subjects completed	42
Sex	Male and female
Age	Mean: 52 years

Inclusion criteria

Serum total cholesterol levels greater than or equal to 220mg/dl at two consecutive visits two weeks apart.

Exclusion criteria

Older than 70 years; history of drug or alcohol abuse; impaired hepatic function test results greater than 20 percent above normal; unstable angina; myocardial infarction or coronary bypass surgery within six months; diabetes mellitus; known secondary hypercholesterolemia due to nephrotic syndrome or hyperthyroidism; serum creatinine level greater than 2.0 mg/dl; or use of lipid-lowering agents within one month prior to enrollment.

End points

Lipid profiles from fasting blood samples were determined before and after the two-week washout period, as well as after 6 and 12 weeks of treatment. Total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum glucose were determined.

Results
The baseline serum TC level of 262 +/– 34 mg/dl was reduced to 247 +/– 40 mg/dl ($p < 0.001$) after 12 weeks of standardized garlic treatment, a reduction of 6 percent. This reduction was significant compared with a 1 percent reduction with placebo ($p < 0.01$). LDL-C was reduced by 11 percent by garlic treatment and 3 percent by placebo ($p < 0.05$). No significant changes were recorded in HDL-C, TG, serum glucose, blood pressure, and other monitored parameters.

Side effects
In general, garlic tablets were well tolerated without any significant odor problems. One patient complained of belching and bad taste.

Authors' comments
Treatment with standardized garlic, 900 mg/day, produced a significantly greater reduction in serum TC and LDL-C than placebo.

Reviewer's comments
This is a relatively well-designed and well-run study. The reduction in serum cholesterol and LDL cholesterol in the treatment group was actually quite modest compared to control. The treatment length was appropriate. The two groups were comparable, but the randomization process was not described. (3, 5)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
De A Santos OS, Grunwald J (1993). Effect of garlic powder tablets on blood lipids and blood pressure—Six month placebo controlled, double blind study. *The British Journal of Clinical Research* 4: 37-44.

Trial design
Parallel. Patients were instructed to follow a low-fat/low-cholesterol diet.

Study duration	6 months
Dose	1 (900 mg powder) tablet daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	60
No. of subjects completed	52
Sex	Male and female
Age	43-60 years

Inclusion criteria
Patients with total cholesterol values over 6.5 mmol/l.

Exclusion criteria
Patients treated with other antihypertensive agents or lipid-lowering agents, severe forms of hypertension and hyperlipidemia, and serious illness.

End points
Blood pressure was measured at baseline and then monthly. Serum cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured at baseline and after three and six months. General well-being was assessed monthly.

Results
Serum cholesterol in the garlic group was statistically reduced after six months compared to placebo ($p < 0.05$). Initial serum cholesterol in the garlic group was reduced from 6.92 to 6.31 mmol/l, a 9 percent reduction. Values for LDL were reduced by nearly 10 percent by garlic and 6 percent by placebo. Mean systolic blood pressure was reduced in the garlic group by 17 percent, from 145 to 120 mmHg ($p < 0.001$). Mean diastolic blood pressure was also reduced, from 90 to 80 mmHg ($p < 0.01$). Blood pressure remained unchanged in the placebo group. Well-being was improved in the active group by 20 percent ($p < 0.001$).

Side effects
No significant side effects.

Authors' comments
Patients given dietary advice and treatment with standarized garlic tablets

produced a significantly greater reaction of total cholesterol and blood pressure than that of placebo.

Reviewer's comments
This study was flawed by the inadequately described statistical methods, blinding, and randomization. The treatment length was appropriate. (1, 5)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Melvin KR, Chappell MA (1996). Effects of garlic powder tablets on patients with hyperlipidaemia in Canadian clinical practice. *European Journal of Clinical Research* 8: 15-36.

Trial design
Crossover. At beginning of trial subjects were randomized to placebo or garlic; on day 30 both groups were given garlic; and on day 60 subjects were again blinded to the original placebo or garlic groups.

Study duration	4 months
Dose	1 (300 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 clinical practice
No. of subjects enrolled	34
No. of subjects completed	19
Sex	Male and female
Age	41-77 years (mean: 54)

Inclusion criteria
Elevated cholesterol and off all other drug therapy.

Exclusion criteria
None mentioned.

End points
Physical exam (clinical history, pill compliance, weight, blood pressure, and diet status) and biochemical lipid profiles in fasting state were taken at baseline and at each 30-day visit.

Results
Total serum cholesterol levels decreased by 12 percent ($p < 0.03$) on average by day 120 in the active treatment group, from an average of 6.99 mmol/l at baseline to 6.09 mmol/l. The placebo group did not show a significant decrease in cholesterol. No significant effect on serum triglycerides was seen in either group. High-density lipoprotein levels increased with garlic but did not reach statistical significance.

Side effects
None listed.

Authors' comments
Garlic powder tablets have a role in cholesterol management as an adjunctive therapy in most cases of significant hyperlipidemia.

Reviewer's comments
This study had a small sample size with a wide age range, and a very moderate reduction in serum cholesterol was observed in these patients. Also, 30 days minimum active treatment (e.g., placebo group from days 30 to 60) may not be long enough to notice effects. The randomization and blinding were not adequately described. (1, 3)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Vorberg G, Schneider B (1990). Therapy with garlic: Results of a placebo-controlled, double-blind study. *The British Journal of Clinical Practice* S69: 7-11.

Trial design
Parallel. Pretrial washout period of 14 days.

Study duration	4 months
Dose	900 mg daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Male and female
Age	Mean: 50 years

Inclusion criteria
Serum cholesterol between 230 and 350 mg/dl after 14-day washout period.

Exclusion criteria
Patients receiving therapy for diabetes mellitus, advanced renal insufficiency, or for lipid lowering.

End points
Cholesterol, triglycerides, and blood pressure were measured before the study, at the end of the washout period, and at 4, 8, 12, and 16 weeks after beginning of therapy.

Results
Total cholesterol in the garlic group dropped by week 8 and continued through week 16, from 294 to 232 mg/dl, 21 percent of the starting value; this change was significant ($p < 0.001$). Reductions in triglyceride levels were also significantly different from placebo at week 16 ($p < 0.05$). Blood pressure also dropped significantly. In addition, results of a self-evaluation questionnaire indicated that patients in the drug group had a greater feeling of well-being.

Side effects
None reported.

Authors' comments
The main finding of our study was the reduction in serum cholesterol by the garlic preparation. Blood pressure and triglyceride reductions were also significantly different between garlic and placebo groups, particularly with respect to change from baseline values. All these effects increased continuously during the 16-week treatment period.

Reviewer's comments
The garlic reduced cholesterol and triglycerides compared to placebo. The length of the trial was appropriate, but the randomization and blinding were not described in sufficient detail. (1, 5)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Adler AJ, Holub BJ (1997). Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. *American Journal of Clinical Nutrition* 65 (2): 445-450.

Trial design
Parallel. Four-arm, double-placebo trial: (1) placebo, (2) garlic, (3) fish oil (12 g/day providing 3.6 g n-3 fatty acids), and (4) both garlic and fish oil. Three-week run-in phase.

Study duration	3 months
Dose	1 (300 mg) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double/single-blind
Blinding adequate	No

Placebo	Yes
Drug comparison	Yes
Drug name	Fish oil
Site description	Single center
No. of subjects enrolled	50
No. of subjects completed	46
Sex	Male
Age	Mean: 45.9 years

Inclusion criteria
Total cholesterol concentration >5.2 mmol/l; medications were allowed as long as they were not initiated within four weeks of the beginning of the study.

Exclusion criteria
Subjects taking lipid-altering or blood pressure-altering medications or supplements within four weeks of study start, with diabetes mellitus, or with cardiovascular disease.

End points
Fasting blood samples were taken at weeks 0, 3, 6, 9, and 12, and were analyzed for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Blood pressure and heart rate were measured. Fatty acid composition of total serum phospholipid was analyzed at weeks 0 and 12. Two three-day dietary records were kept.

Results
In the placebo group, mean serum total cholesterol, LDL-C, and triacylglycerols were not significantly changed in relation to baseline. Mean group total cholesterol concentrations were significantly lower with garlic + fish oil (–12.2 percent) and with garlic (–11.5 percent) after 12 weeks but not with fish oil alone. Mean LDL-C concentrations were reduced with garlic + fish oil (–9.5 percent) and with garlic (–14.2 percent) but were raised with fish oil (+8.5 percent). Mean triacylglycerol concentrations were reduced with garlic + fish oil (–34.3 percent) and fish oil alone (–37.3 percent). The garlic groups (with and without fish oil) had significantly lower ratios of total cholesterol to HDL-C and LDL-C to HDL-C. Mean systolic, diastolic, and arterial blood pressures for all subjects at entry were 120.1, 80.0, and 94.0 mmHg, respectively. By week 12, reductions of 2.4 to 4.2 percent ($p < 0.05$ or $p < 0.005$, respectively) in mean systolic, diastolic, and arterial pressures were found for all three treatment groups (garlic alone, fish oil alone, and garlic + fish oil) relative to the placebo group.

Side effects
Odor due to garlic was reported in 20 percent of the subjects taking garlic pills. One subject reported a slight feeling of nausea with fish oil.

Authors' comments
Garlic supplementation significantly decreased both total cholesterol and LDL-C, whereas fish oil supplementation significantly decreased triacylglycerol concentrations and increased LDL-C concentrations in hypercholesterolemic men. The combination of garlic and fish oil reversed the moderate fish oil-induced rise in LDL-C.

Reviewer's comments
In this study, the garlic supplement alone reduced total cholesterol and LDL cholesterol. Garlic pills and placebo pills were administered in a double-blinded manner, but fish oil capsules and oil placebo capsules were only single-blinded. There was no description of the randomization process. (1, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Neil HAW, Silagy CA, Lancaster T, Hodgeman J, Vos K, Moore JW, Jones L, Cahill J, Fowler GH (1996). Garlic powder in the treatment of moderate hyperlipidemia: A controlled trial and meta-analysis. *Journal of the Royal College of Physicians of London* 30 (4): 329-334. (Further analysis reported in Byrne DJ, Neil HAW, Vallance DT, Winder AF [1999]. *Clinica Chimica Acta: International Journal of Clinical Chemistry* 285 [1-2]: 21-33.)

Trial design
Parallel. During a preliminary six-week screening period, dietary guidelines were given: a daily intake of less than 300 mg cholesterol and about 35 g of fiber was recommended.

Study duration	6 months
Dose	1 (300 mg powder) capsule 3 times daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	115
No. of subjects completed	106
Sex	Male and female
Age	35-64 years

Inclusion criteria
Total cholesterol concentration of 6.5 to 9.0 mmol/L on screening and a repeat fasting concentration of 6.0 to 8.5 mmol/L, with a low-density lipoprotein cholesterol of 3.5 mmol/L or above.

Exclusion criteria
Fasting triglyceride concentration of 5.6 mmol/L or above; high-density lipoprotein cholesterol concentration of 2.0 mmol/L or above; hyperlipidemia secondary to any recognized cause; treatment with a lipid-lowering drug; hospitalization for severe illness within the previous three months; and pregnancy or breast-feeding.

End points
Concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein (apo) A1 and B, and triglycerides were determined. Blood samples were analyzed six weeks before the trial, at the beginning, and at the end of the trial. The second report analyzed resistance of LDL to oxidation, LDL subfraction composition, and levels of circulating antibody to oxidized LDL.

Results
There were no significant differences between the groups receiving garlic and placebo in the mean concentrations of serum lipids, lipoproteins, or apo A1 or B, by analysis either on intention-to-treat or treatment received. An analysis limited to those subjects with better than 75 percent compliance again found no significant differences. The second report showed no significant difference in oxidative resistance lag time, LDL composition, or levels of antibodies to oxidized LDL.

Side effects
Garlic odor was noted.

Authors' comments
In this trial, garlic was less effective in reducing total cholesterol than suggested by previous meta-analysis. The results do not support the hypothesis that dietary garlic supplementation decreases the susceptibility of isolated LDL to oxidation and that patterns of LDL fractions in plasma might be involved. Levels of lipoprotein in plasma were also not changed. Other mechanisms of cardiovascular benefit are, however, not excluded.

Reviewer's comments
This is a very well conducted and designed study with an appropriate length. There were no significant effects on plasma total cholesterol, HDL or LDL cholesterol, triglycerides, or apolipoproteins compared with the placebo. (5, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
McCrindle BW, Helden E, Conner WT (1998). Garlic extract therapy in children with hypercholesterolemia. *Archives of Pediatric and Adolescent Medicine* 152 (11): 1089-1094.

Trial design
Parallel. Patients were instructed to stop taking lipid-lowering medications for at least eight weeks before the study.

Study duration	2 months
Dose	1 (300 mg) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male and female
Age	Mean: 14.0 years

Inclusion criteria
Eight to eighteen years old, a positive family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease in first-degree relatives, a minimum fasting total cholesterol level at enrollment higher than 4.8 mmol/l (>185 mg/dl), participation in a dietary counseling program, and compliance with a National Cholesterol Education Program Step II diet for at least six months.

Exclusion criteria
Presence of secondary causes of hyperlipidemia, a history of major surgery, or serious illness three months or less prior to enrollment.

End points
Fasting blood samples were taken at baseline and at trial end point. Total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipoprotein(a), apolipoprotein B-100 and A-1, homocysteine, and fibrogen were determined. Blood pressure was monitored along with diet via a food frequency questionnaire.

Results
Baseline lipid values were as follows: total cholesterol 265 mg/dl; LDL cholesterol 206 mg/dl; HDL cholesterol 37 mg/dl; and triglycerides 112 mg/dl. There was no significant relative attributable effect of garlic extract on fasting total cholesterol or LDL cholesterol. Likewise, no significant effect was seen on the levels of HDL cholesterol, triglycerides, apolipoprotein B-100, lipoprotein(a), fibrinogen, homocysteine, or blood pressure (no patients had hypertension at baseline). There was a small effect on apolipoprotein A-1.

Side effects
Minor effects noted: headache, upset stomach, and garlic odor on breath. There were no differences in adverse effects between groups.

Authors' comments
Garlic extract therapy has no significant effect on cardiovascular risk factors in pediatric patients with familial hyperlipidemia.

Reviewer's comments
This is an excellent study that showed no significant reduction in serum lipids or blood pressure compared to placebo. The treatment length was appropriate. (5, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Isaacsohn JL, Moser M, Stein EA, Dudley K, Davey J, Lishkov E, Black HR (1998). Garlic powder and plasma lipids and lipoproteins. *Archives of Internal Medicine* 158 (11): 1189-1194.

Trial design
Parallel. Entry into the study following eight weeks of diet stabilization.

Study duration	3 months
Dose	1 (300 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	2 outpatient clinics
No. of subjects enrolled	50
No. of subjects completed	42
Sex	Male and female
Age	44-70 years

Inclusion criteria
Mean plasma LDL-C level, determined at two visits (four and two weeks before randomization), of 4.1 mmol/l (160 mg/dl) or higher (with no single value <4.0 mmol/l [155 mg/dl]), and a mean plasma triglyceride level lower than 4.0 mmol/l (350 mg/dl).

Exclusion criteria
Secondary cause of hypercholesterolemia including hypothyroidism, nephrotic syndrome (treatment with hormones known to affect lipids, uncontrolled diabetes), unstable angina, or myocardial infarction occurring within two months of entry into the study, active liver disease, chronic renal disease (creatinine level >265 µmol/l [>3mg/dl]), or severe metabolic or endocrine disorders. All lipid-lowering drugs were discontinued six weeks before entry into the study.

End points
Dietary assessment using a three-day diet diary and food rating record was made after four and eight weeks of diet stabilization, and after 12 weeks of treatment. Fasting blood samples were drawn to determine plasma lipid and lipoproteins, apolipoproteins, chemistry profiles, and complete blood counts. Heart rate and blood pressure were also measured.

Results
Baseline levels for total cholesterol were 250 mg/dl and 274 mg/dl for the placebo and garlic groups, respectively. An adjusted percentage of change was calculated and compared between the two groups as the baseline numbers were statistically different. At the conclusion of the trial there were no significant lipid or lipoprotein changes in either placebo or garlic-treated groups and no significant difference between the two groups.

Side effects
Three patients complained of garlic breath, two of body odor. Three patients in both groups complained of gastrointestinal problems.

Authors' comments
Garlic powder (900 mg/d) treatment for 12 weeks was ineffective in lowering cholesterol levels in patients with hypercholesterolemia.

Reviewer's comments
This was a well-conducted study. A small but statistically significant increase in diastolic blood pressure was observed in the placebo group. Otherwise, no significant differences observed between groups. The treatment length was appropriate. (5, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Simons LA, Balasubramaniam S, von Konigsmark M, Parfitt A, Simons J, Peters W (1995). On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. *Atherosclerosis* 113 (2): 219-225.

Trial design
Crossover. After a baseline dietary period of 28 days, subjects were assigned to garlic or placebo for 12 weeks followed by 28 days washout, followed by 12 weeks with alternate treatment. All subjects were placed on an isocaloric, fat-restricted diet.

Study duration	3 months
Dose	1 (300 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	31
No. of subjects completed	29
Sex	Male and female
Age	42-69 years

Inclusion criteria
Mild hypercholesterolemia in the range 6.0 to 7.8 mol/l after 28 days on standard dietary advice; plasma triglyceride below 3.0 mmol/l; not using lipid-regulating, antihypertensive, or antioxidant drugs.

Exclusion criteria
No active renal or liver disease, diabetes, or unstable coronary artery dis-

ease. No intake of garlic or other nutritional supplements throughout the study.

End points
At point of recruitment and continuing throughout the study, each subject received dietary instruction in an isocaloric, fat-restricted diet. Clinical observations and blood sampling were performed every 28 days, for a total of nine visits. Blood pressure was measured, as well as plasma cholesterol and triglycerides.

Results
Comparing the period on garlic with that on placebo, there were no significant differences in plasma cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, plasma triglycerides, lipoprotein(a) concentrations, or blood pressure (baseline 120/80 +/– 14/8 mmHg). Garlic showed no demonstrable effect on oxidizability of LDL, on the ratio of plasma lathosterol to cholesterol (a measure of cholesterol synthesis), or on LDL receptor expression in lymphocytes.

Side effects
Minor gastrointestinal disturbances such as abdominal bloating, nausea, or flatulence; body odor; garlic taste.

Authors' comments
We conclude from the present study in subjects with mild to moderate hypercholesterolemia that garlic powder tablets at a dose of 900 mg/day appeared to have no significant effect on plasma cholesterol or other lipid and lipoprotein parameters.

Reviewer's comments
The garlic supplementation showed no beneficial effect on plasma lipids. The trial had a good crossover/washout design. (3, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference

Superko R, Krauss RM (2000). Garlic powder, effect on plasma lipids, postprandial lipemia, low-density lipoprotein particle size, high-density lipoprotein subclass distribution and lipoprotein(a). *Journal of the American College of Cardiology* 35 (2): 321-326.

Trial design

Parallel. Patients followed the American Heart Association Step I diet for at least two weeks before entry into the trial. Before the laboratory tests, subjects fasted for 16 hours and avoided alcohol for 48 hours.

Study duration	3 months
Dose	1 (300 mg) tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Lipid research clinic
No. of subjects enrolled	50
No. of subjects completed	50
Sex	Not given
Age	Mean: 53 years

Inclusion criteria

Subjects with moderate hypercholesterolemia: low-density lipoprotein cholesterol between 150 and 200 mg/dl and triglycerides <300 mg/dl.

Exclusion criteria

Subjects with heterozygous familial hypercholesterolemia, a systemic disease that could affect blood lipids, body weight greater than 30 percent of ideal, use of lipid-lowering drugs in the preceding two months, or other medications known to change blood lipids.

End points

LDLC, HDLC, very-low-density lipoproteins, low-density lipoproteins, total cholesterol, and triglyceride levels were measured. Apolipoprotein (apo) B and lipoprotein(a) [Lp(a)] levels were also measured, as well as postpriandial triglyceride response.

Results
At the end of the trial, Kwai garlic tablets had no significant effect on levels of fasting triglycerides, postprandial triglycerides, LDL cholesterol, LDL subclass distribution, LDL peak particle diameter, HDL subclass distribution, HDL cholesterol, total cholesterol, Lp(a), or apo B. There were also no changes compared to the placebo group with respect to body mass index, diastolic or systolic blood pressure, or diet variables.

Side effects
None mentioned.

Authors' comments
The double-blind, randomized clinical trial we report confirms this lack of effect of garlic on routine measures of triglycerides, total, LDL, and HDL cholesterol. However, it contributes new information to the field by further revealing no significant effect of 300 mg t.i.d. of Kwai garlic on LDL peak particle diameter, LDL subclass distribution, apo B, Lp(a), HDL subclass distribution, and postprandial lipemia.

Reviewer's comments
This is a good-quality study. (5, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Saradeth T, Seidl S, Resch KL, Ernst E (1994). Does garlic alter the lipid pattern in normal volunteers? *Phytomedicine* 1: 183-185.

Trial design
Parallel. Pretrial two-week washout period.

Study duration	15 weeks
Dose	600 mg daily
Route of administration	Oral
Randomized	Yes

Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	72
No. of subjects completed	68
Sex	Male and female
Age	Mean: 39.2 years

Inclusion criteria
Between 18 and 50 years, and healthy with constant blood baseline measurements before and after two-week pretrial washout period.

Exclusion criteria
Pregnant women, and individuals taking fresh garlic or garlic medication prior to the trial, showing clinical signs of atherosclerotic diseases, impaired liver function, or inflammatory diseases were excluded. Persons taking fibrinolytic agents, anticoagulants, or fibrates were also not admitted.

End points
Baseline measurements were taken at the beginning and end of the two-week washout period, and trial measurements were taken after 5, 10, and 15 weeks of treatment. Total cholesterol, triglycerides, and blood pressure were monitored.

Results
There was a drop in total cholesterol in the garlic group which was significant after ten weeks but insignificant at the 15 weeks measurement (223 to 210 and 214 mg/dl). Triglycerides decreased numerically (124 to 118 mg/dl) without reaching the level of significance. Blood pressure remained constant throughout. No changes occurred in the placebo group.

Side effects
Not mentioned.

Authors' comments
The medication of garlic induces changes in blood lipids, even if these variables had been normal to start with.

Reviewer's comments
This study demonstrated that 600 mg dried garlic per day led to a slight decrease in total cholesterol compared with placebo in volunteers with normal

lipid levels at baseline. In this well-designed and well-conducted study, a level of evidence point was lost because of inappropriate inclusion/exclusion criteria. (5, 5)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels) in diabetics
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Mansell P, Reckless JPD, Lloyd J, Leatherdale B (1996). The effect of dried garlic powder tablets on serum lipids in non-insulin dependent diabetic patients. *European Journal of Clinical Research* 8: 25-26.

Trial design
Parallel.

Study duration	3 months
Dose	1 (300 mg of dried garlic) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Male and female
Age	42-75 years (median: 63)

Inclusion criteria
Non-insulin-dependent diabetics with well-controlled diabetes, on diet or tablets, with a serum total cholesterol between 6.0 and 8.0 mmol/l.

Exclusion criteria
None mentioned.

End points
Blood samples and blood pressure measurements were taken at baseline and after 6 and 12 weeks.

Results
Serum total cholesterol and serum low-density lipoprotein cholesterol in garlic group were reduced ($p < 0.07$ and $p < 0.05$, respectively) at week 6, but not at week 12. High-density lipoprotein cholesterol in the garlic group rose compared to placebo ($p < 0.05$). LDL-C/HDL-C ratio fell at 6 and 12 weeks ($p < 0.05$). There were no differences in very low density lipoprotein cholesterol, HDL-C2 and HDL-C3, triglycerides or in apolipoprotein A1 or B compared with placebo. Garlic tablets also had no effect on fasting blood glucose, HbA1c, serum insulin, or c peptide. It was not mentioned whether there was an effect on blood pressure.

Side effects
Odor noted at least once weekly.

Authors' comments
Dried garlic tablets had a beneficial effect on LDL-C/HDL-C ratio in moderately hypercholesterolemic non-insulin-dependent diabetic patients—a potential reduction in cardiovascular risk. No significant effect on blood pressure or diabetic control.

Reviewer's comments
Although the placebo was identical to treatment, the degree of blinding was not mentioned. The randomization process was not clearly described. Insufficient detail was given for the inclusion and exclusion criteria. However, the outcome measures were clearly defined, and the treatment length was appropriate. (0, 3)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Lipids and lipoproteins** in normal volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Phelps S, Harris WS (1993). Garlic supplementation and lipoprotein oxidation susceptibility. *Lipids* 28 (5): 475-477.

Trial design
Crossover. Two-week treatment periods with a one-week washout period between treatment periods. Subjects' diets were monitored.

Study duration	2 weeks
Dose	6 (100 mg of powdered garlic) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	10
No. of subjects completed	Not given
Sex	Male and female
Age	Mean: 32 years

Inclusion criteria
Healthy, normolipidemics. Smoking and exercise patterns were kept constant throughout the study.

Exclusion criteria
Subjects could not be taking medications that may affect the serum lipids, garlic, or have a significant amount of antioxidants in diet.

End points
Blood samples were drawn at the beginning and end of each test period. Lipids and lipoproteins were analyzed. Diets were monitored with three-day diaries, one per treatment period.

Results
Garlic supplementation did not alter plasma total cholesterol, low-density lipoprotein or high-density lipoprotein cholesterol, or triglyceride levels. Garlic significantly reduced the susceptibility of the apoB-containing lipoproteins to copper-induced oxidation ($p < 0.05$). Only half of the group experienced

this change, with two patients showing remarkable changes. Values with placebo were unchanged.

Side effects
None listed.

Authors' comments
We conclude that 600 mg of Kwai taken for only two weeks significantly decreased the lipoprotein oxidation susceptibility without altering serum cholesterol levels in normal adults.

Reviewer's comments
This was a very brief study with a small sample size. Garlic supplementation reduced apo-B lipoprotein fraction susceptibility to oxidation, but because the sample size was very small, the value of this finding is undetermined in a "real life" setting. Also, randomization, blinding, and dropouts were not adequately described. (0, 5)

Clinical Study: LI 111

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Atherosclerosis**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Koscielny J, Klubendorf D, Latza R, Schmitt R, Radtke H, Siegel G, Kiesewetter H (1999). The antiatherosclerotic effect of *Allium sativum. Atherosclerosis* 144 (1): 237-249.

Trial design
Parallel.

Study duration	4 years
Dose	900 mg powder daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	280
No. of subjects completed	152
Sex	Male and female
Age	40-80 years

Inclusion criteria
Advanced atherosclerosis plaques as measured by ultrasound in the carotid bifurcation and/or the femoral arteries; at least one of the established risk factors such as high systolic blood pressure, hypercholesterolemia, diabetes mellitus, and smoking.

Exclusion criteria
Severe internal diseases such as functional disorders of the heart, circulation, liver, kidney, and lung, decompensated heart failure, severe arrythmias, acute myocardial infarction (<6 months ago), lung emphysema, asthma bronchiale, systolic blood pressure >180 mmHg, hypotension <110 mmHg, renal failure (creatinine >2.0 mg/dl); pregnancy; simultaneous treatment with aspirin, naftidrofuryl, pentoxifylline, omega-3-fatty acid, calcium antagonists, and oral antithrombotic agents; and hemodynamically relevant stenotic lesions in the examined arteries.

End points
Change of plaque volume in the common carotid and femoral artery and changes in the combined intimal-medial thickness (IMT). Plasma viscosity, platelet aggregation, total blood cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose were also measured. Doppler pressure assessments of the brachial, dorsal pedal, and posterior artery, of blood pressure, and of heart rate were obtained.

Results
The arteriosclerotic plaque volume increased by 15.6 percent over four years in the placebo group. In the garlic group a decrease of 2.6 percent was observed. There was a significant difference of 18.3 percent between placebo and garlic groups. Breaking the groups down by sex and age showed differences in results. The age-dependent representation of the plaque volume shows an increase between 50 to 80 years that is diminished with garlic treatment by 6 to 13 percent. Further subgroup analysis found that the reductions compared to placebo were 4.4 percent for men and 58 percent for women. However, there was an unequal age distribution of women in the placebo and garlic groups. The predominately younger women in the pla-

cebo group (aged 40 to 55 years) had a drastic increase in plaque volume (53 percent), while the mainly older women (aged over 55 years) in the garlic group had a plaque reduction of 4.6 percent. Plasma lipid levels and blood pressure measurements were not mentioned.

Side effects
Annoyance with odor.

Authors' comments
These results substantiate that not only a preventative but also possibly a curative role in artherosclerosis therapy (plaque regression) may be ascribed to garlic remedies.

Reviewer's comments
This is a well-conducted and well-designed study with an appropriate treatment length. There was no description of the randomization process. (3, 6)

Clinical Study: Kwai®

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Effect on postmeal lipid levels**
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Rotzsch W, Richter V, Rassoul F, Walper A (1992). Reduction in postprandial lipaemia caused by *Allium sativum:* Controlled double-blind trial involving test persons with low HDL2-cholesterol levels. *Arzneimittel-Forschung/Drug Research* 42 (10): 1223-1227.

Trial design
Parallel. Lipid levels were measured before and after a high-fat meal. Pretrial washout period of one week.

Study duration	1 dose and 6 weeks
Dose	1 (300 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	24
No. of subjects completed	24
Sex	Male and female
Age	23-53 years

Inclusion criteria
Volunteers with low initial high-density lipoprotein 2-cholesterol concentrations in the plasma, below 10 mg/dl in men and 15 mg/dl in women.

Exclusion criteria
None mentioned.

End points
Lipid concentrations in the serum were measured three times each day on the first, twenty-second, and forty-third day of treatment; measurements were taken both before as well as three and five hours after intake of 100 g butter.

Results
The postprandial increase in triglyceride levels was much lower in the garlic group than the placebo group, but it was not statistically significant. However, after six weeks, garlic caused a significant decrease in fasting triglyceride levels compared to placebo. There was an increase in HDL2-cholesterol in the garlic group, but this was not statistically different from placebo.

Side effects
None discussed.

Authors' comments
In everyday life, this would mean that the single administration of garlic together with a high-fat meal will slightly improve triglyceride values, but a major preventive effect will be obtained only by regular administration over longer periods of time.

Reviewer's comments
The single-day treatment to observe postprandial changes in plasma lipids is of limited value. The six weeks of continuous administration led to a reduction in fasting triglycerides. The trial was limited by the small sample size (12 in each group), as well as inadequately described randomization. (2, 5)

Clinical Study: LI 111

Extract name	LI 111
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Increased spontaneous platelet aggregation**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Kiesewetter H, Jung F, Pindur G, Jung EM, Mrowietz C, Wenzel E (1991). Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 29 (4): 151-155.

Trial design
Parallel. Trial preceded by a one-week washout period.

Study duration	1 month
Dose	4 (200 mg powdered garlic) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single general practice
No. of subjects enrolled	120
No. of subjects completed	Not given
Sex	Male and female
Age	19-26 years

Inclusion criteria
Subjects with constantly increased spontaneous thrombocyte (platelet) aggregation. Measurements were made three times during the washout phase (days 0, 3, and 7) and the values measured on days 3 and 7 had to be pathological.

Exclusion criteria
None mentioned.

End points
Spontaneous thrombocyte aggregation was measured during washout phase (days 0, 3, and 7) and on days 14, 21, 28, and 35. Blood pressure, blood glucose, cholesterol, triglycerides, fibrinogen, thrombocyte, and leukocyte count were also determined.

Results
Spontaneous thrombocyte aggregation in the garlic group decreased significantly, by 56.3 percent by the Breddin method and 10.3 percent by the Grotemeyer method. The microcirculation of the skin increased by 47.6 percent, plasma viscosity in garlic group decreased by 3.2 percent, diastolic blood pressure decreased by 9.5 percent (from 74 +/– 9 to 67 +/– 5 mmHg), and blood glucose concentration decreased by 11.6 percent. There was no change in systolic blood pressure, total cholesterol levels, or triglyceride levels. The mean total cholesterol level at baseline for the garlic group was 228 mg/dl.

Side effects
None mentioned.

Authors' comments
The vascular protective effect of garlic, by influencing the mentioned risk parameters for cardiovascular diseases, must be pointed out. Especially interesting is the thrombocyte aggregation inhibiting effect. Thus, garlic may be useful in cases of acetylsalicyclic acid intolerance.

Reviewer's comments
This is a well-designed and well-conducted study showing that garlic powder may be useful for inhibition of thrombocyte aggregation in patients unable to use aspirin. The treatment length was appropriate and the blinding was adequately described. (2, 6)

Product Profile: Pure-Gar®

Manufacturer	**Essentially Pure Ingredients™**
U.S. distributor	**Essentially Pure Ingredients™**
Botanical ingredient	**Garlic clove dried**
Extract name	N/A
Quantity	No information
Processing	Proprietary quick "cool dry" process
Standardization	0.3% allicin
Formulation	Tablet

Source(s) of information: Essentially Pure Ingredients™ Web page (www.essentiallypure.com/products.htm); Lash et al., 1998.

Clinical Study: Pure-Gar®

Extract name	N/A
Manufacturer	Essentially Pure Ingredients™
Indication	**Hypercholesterolemia** (elevated cholesterol levels) in renal transplant patients
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Lash JP, Cardoso, LR, Mesler PM, Walczak DA, Pollak R (1998). The effect of garlic on hypercholesterolemia in renal transplant patients. *Transplantation Proceedings* 30 (1): 189-191.

Trial design
Parallel. Patients were on National Cholesterol Education Program Step One restriction diet.

Study duration	3 months
Dose	1 tablet (680 mg dried garlic) twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	35
No. of subjects completed	35
Sex	Male and female
Age	41-51 years

Inclusion criteria
Renal transplanted patients with total serum cholesterol greater than 240 mg/dL and LDL cholesterol greater than 160 mg/dL by two consecutive fast-

ing determinations, with stable renal allograft function for more than six months.

Exclusion criteria
Triglycerides >500 mg/dL, nephritic syndrome, and use of other hypolipemic medications within a six-month period.

End points
Lipid profile, such as cholesterol, triglycerides, LDL, and HDL, were measured.

Results
Garlic was effective in decreasing both total and LDL cholesterol levels (290 to 275 mg/dl; 193 to 182 mg/dl). This benefit was apparent after six weeks and maintained at 12 weeks. No change was observed in the placebo group in total or LDL cholesterol.

Side effects
One case each of diarrhea and epigastric pain.

Authors' comments
Although garlic had significant beneficial effects, treated patients still had hyperlipidemia which was severe enough to consider the addition of standard pharmacotherapy. There may be a role for garlic in combination therapy with a HMG-CoA reductase inhibitor. It is possible that garlic supplementation could decrease the dosage of the HMG-CoA reductase inhibitor required and thereby minimize the chance for drug toxicity.

Reviewer's comments
In this study, garlic clearly shows cholesterol-lowering effect in renal failure patients. It is a well-designed and well-executed study; however, the randomization process was not described in any detail. (3, 5)

Product Profile: Dried Garlic

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Garlic clove dried**
Extract name	N/A
Quantity	No information
Processing	No information
Standardization	No information
Formulation	Tablet

Source(s) of information: Luley et al., 1986.

Clinical Study: Garlic (Dried)

Extract name	N/A
Manufacturer	None
Indication	**Hyperlipoproteinemia** (elevated blood lipid levels)
Level of evidence	**III**
Therapeutic benefit	**No**

Bibliographic reference
Luley C, Lehmann-Leo W, Moeller B, Martin T, Schwartzkopff W (1986). Lack of efficacy of dried garlic in patients with hyperlipoproteinemia. *Arzneimittel-Forschung/Drug Research* 36 (1): 766-768.

Trial design
Crossover after six weeks. Two studies are reported here. Study 1 had 34 subjects who were given 594 mg/day of an unnamed commercial preparation of dried garlic. Study 2 had 51 subjects who were given 1350 mg/day of a preparation especially prepared for the study.

Study duration	6 weeks
Dose	(1) 3 (66 mg) three times daily; (2) 1 (450 mg) three times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	34, 51
No. of subjects completed	34, 51
Sex	Not given
Age	Not given

Inclusion criteria
Patients with hyperlipoproteinemia types IIa, IIb, and IV.

Exclusion criteria
None mentioned.

End points
Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and several safety parameters were measured every three weeks in both studies. Study 2 had additional tests, including apolipoprotein A and B levels, euglobulin, lysis time, fibrin split products, prothrombin time, whole blood coagulation time, and fibrinogen levels.

Results
Neither dosage of dried garlic showed any significant effect on any of the parameters measured.

Side effects
Bad smell reported in study 2.

Authors' comments
The administration of pills containing dried garlic in the concentration studied should not be recommended as an antiatherosclerotic agent.

Reviewer's comments
No benefit to cardiovascular risk was found from dried garlic pills. The randomization and blinding were not described in any detail. (1, 5)

Product Profile: Spray-Dried Garlic

Manufacturer	**Government Pharmaceutical Organization, Thailand**
U.S. distributor	None
Botanical ingredient	**Garlic clove dried**
Extract name	N/A
Quantity	350 mg
Processing	Spray-dried garlic
Standardization	No information
Formulation	Capsule

Source(s) of information: Plengvidlya et al., 1998.

Clinical Study: Garlic (Dried)

Extract name	N/A
Manufacturer	Government Pharmaceutical Organization, Thailand

Indication	**Hyperlipoproteinemia** (elevated blood lipid levels)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Plengvidlya C, Sitprija S, Chinayon, S, Pasatrat S, Tunkayoon M (1998). Effects of spray dried garlic preparation on primary hyperlipoproteinemia. *Journal of the Medical Association of Thailand* 71 (5): 248-252.

Trial design

Crossover after two months.

Study duration	2 months
Dose	1 (350 mg) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male and female
Age	42-60 years

Inclusion criteria

Patients with primary hyperlipoproteinemia, with moderately increased serum triglycerides and cholesterol.

Exclusion criteria

Patients with complicated diseases, or diseases causing secondary hyperlipoproteinemia, and those previously receiving any lipid-lowering drugs.

End points

Blood samples were taken at baseline and after one, two, three, and four months. Serum lipid profiles, total cholesterol, triglycerides, and HDL-C were determined.

Results
The results showed some trends for reduction of serum cholesterol and serum triglycerides, and elevation of serum high-density lipoprotein cholesterol. However, no statistical significance was demonstrated by analysis of variance for comparison with the baseline and placebo. Baseline lipid levels were as follows: total cholesterol 280 mg/dl; triglycerides 355 mg/dl; and HDL cholesterol 38 mg/dl.

Side effects
None mentioned.

Authors' comments
The lipid-lowering effects of this garlic preparation were not confirmed.

Reviewer's comments
No statistical lowering of serum lipid levels was observed. The sample size was too small, and the randomization and blinding processes were not adequately described. (1, 4)

Clinical Study: Garlic (Dried)

Extract name	N/A
Manufacturer	Government Pharmaceutical Organization, Thailand
Indication	**Diabetes** (NIDDM)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Sitprija S, Plengvidlya C, Kangkaya V, Bhuvapanich S, Tunkayoon M (1987). Garlic and diabetes mellitus phase II clinical trial. *Journal of the Medical Association of Thailand* 70 (2): 223-227.

Trial design
Parallel. Subjects were instructed to have dietary control for the month preceding the experiment and to continue this dietary control during the study.

Study duration	1 month
Dose	350 mg twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No

Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Outpatient clinic
No. of subjects enrolled	40
No. of subjects completed	33
Sex	Male and female
Age	42-60 years

Inclusion criteria
Subjects with non-insulin-dependent diabetes without complication and who had no prior treatment.

Exclusion criteria
None mentioned.

End points
Glucose tolerance test performed after overnight fast (12 hours). Blood glucose and serum insulin were determined at fasting and at 30, 60, 120, and 180 minutes via venous blood. Blood total cholesterol, triglycerides, high-density lipoprotein, and liver function were determined. The tests were measured before and one month after treatment.

Results
Garlic produced an insignificant change in blood glucose and serum insulin levels compared to baseline. There was also no significant change in total cholesterol, triglycerides, or in high-density lipoprotein. The baseline levels were as follows: total cholesterol 228 mg/dl; triglycerides 203 mg/dl; and HDL 42 mg/dl.

Side effects
No significant effects observed.

Authors' comments
Garlic produced no significant change to blood glucose, serum insulin, and lipid profile. Toxic effects to the liver were not observed.

Reviewer's comments
This study was conducted on a small, heterogeneous group of 40 diabetics. Neither the randomization nor blinding processes were adequately described. (1, 5)

Product Profile: Kyolic® Aged Garlic Extract™, HI-PO™ Formula 100

Manufacturer	**Wakunaga of America Co., Ltd.**
U.S. distributor	**Wakunaga of America Co., Ltd.**
Botanical ingredient	**Garlic bulb extract**
Extract name	None given
Quantity	300 mg
Processing	Aqueous ethanol extract of fresh bulb
Standardization	*S*-allylcysteine
Formulation	Capsule

Recommended dose: Take two capsules with a meal twice daily.

DSHEA structure/function: Supports cardiovascular health; supports a healthy heart and overall circulatory function.

Other ingredients: Whey, magnesium stearate (vegetable source).

Comments: Kyolic Aged Garlic Extract also comes in tablet, caplet, and liquid forms. Kyolic Aged Garlic Extract can also be found in combination with various other herbs and vitamins.

Source(s) of information: Product label; information from manufacturer.

Clinical Study: Aged Garlic Extract

Extract name	None given
Manufacturer	Wakunaga of America Co., Ltd.
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Yeh YY, Lin RI, Yeh SM, Evans S (1997). Garlic reduces plasma cholesterol in hypercholesterolemic men maintaining habitual diets. In *Food Factors for Cancer Prevention.* Eds. H Ohigashi, T Osawa, J Terao, S Watanabe, T Yoshikawa. Tokyo: Springer-Verlag, pp. 226-230.

Trial design
Parallel. Pretreatment baseline period of four weeks.

Study duration	5 months
Dose	3 (800 mg) capsules 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	34
No. of subjects completed	34
Sex	Male
Age	35-55 years

Inclusion criteria
Plasma total cholesterol between 220 mg/dl and 285 mg/dl.

Exclusion criteria
Acute or chronic disease of the liver, kidney, skin, digestive system, thyroid, and blood as evaluated from a medical questionnaire and a clinical blood test.

End points
Fasting blood samples drawn at baseline (average of three measurements at one, two, and four weeks of pretreatment), and at two, four, and five months, were analyzed for plasma cholesterol. Three-day food records were taken at baseline and after two and four months of treatment.

Results
After five months of treatment with garlic, the mean plasma level of total cholesterol was reduced by 7 percent (18 mg/dl) and LDL cholesterol was decreased by 10 percent (17 mg/dl) from the baseline values. Levels remained unchanged in the placebo group. Neither garlic nor placebo altered the plasma levels of high-density lipoprotein cholesterol and tricylglycerol. Garlic treatment did not affect body weight, body mass index, or blood pressure.

Side effects
No major side effects were observed. Two subjects complained of mild unpleasant breath, and one reported occasional heartburn.

Authors' comments
We conclude that daily supplementation of aged garlic extract for five months without diet modifications has a mild cholesterol-lowering effect in hypercholesterolemic men.

Reviewer's comments
This study was limited by the small sample size (17 men in each group). The placebo capsules contained a common food ingredient, but there was no mention as to whether their appearance was identical to that of garlic capsules. There was no description of the randomization process either. (1, 5)

Clinical Study: Aged Garlic Extract

Extract name	None given
Manufacturer	Wakunaga of America Co., Ltd.
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Steiner M, Khan AH, Holbert D, Lin RI (1996). A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. *American Journal of Clinical Nutrition* 64 (6): 866-870. (Platelet studies published by Steiner M, Lin RS [1998] *Journal of Cardiovascular Pharmacology* 31 [6]: 904-908.)

Trial design
Crossover. Four-week baseline period, followed by six-month treatment period of garlic or placebo, and then a four-month period with switched treatments. Participants were advised to follow the National Cholesterol Education Program Step 1 diet for the length of the study.

Study duration	10 months
Dose	9 (800 mg) capsules per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	52
No. of subjects completed	41
Sex	Male
Age	32-68 years

Inclusion criteria
Plasma total cholesterol between 220 mg/dl and 290 mg/dl; normal results on a physical examination.

Exclusion criteria
None mentioned.

End points
During the baseline and treatment periods, lipid profiles (total, HDL, and LDL cholesterol, and triglycerols) were analyzed at weekly intervals. Blood pressure was also measured. In a subgroup of ten compliant subjects divided between the garlic and placebo groups, platelet adhesion and aggregation studies were performed at three and six months during the first intervention period, at three months during the second intervention period, and two to three months after termination of the study.

Results
Maximal reduction in total serum cholesterol of 6.1 percent or 7.0 percent in comparison with the average concentration during the placebo administration and baseline evaluation period, respectively. Low-density lipoprotein cholesterol was also decreased by aged garlic extract, 4 percent in comparison with placebo period concentrations. In addition, there was a 5.5 percent decrease in systolic blood pressure and a modest reduction of diastolic blood pressure in response to garlic. Platelet adhesion to fibrogen was reduced by >30 percent during garlic administration. Platelets also required higher concentrations of epinephrine and collagen, but not ADP, to aggregate.

Side effects
Allergy to coating material of the capsules, gastrointestinal complaints, and perception of unusual body odor.

Authors' comments
Dietary supplementation with aged garlic extract has beneficial effects on the lipid profile and blood pressure of moderately hypercholesterolemic subjects. AGE administration can produce an inhibition of some of the platelet functions important for initiating thromboembolic events in the arterial circu-

lation. Together, AGE provides a combination of therapeutic effects directed against the major pathogenic factors of atherosclerosis and associated thrombotic events.

Reviewer's comments
This is a well-designed and well-conducted peer-reviewed study showing a modest decrease in both cholesterol and blood pressure. (5, 6)

Clinical Study: Aged Garlic Extract

Extract name	None given
Manufacturer	Wakunaga of America Co., Ltd.
Indication	**Blood clotting factors** in normal volunteers
Level of evidence	**I**
Therapeutic benefit	**MOA**

Bibliographic reference
Steiner M, Li W (2001). Aged garlic extract, a modulator of cardiovascular risk factors: A dose-finding study on the effects of AGE on platelet functions. *Journal of Nutrition* 131 (3s): 980S-984S.

Trial design
Crossover. There was an initial six-week baseline period during which no treatment was given. Patients were then randomized to receive placebo or AGE three (800 mg) capsules per day for six weeks; the dosage was then raised to six (800 mg) capsules per day for six weeks; and finally the dosage was raised to nine (800 mg) capsules per day for another six weeks. After a two-week washout period, patients were switched to the other treatment for a repeat of the same dosing regimen.

Study duration	18 weeks
Dose	3, 6, or 9 (800 mg) capsules daily (2.4 to 7.2 g daily)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No

Site description	Not described
No. of subjects enrolled	34
No. of subjects completed	28
Sex	Male and female
Age	Not given

Inclusion criteria
Normal individuals in good physical health.

Exclusion criteria
None mentioned.

End points
Every two weeks blood was sampled and processed for adhesion and platelet aggregation studies. Aggregation tests were carried out with the following agonists: arachidonic acid, adenosine diphosphate (ADP), epinephrine, and collagen. Platelet adhesion was tested for all subjects on surfaces coated with collagen, and for a subgroup of subjects on surfaces coated with fibrinogen and von Willebrand factor.

Results
Platelet aggregation using the agonist ADP resulted in a significant increase in the threshold for individuals consuming AGE, compared to baseline and placebo only at the highest dose (7.2 g AGE daily, $p < 0.05$). With the collagen-induced aggregation, all doses of AGE saw a significant increase in the threshold compared to baseline and placebo. For epinephrine-induced aggregation, AGE significantly inhibited aggregation (increased threshold) only at the lower doses (2.4 and 4.8 g) compared to placebo and baseline. At low shear rates (~1/30 s), there were significant, but small, reductions in platelet aggregation to collagen-coated surfaces for the two higher doses (4.8 to 7.2 g AGE). For high shear rates (~1/1200 s) there was a dose response for reduction in platelet adhesion to collagen-coated surfaces; 7.2 g AGE produced the highest reduction. For the subgroup tested for platelet adhesion to fibrinogen- and von Willebrand factor-coated surfaces, adhesion to the former was significantly inhibited by all doses of AGE, with greater inhibition at the two higher doses. Adhesion to von Willebrand factor-coated surfaces was inhibited only at doses of 7.2 g AGE.

Side effects
Side effects included body odor, allergy, and gastrointestinal complaints such as flatulence and heartburn.

Authors' comments
The inhibition of several risk factors achieved by AGE should make it a very useful dietary supplement in the prevention of cardiovascular disease.

Reviewer's comments
This is a good study. (5, 6)

Clinical Study: High Potency Kyolic®

Extract name	None given
Manufacturer	Wagner Probiotics (Wakunaga of America Co., Ltd.)
Indication	**Lipid oxidation** in normal volunteers
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference

Munday JS, James KA, Fray LM, Kirkwood SW, Thompson KG (1999). Daily supplementation with aged garlic extract, but not raw garlic protects low density lipoprotein against in vitro oxidation. *Atherosclerosis* 143 (2): 399-404.

Trial design

Three-arm Latin-square design study: 6 g raw garlic, 2.4 g aged garlic extract, or 0.8 g DL-alpha-tocopherol. Subjects took each supplement for seven days, interrupted by a seven-day washout period with no supplements.

Study duration	7 days
Dose	2 capsules (total of 2.4 g) aged garlic extract daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	DL-alpha-tocopherol and raw garlic
Site description	Single center
No. of subjects enrolled	9
No. of subjects completed	9
Sex	Male and female
Age	24-49 years

Inclusion criteria

Nonsmoking volunteers.

Exclusion citeria
Person who had consumed significant quantities of garlic or taken any medication, including dietary supplements, during the month preceding the study.

End points
At the beginning and the end of each seven-day supplement period, a fasting blood sample was taken and the concentration of plasma lipoproteins and the oxidizability of LDL determined.

Results
Alpha-tocopherol (vitamin E) supplementation produced LDL which was significantly ($p < 0.05$) more resistant to oxidation than LDL isolated from subjects receiving AGE. LDL from subjects receiving AGE was more resistant ($p < 0.01$) to oxidation than LDL from nonsupplemented subjects (i.e., when subjects were on washout periods between treatments). The oxidation resistance of LDL from subjects receiving raw garlic was not significantly different to LDL from subjects receiving no supplements or subjects receiving AGE. The decrease in LDL oxidation resulting from alpha-tocopherol supplementation was consistent. In contrast, that resulting from supplementation of AGE or raw garlic was variable. No significant changes in plasma lipoprotein or triglyceride concentrations were observed.

Side effects
No adverse effects with AGE or alpha-tocopherol; body odor with raw garlic.

Authors' comments
These results suggest that if antioxidants are proven to be antiatherogenic, the combined antioxidant and serum cholesterol-lowering actions of AGE may make it useful in reducing the progression of atherosclerosis.

Reviewer's comments
This study was flawed by the small sample size and short treatment period. Both AGE and raw garlic had unimpressive effects on LDL oxidation compared to vitamin E. There was no placebo due to the inclusion of raw garlic. (1, 5)

Product Profile: Kyolic® Liquid Aged Garlic Extract™

Manufacturer	**Wakunaga of America Co., Ltd.**
U.S. distributor	**Wakunaga of America Co., Ltd.**
Botanical ingredient	**Garlic bulb extract**
Extract name	None given

Quantity	No information
Processing	Aqueous ethanolic extract of the bulb (aged 20 months) and produced without heat
Standardization	*S*-allylcysteine
Formulation	Liquid

Recommended dose: As a dietary supplement, take one-quarter to one-half teaspoon, or 30 to 60 drops (one or two filled 00 size capsules) with a meal twice daily.

Other ingredients: Water, residual alcohol from extraction.

Source(s) of information: Product package; information from manufacturer.

Clinical Study: Kyolic® Liquid Aged Garlic Extract™

Extract name	None given
Manufacturer	Wakunaga of America Co., Ltd.
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Lau BHS, Lam F, Wang-Cheng R (1987). Effect of an odor-modified garlic preparation on blood lipids. *Nutrition Research* 7: 139-149.

Trial design
Three-part study. Part 1 (hyperlipidemic group): 32 patients (ages 45 to 68; 27 finished study) with elevated serum cholesterol and triglycerides. Part 2 (normolipidemic group): 14 patients (ages 18 to 32) with serum cholesterol and triglycerides in normal range. Part 3 (hyperlipidemics): 10 patients (ages 56 to 67), uncontrolled study.

Study duration	6 months
Dose	4 (1 ml, 250 mg active garlic components per ml) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No

Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	56
No. of subjects completed	51
Sex	Male and female
Age	3 different age groups

Inclusion criteria
Healthy volunteers with no obvious medical problems at the time of the study. First study: initial cholesterol in the range of 220 to 440 mg/dl; second study: initial cholesterol in the range of 150 to 200 mg/dl; third study: initial cholesterol in the range of 240 to 380 mg/dl.

Exclusion criteria
Those taking medications, on special diets, smokers, or alcohol users.

End points
Fasting blood measurements of serum cholesterol, triglycerides, and lipoproteins taken at baseline and at monthly intervals.

Results
Lowering of cholesterol, triglycerides, and low density and very low density lipoproteins with a rise of high-density lipoprotein was observed in the majority of hyperlipidemic subjects who took garlic. Part 1 reported that 11 out of 15 subjects had a decrease in serum cholesterol of greater than 10 percent. The effect was significant compared to placebo. Garlic did not significantly influence cholesterol and triglyceride levels of those whose baseline levels were in the normal range. The lowering of lipid levels was not observed during the first and second month of treatment. In fact, the majority showed a rise in lipid values during that period.

Side effects
No serious side effects reported.

Authors' comments
This study conforms previous reports of lowering cholesterol and triglycerides using various garlic preparations. Furthermore, it suggests that odor-modified garlic extract may be used in conjunction with dietary modification for control of hyperlipidemia. Of special interest was the initial rise in cholesterol, triglycerides, and LDL/VLDL with garlic supplementation, suggesting

possible mobilization of tissue lipids into the circulation during this phase of garlic ingestion.

Reviewer's comments
This was a three-part study, each with an inadequate number of participants. Although parts 1 and 2 were placebo controlled, part 3 was not. Blinding appeared to be single, and the randomization process was not described. (1, 5)

Product Profile: Garlic Oil, Ethyl Acetate Extracted

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Garlic clove extract**
Extract name	None given
Quantity	Equivalent of 1 g raw garlic
Processing	Peeled garlic cloves were crushed, extracted in ethyl acetate, the solvent evaporated, and the resultant oil dissolved in soy oil
Standardization	No information
Formulation	Capsule

Source(s) of information: Bordia, Verma, and Srivastava, 1998.

Clinical Study: Garlic Oil, Ethyl Acetate Extraction

Extract name	None given
Manufacturer	None
Indication	**Heart disease; coronary artery disease**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Bordia A, Verma SK, Srivastava KC (1998). Effect of garlic *(Allium sativum)* on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 58 (4): 257-263.

Trial design
Parallel. Two-week pretrial baseline period.

Study duration	3 months
Dose	2 capsules (each equivalent to 1 g raw garlic) twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Not given
Age	51-66 years

Inclusion criteria
Patients who had myocardial infarctions more than six months ago, with or without angina. Those with angina were stable with drugs. All patients stopped intake of nitrates and aspirin two weeks prior to study.

Exclusion criteria
None mentioned.

End points
Two pretrial fasting blood samples were collected at an interval of two weeks to examine baseline parameters. Patients were then evaluated every month for clinical symptoms and side effects. At intervals of one and one-half months and three months of administration, fasting blood samples were obtained and examined for lipid profile, fibrinogen, fibrinolytic activity, and blood sugar levels.

Results
Patients taking garlic showed a significant reduction in total cholesterol (from 252.9 to 220.5 mg/dl, 12.8 percent) and triglycerides (15.2 percent) compared to baseline (both $p < 0.01$) after three months of treatment. Their HDL-C and fibrinolytic activity increased significantly (22.3 percent and 55.1 percent, respectively) compared to baseline ($p < 0.05$ and $p < 0.01$, respectively). There was no change in fibrinogen levels. Those on placebo had no

significant changes to any of the parameters compared to baseline. Neither group showed any change to blood glucose levels.

Side effects
None listed.

Authors' comments
In the light of these data and those of others on the lipid-regulating effects of garlic coupled with its enhanced fibrinolytic activity and anticoagulant, eicosanoid modulatory, and antioxidant effects, garlic might find a place among the arsenal of dietary agents showing protection against the diseases of the cardiovascular system and possibly other diseases as well.

Reviewer's comments
This study had clear and statistically positive results: cholesterol was lowered by 13 percent at three months; triglycerides were lowered by 15.2 percent; HDL increased by 22.3 percent; and platelet aggregation was inhibited. Neither the randomization process nor the placebo were described in any detail. It is unclear if this trial was blinded or open. (1, 6)

Clinical Study: Garlic Oil, Ethyl Acetate Extraction

Extract name	None given
Manufacturer	None
Indication	**Coronary heart disease patients with hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Bordia A (1981). Effect of garlic on blood lipids in patients with coronary heart disease. *The American Journal of Clinical Nutrition* 34 (10): 2100-2103.

Trial design
Parallel. Two-part study. Part 1 included 20 healthy individuals given garlic for six months followed by two months without garlic. Part 2 included 68 coronary heart disease patients who were divided into two groups and given either garlic or placebo for ten months.

Study duration	10 months
Dose	0.25 mg oil per kg body weight in 2 divided doses; e.g., 15 mg/60 kg person
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	68
No. of subjects completed	62
Sex	Not given
Age	42-62 years

Inclusion criteria
Patients with coronary heart disease with serum cholesterol levels from 250 to 350 mg/dl.

Exclusion criteria
Patients with hyperlipidemia secondary to other conditions such as nephrotic syndrome, liver, pancreas or biliary tract disease, or uncontrolled diabetes and other endocrinological diseases; patients with serious complications or severe hyperlipidemia requiring specific therapy and strict dietary restriction.

End points
Fasting blood samples were collected initially (mean of two samples at a one-week interval) and then after every month. Samples were analyzed for serum cholesterol, triglycerides, phospholipids, and lipoproteins.

Results
In the first part of the study, serum cholesterol dropped (233 to 200 mg/dl, $p < 0.05$), serum triglycerides dropped (110 to 92 mg/dl, $p < 0.05$), and high-density lipoprotein increased (29 to 41 mg/dl, $p < 0.001$) after six months. In part 2, garlic administration raised serum cholesterol in the first month but decreased it by 18 percent after eight months (298 to 244 mg/dl, $p < 0.05$). Serum cholesterol continued to decrease for two months after treatment had stopped (to 228 mg/dl). Serum triglycerides also decreased significantly ($p < 0.05$). There was no change in these levels in the control group. By the end of 8 months, the HDL levels increased ($p < 0.001$) while the LDL levels

decreased ($p < 0.05$). The cholesterol/phospholipid ratio reduced following garlic administration but not with placebo.

Side effects
Epigastric discomfort, diarrhea.

Author's comments
The essential oil of garlic has shown a distinct hypolipidemic action in patients of coronary heart disease.

Reviewer's comments
Overall, this is a good study showing a reduction in cholesterol with ethylacetate extract of garlic oil over eight months. (3, 6)

Product Profile: Garlic Oil, Cold Pressed

Manufacturer	**General Nutrition Research Laboratories**
U.S. distributor	None
Botanical ingredient	**Garlic clove extract**
Extract name	None given
Quantity	18 mg oil is equivalent to 9 g raw garlic
Processing	Cold-pressed garlic oil extracted from fresh garlic
Standardization	No information
Formulation	Perle

Other ingredients: Coconut oil (158 mg), glycerin (30 mg), gelatin (54 mg).

Source(s) of information: Barrie, Wright, and Pizzorno, 1987.

Clinical Study: Garlic Oil, Cold Pressed

Extract name	None given
Manufacturer	General Nutrition Research Laboratories
Indication	**Cardiovascular risk factors** in normal volunteers
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Barrie S, Wright J, Pizzorno J (1987). Effects of garlic oil on platelet aggregation, serum lipids and blood pressure in humans. *Journal of Orthomolecular Medicine* 2 (1): 15-21.

Trial design
Crossover after four weeks. Three-week washout between treatment periods.

Study duration	4 weeks
Dose	18 mg of garlic oil (extracted from 9 g of fresh garlic)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	20
No. of subjects completed	20
Sex	Not given
Age	Mean: 26 years

Inclusion criteria
Good health.

Exclusion criteria
Signs of degenerative cardiovascular disease.

End points
Platelet aggregation percentages, serum lipid levels, and blood pressure readings measured before and after each supplementation period.

Results
During garlic administration, there was a significant reduction (16.4 percent) in platelet aggregation ($p < 0.005$), in serum cholesterol (from 195 to 180 mg/dl, $p < 0.001$), and the mean blood pressure (94 to 88 mmHg, $p < 0.009$), as well as a rise in the mean HDL levels (from 56 to 69 mg/dl, $p < 0.001$). In addition, there was a rise in arachidonic acid in red cell phospholipids following garlic administration.

Side effects
None noted.

Authors' comments
The results of this study suggest that garlic has therapeutic potential as an antiatherosclerotic, antithrombotic, and antihypertensive agent in normal healthy adults.

Reviewer's comments
This is a well-designed study overall; however, 20 subjects is too small to judge in a crossover design. (3, 5)

Product Profile: Tegra

Manufacturer	**Hermes Arzneimittel GmbH, Germany**
U.S. distributor	None
Botanical ingredient	**Garlic clove extract**
Extract name	None given
Quantity	5 mg, equivalent to 4 to 5 g fresh garlic
Processing	Steam-distilled garlic oil preparation
Standardization	No information
Formulation	Enteric coated

Other ingredients: Beta cyclodextrin.

Source(s) of information: Berthold, Sudhop, and von Bergmann, 1998a.

Clinical Study: Tegra

Extract name	None given
Manufacturer	Hermes Arzneimittel GmbH, Germany
Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Berthold H, Sudhop T, von Bergmann, K (1998a). Effect of a garlic oil prepa-

ration on serum lipoproteins and cholesterol metabolism. *Journal of the American Medical Association* 279 (23): 1900-1902.

Trial design
Crossover study after 12 weeks. Pretrial single-blind washout period for four weeks, and a four-week single-blind washout between treatment periods.

Study duration	3 months
Dose	5 mg garlic oil twice daily, equivalent to 4 to 5 fresh garlic cloves
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single outpatient clinic
No. of subjects enrolled	26
No. of subjects completed	25
Sex	Male and female
Age	51-66 years

Inclusion criteria
Moderate hypercholesterolemia (total cholesterol 240 to 348 mg/dl and triglycerides <265 mg/dl). Any lipid-lowering drugs or drugs which would interfere with lipid metabolism were not allowed for eight weeks prior to start. No additional intake of garlic or other food supplements allowed.

Exclusion criteria
Active liver or renal diseases, diabetes, thyroid dysfunction, history of coronary heart disease, pathological values in clinical chemistry or routine hematological parameters, and alcohol or drug abuse.

End points
Serum lipoprotein concentrations, cholesterol absorption, and cholesterol synthesis measured at beginning of study and ends of both treatment periods. Food intake was assessed at the end of the treatment periods using seven-day food records. During the last week of each treatment period, cholesterol absorption and endogenous cholesterol synthesis were measured by double isotope feeding using deuterated [D_6]cholesterol and [D_4]sitosterol.

Results
Lipoprotein levels were virtually unchanged at the end of both treatment periods. Cholesterol absorption, cholesterol synthesis, mavalonic acid excretion, and changes in the ratio of lathosterol to cholesterol were not different in garlic and placebo treatment.

Side effects
Garlic odor; slight abdominal discomfort in a few cases caused by garlic and placebo.

Authors' comments
The commercial garlic oil preparation had no influence on serum lipoproteins, cholesterol absorption, or cholesterol synthesis. Garlic therapy for treatment of hypercholesterolemia cannot be recommended on the basis of this study.

Reviewer's comments
Tegra garlic oil is steam distilled and bound to cyclodextrin. The use of this special preparation may affect the bioavailable dose compared to other garlic oil. Otherwise, this is a well-conducted study. (5, 5)

Product Profile: Garlic (Raw)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Garlic clove**
Extract name	N/A
Quantity	No information
Processing	Raw
Standardization	No information

Source(s) of information: Bhushan et al., 1979; Gadkari and Joshi, 1991.

Clinical Study: Garlic (Raw)

Extract name	N/A
Manufacturer	None

Indication	**Hypercholesterolemia** (elevated cholesterol levels)
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Bhushan S, Sharma SP, Singh SP, Agrawal S, Indrayan A, Seth P (1979). Effect of garlic on normal blood cholesterol level. *Indian Journal of Physiology and Pharmacology* 23 (3): 211-214.

Trial design
Parallel. Treatment group was compared to a control group taking nothing.

Study duration	2 months
Dose	10 g of raw garlic daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	1 general practice
No. of subjects enrolled	25
No. of subjects completed	25
Sex	Male
Age	18-35 years

Inclusion criteria
Healthy subjects who had never ingested garlic before with initial cholesterol levels of 160 to 250 mg/dl.

Exclusion criteria
During test period, no intake of any drug, onion, smoking, or tobacco chewing was allowed. Physical activity was restricted.

End points
Fasting blood samples collected and serum cholesterol tested before study and after two months.

Results
There was a significant decrease in serum cholesterol (33.2 mg/dl) in the raw garlic group compared to baseline (15 percent reduction, $p < 0.00001$),

whereas serum cholesterol in the control group did not change significantly. A comparison of the two groups revealed a significant difference ($p < 0.05$).

Side effects
None noted.

Authors' comments
Raw garlic can be advocated for daily ingestion in order to lower one's blood cholesterol level even if it is within normal limits.

Reviewer's comments
This study was flawed by its small sample size and lack of blinding. The randomization process was also not described. (0, 5)

Clinical Study: Garlic (Raw)

Extract name	N/A
Manufacturer	None
Indication	**Cardiovascular risk factors** in normal volunteers
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Gadkari, J, Joshi V (1991). Effect of ingestion of raw garlic on serum cholesterol level, clotting time and fibrinolytic activity in normal subjects. *Journal of Postgraduate Medicine* 37 (3): 128-131.

Trial design
Parallel. Treatment group compared was to a control group taking nothing.

Study duration	2 months
Dose	10 g of raw garlic daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	1 general practice

No. of subjects enrolled	50
No. of subjects completed	50
Sex	Not given
Age	17-22 years

Inclusion criteria
Healthy subjects who had never ingested garlic before.

Exclusion criteria
None mentioned.

End points
Fasting blood samples were taken before the study and after two months of treatment. Serum cholesterol, fibrinolytic activity, and clotting time were measured.

Results
After two months of treatment, there was a significant decrease in serum cholesterol (from 213.3 to 180.0 mg/dl), an increase in clotting time (from 4.14 to 5.02 min), and an increase in fibrinolytic activity in the raw garlic group (all $p < 0.001$), whereas there was no significant change in the control group.

Side effects
None noted.

Authors' comments
Garlic may be useful for prevention of thromboembolic phenomenon.

Reviewer's comments
The outcome measures and inclusion/exclusion criteria were clearly defined and appropriate. However, the study was not blinded, the randomization process was not described, and the effects of garlic on fibrinolysis, cholesterol, and clotting time could be due to other factors. (0, 6)

Ginger

Latin name: ***Zingiber officinale*** **Roscoe** [Zingiberaceae]
Plant parts: **Root, rhizome**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Ginger root (rhizome) is a common spice that has long been esteemed as an appetite stimulant and an aid to digestion. It has been used in China for roughly 2,500 years and is a common ingredient in traditional Chinese herbal formulas. Ginger has a distinct aroma due to its essential oil, which contains approximately 60 components, including geranial and neral. Ginger's flavor is due to its pungent principals, which include gingerols and products formed from gingerols, the shogaols and zingerone. Shogaols and gingerols, especially 6-gingerol, have demonstrated antiemetic activity in animal studies (Awang, 1992; ESCOP, 1996).

Zintona® contains a standardized dried ginger root powder. It is a registered trademark of Dalidar Pharma Ltd. and is registered as an OTC pharmaceutical in several European countries. Dalidar has been acquired by Makhteshim-Agan Industries, Ltd., Israel, a subsidiary of Koor Industries. Several trials were conducted on Zintona supplied by Pharmaton S.A., Switzerland. Zintona is no longer sold in the United States.

WS 1540 is an extract of ginger rhizome. It is manufactured by Dr. Willmar Schwabe GmbH & Co. in Germany. This extract is not available in the United States.

Eurovita Extract 33 (EV ext-33) is a ginger extract with a standardized amount of hydroxy-methoxy-phenyl compounds. It is manufactured by Eurovita A/S and is not available in the United States.

Several studies used generic preparations of powdered ginger root and rhizome. Few details were provided to characterize these ginger preparations. Most studies just described the product as powdered

GINGER SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Zintona®	Dalidar Pharma Ltd., Israel/ None	Dried root powder	Ages 3-6: 250 mg; over 6 yrs: 500 mg before departing and then every 4 h	Motion sickness	4	Yes (I-1, II-1) Trend (III-1) MOA (III-1)
WS 1540	Dr. Willmar Schwabe GmbH & Co., Germany/ None	Extract of rhizome (WS 1540)	2 × 2 (10 mg) capsules	Gastrointestinal motility	1	MOA (II-1)
Eurovita Extract 33	Eurovita A/S, Denmark/None	Standardized to content of hydroxymethoxy-phenyl compounds	170 mg 3 times daily	Osteoarthritis	1	No (I-1)
Generic	None/None	Powdered ginger	0.94-1 g daily	Motion sickness	3	Trend (III-2) MOA (III-1)
			0.5-2 g daily	Nausea	7	Yes (I-1, II-1) Undetermined (II-1, III-3) No (I-1)
			1 g	Gastric motility	1	MOA (I-1)
			4 g daily	Cardiovascular risk factors	1	MOA (III-1)
Generic (raw and stem)	None/None	Chopped ginger root or stem ginger	15 g raw or 40 g stem ginger daily	Cardiovascular risk factors	1	MOA (III-1)

ginger and gave the dose. None of the studies mentioned profiling the ginger for quantities of gingerols, nor were any other chemical analyses mentioned. Bordia, Verma, and Srivastava (1997) remark in their discussion that the sample used in their study was almost 50 percent lower in measured constituents than two other samples which they also obtained. However, they did not specify the constituents they measured or give any values. One study used ginger that complied with the British Pharmacopoeia monograph of 1988 and was supplied by Blackmores Ltd. (Sydney, Australia) (Arfeen et al., 1995). Two studies used powdered ginger specially prepared for the trial by Martindale Pharmaceuticals Pty. Ltd. in England (Phillips, Ruggier, and Hutchinson, 1993; Phillips, Hutchinson, and Ruggier, 1993). Again, however, characterization of the product was not mentioned.

One trial used raw Brazilian ginger root supplied by Toko Rinus, Nijmegen, and stem ginger supplied by Ambition, Polak Import, Rotterdam, both of the Netherlands. No further description was provided (Janssen et al., 1996).

SUMMARY OF REVIEWED CLINICAL STUDIES

Ginger products have been tested in clinical studies for effectiveness in reducing nausea and vomiting due to administration of chemotherapy, emergence from general anesthesia following surgery, morning sickness associated with pregnancy, and, most commonly, for motion sickness. Vertigo, nausea, vomiting, cold sweat, and pallor are typical signs of motion sickness. Motion sickness is often caused by the perception of movement by the inner ear, especially when it conflicts with information from the eyes and other senses. The inner ear contains sensors for motion in the vestibular system. The vomiting reflex is mediated via the vagal and sympathetic pathways of the nervous system and can be stimulated by pain, smell, sight, motion, cytotoxic drugs, and irritants in the stomach.

Agents commonly used to prevent nausea and vomiting include serotonin inhibitors (e.g., ondansetron), dopamine antagonists (metoclopramide, chlorpromazine, promenthazine, etc.), antihistamines (dimenhydrinate, diphenhydramine, meclizine, etc.), corticosteroids, cannabinoids, and benzodiazepines. Scopolamine, given orally, parenterally, or transdermally, is regarded as the most potent drug for the

prophylaxis and treatment of motion sickness. However, the antihistamines, especially dimenhydrinate, are also commonly used (Hardman et al., 1996).

The ability of ginger to inhibit the formation of inflammatory mediators and its antioxidant activity in vitro led to testing an extract for a possible clinical application for osteoarthritis (deterioration of the joints characterized by pain, inflammation, and reduced function). Common first-line treatments for relief of symptoms of rheumatic diseases are the nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin, acetaminophen, indomethacin, ibuprofen, and diclofenac (Hardman et al., 1996).

Zintona

Motion Sickness

Three studies with Zintona demonstrated a benefit for this ginger product on motion sickness. A fourth study indicated that the mode of action of Zintona is gastrointestinal, rather than through the central nervous system.

The first of two good-quality studies compared the ability of Zintona and six other agents (standard pharmaceuticals) to prevent seasickness on a six-hour sea voyage. The trial included 1,475 volunteers who filled out a questionnaire regarding their degree of discomfort, nausea, and vomiting. Zintona was given in a dose of 500 mg (two tablets) two hours prior to departure and again four hours later. Completed questionnaires indicated that all treatments offered some benefit, with no statistical difference between them (Schmid et al., 1994). The other good-quality study included 60 cruise ship passengers, with a history of motion sickness, who received either Zintona (500 mg before sailing and every four hours afterward) or dimenhydrinate (100 mg before sailing and every fours hours afterward) for two days. Both treatments were equally effective in preventing seasickness (Riebenfeld and Borzone, 1999).

In one study, 28 children, four to eight years old, were treated to prevent motion sickness on a two-day trip that included journeying by car, boat, and/or airplane. They were given either Zintona (250 mg for those aged three to six or 500 mg for those older than six, 30 minutes before the trip and every four hours as needed) or dimenhydrinate (12.5 or 25 mg 30 minutes before the trip and every four

hours as needed). As rated by pediatric physicians, Zintona was more effective and had fewer side effects (Cereddu, 1999). The trial was rated as having a trend toward therapeutic benefit by our reviewers, Drs. Karriem Ali and Richard Aranda, due to a lack of detail in the study report.

A three-arm, crossover, mode-of-action study with 38 participants determined that ginger did not prevent motion sickness with the same central nervous system mechanism as dimenhydrinate. The study measured the nystagmus response (involuntary eye movements) to optokinetic stimuli (a moving stripe pattern), vestibular stimuli (water irrigation of the ears), and to being spun in a rotary chair. Ginger, 1g Zintona given 90 minutes before stimuli, had no influence on experimentally induced nystagmus, compared to baseline and placebo. In contrast, dimenhydrinate, 100 mg, reduced the nystagmus response to all stimuli. The authors concluded that ginger most likely acts through a mechanism involving the gastrointestinal tract, in contrast to dimenhydrinate which acts through the central nervous system (Holtmann et al., 1989).

WS 1540

Gastrointestinal Motility

A crossover trial measured the effect of 200 mg ginger extract WS 1540 (corresponding to 2 g ginger root) on gastrointestinal motility in 12 healthy volunteers. Ginger or placebo was given in the morning after fasting and at noon before lunch. Gastroduodenal motility was tested in the morning and for an hour after lunch. In comparison to placebo, ginger increased the number, frequency, and amplitude of gastric contractions in the fasting state and to a lesser degree following a meal (Micklefield et al., 1999).

Eurovita Extract 33

Osteoarthritis

Eurovita Extract 33 (EV ext-33), a ginger extract, was compared to ibuprofen (a NSAID) and placebo in a well-conducted crossover study with 56 participants with osteoarthritis. Each treatment arm,

with daily administration of 510 mg ginger extract, 1200 mg ibuprofen, or placebo, was three weeks in duration with a one-week washout period in between. As a result, ibuprofen was more effective than ginger and placebo in reducing pain, improving range of motion, and reducing consumption of acetaminophen (another NSAID). Benefit from ibuprofen was significantly better than placebo. Ginger was more effective than placebo, but not significantly (Bliddal et al., 2000).

Generic

Motion Sickness

The effect of powdered ginger on experimentally induced motion sickness was tested in two studies, both given low ratings. In the first study, prevention of experimentally induced motion sickness was measured in a one-dose crossover experiment. Motion sickness was induced by stimulation of the vestibular system (inner ear) through irrigating the left ear with water. Ginger, 1 g powdered root given one hour before the procedure, was effective in reducing vertigo but not nystagmus in comparison with placebo. As no statistically significant change in nystagmus was demonstrated, the author suggested that ginger does not directly affect the vestibular system (Grøntved and Hentzer, 1986). The second study was a three-arm, open, experimental study with motion sickness induced by a tilted rotating chair. The study compared the benefit of powdered ginger root (940 mg), dimenhydrinate (100 mg), and placebo (powdered chickweed herb). Administration of ginger allowed the subjects to stay in the chair longer and diminished feelings in their stomachs compared to those in the other two groups (Mowrey and Clayson, 1982).

Another study explored the effects of ginger on motion sickness experienced by Navy cadets. Seventy-nine men were given either ginger (1 g powered root) or placebo (lactose) on their first trip on the high seas. Ginger significantly reduced the tendency to vomit and experience cold sweats. The symptoms of nausea and vertigo were also reduced, but not significantly (Grøntved et al., 1988).

Nausea

A small study included 11 subjects undergoing chemotherapy with 8-methoxy psoralen (8-MOP). The subjects monitored their nausea following 8-MOP treatments with or without the addition of ginger (1.6 g powdered root). As a result, treatment with ginger reduced the nausea score (Meyer et al., 1995). The level of evidence of this trial was low due to poor experimental design.

The ability of ginger to treat postoperative nausea and vomiting was tested in four trials. One trial rated as good quality failed to show a benefit. The other three studies were rated as having undetermined benefit due to poor methodology. The good-quality study was a three-arm study in which females undergoing gynecological laparoscopic surgery received either 500 mg ginger, 1000 mg ginger, or placebo one hour before induction of anesthesia. Three hours after the operation patients were questioned as to whether they had experienced any nausea or vomiting after gaining consciousness. No significant benefit was derived from the ginger (Arfeen et al., 1995).

A larger study with 111 women undergoing gynecological laparoscopic surgery compared ginger and droperidol with placebo in a double-dummy protocol with four arms. All treatments were administered one hour before surgery (ginger 1 g orally; droperidol 1.25 mg intravenously), and the ginger treatment was repeated after surgery. As a result, there were no significant differences in the incidences of postoperative nausea with either treatment alone or with both treatments together (Visalyaputra et al., 1998). Our reviewers, Drs. Ali and Aranda, commented that the sample size was inadequate and the differences in surgical techniques might have affected the results of this study.

In another study, 120 women undergoing laparoscopic surgery were given metoclopramide (10 mg), ginger (1 g), or placebo one hour before induction of anesthesia. In this study the incidence of nausea and vomiting following surgery for both treatment groups was less than with placebo (Phillips, Ruggier, and Hutchinson, 1993). However, Drs. Ali and Aranda rated the benefit as undetermined, as measuring the number of nausea complaints per patients does not have a clear correlation with severity or antiemetic effect.

In a study with 60 women undergoing major gynecological surgery, ginger (1 g) was compared to metoclopramide (10 mg IV) and

placebo in a double-dummy design. The ginger capsules were given one and one-half hours before surgery, and the metoclopramide was given at the induction of anesthesia. As a result of treatment, the ginger and metoclopramide groups both experienced significantly less nausea after surgery compared to the placebo group. There was also less need for additional treatment with metoclopramide after surgery in the active treatment groups (Bone et al., 1990). The level of evidence was rated low due to limitations of the methodology.

Ginger was reported to significantly reduce nausea and vomiting associated with pregnancy in two good-quality studies using a dose of 250 mg powdered ginger four times daily for four days. The first trial included 27 women in a crossover design, in which the women were given either placebo or powdered ginger for four days with a two-day washout period in between. Subjective assessments by the women revealed that 70 percent felt greater relief from ginger (Fischer-Rasmussen et al., 1990). The second study was a larger, parallel, placebo-controlled study with 67 pregnant women that measured nausea and vomiting using a visual analog scale and the five-item Likert scale. Using the Likert scale, 28 out of 32 subjects in the ginger group had relief from nausea compared to 10 out of 35 in the placebo group. Ginger did not have an adverse effect on pregnancy outcome (Vutyavanich, Kraisarin, and Ruangsri, 2001).

Gastric Motility

A crossover trial with 16 healthy volunteers examined the effect of powdered ginger (1 g) or placebo on gastric emptying rates. Paracetamol was administered at the same time as either ginger or placebo, and the mean, peak, and time of peak plasma concentrations of the drug were used as a marker for gastric emptying rates. Ginger did not affect gastric emptying rates, as the paracetamol pharmacokinetics were the same for both groups (Phillips, Hutchinson, and Ruggier, 1993).

Cardiovascular Risk Factors

A placebo-controlled trial explored the benefit of ginger for 60 patients with stable cardiovascular disease. The subjects had a history of heart attack and were taking nitrates and aspirin. The aspirin was stopped two weeks before the study. A dose of 4 g powdered ginger

root for three months did not affect experimentally induced platelet aggregation, fibrinogen levels, blood lipid levels, or blood sugar levels. Only a higher, single dose of 10 g powdered ginger reduced experimentally induced platelet aggregation (Bordia, Verma, and Srivastava, 1997). Omissions in descriptions of trial methodology made this trial difficult to evaluate.

A crossover study examined the possible effect of ginger on platelet activity. Platelets were removed from 18 healthy volunteers following two weeks' administration of either 15 g raw ginger, 40 g cooked stem ginger, or placebo. There was no effect by either form of ginger on platelet activity as measured by stimulated release of thromboxane B2 (Janssen et al., 1996). The description of the preparations used in this trial was insufficient, and the study would have been stronger if a comparison with powdered ginger, the more common form of ginger, was included.

SYSTEMATIC REVIEWS AND META-ANALYSES

A systematic review of randomized controlled trials was conducted on six studies exploring the possible efficacy of ginger for nausea and vomiting. The studies addressed four different clinical conditions: seasickness (one study), morning sickness (one study), chemotherapy-induced nausea (one study), and postoperative nausea (three studies). Only the data from the three studies on postoperative nausea were pooled for statistical analysis (Bone et al., 1990; Phillips, Ruggier, and Hutchinson, 1993; Arfeen et al., 1995). The pooled absolute risk reduction for the incidence of postoperative nausea indicated that 1 g ginger taken before surgery gave no benefit over placebo (Ernst and Pittler, 2000).

ADVERSE REACTIONS OR SIDE EFFECTS

No serious side effects associated with powdered ginger or ginger extracts were reported in the trials reviewed. Occasionally participants reported headache and abdominal discomfort. A comparison trial with adults reported fewer side effects with Zintona (13 percent) compared with dimenhydrinate (40 percent). The doses were 500 mg

and 100 mg, respectively, every four hours for two days (Riebenfeld and Borzone, 1999).

A trial with 28 children reported no side effects for those given ginger, whereas for those taking dimenhydrinate, 69 percent complained of dry mouth. In that trial, children aged three to six years received 250 mg Zintona every four hours for two days and those aged six to eight years received 500 mg every four hours for two days; those taking dimenhydrinate received either 12.5 or 25 mg in the same dosing regimen (Cereddu, 1999).

In two trials including a total to 100 pregnant women given 250 mg powdered ginger four times daily for four days, there were no reports of major adverse events or effects on the outcome of pregnancy (Fischer-Rasmussen et al., 1990; Vutyavanich, Kraisarin, and Ruangsri, 2001). Only minor side effects, including headache and abdominal discomfort, were reported.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

German Commission E
British Herbal Compendium (BHC)
World Health Organization (WHO)
European Scientific Cooperative on Phytotherapy (ESCOP)
United States Pharmacopoeia—Drug Information (USP-DI)

Indications

Ginger root is widely recommended for the treatment of dyspepsia and the prevention or prophylaxis of motion sickness (Blumenthal et al., 1998; Bradley, 1992; WHO, 1999; ESCOP, 1996). The *British Herbal Compendium,* the WHO, and ESCOP state that ginger can be used to treat vomiting in pregnancy, while the latter two also suggest ginger for postoperative nausea and vomiting (Bradley, 1992; WHO, 1999; ESCOP, 1996). Other indications listed by the *BHC* include colic, anorexia, bronchitis, and rheumatic complaints (Bradley, 1992). The WHO also lists the following indications: flatulence, colic, vomiting, diarrhea, spasm, colds, flu, appetite stimulation, nar-

cotic antagonist, and inflammation in migraine headache and rheumatic and muscular disorders (WHO, 1999). The *United States Pharmacopoeia—Drug Information* botanical monograph series lists the following reported uses of ginger rhizome: the prevention of nausea and vomiting after operations and the prevention and treatment of vomiting and nausea associated with motion sickness (*USP-DI,* 1998).

Actions stated by the Commission E are antiemetic, positively inotropic, promoting secretion of saliva and gastric juices, cholagogue, and increases tonus and peristalsis in the intestines (Blumenthal et al., 1998). The *BHC* also lists several actions, including carminative, antiemetic, spasmolytic, peripheral circulatory stimulant, and anti-inflammatory (Bradley, 1992).

Doses

Rhizome: 2 to 4 g rhizome daily or equivalent preparations (Blumenthal et al., 1998; WHO, 1999)

- Powdered rhizome: single doses of powdered rhizome, 1 to 2 g, or 0.25 to 1 g three times daily (Bradley, 1992); 0.5 to 2 g of the powdered drug daily or divided doses (adults and children over six years) (ESCOP, 1996)

Tincture:

- Weak ginger tincture BP: (1:5, 90 percent ethanol) 1.5 to 3 ml three times daily (Bradley, 1992)
- Strong ginger tincture BP: (1:2, 90 percent ethanol), 0.25 to 0.5 ml three times daily (Bradley, 1992)

Note: The *BHC,* WHO, and *USP-DI* suggest specific dosages for certain indications:

As an antiemetic: single doses of powdered rhizome, 1 to 2 g (Bradley, 1992)

For motion sickness: (adults and children over six years) 0.5 g, 2 to 4 times daily (WHO, 1999); 1 g ginger 30 to 60 minutes before travel (*USP-DI,* 1998)

For dyspepsia: 2 to 4 g daily, as powdered plant material or extracts (WHO, 1999)

For postoperative nausea or vomiting: 1 g ginger taken 30 to 60 minutes before surgery (*USP-DI,* 1998)

Treatment Period

No restrictions are listed by ESCOP (1996).

Contraindications

The Commission E and WHO suggest that ginger should be used only after consultation with a physician when the patient has gallstones (Blumenthal et al., 1998; WHO, 1999). The WHO also states that patients taking anticoagulant drugs or those with blood coagulation disorders should consult their physicians before self-medicating with ginger (WHO, 1999). The *USP-DI* suggests that pharmacologic doses of ginger are not recommended for children and pregnant or breastfeeding women (*USP-DI,* 1998). The *BHC* and ESCOP list no known contraindications (Bradley, 1992; ESCOP, 1996).

Adverse Reactions

ESCOP lists heartburn as a possible adverse reaction, while the Commission E states that ginger has no known adverse reactions (ESCOP, 1996; Blumenthal et al., 1998). The *USP-DI* also lists minor heartburn as the only reported adverse reaction to ginger (*USP-DI,* 1998).

Precautions

ESCOP has no reported precautions for ginger, while the WHO suggests that it is not recommended for children less than six years of age (ESCOP, 1996; WHO, 1999). The *USP-DI* suggests that patients with an increased risk of hemorrhage or those taking anticoagulants should use ginger with caution (*USP-DI,* 1998).

Drug Interactions

Although the Commission E states no known drug interactions, the WHO states that ginger may affect bleeding times and immunological parameters owing to its ability to inhibit thromboxane synthase and to act as a prostacyclin agonist; the ESCOP claims that ginger may enhance absorption of sulfaguanidine (Blumenthal et al., 1998; WHO, 1999; ESCOP, 1996).

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DETAILS ON GINGER PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Ginger

Product Profile: Zintona®

Manufacturer	**Dalidar Pharma Ltd., Israel**
U.S. distributor	None
Botanical ingredient	**Ginger root**
Extract name	**Zintona**
Quantity	250 mg
Processing	Dried root powder
Standardization	Pungent phenolic compounds
Formulation	Capsule

Recommended dose: Take two capsules one-half hour prior to travel or meals. Up to two capsules may be taken every four hours during travel.

DSHEA structure/function: Maintains a calm stomach, especially during travel.

Cautions: As with any supplement, contact a doctor if currently taking prescription medicine, or if pregnant or nursing a baby.

Other ingredients: Gelatin, colloidal anhydrous silica, sodium lauryl sulfate.

Source(s) of information: Quanterra™ Stomach Comfort product package (©1999 Warner-Lambert Co.); Riebenfeld and Borzone, 1999.

Clinical Study: Zintona®

Extract name	Zintona
Manufacturer	Pharmaton S.A., Switzerland (Dalidar Pharma Ltd., Israel)
Indication	**Motion sickness; seasickness**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference

Schmid R, Schick T, Steffen R, Tschopp A, Wilk T (1994). Comparison of seven commonly used agents for prophylaxis of seasickness. *Journal of Travel Medicine* 1 (4): 203-206.

Trial design

Parallel. Subjects received one of seven substances frequently used to prevent seasickness and matching placebo of another substance in a double-dummy method. Nobody received only placebo. The comparison medications were Touristil (cinnarizine 20 mg, domperidone 15 mg), Marzine (cyclizine 50 mg), Dramamine (dimenhydrinate 50 mg, caffeine 50 mg), Peremesin (meclozine 25 mg, caffeine 20 mg), Stugeron (cinnarizine 25 mg), and Scopoderm TTS (scopolamine 0.5 mg). In most cases, subjects took the medication two hours prior to departure. For Touristil and Zintona an additional dose was administered four hours later. Stugeron and Scopoderm TTS were administered the previous evening. A second dose of Stugeron was given the following morning. The whale-watching tour lasted six hours and went out on high seas.

Study duration	1 day
Dose	500 mg 2 hours prior to departure and after 4 hours
Route of administration	Oral

Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Touristil, Marzine, Dramamine, Peremesin, Stugeron, Scopoderm TTS
Site description	Ship
No. of subjects enrolled	1741
No. of subjects completed	1475
Sex	Male and female
Age	16-65 years

Inclusion criteria
Tourists participating in a whale-watching tour in Norway between the ages of 16 and 65 years old.

Exclusion criteria
Pregnant or nursing women, persons who had used antiemetic or anti-allergic drugs within the past 48 hours, patients with glaucoma, and persons with a history of adverse reactions to any of the substances to be tested.

End points
The outcome measures were vomiting, malaise (modified Graybiel criteria), and subjective reports of adverse events. The information was collected via a questionnaire gathered at the end of the trip.

Results
Questionnaires were completed by 85.5 percent of volunteers (n = 1489). Those who tried to avoid seasickness by fixing their eyes on the horizon, by putting cotton in their ears, or by wearing a "sea band" on the wrist were excluded from analysis. None of the study medications offered complete protection from seasickness. All had similar rates of efficacy compared to an earlier trip without prophylaxis when 80 percent got sick. No statistical difference was seen between treatments. In each treatment group, 4.1 to 10.2 percent experienced vomiting and 16.4 to 23.5 percent experienced malaise (nausea and discomfort).

Side effects
No serious adverse reactions reported. Sleepiness and tiredness were reported generally for all seven agents.

Authors' comments
Six of the seven medications may be recommended for prevention of seasickness; Scopolamine TTS seems the least attractive. Ginger was as potent as the others.

Reviewers' comments
The ginger root product (Zintona) demonstrated similar efficacy to the pharmaceutical agents tested. The experimental design did not include a baseline measurement of nausea/vomiting sensitivity. This study is of a type similar to a phase II clinical development trial; however, no conclusive phase I type (effective and toxic dose ranges) data were presented or referenced. (3, 5)

Clinical Study: Zintona®

Extract name	Zintona
Manufacturer	Dalidar Pharma Ltd., Israel
Indication	**Motion sickness; seasickness**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Riebenfeld D, Borzone L (1999). Randomized double-blind study comparing ginger (Zintona®) and dimenhydrinate in motion sickness. Reviewed and edited by Fulder S and Brown D. *Healthnotes Review of Complementary and Integrative Medicine* 6 (2): 98-101.

Trial design
Parallel. Cruise ship passengers received either Zintona or dimenhydrinate (100 mg one-half hour before sailing and 100 mg every four hours) for two days.

Study duration	2 days
Dose	500 mg one-half hour before sailing and every 4 hours thereafter
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes

Drug name	Dimenhydrinate (Dramamine)
Site description	Cruise ship
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Male and female
Age	10-77 years (mean: 37)

Inclusion criteria
Cruise ship passengers with a history of motion sickness.

Exclusion criteria
Not mentioned.

End points
Therapeutic effectiveness was evaluated by the following parameters: a physician's examination of general condition, especially central nervous system and gastrointestinal function; severity of motion sickness symptoms rated according to a point system by physicians; and subjects' self-reported assessment of severity of motion sickness.

Results
Twenty-one patients taking Zintona reported very good results compared to 15 in the dimenhydrinate group. The ship's physician reported equal results (primarily good or very good) for both Zintona and dimenhydrinate (statistical improvement for both $p < 0.05$). General conditions, such as malaise, appetite, and vomiting, improved equally well in both groups. Change in degree of motion sickness was slightly (nonsignificant) better for dimenhydrinate for treatment of motion sickness.

Side effects
Side effects in the Zintona group (13.3 percent) were significantly less than in the dimenhydrinate group (40 percent) ($p < 0.001$). Drowsiness and headache were reported with Zintona, while dimenhydrinate was associated with drowsiness, gastric distress, and cold sweats.

Authors' comments
Zintona is as effective as dimenhydrinate for treatment of motion sickness and has a lower incidence of side effects.

Reviewers' comments
The study, as designed, allowed for noninferiority comparison to the existing treatment, but the analysis of treatment based upon primarily subjective assessment methods would have benefited from a placebo arm. The study did not include a general gastrointestinal history or otherwise rule out comorbid conditions. The sample size was probably appropriate, given the significant

results; however, no power calculation was presented. The trial length was adequate. It is unclear if the adverse events were intrinsic to the clinical syndrome of motion sickness. (Edited version of the paper reviewed) (5, 6)

Clinical Study: Zintona®

Extract name	Zintona
Manufacturer	Dalidar Pharma Ltd., Israel
Indication	**Motion sickness**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Cereddu P (1999). Motion sickness in children: Results of a double-blind study with ginger (Zintona®) and dimenhydrinate. Reviewed and edited by Fulder S and Brown D. *Healthnotes Review of Complementary and Integrative Medicine* 6 (2): 102-107.

Trial design
Parallel. Subjects received either Zintona (ages three to six years: 250 mg 30 minutes before beginning a two-day trip [by car, boat, and/or airplane], then 250 mg every four hours as needed; ages six and above: 500 mg in the same pattern) or dimenhydrinate (12.5 mg or 25 mg 30 minutes before beginning the trip and 12.5 or 25 mg every four hours as necessary). There was a one-week washout period before the trial, and no drugs similar to those being tested were given during this time.

Study duration	2 days
Dose	3 to 6 years, 250 mg every 4 hours; 6+ years, 500 mg every four hours
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Dimenhydrinate (Dramamine)
Site description	Travel in car, boat, or airplane
No. of subjects enrolled	28

No. of subjects completed	28
Sex	Male and female
Age	4-8 years

Inclusion criteria
Children with previous history of motion sickness which was determined by a questionnaire.

Exclusion criteria
Children younger than three years of age, concomitant illnesses, anemic, or could not cooperate with the study design.

End points
The severity of motion sickness was determined by the pediatric physician and included subjective symptoms (vertigo, body temperature, headache, increased salivation, stomachache, nausea, dryness of mouth) and objective symptoms (pallor, cold sweat).

Results
In the physicians' ratings, Zintona was reported as having good results in 100 percent of the subjects while dimenhydrinate rated good in only 31 percent and modest results in 69 percent. Therapeutic effect was noted within 30 minutes in the Zintona group compared with 60 minutes for the dimenhydrinate ($p < 0.00001$).

Side effects
No subject taking Zintona reported any side effects, while 69.23 percent of cases in the dimenhydrinate group complained of dry mouth and 23.07 percent had vertigo.

Author's comments
This small study provides some indication that a safe traditional medicinal food is quite effective in decreasing vertigo, nausea, sweating, pallor, and, in general, the symptoms of motion sickness.

Reviewers' comments
It is unclear whether each subject experienced the same mode(s) and duration of travel. Given the day-to-day variance in the study population, the described and applied statistical methods are inadequate. The randomization method used did not create well-matched groups with respect to history and severity of motion sickness. Because the data collected were relative-subjective, this difference could serve as a confounder both toward overestimating and underestimating efficacy (i.e., a subject with severe symptoms could either be more refractory to treatment effects or could experience, and so report, a greater relative sense of symptomatic relief). The washout period was an interesting idea, but not of any apparent value in this trial. The refer-

ences presented regarding the dosage range involved studies of significantly older patients. This is concerning, as pediatric dosing—especially in patients under six years of age—warrants thorough study and consideration for any agent. The circumstance of unsubstantiated dosage choices in vulnerable subjects in this study demands mention here again, that this study is of a type most similar to a phase II clinical development trial, yet no conclusive phase I type data (effective and toxic dose ranges) were presented or referenced. The trial length was likely adequate. (Edited version of the paper reviewed) (1, 3)

Clinical Study: Zintona®

Extract name	Zintona
Manufacturer	Pharmaton S.A., Switzerland (Dalidar Pharma Ltd., Israel)
Indication	**Motion sickness; induced nystagmic activity**
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Holtmann S, Clarke AH, Scherer H, Hohn M (1989). The anti-motion sickness mechanism of ginger, a comparative study with placebo and dimenhydrinate. *Acta Otolaryngologica* 108 (3-4): 168-174.

Trial design
Crossover. Three-arm study: subjects were given either ginger, dimenhydrinate (100 mg), or placebo (lactose). Preparations were administered 90 minutes before stimulus routines. There were washout periods of 48 hours between sessions.

Study duration	1 day
Dose	1000 mg single dose
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Dimenhydrinate (Dramamine)

Site description	Single center
No. of subjects enrolled	38
No. of subjects completed	38
Sex	Male and female
Age	22-34 years (mean 26.3)

Inclusion criteria
Subjects with a distinct, symmetrical response to caloric and rotatory vestibular stimuli and normal gain in the optokinetic test.

Exclusion criteria
Subjects exhibiting a spontaneous nystagmus in their electronystagmography (ENG) recording with an intensity of more than 1 degree per second were also excluded from the study.

End points
The extent to which nystagmic activity (involuntary movements of the eye), induced by vestibular stimuli (water irrigation of the ears), optokinetic stimuli (a moving strip pattern), and being spun in a rotary chair, was affected was measured in a model for testing motion sickness. Eye movements were recorded using standard ENG equipment, and the evaluation was performed by automatic nystagmus analysis.

Results
Ginger root had no influence on the experimentally induced nystagmus, compared with baseline and placebo. Dimenhydrinate was found to cause a reduction in the nystagmus response to caloric, rotatory, and optokinetic stimuli. It can be concluded that neither the vestibular nor the oculomotor system, both of which are of decisive importance in the occurrence of motion sickness, are influenced by ginger.

Side effects
None mentioned.

Authors' comments
The mechanism of action of ginger is of a different nature than the CNS mechanism of action of the commonly used anti-motion sickness drugs. These reports and findings lend support to the thesis that the antiemetic mechanism of action of powdered ginger root is of gastrointestinal nature.

Reviewers' comments
The sample size may have been appropriate; however, no power calculation was presented. The trial had a very poor presentation of data. The data were not clearly presented in one bar graph, and other graphs and charts did not allow for assessment of statistical significance between groups. It is unclear

whether lactose is sufficiently gastrointestinally inactive to serve as a placebo in this study. The treatment length was adequate. (1, 4)

Product Profile: WS 1540

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	None
Botanical ingredient	**Ginger rhizome extract**
Extract name	**WS 1540**
Quantity	100 mg, corresponding to 1 g ginger root
Processing	No information
Standardization	No information
Formulation	Capsule

Source(s) of information: Micklefield et al., 1999.

Clinical Study: WS 1540

Extract name	WS 1540
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Gastroduodenal motility**
Level of evidence	**II**
Therapeutic benefit	**MOA**

Bibliographic reference
Micklefield GH, Redeker Y, Meister V, Jung O, Greving I, May B (1999). Effect of ginger on gastroduodenal motility. *International Journal of Clinical Pharmacology and Therapeutics* 37 (7): 341-346.

Trial design
Two-period crossover trial. Ginger or placebo were given at 8 a.m. after fasting and at 12 noon before a meal. Seven days elapsed between experiments.

Study duration	1 day
Dose	2 (100 mg extract) capsules twice daily
Route of administration	Oral

Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Laboratory
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male
Age	24-44 years

Inclusion criteria
Male volunteers aged 18 to 50 years.

Exclusion criteria
Symptoms or anamnestic indications of gastrointestinal disorders or serious abdominal surgeries (except appendectomies), other severe disorders, and any concomitant medication.

End points
Fasting and postprandial (up to one hour after a meal) gastroduodenal motility was recorded using a manometric catheter. The motility parameters, including the number, the frequency, and the amplitude of contractions, were measured in the gastric corpus, antrum, and duodenum. The phases of the migrating motor complex (MMC) were as follows: phase I motor quiescence; phase II pressure waves >10 mmHg at a rate higher than two per ten minutes; and phase III rhythmic contractile activity at maximum frequency (two per minute in the antrum for at least one minute, 10 to 12 per minute in the duodenum for at least two minutes).

Results
In the fasting state, ginger significantly increased the number and frequency of contractions during phase II in the corpus and phase III in the antrum. The only significant effect on the duodenum was the frequency of contractions during phase II. Postprandially, ginger significantly increased the number and frequency of contractions in the corpus and amplitude in the antrum but otherwise showed only a trend toward activity compared to placebo. Ginger had no effect on the postprandial motility index compared to placebo.

Side effects
None observed.

Authors' comments
Oral ginger improves gastroduodenal motility in the fasting state and after a standard test meal.

Reviewers' comments
The small sample size was acceptable for this physiologic study (mechanism of action). The trial length was adequate. (3, 4)

Product Profile: Eurovita Extract 33

Manufacturer	**Eurovita A/S, Denmark**
U.S. distributor	None
Botanical ingredient	**Ginger root extract**
Extract name	**EV ext-33**
Quantity	No information
Processing	No information
Standardization	Hydroxy-methyl-phenyl compounds
Formulation	Capsule

Source(s) of information: Bliddal et al., 2000.

Clinical Study: Eurovita Extract 33

Extract name	EV ext-33
Manufacturer	Eurovita A/S, Denmark
Indication	**Osteoarthritis**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Bliddal H, Rosetzsky A, Schlichting P, Weidner MS, Andersen LA, Ibfelt H-H, Christensen K, Jensen ON, Barslev J (2000). A randomized, placebo-controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. *Osteoarthritis and Cartilage* 8 (1): 9-12.

Trial design
Crossover. One-week washout period preceded three three-week treatment periods. Patients received either ginger extract, ibuprofen (400 mg three times daily), or placebo. Acetaminophen was given as a rescue drug during

the washout period and during the rest of the study in a maximum dose of 3 g daily.

Study duration	3 weeks
Dose	170 mg three times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Ibuprofen
Site description	Multicenter
No. of subjects enrolled	75
No. of subjects completed	56
Sex	Male and female
Age	24-87 years (mean: 66)

Inclusion criteria
Outpatients fluent in Danish, over the age of 18, with clinical dysfunction and pain due to osteoarthritis of the hip or knee. Mean duration of osteoarthritis was 7.7 years, and mean Lequesne index was 11.8 at entry.

Exclusion criteria
Exclusion criteria included rheumatoid arthritis, neurological disorders, severe medical diseases, and dementia. No injections in joints were accepted within six months before the study start.

End points
The primary outcome measure was a 100 mm visual analog scale (VAS) for pain assessment. Other end points included the Lequesne index for either hip or knee, range of motion, consumption of acetaminophen, and the investigator's preference of medication in the different treatment periods. Measurements were taken at baseline (after the washout period) and at the end of each treatment period. Patients also kept a diary with a four-point Likert pain scale during each treatment period.

Results
For the VAS, a ranking of efficacy was found for the three treatment periods: ibuprofen > ginger extract > placebo ($p < 0.0001$). The same ranking trend was found for the rescue medication (acetaminophen) consumption ($p < 0.01$). The Lesquesne index changed positively during treatment, also with

the same ranking of treatment efficacy. For these tests, there were significant differences between ibuprofen and ginger extract and between ibuprofen and placebo, but there was no significant difference between ginger extract and placebo. The patients' diaries were not assessable, as many were not filled out properly. No differences in range of motion were noted in any of the treatment periods. Investigators had a 66 percent preference in favor of ibuprofen for all periods.

Side effects
Four patients withdrew due to side effects: intestinal strangulation (placebo); restless legs (placebo); bad taste (ginger); and nausea (ibuprofen). Other adverse events were mostly gastrointestinal: bad taste; dyspepsia; changes in stools/intestinal trouble; or nausea. Three patients had allergic reactions (one in each treatment group).

Authors' comments
This study demonstrates a ranking of efficacy on pain level and function in patients with osteoarthritis of the hip or knee with ibuprofen being more effective than ginger extract (E.ext-33) and placebo. However, a carryover effect may blur possible effects of the later treatment periods, and based on the present results, caution should be observed in the interpretation of a crossover study of ginger extract.

Reviewers' comments
This study is of a type most similar to a phase II or IV clinical development trial; however, no conclusive phase I type (effective and toxic dose ranges) data were presented or referenced. In such an experimental circumstance, only a positive result can be considered definitive, as a negative result may occur simply due to an ineffective dosing regimen. Therefore, the results presented apply only to the particular standardized ginger extract (Eurovita 33). Lack of therapeutic benefit cannot be assumed categorically for all ginger preparations. The trial length was potentially inadequate, given that the dose-response pharmacokinetics of ginger are unknown. (5, 6)

Product Profile: Ginger (Powdered)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Ginger root**
Extract name	N/A
Quantity	No information
Processing	Powdered plant material
Standardization	No information
Formulation	Capsule

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	None
Indication	**Motion sickness; vertigo and nystagmus**
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Grøntved A, Hentzer E (1986). Vertigo-reducing effect of ginger root, a controlled clinical study. *ORL; Journal for Oto-rhino-laryngology and Its Related Specialties* 48 (5): 282-286.

Trial design
Crossover study. At least 48 hours between one-day sessions in which either ginger or placebo was administered one hour before testing.

Study duration	1 day
Dose	1 g of powdered ginger root
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	8
No. of subjects completed	8
Sex	Not given
Age	16-56 years (median: 33.5)

Inclusion criteria
Healthy volunteers.

Exclusion criteria
Persons having spontaneous nystagmus, food allergy, or abnormal otomicroscopy were excluded.

End points
Subjects were adapted to darkness and placed supine with their head bent

30 degrees forward. The vestibular system was stimulated by irrigating the left ear with water. The provoked nystagmus was recorded by electronystagmography. The subject evaluated the degree of vertigo on a scale of 0 to 5. Recording of vertigo and nystagmus was carried out three times at 20-minute intervals after intake of treatment.

Results
Ginger root reduced the induced vertigo significantly compared to placebo ($p < 0.05$). There was no statistically significant action upon the duration or the maximum slow-phase velocity of nystagmus.

Side effects
None reported by the subjects.

Authors' comments
Ginger root reduced the induced vertigo significantly better than placebo. Investigations indicate that ginger root, similar to sympathomimetics and parasympatholytics, dampens the induced vestibular impulses to the autonomic centers of the central nervous system and possibly the cerebral cortex. Ginger root does not appear to affect the vestibular system directly, as no statistically significant change in nystagmus was demonstrable.

Reviewers' comments
The sample size may not have been appropriate; no power calculation was presented. The washout period was brief and not of fixed duration, but likely adequate if ginger's mechanism is direct (versus centrally mediated). (3, 3)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	None
Indication	**Motion sickness**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Mowrey D, Clayson D (1982). Motion sickness, ginger and psychophysics. *The Lancet* 1 (8273): 655-657.

Trial design
Parallel. Three-arm study. Subjects were told that they were to be given either dimenhydrinate or harmless herbs. Subjects were given either dimenhydrinate

(100 mg), powdered ginger (940 mg), or placebo (powdered chickweed herb) 20 to 25 minutes before testing.

Study duration	1 day
Dose	2 capsules (total of 940 mg of powdered ginger)
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Dimenhydrinate (Dramamine)
Site description	Laboratory
No. of subjects enrolled	36
No. of subjects completed	36
Sex	Male and female
Age	18-20 years

Inclusion criteria
Subjects were selected based on self-rated extreme or very high susceptibility to motion sickness.

Exclusion criteria
None mentioned.

End points
Subjects were blindfolded and placed on a tilted, rotating chair for up to six minutes. They were asked to quantify the feelings in their stomachs every 15 seconds. The experiment was stopped if the subject vomited.

Results
None of the subjects in the placebo and dimenhydrinate groups was able to stay in the chair for six minutes, whereas half of the subjects in the ginger group stayed for the full time ($p < 0.001$). The magnitude of gastrointestinal sensations was greatest with placebo, intermediate with dimenhydrinate, and lowest with ginger.

Side effects
None noted.

Authors' comments
Powdered ginger was superior to dimenhydrinate in preventing gastrointestinal symptoms of testing motion sickness.

Reviewers' comments
The "time in chair" measurements imply superiority of ginger over placebo. The validity of chickweed as a placebo in this study is a concern. Subjects were also not evaluated for other medications, gastrointestinal and central nervous system disorders, or other relevant medical history. The experimental design did not sufficiently control the variables involved in the unknown nature of the physiologic mechanism, analytic method, and pharmacokinetics. The experimental and analytical methods did not produce a convincing picture from the data. Indeed, the analytical methodology was as much of an experimental variable as the tested agents. Power function analysis should have been established first without treatment, then with an effective agent versus a valid placebo. It is not clear whether the pharmacokinetics of ginger are amenable to a study of ±30 minutes duration. (1, 3)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	Dispensary at Odense University Hospital, Denmark
Indication	**Motion sickness; seasickness**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Grøntved A, Brask T, Kambskard J, Hentzer E (1988). Ginger root against seasickness, a controlled trial on the open sea. *Acta Otolaryngologica* 105 (1-2): 45-49.

Trial design
Parallel. Conditions of heavy seas, a few days from port.

Study duration	4 hours
Dose	1 g of powdered ginger root
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Fully rigged training ship
No. of subjects enrolled	80
No. of subjects completed	79
Sex	Male
Age	16-19 years (median: 17)

Inclusion criteria
Subjects not accustomed to high seas and not especially susceptible to motion sickness.

Exclusion criteria
None mentioned.

End points
Every hour for four hours, subjects noted a score for each of the following seasickness symptoms: nausea, vertigo, vomiting, and cold sweats.

Results
Ginger root significantly reduced the tendency to vomit and cold sweat compared to placebo ($p < 0.05$). Ginger root also reduced the symptoms of nausea and vertigo but not significantly.

Side effects
None reported.

Authors' comments
Powdered ginger has at least some effect on symptoms of motion sickness. Contrary to all conventionally used anti-motion sickness drugs, no side effects were reported.

Reviewers' comments
The sample size may not have been appropriate; no power calculation was presented. A larger sample size may have provided greater data resolution. (3, 3)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	None

Indication	**Nausea due to chemotherapy agent**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Meyer K, Schwartz J, Crater D, Keyes B (1995). *Zingiber officinale* (ginger) used to prevent 8-MOP-associated nausea. *Dermatology Nursing* 7 (4): 242-244.

Trial design
Linear comparison. Nausea due to chemotherapy agent 8-MOP alone was noted before the trial and then compared to nausea felt after administration of both 8-MOP and ginger. Ginger was administered 30 minutes prior to 8-MOP ingestion.

Study duration	Not given
Dose	3 capsules of 530 mg each (1.6 g total)
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Hospital
No. of subjects enrolled	11
No. of subjects completed	11
Sex	Male and female
Age	23-80 years (median: 54)

Inclusion criteria
Patients undergoing monthly photopheresis therapy (psoralen, 8-MOP) and who regularly complained of nausea as a result.

Exclusion criteria
None mentioned.

End points
Patients completed a survey, rating their nausea on scale of 0 to 4 (no nausea to severe nausea). Serum was drawn to assess 8-MOP levels.

Results
Total score for nausea decreased from 22.5 (individual average 2.045) prior

to the trial, to 8.0 (individual average 0.727) after administration of ginger. Serum levels of 8-MOP remained therapeutic in 10 out of 11 patients (the one patient with subtherapeutic levels had connective tissue disease with gastrointestinal involvement).

Side effects
Three patients described heartburn symptoms.

Authors' comments
As a nonprescription item with minimal side effects, ginger is worth a trial as an antiemetic in both photopheresis and other therapies involving psoralen.

Reviewers' comments
This trial had an exceptionally poor experimental design and discussion. The trial used a subjective assessment of a subjective condition without blinding or placebo. Comparing experimental results to memory of prior experiences is not sound methodology. The MOP levels were not compared to a baseline level for this patient group. No justification or explanation was given for administering ginger 30 minutes prior to administering 8-MOP; the pharmacokinetics of this agent are not well established. (1, 3)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	Blackmores Ltd., Australia
Indication	**Nausea and vomiting** (postoperative)
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Arfeen Z, Owen H, Plummer, JL, Ilsley AH, Sorby-Adams RAC, Doecke CJ (1995). A double-blind randomized controlled trial of ginger for the prevention of postoperative nausea and vomiting. *Anaesthesia and Intensive Care* 23 (4): 449-452.

Trial design
Parallel. Patients received diazepam (10 mg) as oral presurgery medication plus two study medication capsules, one hour before induction of anesthesia. There were three groups of patients. They received either two placebo capsules, one capsule of 500 mg ginger plus one placebo capsule, or two capsules containing 500 mg ginger. Anesthesia was induced using thio-

pentone 4 to 5 mg/kg followed by vecuronium 0.1 mg/kg. Intraoperative and postoperative analgesia was provided by intravenous morphine.

Study duration	1 day
Dose	1 or 2 capsules of 500 mg ginger powder
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	108
No. of subjects completed	108
Sex	Female
Age	19-70 years (mean: 32.3 years)

Inclusion criteria
Patients between 18 and 75 years undergoing gynecological laparoscopic surgery, American Society of Anesthesiology (ASA) physical status 1 or 2, under general anesthesia.

Exclusion criteria
Patients with known allergy to ginger or intolerance to spicy foods, who were pregnant or lactating, or receiving other antiemetic treatment.

End points
Three hours after the operation, patients were questioned as to whether they had experienced any nausea or vomiting since regaining consciousness. Nausea was graded as either present with one of three categories of severity or as absent, and vomiting was categorized as present or absent.

Results
The incidence of nausea and vomiting increased slightly but nonsignificantly with increasing dose of ginger. The incidence of moderate or severe nausea was 22 percent for placebo, 23 percent for 500 mg ginger, and 36 percent for 1000 mg ginger. The incidence of vomiting was 17 percent, 14 percent, and 31 percent in groups receiving 0, 500, and 1000 mg ginger, respectively.

Side effects
Flatulence, bloated feeling, and heartburn were reported in the ginger group.

Authors' comments
Powdered ginger (British Pharmacopoeia grade, 1988) is ineffective in reducing the incidence of postoperative nausea and vomiting.

Reviewers' comments
This is an excellent study. The subjects were limited to ASA 1 and 2 females. The inclusion of morphine in the anesthetic regimen and variations in surgical technique are covariables. The results may have been different for different surgeons or anesthetic techniques. The trial length was adequate. (3, 6)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	Pharmacy Department of Mahidol University, Thailand
Indication	**Nausea and vomiting** (postoperative)
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Visalyaputra S, Petchpaisit N, Somcharoen K, Choavaratana R (1998). The efficacy of ginger root in the prevention of postoperative nausea and vomiting after outpatient gynaecological laparoscopy. *Anaesthesia* 53 (5): 506-510.

Trial design
Parallel. Ginger and/or droperidol were given using a double-placebo method yielding 4 groups. Group 1: placebo capsules and 0.5 ml IV saline; group 2: placebo capsules plus 1.25 mg droperidol IV; group 3: two capsules of 0.5 g powdered ginger root plus saline IV; group 4: two capsules of 0.5 powdered ginger plus 1.25 mg droperidol IV. Study medications were taken one hour before induction of anesthesia induced with thiopentone (5 mg/kg) and fentanyl (1 µg/kg). One-half hour before discharge, every patient received another two capsules of either ginger root (0.5 g per capsule) or placebo. Paracetamol tablets were given for postoperative pain.

Study duration	1 day
Dose	2 (0.5 g) capsules before and after surgery
Route of administration	Oral
Randomized	Yes
Randomization adequate	No

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Droperidol
Site description	Single center
No. of subjects enrolled	120
No. of subjects completed	111
Sex	Female
Age	Mean: 32.75 years

Inclusion criteria
Women age 20 to 40 years with ASA grade 1 or 2 who were scheduled for elective gynecological diagnostic laparoscopy.

Exclusion criteria
Patients who had received opioids or antiemetic drugs within 24 hours of the operation.

End points
The incidence and severity of nausea as well as the frequency of vomiting were recorded during the period in the recovery room and for 24 hours afterward. The degree of dizziness and sedation upon arrival into the recovery room were also recorded.

Results
There were no significant differences in the incidences of postoperative nausea, which were 32 percent, 20 percent, 22 percent, and 33 percent, and vomiting which were 35 percent, 15 percent, 25 percent, and 25 percent in the placebo, droperidol, ginger, and ginger plus droperidol groups, respectively.

Side effects
Not addressed.

Authors' comments
Ginger powder in the dose of 2 g, droperidol 1.25 mg, or both are ineffective in reducing the incidence of postoperative nausea and vomiting after gynecological laparoscopy.

Reviewers' comments
This trial had an insufficient sample size, and the variations in surgical technique may have affected the ability of this study to produce statistically sig-

nificant results. The subjects were limited to ASA 1 and 2, middle-aged females. The trial length was adequate. (3, 5)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	Martindale Pharmaceuticals Pty Ltd., UK
Indication	**Nausea and vomiting** (postoperative)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Phillips S, Ruggier R, Hutchinson SE (1993). *Zingiber officinale* (ginger)—An antiemetic for day case surgery. *Anaesthesia* 48 (8): 715-717.

Trial design
Parallel. Three study groups: group A given two capsules of metoclopramide (10 mg total); group B given two capsules of powdered ginger root (1 g total); and group C given placebo. Study medications were administered one hour before induction of anesthesia. Anesthesia was induced with propofol 2.5 mg/kg and fentanyl 1 to 2 µg/g followed by atracurium 0.3 mg/kg.

Study duration	1 day
Dose	2 (500 mg) capsules of powdered ginger root
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Metoclopramide
Site description	Single center
No. of subjects enrolled	120
No. of subjects completed	120
Sex	Female
Age	Mean: 33.6 years

Inclusion criteria
Gynecological patients, ASA grades 1 to 3, scheduled for elective laparoscopic surgery as day patients.

Exclusion criteria
Patients who were pregnant or had ingested alcohol, opioids, or antiemetics in the 24 hours before surgery.

End points
Nausea and vomiting were observed at discharge from recovery room, at hospital discharge, and 24 hours postoperatively. The presence of pain and possible side effects were also recorded.

Results
The incidence of nausea and vomiting was similar in patients given metoclopramide and ginger (27 percent and 21 percent, respectively) and less than those who received placebo (41 percent).The requirement for postoperative antiemetics was lower in those patients receiving ginger. The requirements for postoperative analgesia recovery time and time until discharge were the same in all groups.

Side effects
There was no difference in the incidence of side effects between the three groups.

Authors' comments
Ginger is an effective and promising antiemetic suitable for day case patients with no documented side effects.

Reviewers' comments
The sample size may have been appropriate, given the significant results; however, no power calculation was presented. The standard/threshold for administering antiemetic treatment was not presented. Postoperative antiemetic regimen variation is a confounding covariable. Measuring the number of nausea complaints per patient does not have a clear correlation with severity or antiemetic efficacy. The anesthetic agent used, propofol, has known antiemetic effects. Perhaps the most relevant statements were that the mean time from induction to discharge was the same in all groups. Therefore there was no demonstrated impact on the parameter of primary motivation for the study—"delayed hospital discharge." "Antiemetics required more often" sounds convincing; however, it is meaningless without an established standard/threshold for treatment. Even then, it says more about the efficacy of the postoperative antiemetic regimen than it does the preoperative prophylaxis. The trial length was adequate. (3, 4)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	Pharmacy Department at St. Bartholomew's Hospital, England
Indication	**Nausea and vomiting** (postoperative)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Bone ME, Wilkinson DJ, Young JR, McNeil J, Charlton S (1990). Ginger root—A new antiemetic: The effect of ginger root on postoperative nausea and vomiting after major gynecological surgery. *Anaesthesia* 45 (8): 669-671.

Trial design
Parallel. Ginger was compared to placebo and metoclopramide. Group 1 was given two capsules powdered ginger root (total 1 g) and placebo injection. Group 2 was given placebo capsules and metoclopramide (10mg) IV. Group 3 was given a double placebo. Capsules were given at the time of premedication and 1.5 hours before surgery, and intravenous medication was given at the induction of anesthesia. Patients were premedicated intramuscularly with papaveretum and scopolamine (hyoscine). Anesthesia was induced with a sleep dose of thiopentone, followed by alcuronium or vecuronium. Both ginger and placebo capsules were flavored with a "nonactive chemical essence of ginger." Nausea and vomiting after surgery were treated with metoclopramide, 10 mg intramuscularly, as required. Papaveretum or paracetamol was administered upon request for pain.

Study duration	1 day
Dose	2 capsules (500 mg) powdered ginger
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Metoclopramide
Site description	Hospital
No. of subjects enrolled	60
No. of subjects completed	60

Sex	Female
Age	16-65 years (mean: 40.6)

Inclusion criteria
Patients with ASA grades 1 or 2, scheduled for major gynecological surgery.

Exclusion criteria
Patients who received opioid analgesia or antiemetics in the 24 hours before surgery.

End points
Patients were observed for symptoms of nausea and vomiting after recovery from anesthesia in recovery room, and at 4, 12, and 24 hours after the operation.

Results
Significantly fewer incidences of nausea were recorded in the group that received ginger root compared with placebo ($p < 0.05$). The number of incidences of nausea in the groups that received either ginger root or metoclopramide were similar. The administration of an antiemetic after the operation was significantly greater in the placebo group compared to the other two groups ($p < 0.05$).

Side effects
Very low and did not differ between treatments.

Authors' comments
Ginger root significantly reduced the incidence of postoperative emetic sequelae compared to placebo and had the same effect as metoclopramide.

Reviewers' comments
The nausea/vomiting data (N/V) were grouped rather than presented as individual numbers for each period. No prior history of predisposition to N/V was mentioned, e.g., CNS (vestibular) or GI disorders, or emetogenic medications taken. The sample size may not have been appropriate, as no power calculation was presented. The placebo group was older with a lower incidence of postoperative N/V and motion sickness and had shorter surgical times. The ginger group received more papaveretum intraoperatively. The nonuniform administration of papaveretum and paracetamol for postoperative analgesia creates a potentially confounding covariable. The administration of scopolamine (hyoscine) as an antiemetic creates a covariable which is a potential cofounder; unrecognized synergetic or other interactions are possible given that the mechanism of action of ginger is unknown. No reference was presented to demonstrate that the ginger flavoring used for the ginger and placebo pills lacks antiemetic or other potentially confounding bioactivity. The trial length was adequate. (3, 3)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	None
Indication	**Severe nausea and vomiting in pregnancy** (hyperemesis gravidarum)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U (1990). Ginger treatment of hyperemesis gravidarum. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 38 (1): 19-24

Trial design
Crossover. Four-day treatment periods with a two-day washout period in between.

Study duration	4 days
Dose	250 mg 4 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Hospital (OB/GYN department)
No. of subjects enrolled	30
No. of subjects completed	27
Sex	Female
Age	18-39 years (mean: 26.4)

Inclusion criteria
Pregnant women admitted to the hospital with hyperemesis (nausea and vomiting) before the twentieth week of gestation and with symptoms lasting more than two days.

Exclusion criteria
Inability to take capsules. Subjects with gastrointestinal symptoms with probable origin in gallbladder or liver disease, duodenal ulcer, pancreatitis, etc.

End points
The severity and relief of symptoms were assessed using scoring systems. The severity score, conducted before the trial, noted the degree of nausea, vomiting, and weight loss. The relief score, evaluated on days 5 and 11 (after treatment) included a subjective assessment by the patient. Subjects were also observed for acetonuria and disturbance of hematocrit values.

Results
Subjective assessments by the women revealed that 70.4 percent stated preference to the period in which they received the ginger capsules,14.8 percent preferred the placebo, and the remainder were unable to state a preference. The relief scores showed a significantly greater relief for ginger, especially in reducing the number of attacks of vomiting and the degree of nausea.

Side effects
No side effects were reported. No deformed infants were born. One spontaneous abortion occurred.

Authors' comments
Powdered root of ginger in daily doses of 1 g during four days was better than placebo in diminishing or eliminating vomiting during pregnancy.

Reviewers' comments
This is a good-quality study. No justification was given for the length of the washout period (two days). The subjective scale is not balanced between exacerbation and amelioration. The trial length was adequate. (5, 4)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	None
Indication	**Nausea and/or vomiting in pregnancy**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Vutyavanich T, Kraisarin T, Ruangsri R-A (2001). Ginger for nausea and vomiting in pregnancy: Randomized, double-masked, placebo-controlled trial. *Obstetrics and Gynecology* 97 (4): 577-582.

Trial design
Parallel. Subjects were advised to divide their meals into frequent small ones low in fat and rich in carbohydrates.

Study duration	4 days
Dose	1 (250 mg) capsule 4 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	University hospital
No. of subjects enrolled	70
No. of subjects completed	67
Sex	Female
Age	Mean: 28.5 years

Inclusion criteria
Women who had attended an antenatal clinic before 17 weeks gestation and had nausea of pregnancy, with or without vomiting.

Exclusion criteria
Subjects were excluded if they had other medical disorders such as gastrointestinal diseases or hepatitis that may manifest with vomiting or nausea; were mentally retarded; had geographic or language barriers; had taken other medication in the previous week that might alleviate or aggravate nausea or vomiting; were unable to take the medication as prescribed; or were otherwise unable to participate in the trial.

End points
The primary outcome was improvement in symptoms of nausea. A visual analog scale and a Likert scale were used to measure nausea. Subjects completed a visual analog scale at their first visit and twice daily for the four days of treatment (at noon and bedtime). The five-item Likert scale was used at the one-week follow-up visit to assess the patients' response to ginger or placebo. Patients also recorded the number of vomiting episodes in the 24 hours prior to treatment and on each of the treatment days. Other secondary end points included side effects and adverse effects on pregnancy such as preterm birth, abortion, perinatal death, congenital anomaly, and delivery mode.

Results
The visual analog scores (after therapy minus baseline) of the subjects taking ginger decreased significantly as compared to the placebo group scores ($p = 0.014$). The number of vomiting episodes was also significantly decreased in the ginger group compared to the placebo group ($p < 0.001$). Using the Likert scale, 28 out of 32 subjects in the ginger group had improvement in symptoms of nausea compared to 10 of 35 in the placebo group ($p < 0.001$).

Side effects
Minor side effects occurred in both groups. Effects reported in the ginger group included headache, abdominal discomfort, heartburn, and diarrhea. Ginger did not have an adverse effect on pregnancy outcome.

Authors' comments
A significant improvement in nausea scores was found in subjects who received ginger compared with those who received placebo. Ginger also significantly reduced the mean number of vomiting episodes during the four days of treatment.

Reviewers' comments
Dietary modification to small, low-fat, carbohydrate-rich meals is a potential confounding variable. Compliance with prescribed diet was not assessed/reported. The ginger preparation used was well described but not chemically characterized (i.e., fresh Thai ginger, dried at 60°C for 24 hours, and ground into powder). The treatment length was adequate. (5, 6)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	Martindale Pharmaceuticals Pty Ltd., UK
Indication	**Gastric motility; gastric emptying rate**
Level of evidence	**I**
Therapeutic benefit	**MOA**

Bibliographic reference
Phillips S, Hutchinson S, Ruggier R (1993). *Zingiber officinale* does not affect gastric emptying rate: A randomized, placebo-controlled, crossover trial. *Anaesthesia* 48 (5): 393-395.

Trial design
Crossover study. Patients received two capsules of either ginger or placebo

in each study period. After at least a week they switched treatments. Before each study period, subjects abstained from alcohol and paracetamol for 24 hours and fasted for at least two hours.

Study duration	1 day
Dose	2 capsules (500 mg) powdered ginger root
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Hospital
No. of subjects enrolled	16
No. of subjects completed	16
Sex	Male and female
Age	Not given

Inclusion criteria
Healthy volunteers at least 18 years old.

Exclusion criteria
Patients who were pregnant, had a gastrointestinal disease, or were taking any medication that affected gastric emptying.

End points
Gastric emptying was measured using a paracetamol absorption technique. The rate of gastric emptying was assessed by comparing the mean, peak, and time of peak plasma paracetamol concentrations, time to first detection of paracetamol in plasma, and the area under the paracetamol concentration time curve. Venous blood was taken at the same time as capsule administration and every 15 minutes for two hours.

Results
Ingestion of ginger did not affect gastric emptying. The mean and peak plasma paracetamol concentrations were similar in both groups.

Side effects
None reported by subjects.

Authors' comments
The antiemetic effect of ginger is not associated with an effect on gastric emptying.

Reviewers' comments
No documentation is given to support the assumption that ginger smell and taste additives have no gastrointestinal or pharmacologic effect. It is unclear whether lactose is suitably gastrointestinally inactive to serve as a placebo. The trial length was adequate. (5, 5)

Clinical Study: Ginger (Powdered)

Extract name	N/A
Manufacturer	None
Indication	**Cardiovascular risk factors; coronary artery disease**
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Bordia A, Verma SK, Srivastava KC (1997). Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenumgraceum* L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 56 (5): 379-384.

Trial design
Parallel. Ginger was administered in two different doses: 4 g daily for three months and 10 g as a single dose. *Note:* Fenugreek was tested separately and that information is not included in this summary.

Study duration	3 months
Dose	4 g powdered ginger daily, or 10 g single dose
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	Yes
Drug comparison	No

Site description	Not described
No. of subjects enrolled	60
No. of subjects completed	Not given
Sex	Not given
Age	Not given

Inclusion criteria
Patients with healed myocardial infarction (>6 months) with or without angina, all stable in their symptoms. All subjects were taking nitrates and aspirin; the aspirin was stopped two weeks before the study.

Exclusion criteria
Not mentioned.

End points
Two blood samples were collected before the trial at an interval of two weeks. During the three-month trial, patients were evaluated every month for clinical symptoms. Blood samples were collected after one and one-half months and three months. Blood samples were examined for lipid profile (total serum cholesterol, triglycerides, and HDL-C), blood sugar, plasma fibrinogen, fibrinolytic activity, and platelet aggregation.

Results
Ginger given at 4 g daily did not affect adenosine diphosphate (ADP)- and epinephrine-induced platelet aggregation, or fibrinolytic activity, fibrinogen levels, blood lipids, or blood sugar. However, a single dose of 10 g powdered ginger produced a significant reduction in platelet aggregation after four hours. Both ADP- and epinephrine-induced platelet aggregation were reduced significantly ($p < 0.05$).

Side effects
None noted.

Authors' comments
Ginger's antiartherosclerotic effect could be related to its antioxidant property and/or eicosanoid metabolism, since it did not affect the blood lipids, fibrinolytic activity, and fibrinogen level.

Reviewers' comments
No data were given concerning subjects' medications, medical history (comorbid conditions), or demographics. The sample size may not have been appropriate; no power calculation was presented. This study is of a type more similar to a phase IV clinical development trial; however, no conclusive phase I type (effective and toxic dose ranges) data were presented or referenced. Stopping aspirin in these patients carries a risk which is unwarranted

given the lack of any preliminary data demonstrating clear therapeutic efficacy. The dosage choices of 4 and 10 g were beyond the standard range for other trials. The trial length was apparently adequate. (0, 3)

Product Profile: Ginger (Raw), Stem Ginger

Manufacturer	**Toko Rinus, the Netherlands (root), Ambition, Polak Import, the Netherlands (stem)**
U.S. distributor	None
Botanical ingredient	**Ginger root and stem**
Extract name	N/A
Quantity	No information
Processing	Raw root or stem were cut up and put into custard
Standardization	No information

Source(s) of information: Janssen et al., 1996.

Clinical Study: Ginger (Raw), Stem Ginger

Extract name	N/A
Manufacturer	Toko Rinus, the Netherlands (root); Ambition, Polak Import, the Netherlands (stem)
Indication	**Cardiovascular risk factors; antiplatelet effect**
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference

Janssen PLTMK, Meyboom S, van Staveren WA, de Vegt F, Katan MB (1996). Consumption of ginger (*Zingiber officinale* Roscoe) does not affect ex vivo platelet thromboxane production in humans. *European Journal of Clinical Nutrition* 50 (11): 772-774.

Trial design

Crossover study. Three consecutive two-week periods. Three treatments:

15 g of raw ginger root daily, 40 g of cooked stem ginger daily, or placebo; all supplied in vanilla custard.

Study duration	2 weeks
Dose	15 g of raw ginger root; 40 g stem ginger
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	18
No. of subjects completed	18
Sex	Male and female
Age	Mean: 22 years

Inclusion criteria
Healthy subjects, nonsmokers, with normal values in routine lab tests.

Exclusion criteria
Subjects with urinary protein or glucose or high blood pressures.

End points
Fasting venous blood was drawn to measure thromboxane B2 production in maximally stimulated platelet-rich plasma at day 12 and day 14 of each treatment period.

Results
Daily treatment of ginger root or stem ginger for 14 days did not affect maximum ex vivo platelet thromboxane B2 production ($p = 0.616$). There was no significant effect on thromboxane production relative to placebo for raw ginger or stem ginger, and no effect of treatment order.

Side effects
None reported.

Authors' comments
The putative antithrombotic activity of ginger in humans cannot be confirmed.

Reviewers' comments

In the "Design and Treatments" section, it is evident that the trial was not conducted in a blinded fashion. The subjects were given their treatment materials to take home on the weekends to mix on their own. It is difficult to imagine how this could have been accomplished without the treatment groups being unblinded. The "cooked stem ginger" preparation was unusual enough that it should have been clearly described botanically, as well as its cooking protocol. The power calculation for this study was presented only by reference to a previous paper written by this author. The number of samples drawn per subject per treatment period was small. For some reason the effects of dry ginger root powder—the most common dosage form—were not evaluated in this study. Due to the broad variation in what could be considered "fresh" Brazilian ginger root or "cooked stem," the results of this study cannot be generally extrapolated to other ginger products/preparations. The trial length was adequate. (1, 4)

Ginkgo

Other common names: **Maidenhair tree**
Latin name: ***Ginkgo biloba* L.** [Ginkgoaceae]
Plant part: **Leaf**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

The ginkgo tree is native to China. It is the last surviving member of its family (Ginkgoaceae) and more closely resembles ancient ferns than deciduous trees. Ginkgo is extremely hardy, and specimens over one thousand years old have been reported in China, Korea, and Japan. The seeds have been used therapeutically in China and eastern Asia for over 2,000 years. Therapeutic use of the leaves has gained popularity in the past 40 years (Schulz, Hänsel, and Tyler, 2001).

Most of the ginkgo leaf products on the market are concentrated extracts with a ratio of roughly 50 parts leaf to 1 part extract. This means that the manufacturing procedure, which uses an acetone-water extraction and several purification steps, yields one kilogram of final product from 50 kilograms of dried ginkgo leaves. Standardized leaf extracts generally contain 22 to 27 percent flavonol glycosides, 5 to 7 percent terpene lactones (2.8 to 3.4 percent ginkgolides A, B, and C, and 2.6 to 3.2 percent bilobalide), and less than 5 ppm ginkolic acids. While many ginkgo constituents are purported to contribute to the herb's therapeutic effect, some of the constituents have been linked to specific pharmacological actions. The ginkgo flavonol glycosides are efficient free-radical scavengers, the ginkgolides inhibit platelet-activating factor, and the ginkgolides and bilobalide have demonstrated neuroprotective properties (Schulz, Hänsel, and Tyler, 2001; Foster and Tyler, 1999).

Ginkgold® and Ginkoba® are manufactured by Dr. Willmar Schwabe GmbH & Co. in Germany and are marketed in the United States by Nature's Way Products, Inc., and Pharmaton Natural Health

GINKGO SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Single Ingredient Products						
Ginkgold®; Ginkoba®	Dr. Willmar Schwabe GmbH & Co., Germany/ Nature's Way Products, Inc.	Leaf extract (EGb 761®)	120-240 mg per day, up to 600 mg per day	Normal cognitive functioning	4	Yes (I-1, II-1) Trend (II-1) No (II-1)
				Age-related cognitive impairment	6	Yes (I-3, II-2) No (I-1)
	Pharmaton Natural Health Products		120 or 240 mg per day	Dementia/ Alzheimer's disease	4	Yes (I-3, III-1)
			120-240 mg per day	Cerebrovascular insufficiency	6	Yes (I-2, II-1, III-2) Trend (III-1)
			120 or 240 mg per day	Peripheral vascular disease	5	Yes (I-1, II-1, III-3)
			120 or 240 mg per day	Tinnitus (ringing in the ears)	1	Yes (I-1)
				Sudden hearing loss	1	Trend (II-1)

			160 or 320 mg per day	Protection against hypoxia	1	Yes (III-1)
				Antioxidant effects	1	Yes (III-1)
			40-240 mg per day	Electrophysiological effects	3	MOA (II-1, III-2)
Ginkai™* (US), Kaveri® (EU), Ginkyo® (EU)	Indena S.p.A., Italy; Lichtwer Pharma AG, Germany/ Lichtwer Pharma U.S., Inc.	Leaf extract (LI 1370; GinkgoSelect™)	150 mg per day	Age-related cognitive impairment	4	Yes (I-1, III-2) Undetermined (III-1)
				Cognitive functioning after brain aneurysm operation	1	Yes (II-1)
				Normal cognitive functioning	1	Yes (II-1)
				Tinnitus (ringing in the ears)	1	No (I-1)
			112.5 or 300 mg per day	Microcirculation	2	Yes (III-2)
			240 mg	Sleep quality (REM latency)	1	MOA (I-1)

GINKGO SUMMARY TABLE (continued)

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
GK501™	Pharmaton S.A., Switzerland/None	Leaf extract (GK 501™)	120-360 mg per day	Normal cognitive functioning	2	Yes (I-2)
Ginkgoforce	Bioforce AG, Switzerland/Bioforce USA	Alcoholic tincture of fresh leaves	60-120 drops per day	Age-related memory impairment	1	Trend (II-1)
Combination Product						
Ginkoba M/E™ (US), Gincosan ® (EU)	Pharmaton S.A., Switzerland/ Pharmaton Natural Health Products	Ginkgo leaf extract (GK501™) and ginseng root extract (G115®)**	80-960 mg daily	Cognitive functioning	3	Yes (I-1, II-1, III-1)

*Products that contain the Indena S.p.A GinkgoSelect extract as a single ingredient are listed below. The extract has been tested clinically but the final formulation has not.

Product Name	Manufacturer/Distributor
Ginkgo Biloba 24%	Enzymatic Therapy
GB24™	Thorne Research
Ginkgo Biloba	Swanson Health Products

**See the ginseng profile for information on the ginseng root extract G115.

Products, respectively. These products contain a patented ginkgo leaf extract called EGb 761® (50:1), which is characterized as containing 24 percent flavonol glycosides and 6 percent terpene lactones. EGb 761 is sold in Europe in products named Tanakan®, Rökan®, and Tebonin® forte.

Ginkai™ contains the ginkgo leaf extract LI 1370 which is standardized to contain 25 percent ginkgo flavonol glycosides and 6 percent terpenoids (ginkgolides and bilobalide). LI 1370 is manufactured by Lichtwer Pharma AG in Germany and contains the GinkgoSelect™ extract manufactured by Indena S.p.A., Italy. Ginkai is sold in the United States by Lichtwer Pharma U.S., Inc. LI 1370 is sold in Europe as Ginkyo® and Kaveri®. GinkgoSelect is also sold in the United States under the names Ginkgo Biloba-24% (Enzymatic Therapy®), GB24™ (Thorne Research), and Ginkgo Biloba (Swanson Health Products).

GK501™ is manufactured in Switzerland by Pharmaton S.A. It is characterized as containing 24 percent ginkgo flavonol glycosides and 6 percent terpene lactones. GK501 is not sold in the United States as a single-ingredient product.

Ginkoba M/E™ is a combination product that contains extracts of ginkgo leaves (GK501) and ginseng root (G115®). GK501 is characterized as containing 24 percent ginkgo flavonol glycosides and 6 percent terpene lactones, and G115 contains 4 percent ginsenosides. Ginkoba M/E is manufactured by Pharmaton S.A. in Switzerland and sold in the United States by Pharmaton Natural Health Products. This product is sold in Europe as Gincosan®.

Ginkgoforce, sold as Geriaforce in Europe, is a liquid tincture of fresh ginkgo leaves. Ginkgoforce has a plant-to-extract ratio of 1:9 and is made with 62 percent alcohol. Ginkgoforce is produced by Bioforce AG in Switzerland and sold by Bioforce USA in the United States.

SUMMARY OF REVIEWED CLINICAL STUDIES

Ginkgo products have been tested in clinical studies for their ability to improve cognitive function in a range of subjects, from normal healthy adults and those with age-related impairment to those with early-stage dementia and Alzheimer's disease. Ginkgo products have

also been tested for treatment of cognitive dysfunction attributed to insufficient blood flow to the brain, termed cerebrovascular insufficiency or vascular dementia.

Dementia is a clinical syndrome characterized by losses of cognitive and emotional abilities that are sufficient to interfere with daily functioning and quality of life. The American Psychiatric Association, in its *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) (2000), defines the diagnostic features of dementia as memory impairment, deterioration of language function (aphasia), impaired ability to execute activities despite intact muscles, senses, and comprehension of the task (apraxia), and disturbances in executive functioning (the ability to think abstractly and to plan, initiate, sequence, monitor, and conclude complex behavior). Dementia can be mild (work and social activities are impaired but the capacity for independent living remains), moderate (independent living is hazardous and some supervision is required), or severe (daily living activities are impaired, continuous supervision is required, and the person is largely incoherent or mute). Dementia can be caused by Alzheimer's disease, vascular disease, human immunodeficiency virus (HIV), head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, substance abuse, and other medical conditions.

Alzheimer's disease is observed as a gradual and progressive cognitive decline. Diagnosis of Alzheimer's disease is often made once other causes of dementia have been ruled out, due to a lack of laboratory markers. Cerebrovascular disease can cause vascular dementia diagnosed by characteristic neurological signs or laboratory evidence. Symptoms include transient ischemic attacks (ministrokes), hemipareses, tinnitus (ringing in the ears), dizziness, headache, and anxiety (Schulz, Halama, and Hoerr, 2000).

Ginkgo has also been tested in treatment of cramping and pain in the legs while walking, a condition termed intermittent claudication. This condition is due to mild to moderate peripheral arterial disease (peripheral arterial occlusive disease), in which narrowing of the arteries limits the blood supply to the legs. Early stages of the disease are without symptoms, but later stages are associated with leg pain and muscle cramps upon walking and, ultimately, ischemic ulceration, gangrene, and tissue loss. The stages have been classified in a system according to Fontaine: stage I represents those who are

asymptomatic with isolated arterial stenosis of the lower limbs; stage II is mild to moderately severe leg pain and muscle cramps upon walking; stage III are those with pain while resting; and stage IV are those with ulcerations and gangrene. Ginkgo has been tested in the treatment of stage IIb, in which subjects have a pain-free walking distance of 200 meters or less (Peters, Kieser, and Holscher, 1998).

EGb 761

By far, the majority of clinical trials on ginkgo have been conducted on products containing the EGb 761 extract. We include here a total of 32 controlled clinical studies covering indications of cognitive function (normal and age-related impairment), dementia (including Alzheimer's disease), insufficient blood flow to the brain or extremities, tinnitus, and antioxidant effects.

Normal Cognitive Functioning

Four trials that looked at the effect of EGb 761 on cognitive function in normal volunteers reported mixed results. The largest study, including 203 adults over 60 years old without cognitive impairment, did not report any benefit from Ginkoba, 40 mg three times daily for six weeks, compared to placebo. The study used a battery of tests to measure cognitive function as well as a self-reported memory function questionnaire and a global rating by a companion (Solomon et al., 2002). Another trial included 40 volunteers (55 to 88 years old) who took 120 mg extract or placebo for six weeks and reported improvements in speed of mental processing following treatment. Participants receiving treatment judged their memory as improved, but objective memory tests did not reveal any statistical improvement (Mix and Crews, 2000). Two small crossover trials examined the effect of one dose of ginkgo on reaction time and memory. In both trials, memory improved one hour after administration of 600 mg extract. One of the trials, with eight women aged 25 to 40 years, reported a selective but marked improvement in working memory (Hindmarch, 1986). The other trial, with 12 females, mean age 22 years, failed to replicate the benefit to working memory but did find evidence of improved secondary memory (Warot et al., 1991). Other

measurements of reaction time or the activity of the central nervous system in general did not change in either trial.

Age-Related Cognitive Impairment

Five good-quality trials looked at elderly people with cognitive impairment attributed to aging. All trials used cognitive test batteries, four of them computerized. The patients in these trials all satisfied the criteria of age-associated memory impairment and, in the more extreme trials, mild cognitive impairment. All trials showed statistically significant benefits to one or more aspects of cognitive function, including attention, information processing, and both short- and long-term memory. Four trials ranged in length from three months to one year and used a dose of 120 or 160 mg extract per day. Improvement was observed after one month (Rai, Shovlin, and Wesnes, 1991; Wesnes et al., 1987; Israel et al., 1987; Taillandier et al., 1986). The largest trial (122 subjects) and longest running (one year) reported an increase in the Geriatric Clinical Evaluation score after three months of treatment with continued improvement for the remainder of the year (Taillandier et al., 1986). The fifth trial, which included a series of one-day experiments, showed improvement in a computerized test of information processing completed one hour after taking doses of 320 or 600 mg extract (Allain et al., 1993).

Age-Related Cognitive Impairment/Dementia and Alzheimer's Disease

A study included elderly adults with either dementia or non-demented age-associated memory impairment. A total of 214 participants with a mean age of 83 years included 63 with dementia due to Alzheimer's disease or vascular origins and 151 with age-related memory loss. The majority of the Mini-Mental State Examination (MMSE) scores were in the range of 12 to 24, signaling moderate impairment. The participants were divided into three groups for the initial three months and given 160 or 240 mg EGb 761 or placebo. The groups taking EGb 761 were randomized again to either continue with ginkgo or to take placebo for the rest of the six-month study. The initial placebo group continued to take placebo. An intention-to-treat analysis showed no effect on neuropsychological testing, clinical assessment of symptoms, depressive mood, self-perceived memory,

health, or behavior in either the relatively small group that took ginkgo (79) or the placebo group (44) for the entire six months. In addition, no beneficial effects were observed due to the higher ginkgo dose or longer duration of treatment. In short, none of the subgroups benefited from ginkgo compared to placebo (van Dongen et al., 2000).

Dementia and Alzheimer's Disease

Four good-quality trials, two large and two small, found a benefit from treatment with ginkgo on dementia. The two large well-conducted positive trials included a combined total of 293 patients with either Alzheimer's disease or vascular (multiple infarct) dementia. One study used a dose of 240 mg per day and continued for six months (Kanowski et al., 1997). The other used a dose of 120 mg per day and lasted for one year (Le Bars et al., 1997). In both studies, the treatment groups showed improvement after six months of dosing according to the following scales: Sundrom-Kurztest (SKT) (a brief test of cognitive function, memory, and attention), Clinical Global Impressions (CGI) (clinicians' interview-based quantified judgment of the amount of change in overall impairment), Alzheimer's Disease Assessment Scale (ADAS-cog) (a performance-based cognitive test that objectively evaluates memory, language, praxis, and orientation), and Geriatric Evaluation by Relatives Rating Instrument (GERRI) (an inventory completed by the caregiver) (Kanowski et al., 1997; Le Bars et al., 1997). According to our reviewer, Dr. Keith Wesnes, this well-known ginkgo study shows a benefit from ginkgo comparable to current pharmacological therapies of choice, e.g., Aricept. A reanalysis of the Le Bars and colleagues (1997) study included a stratification of Alzheimer's patients according to severity of cognitive impairment. The relative changes from baseline depended upon the severity of the disease. Significant improvement compared to baseline according to the ADAS-cog and GERRI was observed in those with mild cognitive impairment (MMSE more than 23). While in patients with moderate to severe dementia (MMSE less than 23), there was less deterioration in the EGb 761 group compared to baseline than that observed in the placebo group (Le Bars et al., 2002). The two small trials had a combined total of 58 patients with Alzheimer's disease who were given 240 mg per day for three

months. The studies demonstrated improvement with treatment, compared with placebo, according to the SKT test (Maurer et al., 1997; Hofferberth, 1994).

Cerebrovascular Insufficiency

Six trials looked at cognitive function in elderly people with dysfunction attributed to insufficient blood flow to the brain. Symptoms of this disorder, called cerebrovascular insufficiency or cerebroorganic psychosyndrome, include transient ischemic attacks, hemipareses, tinnitus, dizziness, headache, and anxiety. Five of the six studies used doses of 120 or 160 mg per day for seven weeks to six months and reported clear and significant benefits in cognitive function that were based upon either performance or subjective ratings. Two of these studies, with a total of 92 subjects, were deemed to be of excellent quality and reported improvement in short-term memory, awareness, and rate of learning (Grassel, 1992; Halama, Bartsch, and Meng, 1988). In the third good-quality, but small, study with 24 subjects, changes in electroencephalogram (EEG) patterns in the treatment group correlated with a reduction in abnormally elevated venous microembolism (a laboratory indicator of blood platelet aggregation). This result indicated an improvement in blood flow may play a role in the clinically observed cognitive improvement (Hofferberth, 1991b). Two other studies had clearly defined positive end points in cognitive function, saccadic eye movement, and EEG changes (Hofferberth, 1989), as well as symptoms of tinnitus, anxiety, attention, higher function, and memory (Arrigo, 1986), but failed to describe the blinding and randomization processes. The sixth study of this group included 20 patients who were depressed, in addition to having cerebrovascular insufficiency. Following a dose of 240 mg per day for two months, there were patterns of improvement in reaction times and depression symptoms in the treatment group in comparison with the placebo group (Halama, 1990).

Peripheral Vascular Disease

Five trials looked at effects of ginkgo on peripheral vascular disease stage IIb according to Fontaine. Subjects had intermittent claudication (leg pain and cramps) and a pain-free walking distance of less than 200 meters. Four of the five trials were placebo controlled

and showed important improvements in pain-free walking distances for patients following treatment of 120 mg extract per day for six months. None of the studies indicated any gross improvement in blood flow of the ischemic leg as measured in Doppler studies comparing blood pressure in the ankle to blood pressure in the arm. One excellent-quality, parallel, placebo-controlled trial that included a total of 54 patients reported an increase in pain-free walking distance from 94.5 m to 147 m following treatment. There was also a 42 percent increase in total walking distance for the treatment group, compared to an 8 percent increase in the placebo group (Blume, Kieser, and Holscher, 1996). Three other studies, with a total of 225 subjects, reported similar findings (Bauer, 1984; Thomson et al., 1990; Peters, Kieser, and Holscher, 1998). A six-month dose-response study reported significantly greater increases in pain-free walking distance and maximum walking distance with a doubling of the standard dose; the trial compared the usual 120 mg per day to 240 mg per day (Schweizer and Hautmann, 1999).

Tinnitus

A well-conducted trial focusing on tinnitus (the perception of sound in the absence of external stimuli or "ringing in the ears") reported a clear clinical benefit for those taking ginkgo. In this trial which included 78 patients with tinnitus for at least the previous two months, a dose of 120 mg extract per day produced a statistical reduction in sound volume after ten weeks compared to baseline. No significant change was noted in the placebo group (Morgenstern, 1997).

Sudden Hearing Loss

A trial with 78 adults with sudden hearing loss (of at least 15 dB, within ten days before entry into the study) compared a dose of 24 mg to 240 mg daily for two months. A large majority of subjects in both groups recovered their hearing. The higher dose showed an advantage over the lower dose for those without tinnitus, but not for those with tinnitus (Burschka et al., 2001).

Protection Against Hypoxia

A poorly described placebo-controlled pilot trial using eight healthy male volunteers showed that 160 mg extract per day for two weeks helped reduce the deficits in both attention and saccadic eye movements produced by hypoxia (lack of oxygen to the brain) (Schaffler and Reeh, 1985).

Antioxidant Effects

Another placebo-controlled pilot study demonstrated that taking EGb 761 before surgery limited oxidative stress in plasma and showed signs of improving patient recovery. The study included 15 patients undergoing coronary bypass surgery who were given 320 mg extract per day or placebo for five days before surgery (Pietri et al., 1997).

Electrophysiological Effects

Three studies explored the effect of EGb 761 on brain electroencephalogram recordings. Two of the studies suggested an increase in alpha activity that was consistent with a nootropic or cognitive enhancing action (Itil and Martorano, 1995; Luthringer, d'Arbigny, and Macher, 1995). The third study did not report any clear effect on the EEG profile (Kunkel, 1993). The studies used doses ranging from 40 to 160 mg extract and were all short term with testing following either one treatment or at most five days of treatment.

LI 1370

We reviewed ten studies conducted on ginkgo extract LI 1370. Three of four trials showed a benefit for age-related cognitive impairment. A benefit was also observed for subjects recovering from a brain aneurysm and subsequent operation, as well as normal volunteers. LI 1370 appeared to benefit microcirculation in two studies but showed no benefit for tinnitus in another. A sleep study indicated that LI 1370 does not have cholinergic activity.

Age-Related Cognitive Impairment

The largest trial, which included a total of 209 outpatients, mean age 69, with cerebral insufficiency, reported a significant improvement after six weeks in forgetfulness, depression, and headache with treatment of 150 mg extract per day in comparison to placebo. After 12 weeks, there was significant improvement in additional symptoms of memory gaps, difficulty concentrating, tendency to fatigue, lack of drive, and tinnitus in comparison to placebo (Bruchert, Heinrich, and Ruf-Kohler, 1991). Another good-quality three-month trial with 86 subjects with cerebral insufficiency due to old age reported similar findings. Significant improvement was seen in short-term memory, attention to tasks, and subjective performance from the sixth week onward with a dose of 150 mg extract per day in comparison to placebo (Vesper and Hansgen, 1994).

A trial studied 50 elderly people with failing mental performance. Significant benefits to cognitive function according to both psychometric and neurophysiologic tests were observed after three weeks of treatment compared with placebo. LI 1370 was given in a dose of 50 mg three times daily for six weeks (Hofferberth, 1991a). However, the methodology of the trial was considered poor.

A pilot study with 15 subjects measured EEG changes in mildly impaired subjects with age-related signs of cerebral insufficiency. Treatment with 150 mg LI 1370 for three months did not cause a general change in EEG activity. However, when the subjects were stressed by sleep deprivation, causing a reversible decrease in mental performance, there were significant changes in theta waves and the alpha slow-wave sleep index in the ginkgo group compared to the placebo group. The authors concluded that ginkgo causes EEG changes that are situation and stimulus dependent (Schulz, Jobert, and Breuel, 1991).

Brain Aneurysm

A good-quality trial included 42 people recovering from brain aneurysms and subsequent operations. After 12 weeks of treatment with 150 mg LI 1370 per day, a statistically significant improvement was seen in reaction times, the number of errors, and short-term ver-

bal memory in comparison to baseline and to the placebo group (Maier-Hauff, 1991).

Normal Cognitive Functioning

A dose-comparison trial included 31 healthy volunteers who showed improved performance in short-term memory tasks after two days' dosing with quantities of 50 and 100 mg extract three times daily or 120 mg and 240 mg once daily compared to placebo. More improvement occurred in a subset of older volunteers, but there was no indication of a dose-response relationship for the group as a whole (Rigney, Kimber, and Hindmarch, 1999). Our reviewer, Dr. Wesnes, commented that the authors did not state their method of blinding the five different treatments, nor did they give the rationale for the different dosage regimens.

Tinnitus

A large study included 909 healthy volunteers who had had tinnitus for over a year. They were treated with 50 mg three times daily or placebo for three months. As a result, there was no significant benefit for ginkgo over placebo (Drew and Davies, 2001).

Microcirculation

Two trials demonstrated improvements to microcirculation; one of them also showed improvements in retinal circulation, while the other also showed improvements in blood flow in nail fold capillaries. The first study included a group of 24 hypertensive individuals, with fundus hypertonicus who were treated with 300 mg per day LI 1370 or placebo for six weeks. Retinal blood flow increased, circulation time decreased, and blood viscosity decreased compared to the placebo group (Koza, Ernst, and Sporl, 1991). The second study was a small crossover study with single doses (45 ml solution) containing either 112.5 mg dry extract or a placebo (composed of inactive excipients in the formulation) given to ten healthy subjects. The result was a 15.6 percent decrease in erythrocyte aggregation and a 57 percent increase in blood flow in nail fold capillaries in the ginkgo group (Jung et al., 1990).

Sleep Quality (REM Latency)

A small mode-of-action study explored whether LI 1370 had cholinergic activity, as measured by its effect on latency to rapid eye movement (REM) in sleep. Ten healthy volunteers were given placebo or 240 mg ginkgo two hours before going to bed in a sleep lab. No comparative effect on sleep was measured. However, the authors did not rule out a cholinergic mechanism for LI 1370, as REM sleep can be affected by other factors such as noradrenaline or serotonin function (Murray, Cowen, and Sharpley, 2001).

GK501, Ginkoba M/E

Cognitive Functioning

Cognitive function and attention speed scores improved in a good-quality pilot trial with 20 young volunteers given single doses of 120, 240, or 360 mg GK501 extract. Dose-dependent improvements in attention appeared two and one-half hours after dosing with 240 and 360 mg and were still present after six hours. Changes in speed of memory and accuracy of information did not follow a pattern (Kennedy, Scholey, and Wesnes, 2000).

Another study examined the effects of ginkgo extract GK501, ginseng extract G115, the combination of the two (Ginkoba M/E), and placebo on cognitive functioning up to six hours after dosing in 20 young volunteers. There was a dose-dependent improvement in speed in an arithmetic task (serial threes) with doses of 120, 240, and 360 mg of ginkgo extract. Ginseng improved accuracy and slowed responses in the serial sevens arithmetic task with doses of 200, 400, and 600 mg. Ginkoba M/E produced a sustained increase in the number of serial sevens responses with a dose of 320 mg. Higher doses of 640 and 960 mg also improved accuracy in both serial threes and serial sevens tests (Scholey and Kennedy, 2002).

The product combining extracts GK501 and G115 (Ginkoba M/E) was tested for its effect on cognitive function in three additional trials. Improvements in quality of memory were demonstrated in all three studies, reflecting selective improvement in the ability to store and retrieve information from short- and long-term memory. Other cognitive aspects such as attention were not improved. The first study com-

pared the effects of three doses (80, 160, and 320 mg) for three months on healthy volunteers with neurasthenia (fatigue, lack of motivation, and feelings of inadequacy) (Wesnes et al., 1997). The second study included a large number (256) of healthy, middle-aged volunteers given either 320 mg or placebo daily for three and one-half months. In this trial, benefits persisted 14 days after termination of treatment (Wesnes et al., 2000). The third study compared single doses of 320, 640, or 960 mg of the combination in a small study with healthy young volunteers (Kennedy, Scholey, and Wesnes, 2001).

Geriaforce (Ginkgoforce)

Age-Related Memory Impairment

A large trial (197 subjects) conducted on people with age-induced memory disorders compared two doses of Ginkgoforce (60 or 120 drops per day) with placebo in a six-month trial. The results of the trial were partly compromised by not training the subjects on tests prior to the study, with the result that training effects appeared on all assessments. Nonetheless, improvements were greater with ginkgo on the Benton test measuring visual short-term memory (Degenring and Brautigam, 1999).

META-ANALYSES AND SYSTEMATIC REVIEWS

Several meta-analyses and systematic reviews of the clinical literature on ginkgo have been published. A summary of analyses of trials treating Alzheimer's disease, dementia, cerebral insufficiency, intermittent claudication (a symptom of peripheral arterial disease), and tinnitus is given in this section.

An objective measure of the effect of ginkgo (products not differentiated) on cognitive function in patients with Alzheimer's disease was attempted in a meta-analysis of randomized, placebo-controlled, double-blind studies. The four studies that met the inclusion criteria contained a total of 212 subjects treated with ginkgo and 212 with placebo. The authors found a small but significant effect after three to six months of treatment with 120 to 240 mg ginkgo extract, EGb 761, compared to placebo. The modest effect size (0.40, $p < 0.0001$), calculated from reported p-values for cognitive measures and sample

sizes, translated into a 3 percent difference in the Alzheimer's Disease Assessment Scale-cognitive subset (Oken, Storzbach, and Kaye, 1998). Published one year later, a systematic review of the treatment of dementia with ginkgo (EGb 761) included nine double-blind, randomized, placebo-controlled trials. The authors concluded that the majority of trials support the notion that ginkgo is efficacious in delaying the clinical deterioration of patients with dementia, or in bringing about symptomatic improvement. However, the authors also commented that none of the trials were flawless or completely convincing (Ernst and Pittler, 1999).

An evaluation of the treatment of age-related cognitive impairment or dementia of any type with any ginkgo extract compared to placebo was undertaken in a meta-analysis including 33 randomized, double-blind studies. The authors concluded that, compared to placebo, ginkgo showed significant benefit for cognition at doses less than 200 mg/day and more so with doses more than 200 mg/day, both for 12 weeks (95 percent CI –1.09,–0.05, $p = 0.03$; 95 percent CI –1.12 to 0.0, $p = 0.008$). Benefits in cognition were also found following 24 weeks with any ginkgo dose (95 percent CI –0.32 to –0.02, $p = 0.03$). Activities of daily living also showed a benefit with doses less than 200 mg/day for 12 weeks. Measures of mood and emotional function showed benefit compared to placebo with doses less than 200 mg/day in treatment lasting 12 weeks and in shorter durations. The authors concluded that overall there is promising evidence of improvement in cognition and function associated with ginkgo. However, they also commented that many of the earlier trials used unsatisfactory methods and were small in size. They could also not rule out publication bias and expressed the need for a large trial using modern methodology and intention-to-treat analysis (Birks et al., 2002).

A meta-analysis of studies exploring the efficacy of the ginkgo preparation LI 1370 (Kaveri® forte) in aged patients with cerebral insufficiency included 11 randomized, placebo-controlled, double-blind trials. In most studies the dose was 150 mg extract per day. The parameters examined were single symptoms, total score of clinical symptoms, and global effectiveness. All single-symptom scores that were analyzed demonstrated superiority compared to placebo. In eight studies, upon which analysis of the total score of clinical symptoms could be conducted, seven of the studies confirmed LI 1370's effectiveness compared to placebo, and one study found no differ-

ence between the two. Global effectiveness, as evaluated by physicians and patients, was confirmed in five of six studies that allowed this analysis (Hopfenmuller, 1994).

Significant increases in pain-free walking distance compared to placebo for patients with intermittent claudication was reported in a meta-analysis of eight randomized, placebo-controlled, double-blind studies. Overall, the increase was 34 meters (37 yards). The dose was either 120 mg or 160 mg of various ginkgo extracts, and the length of treatment for the majority of the trials was 24 weeks, with one trial lasting six weeks and another for 12 weeks (Pittler and Ernst, 2000).

A systematic review summarized randomized, controlled trials using ginkgo for tinnitus. Five studies fulfilled the entry criteria, and the results of these studies suggest that ginkgo is effective in treating tinnitus. One study produced a negative result, but the dose used in the study was much lower (29 mg extract daily) than the usual 120 to 160 mg extract per day used in the other studies. The studies used several different products with either liquid or solid formulations, different routes of administration (one trial used injections), and different lengths of treatment (two weeks to three months). The variability in methodology, end point measurement, dose, and patient classification made a firm conclusion about efficacy difficult (Ernst and Stevinson, 1999).

Alzheimer's disease is associated with a deficiency of the neurotransmitter acetylcholinesterase. A relatively new class of drugs that delays the decomposition of the neurotransmitter has been shown to enhance the cognitive performance of persons with that disease. A comparison of efficacy studies of acetylcholinesterase inhibitors with efficacy studies of ginkgo extract EGb 761 was published. The study results were compared using intent-to-treat analyses of the Alzheimer's Disease Assessment Scale (ADAS-Cog) scores. Two ginkgo studies were compared with one study each for the following acetylcholinesterase inhibitors: rivastigmine, tacrine, metrifonate, and donepezil. The authors reported finding a similar delay in disease progression over a six-month period with both types of treatment (Wettstein, 1999/2000).

ADVERSE REACTIONS OR SIDE EFFECTS

Adverse effects noted in the reviewed trials included abdominal complaints, nausea, and dyspepsia. A meta-analysis published in 1998 noted that the incidence of adverse effects was not different from placebo in the four studies reviewed. In these studies the dose was either 120 to 240 mg per day for three to six months and a total of 424 subjects were included (Oken, Storzbach, and Kaye, 1998). A large postmarketing surveillance study including 1,357 doctors who treated 10,815 patients with dementia with ginkgo extract (LI 1370) reported only mild adverse events in 1.7 percent of patients. The main adverse symptoms observed were nausea (0.34 percent), headache (0.22 percent), stomach complaints (0.14 percent), and allergic reactions (0.09 percent) (Burkard and Lehrl, 1991).

Five case reports of bleeding that may be linked to ginkgo were reported between 1996 and 1998. Three of the patients were reported to have been in good health, one 33 years old and the others aged 61 and 72 years (Rowin and Lewis, 1996; Gilbert, 1997; Vale, 1998). Two had cardiovascular disease and were already taking anticoagulants (aspirin, warfarin) (Matthews, 1998; Rosenblatt and Mindel, 1997).

These reports raised concerns regarding ginkgo and its possible effects on blood thinning and/or interactions with other blood thinners. Five clinical studies that have explored this topic are summarized here. Two studies indicate that ginkgo might inhibit platelet aggregation, but none indicate any alteration in bleeding times. One study indicates a lack of interaction with the blood thinner warfarin.

A study reported inhibition of ex vivo platelet aggregation in 12 volunteers administered 240 mg EGb 761 extract for seven days (Klein, 1988). In another study with six healthy males, administration of a single dose of 600 mg EGb 761 extract reduced ex vivo platelet aggregation but did not alter prothrombin bleeding time or skin bleeding time (Guinot et al., 1989). A trial with 50 healthy male volunteers given 240 mg EGb 761 per day or placebo for seven days in a crossover design reported no alteration of bleeding time, coagulation parameters, or platelet activation (Kohler, Funk, and Kieser, in press). Another crossover study which also included 50 healthy males reported no additional effect on bleeding times or platelet aggregation (agonists included adenosine diphosphate, epinephrine, platelet activating factor, and collagen) when 120 mg EGb 761 was administered

along with 500 mg aspirin (Wolf, in press). A double-blind, crossover study with 21 middle-aged patients on stable long-term warfarin treatment found that the addition of 100 mg ginkgo extract (Bio-Biloba®, Pharma Nord ApS, Denmark) over four weeks did not alter International Normalized Ratio (INR) values, a standardized measurement of clotting time (Engelsen, Nielsen, and Winter, 2002).

Some indications from animal studies suggest that ginkgo extract may inhibit monoamine oxidase (MAO). MAO inhibitors are used to elevate mood in depressed individuals, but their use as antidepressants has been limited due to concerns over interactions with foods high in tyamine content (e.g., cheese) and many drugs. A small pilot study with ten subjects determined that 129 mg EGb 761 extract per day for one month had no effect on MAO in the brain, neither MAO_A or MAO_B. The authors point out that this study does not rule out MAO inhibition in peripheral organs. However, no reports of adverse events suggest significant MAO inhibition (Fowler et al., 2000).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

German Commission E
World Health Organization (WHO)

Indications

The German Commission E approves of the use of a dry extract of the dried leaf that is manufactured using acetone/water with subsequent purification steps, without addition of concentrates or isolated ingredients, and with a drug/extract ratio of 35 to 67:1, on average 50:1. The Commission E and World Health Organization further stipulate that the preparation contain 22 to 27 percent flavone glycosides and 5 to 7 percent terpene lactones, of which approximately 2.8 to 3.4 percent consists of ginkgolides A, B, and C and 2.6 to 3.2 percent bilobalide. The level of ginkgolic acids is below 5 mg/kg. Both organizations indicate use in cases of dementia syndromes (in primary degenerative dementia, vascular dementia, and mixed forms of both) with symptoms including memory deficits, disturbances in concen-

tration, depressive emotional condition, dizziness, tinnitus, and headache; improvement of pain-free walking distance in peripheral arterial occlusive disease in stage II of Fontaine (intermittent claudication); and vertigo and tinnitus of vascular and involutional origin (Blumenthal et al., 1998; WHO, 1999).

Doses

Extract:

- Dry: 120 to 240 mg daily in two or three divided doses (WHO, 1999)
- Fluid: (1:1), 0.5 ml three times daily (WHO, 1999)

Note: The Commission E suggests specific dosages for certain indications:

- For demential syndromes: 120 to 240 mg native dry extract in two or three doses daily (Blumenthal et al., 1998)
- For walking improvement, vertigo, and tinnitus: 120-160 mg native dry extract in two or three doses daily (Blumenthal et al., 1998)

Treatment Period

The Commission E suggests these treatment lengths for the following indications: for demential syndromes, treatment length depends on severity of symptoms but should last at least eight weeks for chronic illnesses; for walking improvement, treatment should be at least six weeks; and for vertigo and tinnitus, administration for more than six to eight weeks has no therapeutic benefit (Blumenthal et al., 1998).

Contraindications

The Commission E and the WHO list the following contraindication: hypersensitivity to *Ginkgo biloba* preparations (Blumenthal et al., 1998; WHO, 1999).

Adverse Reactions

The following adverse reactions are listed as occurring infrequently by the Commission E and the WHO: stomach or intestinal

upsets, headaches, or allergic skin reaction (Blumenthal et al., 1998; WHO, 1999).

Precautions

The Commission E and the WHO list no known precautions (Blumenthal et al., 1998; WHO, 1999).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998).

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DETAILS ON GINKGO PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Ginkgo Products

Product Profile: Ginkgold®

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	**Nature's Way Products, Inc.**
Botanical ingredient	**Ginkgo leaf extract**
Extract name	**Egb 761®**
Quantity	60 mg
Processing	Plant to extract ratio 50:1, acetone 60% m/m
Standardization	24% flavone glycosides, 6% terpene lactones
Formulation	Tablet

Recommended dose: One tablet two times daily with water at meals. For intensive use, take up to two tablets two times daily with water.

DSHEA structure/function: For improved mental sharpness, concentration, memory, cognitive activity. Supports healthy circulation to the brain as well as the extremities. Maintains healthy blood vessel tone and reduces blood viscosity.

Other ingredients: Cellulose, starch, modified cellulose, silica, magnesium stearate, titanium dioxide, caramel.

Comments: EGb 761 is sold in Europe as Tanakan®, Rökan®, and Tebonin® forte.

Source(s) of information: Product package and label; information provided by distributor.

Product Profile: Ginkoba®

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	**Pharmaton Natural Health Products**
Botanical ingredient	**Ginkgo leaf extract**
Extract name	**EGb 761®**
Quantity	40 mg
Processing	Plant to extract ratio 50:1
Standardization	24% ginkgo flavone glycosides and 6% terpene lactones
Formulation	Tablet

Recommended dose: One tablet three times daily with water at mealtimes. Optimal effectiveness has been shown after four weeks with continuous uninterrupted use.

DSHEA structure/function: Improves memory and concentration and enhances mental focus by safely increasing the flow of oxygen to the brain. Sharpens mental focus, enhances memory and concentration, and helps contribute to an overall sense of healthy well-being by increasing the natural blood flow of oxygen to the brain.

Cautions: In case of accidental overdose, seek the advice of a professional immediately. If taking a prescription medicine, pregnant or lactating, please contact a doctor before taking Ginkoba. No information is available on the use of ginkgo biloba extract in children under the age of 12.

Other ingredients: Hydroxypropyl methyl cellulose, lactose, talc, polyethylene glycol, magnesium stearate, titanium dioxide, synthetic iron oxides.

Comments: EGb 761 is sold in Europe as Tanakan®, Rökan®, and Tebonin® forte.

Source(s) of information: Product package and insert (© Boehringer Ingelheim Pharmaceuticals Inc., 2000).

Clinical Study: Ginkoba®

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Cognitive functioning** in normal elderly volunteers
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R (2002). Ginkgo for memory enhancement: A randomized controlled trial. *Journal of the American Medical Association* 288 (7): 835-840.

Trial design
Parallel.

Study duration	6 weeks
Dose	1 (40 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	230
No. of subjects completed	203
Sex	Male and female
Age	60-82 years (Mean: 69.3)

Inclusion criteria
Community-dwelling subjects over 60 years old without cognitive impairment (Mini-Mental State Examination scores greater than 26), and generally in good health, with a companion with whom they came in contact regularly (>four times per week for at least one hour) and who was willing to complete a questionnaire. All subjects were independent in daily living tasks such as shopping, managing finances, and transportation.

Exclusion criteria
Subjects were excluded if they had a history of neurologic or psychiatric disorder, had taken antidepressants or other psychoactive medications in the past 60 days, or had a life-threatening illness in the past five years.

End points
The outcome measures, except the companion's questionnaire, were assessed at the beginning and end of the study. These included tests of memory and learning (California Verbal Learning Test, the Logical Memory subscale of the Wechsler Memory Scale-Revised [WMS-R], and the Visual Reproduction subscale); tests of concentration and attention (Stroop Test, Digit Span [WMS-R], Mental Control [WMS-R], Digit Symbol subscale of the Wechsler Adult Intelligence Scale-Revised [WAIS-R]); expressive language tests (Controlled Category Fluency test, Boston Naming Test). The subjects also completed a memory questionnaire. The subjects' companions completed a global evaluation (based on the Caregiver Global Impression of Change [CGIC] rating scale) only at the end of the study.

Results
Compared to the placebo group, the subjects in the ginkgo group did not perform significantly better on any of the outcome measures.

Side effects
Not evaluated.

Authors' comments
These data suggest that when taken following the manufacturer's instructions, this compound provides no measurable benefit in cognitive function to elderly adults with intact cognitive function.

Reviewer's comments
This trial was compromised by learning effects on most tests, due to the absence of prestudy training and use of tests that are known to have training effects. Also, memory was assessed at only one time point and effects might have been seen at other times. The main author was not blinded, a very unusual practice that would have prevented publication in some scientific journals. (3, 6)

Clinical Study: Ginkgold®

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Cognitive functioning** in normal volunteers
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Mix JA, Crews WD (2000). An examination of the efficacy of *Ginkgo biloba* extract EGb 761 on the neuropsychologic functioning of cognitively intact older adults. *The Journal of Alternative and Complementary Medicine* 6 (3): 219-229.

Trial design
Parallel.

Study duration	6 weeks
Dose	3 (60 mg capsules) daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	48
No. of subjects completed	40
Sex	Male and female
Age	55-88 years

Inclusion criteria
No history of significant neurocognitive impairment and a total score of 24 or more on the Mini-Mental State Examination (MMSE).

Exclusion criteria
Histories of active or clinically significant cardiovascular, neurologic, pulmonary, endocrine, renal, hepatic, gastrointestinal, hematologic, or oncologic diseases/disorders; uncontrolled hypertension; learning disabilities; psychi-

atric or substance abuse disorders; treatment with anticoagulant or psychotropic medications; histories of bleeding disorders or hemorrhagic stroke; uncorrected vision; or hearing or motor difficulties that could have possibly precluded their participation and/or compliance with all of the neuropsychologic procedures.

End points
A series of neuropsychologic tests designed to measure cognitive and behavioral functioning were administered prior to treatment and after six weeks. Tests included the MMSE, Stroop Color and Word Test, Trail Making Test, and the Wechsler Memory Scale—Revised Logical Memory I and II and Visual Reproduction I and II subsets. A self-report questionnaire was administered during the second assessment.

Results
Participants who received EGb 761 exhibited significantly more improvement on a task assessing speed of processing abilities by the end of the treatment as compared to placebo. Trends favoring improved performances in EGb 761 group were also demonstrated in three of the four remaining tasks that involved a timed, speed of processing component, although they did not reach statistical significance. Significantly more participants in the EGb 761 group rated their overall abilities to remember by the end of the treatment as "improved," as compared to the placebo group. In contrast, no significant differences were found between the EGb 761 and placebo groups on any of the four objective memory measures.

Side effects
No notable adverse reactions were reported.

Authors' comments
Ginkgo biloba extract EGb 761 may prove efficacious in enhancing certain neurocognitive functions/processes of cognitively intact older adults.

Reviewer's comments
Soundly conducted and excellently reported study. This is one of the few trials on cognitive function in normal, healthy volunteers. The only possible caveat is that the statistical outcome is dependent on one-tailed testing. (5, 6)

Clinical Study: EGb 761®

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany

Indication	**Cognitive functioning** in normal volunteers
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Hindmarch I (1986). Effect of *Ginkgo biloba* extract on short-term memory. *Presse Medicale* 15 (31): 1592-1594.

Trial design
Crossover. Two Latin squares, treatment with one of three doses of EGb 761 (120 mg, 240 mg, and 600 mg extract) or placebo, administered one hour prior to testing. The four treatments were separated by one-week washout intervals.

Study duration	1 day
Dose	120, 240, and 600 mg of EGb 761 extract
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	8
No. of subjects completed	8
Sex	Female
Age	25-40 years (mean: 32)

Inclusion criteria
Healthy female volunteers in good physical condition with no history of disease (cardiovascular, gastric, hepatic, renal, psychiatric).

Exclusion criteria
Any drug therapy (except contraceptives) and confirmed or suspected pregnancy.

End points
Tests consisted of Critical Flicker Fusion Test (CFF) to measure the activity of the central nervous system (CNS) as a whole; Choice Reaction Time (CRT) to measure sensorimotor performance; memory test to measure

short-term memory and rapid discriminant memory; and a 10 cm visual analog scale to evaluate subjective effects.

Results
Short-term memory as assessed by the Sternberg technique was significantly improved one hour after administration of 600 mg ginkgo ($p < 0.0001$). Analysis of mean reaction times from the pooled data of the positive and negative tests shows a significant difference ($p < 0.05$) between placebo and EGb 761. No significant differences were seen in either the Flicker Fusion or Choice Reaction Time Tests.

Side effects
None mentioned in paper.

Author's comments
Only the Sternberg test was modified to a significant degree by administration of EGb 761, suggesting a specific action of the product on central cognitive processes. These findings point to a potential for use of *Ginkgo biloba* extract in the treatment of patients suffering from senile or presenile dementia in whom memory disorders are among the principal clinical symptoms.

Reviewer's comments
This is the first volunteer study of ginkgo with automated cognitive function tests. The sample was small, and the effect was restricted to 1 dose (600 mg) and one of three tests (Sternberg), but the significance of the effect was high. This finding was not replicated in another trial with 12 females using the same dose and tests (Warot et al., 1991). The randomization process was not adequately described and withdrawals and dropouts were not described. (Translation reviewed) (2, 5)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Cognitive functioning** in normal volunteers
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Warot D, Lacomblez L, Danjou P, Weiller E, Payan C, Puech AJ (1991).

Comparative effects of *Ginkgo biloba* extracts on psychomotor performance and memory in healthy volunteers. *Therapie* 46 (1): 33-36.

Trial design
Crossover. Latin square, with two different ginkgo preparations and matching placebos. Three courses of treatment (600 mg unidentified ginkgo preparation, 600 mg Tanakan and placebo) were separated by one-week intervals. The treatments were given as one acute dose preceding evaluations. Consumption of alcohol and caffeinated beverages was prohibited on the evening before and on the day of evaluation visits.

Study duration	1 day
Dose	600 mg extract
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Unidentified ginkgo preparation
Site description	Not described
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Female
Age	19-30 years (mean: 22.3)

Inclusion criteria
Healthy female volunteers with normal scores on Cattell's self-analysis scale, the Eysenck Personality Inventory, and the Mini-Mult test.

Exclusion criteria
None mentioned.

End points
Psychomotor performance and memory were evaluated before and one hour after oral administration of the drugs. Four psychometric tests were employed for analysis: Critical Flicker Frequency (CFF), Choice Reaction Time, memory test (number recognition or Sternberg test), and images (used to explore free recall and recognition of images). Self-evaluation scales in the form of 11 visual analog scales were completed by the subjects to evaluate mood and wakefulness.

Results
No significant change was observed in the CFF threshold, the choice reaction time, and the subjective evaluation measured by the visual analog scales. In the memory test, significant differences were found between placebo and Tanakan ($p < 0.01$) and between Tanakan and the unidentified ginkgo product ($p = 0.05$). Memory performances were maintained one hour after taking Tanakan, while scores obtained after the administration of the unidentified ginkgo or placebo were reduced.

Side effects
None mentioned in paper.

Authors' comments
In order to verify the clinical relevance of these results, the tests need to be repeated in older, healthy volunteers with age-associated memory impairment.

Reviewer's comments
This study with 50 percent more volunteers failed to replicate working memory benefit seen in Hindmarch (1986), but it did find evidence of improved secondary memory (clear benefit of ginkgo on recall scores). Though authors suggest proactive interference may account for effects, this is unlikely. The study participants were not allocated to groups in a randomized manner. (Translation reviewed) (3, 5)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Ipsen, France (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Age-related memory impairment**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Rai GS, Shovlin C, Wesnes KA (1991). A double-blind placebo-controlled study of *Ginkgo biloba* extract (Tanakan) in elderly outpatients with mild to moderate memory impairment. *Current Medical Research and Opinion* 12 (6): 350-355.

Trial design
Parallel. Two weeks prior to the trial patients underwent training on the test procedures.

Study duration	6 months
Dose	1 (40 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	1 hospital geriatric department
No. of subjects enrolled	31
No. of subjects completed	27
Sex	Male and female
Age	54-89 years (mean: 76)

Inclusion criteria
Patients over the age of 50 showing signs of mild to moderate memory impairment of organic origin as classified by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS, now the NINDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now the Alzheimer's Association) for a minimum of three months prior to screening.

Exclusion criteria
Patients presenting with memory problems due to physical illness, metabolic, endocrine, nutritional, neurological, or cardiac disease; functional disorders such as depression; evidence of renal or hepatic failure; presence of severe cardiac disease; myocardial infarction within the preceding six months; poorly controlled diabetes; epilepsy or malignant disease; those on drugs acting on cerebral metabolism or cerebral blood flow; uncooperative patients; and those with a history of drug or alcohol abuse.

End points
Patients were assessed two weeks before the trial, at baseline, and after 12 and 24 weeks of treatment using the following psychometric tests: the Folstein Mini-Mental State Examination; the Kendrick Battery for the detection of dementia in the elderly; a computerized version of the digit recall task; a computerized version of a classification task; latency of auditory event-related potential (ERP), i.e., P300; and an EEG. Change in performance

over time was assessed by subtracting the initial score from the test score at week 12 or week 24.

Results
The results in patients receiving ginkgo extract were significantly superior to placebo on the digit copying subtest of the Kendrick Battery at both week 12 ($p = 0.022$) and week 24 ($p = 0.017$), and on the median reaction time of the classification task at 24 weeks ($p = 0.026$). The EEG between 1 and 3 Hz also showed a statistically significant decrease in the active treatment group for this frequency compared to placebo.

Side effects
None mentioned in paper.

Authors' comments
The findings of an improvement on the digit copying subtest and an improvement in speed on the classification task, both at week 24, confirm that ginkgo extract EGb 761 has a beneficial effect on mental efficiency in elderly patients showing mild to moderate impairment of organic origin.

Reviewer's comments
This is a replication in a different site with differing tests of Wesnes and colleagues (1987) showing that ginkgo improves cognitive function in what is today termed mild cognitive impairment. The trial is small but supportive of beneficial effects. (5, 5)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Ipsen, France (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Age-related cognitive impairment**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Wesnes K, Simmons D, Rook M, Simpson P (1987). A double-blind placebo-controlled trial of Tanakan in the treatment of idiopathic cognitive impairment in the elderly. *Human Psychopharmacology* 2: 159-169.

Trial design
Parallel. Pretrial washout period of one to three weeks. Patients were trained on the experimental tasks before the trial began.

Study duration	3 months
Dose	1 (40 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	58
No. of subjects completed	54
Sex	Male and female
Age	62-85 years

Inclusion criteria
Patients who showed mild impairment of everyday functioning using the Crichton Geriatric Behavioral Scale for diagnosis of dementia (a score of 14 or more on the scale, without scoring more than 3 on any individual item).

Exclusion criteria
Patients were excluded if there was a predisposing cause for their symptoms, such as infection, drug toxicity, metabolic, endocrine, or nutritional disease; or if they had a neurological disorder, such as chronic subdural hematoma or cerebral neoplasia. Patients with a possible psychiatric cause for their condition, such as depression, were also excluded, as were those with renal, hepatic, or cardiac insufficiency, with diabetes mellitus, or with malignant disease. Medication with psychotropic drugs was not permitted during the trial.

End points
Cognitive efficiency was measured prior to the trial start, and then at monthly intervals, using a battery of tests of mental ability comprising both computerized and pencil-and-paper tasks. Quality of life was assessed using a behavioral questionnaire both before and after the study.

Results
Results of the tests were combined using two different methods. Both groups improved in accuracy during weeks 8 and 12 compared to baseline. The ginkgo group's reaction times were significantly faster during week 4 and showed trends toward maintaining this level during weeks 8 and 12. No improvement was seen in the placebo group. There was a notable increase

in interest taken in everyday activities for the ginkgo group ($p = 0.015$) but not for the placebo group.

Side effects
Tolerance was very good. One ginkgo patient complained of constipation that resolved itself without interruption of treatment.

Authors' comments
Overall the findings from this study, that ginkgo has a favorable effect on mental efficiency in this population, suggest that the drug could prove effective in the treatment of the early stages of primary degenerative dementia.

Reviewer's comments
This is the first study using computerized tests of cognitive function in elderly impaired patients. It showed clear benefits to accuracy and speed of cognitive function plus improvements to quality of life. The authors used one-tailed testing, but the results would have been significant with two-tailed testing. The sample size was fair but probably at the lower end required to detect an effect in this population. (5, 6)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Ipsen, France (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Age-related cognitive impairment**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Israel L, Dell Accio E, Martin G, Hugonot R (1987). *Ginkgo biloba* extract and memory training programs comparative assessment on elderly out-patients. *Psychologie Medicale* 19 (8): 1431-1439.

Trial design
Parallel. Four treatment arms: treatment with either ginkgo or placebo, and with or without memory training. Patients assigned to the memory training program met with a psychologist once a week for three months.

Study duration	3 months
Dose	2 ml twice daily (160 mg extract per day)

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	80
No. of subjects completed	75
Sex	Male and female
Age	56-83 years (mean: 68.4)

Inclusion criteria
Subjects over 55 years of age who complained about beginning disorders of their cognitive functions (score of 20 to 26 on the Folstein MMSE) and without a depressive syndrome (score <18 on the Yesavage Geriatric Depression Scale [GDS]).

Exclusion criteria
Patients with an acute or chronic associated disease of relative severity; manifest depressions in their case history; patients who were not able to discontinue for the duration of the study a treatment concerning vasoregulation or cerebral metabolism.

End points
Patients were assessed at baseline and after three months using three assessments: the psychologist conducted a series of memory tests; the physician rated the scale of mental dynamics and repercussions of the symptoms on the patient's daily life; and the patient rated himself or herself using the Geriatric Depression Scale, the scale of difficulties of daily living, and questions judging his or her satisfaction with the treatment.

Results
Ginkgo treatment significantly improved immediate memory ($p < 0.01$) and training sessions also improved this factor ($p < 0.01$), though the effects were not additive. Improvement was not seen in patients receiving placebo alone. General evocation memory was significantly improved by training sessions ($p < 0.01$) but not by ginkgo. Neither ginkgo nor training improved learning. Mental fluidity and control was improved in both ginkgo groups ($p < 0.005$), but not by memory training.

Side effects
One ginkgo patient complained of nausea and dyspepsia.

Authors' comments
Whenever possible, a therapeutic combination of ginkgo and memory training has to be recommended since its conjugate action allows patients to obtain a better adaptation to everyday life.

Reviewer's comments
Well-conducted trial in elderly mildly impaired volunteers showing benefits of ginkgo on memory and giving probable evidence that training plus ginkgo is the best overall combination for "immediate memory." The randomization process was not adequately described and the data summary was insufficient (does not permit an alternative analysis or replication). (Translation reviewed) (3, 5)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Ipsen, France (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Age-related cognitive impairment**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Taillandier J, Ammar A, Rabourdin JP, Ribeyre JP, Pichon J, Niddam S, Pierart H (1986). *Ginkgo biloba* extract in the treatment of cerebral disorders due to aging: A longitudinal multicenter double-blind placebo-controlled drug trial. *La Presse Medicale* 25 (31): 1576-1583.

Trial design
Parallel.

Study duration	1 year
Dose	2 (2 ml) doses daily (equivalent to 160 mg/day ginkgo extract)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	4 centers
No. of subjects enrolled	166
No. of subjects completed	122
Sex	Male and female
Age	60-97 years (mean: 82)

Inclusion criteria
Patients over 60 years of age with disorders related to cerebral aging (or signs of chronic cerebral insufficiency), Geriatric Clinical Evaluation Scale (GCES) total score between 21 and 113. Patients also had to be living in the retirement home for at least two months.

Exclusion criteria
Patients were excluded if they had any serious chronic disease or associated pathological disorders: psychosis (chronic delirium, mania, depression); severe neurosis (hysterical, obsessive); neoplasms regardless of the site; chronic alcoholism, etc.

End points
Effectiveness was judged according to the GCES. The examining physician also judged the general clinical state of the patient according to the following classifications: disease absent, mild, moderate, moderately severe, significant, or severe. Assessments were carried out at baseline and at 3, 6, 9, and 12 months.

Results
The ginkgo group showed a significant improvement in the GCES after three months. Improvement continued and after one year reached 17 percent. In comparison, improvement in the placebo group became significant only after one year, reaching 7 percent. The two groups were significantly different after three months ($p = 0.01$). Disease severity was significantly different after six months, when the percentage of patients whose condition was "mild" increased from 25 percent to 37 percent in the ginkgo group and decreased from 23 percent to 16 percent in the placebo group. The clinician judged that 58 percent of patients in the ginkgo group had improved compared to 43 percent of patients in the placebo group.

Side effects
Three patients (one in the ginkgo group) complained of digestive disorders and had to stop treatment.

Authors' comments
The use of the GCES permitted the conclusion at the end of this study that *Ginkgo biloba* extract is effective in disorders due to cerebral aging.

Reviewer's comments
Large and early study of ginkgo in "cerebral disorders due to aging" showing significant benefit in the GCES from three months on. The study was flawed, however, by the inadequate description of both the randomization and the statistical analysis. (Translation reviewed) (3, 5)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Ipsen, France (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Age-related memory impairment**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Allain H, Raoul P, Lieury A, LeCoz F, Gandon JM, d'Arbigny P (1993). Effect of two doses of *Ginkgo biloba* extract (EGb 761) on the dual-coding test in elderly subjects. *Clinical Therapeutics* 15 (3): 549-558.

Trial design
Crossover. Latin-square study design with three treatments, each separated by six-day intervals. The treatments were 320 mg extract, 600 mg extract, and placebo. Each was given one hour before psychometric testing.

Study duration	1 day
Dose	320 mg or 600 mg extract
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	18

No. of subjects completed	Not given
Sex	Male and female
Age	60-80 years (mean: 69.3)

Inclusion criteria
Elderly patients with slight age-related memory impairment, nondemented, reporting a cognitive impairment reflected objectively by a difference of more than one standard deviation in comparison with a group of young subjects on an inclusion memory test. Subjects were receiving no treatment for their cognitive impairment.

Exclusion criteria
None mentioned.

End points
Psychometric testing used a dual-coding technique which evaluates the memory coding of verbal material and images in relation to variable presentation times (1920, 960, 480, 240, and 120 ms). The presentation of each series was followed by an immediate recall test. The point at which the presentation time is too short to allow for verbal coding and storage was considered the breaking point.

Results
Overall analyses showed no significant differences between the three treatments on word recall, drawing recall, or the drawings versus words recalled ($p = 0.06$). In the groups treated with ginkgo extract compared to the placebo group, the breaking point was significantly shifted ($p < 0.05$) toward a shorter presentation time (480 ms for ginkgo versus 960 ms for placebo), and dual coding was observed at 960 ms (versus 1920 ms for placebo).

Side effects
No adverse effects were reported by any of the subjects.

Authors' comments
In comparison with placebo, 320 or 600 mg of ginkgo extract improved the performance on the dual-coding test one hour after administration in elderly subjects with slight memory impairment. The values obtained after treatment with ginkgo extract were closer to the values observed in young healthy subjects.

Reviewer's comments
Well-run acute-dose, three-way crossover study in elderly patients satisfying age-associated memory impairment criteria showing the benefit of ginkgo in a computerized test of information processing. This is an interesting study with novel technique, and good design plus analysis. (4, 6)

Clinical Study: EGb 761®

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Age-related memory impairment; Alzheimer's disease; vascular dementia**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference

van Dongen MCJM, van Rossum E, Kessels AGH, Sielhorst HJG, Knipschild PG (2000). The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: New results of a randomized clinical trial. *Journal of the American Geriatrics Society* 48 (10): 1183-1194.

Trial design

Parallel. Initially a three-arm study, becoming a five-arm study. After a three-week run-in period with placebo, subjects were randomized to receive one of three treatments: 160 mg/day ginkgo extract; 240 mg/day ginkgo extract; or placebo. After three months, the subjects taking ginkgo were randomized again to either continue taking ginkgo with the same dose or to take placebo for another three months. Those in the initial placebo group continued to take placebo throughout the study.

Study duration	6 months
Dose	2 tablets per day (either 160 or 240 mg per day)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	256
No. of subjects completed	196
Sex	Male and female
Age	Mean: 82.9 years

Inclusion criteria
Patients at least 50 years old with dementia, including those with Alzheimer's disease and vascular dementia, according to ICD-10 and DSM-III-R, and nondemented patients with age-associated memory impairment.

Exclusion criteria
Exclusion criteria included the following: severe depression; inadequate level of premorbid intelligence; insufficient compliance; a placebo response during three-week washout period; expectation of premature withdrawal; serious comorbidity (particularly pathological conditions considered as nontreatable underlying causes of dementia and cognitive disorders or sources of interference with the trial conduct: brain traumata, tumors, various neurological disorders, severe infectious diseases, or absorption disorders); or taking impermissible cointerventions (e.g., antiparkinson medication, antipsychotic drugs, neuroleptics, antidepressants, cholinergic therapy, or vasoactive drugs).

End points
Outcome measures were assessed at baseline and after 4, 8, 12, 18, and 24 weeks of treatment. The outcome measures included the Zahlennachsprechen Test G (ZN-G, digit span test to test short-term memory); the Wortliste (WL, tests verbal learning); the Zahlen-Verbindungs-Test G (ZVT-G, version of trail-making test that measures planning and organization and cognitive speed); the Sandoz Clinical Assessment-Geriatric Scale (SCAG, rating scale for geriatric symptoms); the Geriatric Depression Scale; self-perceived health status; self-perceived memory status; and the Nürnberger Alters Alltagsaktivitäten Skala (NAA; Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living). The ZVT-G, ZN-G, WL, and NAA are all components of the Nürnberger Alters Inventar (NAI; Nuremberg Gerontopsychological Inventory).

Results
Sixty-three demented and 151 nondemented patients were randomized into the study. The MMSE baseline scores of 80 percent of the population were between 12 and 24, signaling moderate impairment. In general, there was not a dramatic shift in the scores for most of the outcome measures during the treatment with either ginkgo (both doses) or placebo. Intention-to-treat analysis showed no effect on any outcome measure for those given ginkgo ($n = 79$) compared with placebo ($n = 44$) for the entire six-month period.

Side effects
The most common side effects were dizziness, nervousness, and headache. Incidence of side effects was similar in all groups.

Authors' comments
The authors conclude that the trial has failed to reproduce the beneficial effects of ginkgo in older patients with dementia and age-associated memory impairment demonstrated by many previous trials.

Reviewer's comments
This trial was conducted with great care and expertise. My only concern is that there were so many subgroups of patients that this added much variability to the analysis. Nevertheless, a clear negative finding. (5, 6)

Clinical Study: EGb 761®

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Alzheimer-type or multi-infarct dementia**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Kanowski S, Herrmann WM, Stephan K, Wierich W, Horr R (1997). Proof of efficacy of the *Ginkgo biloba* special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Phytomedicine* 4 (1): 3-13. (Also published in Kanowski S, Herrmann WM, Stephan K, Wierich W, Horr R [1996] *Pharmacopsychiatry* 29 [2]: 47-56.)

Trial design
Parallel. Single-blind placebo run-in period of four weeks.

Study duration	6 months
Dose	2 (120 mg) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	41 practices
No. of subjects enrolled	216
No. of subjects completed	156
Sex	Male and female
Age	55-82 years

Inclusion criteria
Outpatients, at least 55 years of age with presenile and senile primary degenerative dementia of the Alzheimer's type (DAT) and multi-infarct dementia (MID) according to DSM-III-R; between 6 and 18 points in the Syndrom-Kurztest; between 13 and 25 points in the MMSE (Mini-Mental State Examination); no pronounced cerebral atrophy; and in whom the necessity for full-time care can probably be avoided or postponed.

Exclusion criteria
Patients with disturbances of consciousness, suffering from other cerebral diseases, depression, psychosis, disorders due to cerebral ischemia of hemorrhage, epilepsy, and dementia of an origin other than those defined in the inclusion criteria; unstable metabolism due to severe cardiovascular insufficiency; noncompensated arrhythmia; severe chronic pulmonary diseases; hepatic and renal disorders; hyper- or dehydration; malign hypertension; gastrointestinal disorders leading to uncertain resorption of the investigational drug; diseases that prevented adequate test performance (e.g., noncompensated dysopia and defective hearing), lack of cooperation; the inability to comprehend the instructions; and intake of drugs which might have interfered with the assessment of efficacy (such as psychostimulants, nootropics, centrally acting vasoactive substances, psychotropic substances, and reserpine).

End points
Evaluations at baseline and after 12 and 24 weeks. Adverse events were additionally recorded after 6 and 18 weeks. Three primary parameters were measured: psychopathological assessment using the Clinical Global Impressions scale (CGI), syndrome-relevant cognitive performance according to the Syndrom-Kurztest (SKT), and behavior according to the Nurnberger Alters-Beobachtungsskala (NAB).

Results
The 156 patients who completed the study in accordance to protocol were evaluated according to the following response criteria: changes in the CGI to "much improved" or "very much improved"; a decrease in the SKT score by 4 points; and a decrease in NAB score of 2 points. The frequency of therapy responders in the two treatment groups differed significantly in favor of EGb 761, with $p < 0.005$ in Fisher's Exact Test. The intent-to-treat analysis of 205 patients led to similar efficacy results.

Side effects
A relationship between the study drug and adverse events was considered possible in only five patients. These were allergic skin reactions, gastrointestinal complaints, and headache.

Authors' comments
The results of this clinical study lead to the conclusion that the ginkgo biloba extract EGb 761 is of clinical efficacy in the treatment of outpatients with dementia of the Alzheimer's type and multi-infarct dementia.

Reviewer's comments
Probably the best study conducted on ginkgo and dementia. Clear benefits on SKT and CGI and excellent reporting. (5, 6)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Alzheimer-type or multi-infarct dementia**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF (1997). A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. *The Journal of the American Medical Association* 278 (16): 1327-1332. (This study was reanalyzed and published in Le Bars PL, Kieser M, Itil KZ [2000]. *Dementia and Geriatric Cognitive Disorders* 11 [4]: 230-237; and reanalyzed again in Le Bars PL, Velasco FM, Ferguson JM, Dessain EC, Kieser M, Hoerr R [2002] *Neuropsychobiology* 45 [1]: 19-26.)

Trial design
Parallel. Trial was preceded by a two-week, single-blind placebo run-in phase.

Study duration	1 year
Dose	3 (40 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No

Site description	6 centers
No. of subjects enrolled	327
No. of subjects completed	137
Sex	Male and female
Age	45-90 years (mean: 69)

Inclusion criteria
Forty-five years of age or older, diagnosis of uncomplicated dementia according to *Diagnostic and Statistical Manual of Mental Disorders* and *International Statistical Classification of Diseases* criteria, either Alzheimer-type or multi-infarct dementia, a Mini-Mental State Examination (MMSE) score of 9 to 26 (inclusive), and a Global Deterioration Scale score of 3 to 6 (inclusive).

Exclusion criteria
Significant medical conditions including cardiac disease, insulin-dependent diabetes, liver disease, chronic renal insufficiency, another psychiatric disorder as a primary diagnosis, and brain mass or intracranial hemorrhage determined by computed tomography (CT) or magnetic resonance imaging (MRI).

End points
Primary outcome measures were assessed at baseline and at 12, 26, and 52 weeks. They were cognitive impairment according to the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog); daily living and social behavior according to the Geriatric Evaluation by Relatives Rating Instrument (GERRI); and general psychopathology according to the Clinical Global Impression of Change (CGIC). Safety assessments were performed after 4, 12, 26, 39, and 52 weeks.

Results
After six months, the placebo group showed a worsening and the ginkgo group showed minimal improvement resulting in statistically significant differences in favor for ginkgo for the ADAS-cog (1.3 points, $p = 0.04$) and the GERRI (0.12 points, $p = 0.02$). In the one-year intent-to-treat analysis, the ginkgo group had an ADAS-cog score 1.4 points better than the placebo group ($p = 0.04$) and a GERRI score 0.14 points better than the placebo group ($p = 0.0004$). On the ADAS-cog, 27 percent of patients treated with ginkgo achieved at least a four-point improvement, compared with 14 percent taking placebo ($p = 0.005$); on the GERRI, 37 percent were considered improved with ginkgo, compared with 23 percent taking placebo ($p = 0.003$). No difference was seen in the CGIC. The results were reanalyzed following application of a stratification based on the severity of the cognitive impairment in a population of 263 intent-to-treat cases with Alzheimer's disease. In stratum 1, with 122 subjects with MMSE > 23, there was no significant change in ADAS-cog or GERRI for the placebo group. The EGb 761 group

showed significant improvement compared to baseline (ADAS-cog 1.7 points; GERRI 0.09 points). There was no significant difference between the two groups. In stratum 2, with 114 subjects with MMSE < 14, the placebo group deteriorated compared to baseline (ADAS-cog 4.1 points; GERRI 0.18 points). The EGb 761 group showed an insignificant impairment from baseline. However, there was a significant difference between the two treatment groups. A small group of 35 subjects with an MMSE < 15 showed significant decline in the placebo group and an insignificant decline in the EGb 761 group. The difference between the two groups was similar to that in stratum 2.

Side effects
No significant differences compared with placebo were observed in the number of patients reporting adverse events or in the incidence and severity of these events.

Authors' comments
EGb 761 was safe and appears capable of stabilizing and, in a substantial number of cases, improving the cognitive functioning of demented patients for six months to one year. Although modest, the changes induced by EGb were objectively measured by the ADAS-cog and were of sufficient magnitude to be recognized by caregivers in the GERRI. The six-month analysis, unlike the one-year analysis, was obtained with a high rate of patient participation (79 percent of intent-to-treat population). The retrospective stratification analysis showed that the relative changes from baseline depended heavily on the severity at baseline. Improvement was observed in the group of patients with very mild to moderate cognitive impairment, while in more severe dementia, the mean EGb 761 effect should be considered more in terms of stabilization or slowing down of worsening, as compared to the greater deterioration observed with placebo.

Reviewer's comments
This is the most famous ginkgo study. It is well conducted and written up and shows a benefit comparable to current pharmacological therapies of choice, e.g., Aricept. The third analysis of this study shows the ADAS-cog effect is best in the MMSE <24 group compared to the effect in the MMSE >23 group. This information is worthy of comment. (5, 6)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Alzheimer-type dementia**

Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Maurer K, Ihl R, Dierks T, Frolich L (1997). Clinical efficacy of *Ginkgo biloba* special extract EGb 761 in dementia of the Alzheimer type. *Journal of Psychiatry Research* 31 (6): 645-655.

Trial design
Parallel. Trial preceded by a seven-day run-in phase.

Study duration	3 months
Dose	6 (40 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	20
No. of subjects completed	18
Sex	Male and female
Age	51-75 years

Inclusion criteria
Age 50-80; Hachinski Ischemic Score less than or equal to 4; mild to moderate Alzheimer-type senile dementia (mean Brief Cognitive Rating Scale [BCRS] score 3 to 5); and normal CT finding or a diffuse, possibly asymmetric, atrophy.

Exclusion criteria
Advanced Alzheimer's dementia (inpatient care or constant nursing by another person for daily tasks); intellectual degeneration, states of confusion, or dementia syndromes of another origin, e.g., multi-infarct dementia (Hachinski Ischemic Score > 7); pseudodementia; nonorganic depressive illness or schizophrenic decompensation; aphasia or sensory, motor, and/or visual disturbances that could interfere with psychometric tests; severe organic diseases; neoplasia of any localization; epilepsy; cerebrovascular malformation; alcohol or drug abuse; vasoactive drugs, nootropics, and/or long-term treatment with other drugs proscribed during the study; and lack of patient cooperation already during the run-in phase.

End points
The primary outcome measure was the sum score in the Syndrom-Kurztest. Other psychometric tests, including the trailmaking test (Zahlen Verbindungs Test [ZVT]), Alzheimer's Disease Assessment Scale (ADAS), Clinical Global Impression, and EEG topography, were evaluated descriptively. Patients were assessed at baseline and after one, two, and three months.

Results
Although the EGb 761 group, with a mean sum score of 19.67 points in the SKT, had a poorer baseline level than the placebo group (18.11 points), it improved to 16.78 points with treatment, whereas the placebo group deteriorated to 18.89 points. The differences between the baseline and final values formed the basis for a statistical group comparison, which gave a result favorable to EGb 761, at a significance level of $p < 0.013$. In addition, certain favorable trends were found at the psychopathological (CGI) and dynamic functional (EEG findings) levels. Intergroup differences in the ADAS cognitive and noncognitive subscales did not reach statistical significance, probably because of the small sample size.

Side effects
None reported.

Authors' comments
The results of this trial can be interpreted as evidence of effectiveness of *Ginkgo biloba* special extract EGb 761 in mild to moderate dementia, and of local effects in the central nervous system.

Reviewer's comments
This trial had a small sample but was well conducted and reported with a clear benefit on a good cognitive end point, SKT, in patients with mild/moderate Alzheimer's disease. Some support in CGI and EEG as well. (5, 5)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Alzheimer-type dementia**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Hofferberth B (1994). The efficacy of EGb 761 in patients with senile dementia of the Alzheimer type, a double-blind, placebo-controlled study on different levels of investigation. *Human Psychopharmacology* 9: 215-222.

Trial design
Parallel.

Study duration	3 months
Dose	6 (40 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	42
No. of subjects completed	40
Sex	Male and female
Age	50-75 years

Inclusion criteria
Hospitalized patients with the clinical diagnosis of incipient senile dementia of the Alzheimer type, aged between 50 and 75 years, Blessed Dementia Scale: sum part A: 0-16, sum part B: 9.5 to 30.5; Hachinski Ischemic Score < 4; normal or diffuse and possible asymmetrically atrophic CT findings.

Exclusion criteria
Those with advanced Alzheimer's dementia; those suffering from intellectual deterioration of confusedness and/or dementia syndrome of other origin including multi-infarctional dementia, Pick's disease, alcoholic dementia, Parkinson's disease, Huntington's disease, lateral amyotrophic sclerosis, chronic subdural hematoma, brain tumors, and dementias based on infectious, toxic, or metabolic/endocrinological factors; those with pseudodementia; those subject to a severe depressive condition; pronounced sensory or motor disturbances; those suffering from severe organic conditions, neoplasias, epilepsy, cerebrovascular malformation, alcohol or drug abuse; patients who were pregnant or not willing to cooperate; or receiving therapy with vasoactive agents, nootropics, psychotonics, tranquilizers, and/or depressants.

End points
The Syndrom-Kurztest (SKT) was the target parameter. Secondary parameters included the saccade test, reaction performance, the Sandoz Clinical Assessment Geriatric Scale (SCAG), and electroencephalography (EEG). Subjects were evaluated at baseline and then at monthly intervals.

Results
Baseline mean values for the SKT were 17 for the treatment group and 15 in the placebo group. After three months, the SKT mean value dropped to 12 in the treatment group, whereas it increased to 17 in the placebo group. The difference between the groups was highly significant after one, two, and three months ($p = 0.00017$, $p = 0.00017$, and $p = 0.00043$, respectively). A superiority of the active substance was found in all five subscales of the SCAG. In addition, the efficacy of the preparation could be clarified in two further neurophysiological examinations (saccade test and EEG). The change in behavior of the patient documented by the subjective final assessment of the examining physician, which is also visible in various items and groups of factors of the SCAG, confirms the other positive results.

Side effects
No side effects recorded during trial.

Author's comments
The proof of efficacy of a preparation aimed at improving cerebral performance may be considered as established if, in each of the target variables, significant changes can be demonstrated by comparison with the control group in two out of three independent examination levels. In this clinical trial, EGb 761 meets this requirement.

Reviewer's comments
This small sample of dementia (Alzheimer's-type) patients responded very clearly to EGb 761 on SKT—a valid and important test of cognitive function, supported by rating scales and EEG. The study was flawed by the inappropriate randomization and the lack of description of withdrawals and dropouts. (2, 6)

Clinical Study: Rökan®

Extract name	EGb 761
Manufacturer	Intersan GmbH, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Cerebrovascular insufficiency**

Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Grassel E (1992). The effect of *Ginkgo biloba* extract on mental performance: Double-blind study conducted under computerized measurement conditions in patients with cerebral insufficiency. *Fortschritte der Medizin* 110 (5): 73-76.

Trial design
Parallel. Four-week washout period before the study.

Study duration	6 months
Dose	2 (80 mg extract) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	3 trial centers
No. of subjects enrolled	72
No. of subjects completed	53
Sex	Male and female
Age	Mean: 63.8 years

Inclusion criteria
Outpatients under 80 years of age with cerebral insufficiency diagnosed on the basis of case histories, with short-term memory capacity IQ lower than Mehrfachwahl Wortschatz Intelligence Test (MWT) IQ (multiple choice vocabulary intelligence test). Patients also had to be able to read text on a computer monitor and had to have an MWT IQ greater than 80.

Exclusion criteria
Patients with neurological diseases of a different origin, those with recent myocardial infarction or severe cardiac arrhythmias, severe hepatic insufficiency, severe renal insufficiency, or pregnancy.

End points
Psychometric performance tests, computerized recordings of short-term memory capacity and basic learning rate, were administered. Testing was done at baseline and at 6, 12, and 24 weeks.

Results
For the ginkgo group, there was a statistically significant improvement in short-term memory capacity after six weeks ($p < 0.005$) and of learning rate after 24 weeks ($p < 0.0001$), compared to baseline. The placebo group showed no significant change compared to baseline. Comparison between the groups showed a statistically significant difference in the short-term memory capacity and learning rate at the end of the 24-week treatment phase (both $p < 0.01$).

Side effects
Four patients in the ginkgo group reported the following adverse events: alopecia, bloating, nausea with gastric pain, or facial flush.

Author's comments
Treatment with *Ginkgo biloba* extract EGb 761 results in improvement of the basic mental performance (especially "capacity for conscious information processing").

Reviewer's comments
Good study showing significant improvement in memory and learning in elderly cerebral insufficiency patients using computerized tests. More information on the tasks would have been welcomed. The only flaw was that the raw data used to evaluate the actual "effect size" were not given. (Translation reviewed) (5, 6)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Cerebrovascular insufficiency**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Halama P, Bartsch G, Meng G (1988). Randomized, double-blind study on the efficacy of *Ginkgo biloba* extract. *Fortschritte der Medizin* 106 (19): 408-412.

Trial design
Parallel.

Study duration	3 months
Dose	3 (40 mg extract) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	1 neurology practice
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Male and female
Age	55-85 years

Inclusion criteria
Outpatients aged above 55 years and diagnosed with mild to medium cerebrovascular insufficiency (Hachinski score > 7, Crichton degree 1 to 3).

Exclusion criteria
Patients with the following diseases or symptoms were excluded: psychosis or neurosis; primary degenerative dementia; secondary insufficiency of cerebral performance (due to intoxication, metabolic disorder, alcoholism, etc.); epilepsy or other severe diseases (e.g., myocardial infarction in the past six months, severe renal insufficiency, severe, life-threatening arrhythmias, malignoma); as well as patients who were not sufficiently cooperative.

End points
The primary outcome measure was the Sandoz Clinical Assessment-Geriatric score evaluating cognitive disturbances, social behavior, lack of initiative, affective disturbances, and somatic disturbances. Additional tests included the Crichton Geriatric Behavioral Rating Scale (CRBRS), the background-interference method (Hintergrund-Interferenz-Verfahren [HIV]), the Syndrom-Kurztest (SKT), and craniocorpography (CCG). Dizziness, tinnitus, headache, and hearing deficit were investigated by questioning the patients. Assessment was completed at baseline and at weeks 4, 8, and 12.

Results
After 12 weeks, the ginkgo group values for total SCAG score dropped on average by 9 points, whereas they remained unchanged in the placebo group. The difference between the groups was highly significant (p = 0.00005). In addition, short-term memory and mental awareness improved, tinnitus improved compared to the placebo group (twelfth week: p = 0.035),

hearing deficits remained unchanged in both groups, headache improved compared to placebo, and dizziness significantly improved in the ginkgo group (twelfth week: $p < 0.001$).

Side effects
Mild to moderate headaches in one patient in the ginkgo group.

Authors' comments
On the basis of the results of the present study, *Ginkgo biloba* is very well suited for the treatment of disturbances of cerebral performance of vascular origin.

Reviewer's comments
Well-designed and well-conducted study with clear and marked improvements in SCAG, particularly items for cognitive and somatic disturbances, plus improvements to SKT for cognitive function plus reduction in dizziness. (Translation reviewed) (5, 6)

Clinical Study: Rökan®

Extract name	EGb 761
Manufacturer	Intersan GmbH, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Cerebrovascular insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Hofferberth B (1991). Simultaneous determination of electrophysiological, psychometric, and rheological parameters in patients with cerebro-organic psychosyndrome and increased vascular risk—A placebo-controlled double-blind study with *Ginkgo biloba* extract EGb 761. In *Mikrozirkulation in Gehirn und Sinnesorganen.* Eds. R Stodtmeister, LE Pillunat. Stuttgart: Ferdinand Enke Verlag, pp. 64-74.

Trial design
Parallel. Treatment preceded by a two-week placebo washout phase.

Study duration	3 months
Dose	3 (40 mg extract) tablets daily
Route of administration	Oral
Randomized	Yes

Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	24
No. of subjects completed	24
Sex	Male and female
Age	62-74 years

Inclusion criteria
Hospitalized patients with the diagnosis "cerebrovascular risk" on the basis of measurements of the venous microembolism index, the theta proportion in the quantified EEG, and clinical history.

Exclusion criteria
Unclear cardiovascular conditions, such as recent myocardial infarction; congestive heart failure; refractory hypertension; hypotension; uncontrollable diabetes; severe liver, kidney, or gastrointestinal disorders; progressive neurological diseases or brain tumors; and patients with stenoses in the carotid or the cerebral circulation or transient ischaemic attack (TIA).

End points
Patients were examined prior to the placebo phase, at baseline, and after 4 and 12 weeks of therapy. Patients were assessed according to quantified EEG, the saccade test, Vienna Determination Unit (VDU), and venous microembolism index (VMI) (a laboratory indicator of platelet aggregation).

Results
After four weeks of treatment, there was an improvement in the ginkgo group compared with the placebo for all measured parameters. The theta-wave component of the theta/alpha ratio fell significantly ($p < 0.01$, between group comparison). Latency time for saccadic eye movements fell at both four weeks ($p < 0.01$) and 12 weeks ($p < 0.001$). The number of correct answers in the VDU reaction test was increased (statistically significant after four weeks). The VMI decreased continuously in the ginkgo group, whereas in the placebo group there was no change ($p < 0.001$ at four weeks, between-group comparison).

Side effects
Two patients in the ginkgo group complained of stomachache.

Author's comments
The standardized *Ginkgo biloba* extract EGb 761 used in this study proved to be highly significantly more effective than placebo and thus fulfills the frequently stipulated criterion of a large difference in efficacy from the control.

Reviewer's comments
Another well-conducted study from this investigator showing marked and widespread improvements despite a small parallel group design. However, the randomization process and statistical methods were not adequately described. (Translation reviewed) (3, 5)

Clinical Study: Rökan®

Extract name	EGb 761
Manufacturer	Intersan GmbH, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Cerebrovascular insufficiency**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Hofferberth B (1989). Effect of *Ginkgo biloba* extract on neurophysiological and psychometric findings in patients with cerebro-organic syndrome. *Arzneimittel-Forschung/Drug Research* 39 (8): 918-922.

Trial design
Parallel. Treatment preceded by a two-week washout period.

Study duration	2 months
Dose	3 (40 mg extract) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	36
No. of subjects completed	36

Sex	Male and female
Age	53-69 years (mean: 63)

Inclusion criteria
Hospitalized patients with cerebrovascular syndrome, pathological results in two of the four tests (EEG, saccade test, Vienna Determination Test, or Trail Making Test).

Exclusion criteria
Patients were excluded if they were taking supplementary prohibited medication, such as vasoactive drugs, CNS stimulants, tranquilizers, antihistamines, calcium antagonists, thrombocyte aggregation inhibitors, and anticoagulants. Also excluded were patients with acute heart disease, uncontrolled hypertension, hypotension, unstable diabetes, severe liver and renal disease, and gastrointestinal disease.

End points
Objective assessment by quantified EEG and saccadic eye movements, and by two psychometric tests (Vienna Determination Unit Test; number connection test). Tests were conducted at baseline and after four and eight weeks, except EEG which was conducted at commencement and at the end of treatment.

Results
After both four weeks and eight weeks of therapy, there was a highly significant improvement in the saccadic test in comparison to the placebo group ($p < 0.0001$). Similar improvements were observed in the psychometric tests. The number of correct responses in the Vienna Determination Test increased very significantly at all speed levels in the ginkgo group after four weeks, by which time it had normalized. In the placebo group, no change was documented. Similarly, the time taken in the Trail Making Test decreased dramatically in the ginkgo group after four weeks, while in the placebo group there was only a slight tendency to shorter times. Quantitative EEG analysis before the study and after eight weeks showed a significant decrease in the theta component of patients in the ginkgo group only. After four weeks of therapy, the patients' subjective evaluation of their condition and the doctor's assessment were clearly positive in the active treatment group.

Side effects
Two reports of nausea and one of ankle edema in the ginkgo group.

Author's comments
The results show *Ginkgo biloba* extract to be a therapeutic option in mild and moderate cerebro-organic syndrome.

Reviewer's comments
Well-conducted trial, with modest sample (*n* = 36), showing large benefits on saccadic eye movements, theta-band reduction in EEG, and improved cognitive function on Vienna test plus Trails A. No placebo improvement was seen, although a similar trial (Bruchert, Heinrich, and Ruf-Kohler, 1991) showed ten seconds improvement in placebo in a similar population in a trail-making test. Neither the randomization nor the blinding were adequately described. (Translation reviewed) (1, 6)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Cerebrovascular insufficiency**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Arrigo A (1986). Treatment of chronic cerebrovascular insufficiency with *Ginkgo biloba* extract. *Therapiewoche* 36: 5208-5218.

Trial design
Crossover. Washout periods of 15 days before treatment and between 45-day treatment periods.

Study duration	45 days
Dose	3 doses of 20 drops (40 mg extract) daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	90
No. of subjects completed	80
Sex	Male and female
Age	36-88 years

Inclusion criteria
Patients with cerebral insufficiency of vascular origin (diffuse or localized tissue ischemia, localized stenoses) diagnosed predominantly on an arteriosclerotic basis. Symptoms included transient ischemic attacks, hemipareses, tinnitus, dizziness, headache, and anxiety.

Exclusion criteria
Patients with severe neurological deficits (e.g., agnosia, apraxia) and/or mental deficiency (e.g., atrophy); psychiatric pathology (e.g., hypochondriacal and depressive psychoses); chronic disease processes altering absorption, metabolism, and catabolism of drugs (e.g., gastric resection, hepatic and renal disease, severe insulin-dependent diabetes); and pathological processes that are possibly terminal (e.g., recent myocardial infarction, severe cardiac arrhythmia).

End points
Patients completed a questionnaire regarding their symptoms (e.g., asthenia, insomnia, headache, dizziness, tinnitus, vision, and stress) at baseline and every 15 days thereafter until the end of treatment. The Wechsler Adult Intelligence Scale (WAIS), which monitors general knowledge, vocabulary, language comprehension, social relationships, ability to concentrate, memory, and learning ability, was conducted before treatment and at the end of treatment periods. Other tests administered were Complex Figures According to Rey; Retentive Capacity (Memory Table); Word Recognition; and the Questionnaire for Determining State of Anxiety and Habitually Anxious Behavior (STAI).

Results
Marked improvement in the patients' self-assessment of symptoms was seen for most symptoms by day 30, and for asthenia after 45 days of treatment with ginkgo. According to the objective psychological tests, ginkgo extract improves memory, logical thinking, and vigilance. The WAIS data show that ginkgo acts upon the progressive diminution of intellectual and cognitive facilities. Concentration, retentive capacity, and ability to make logical associations were significantly improved. In the Word Recognition test, the group treated with ginkgo in each phase of the trial showed significantly greater improvement over the group treated with placebo ($p < 0.0001$). Ginkgo had a significant effect on performance compared to placebo in the Memory test ($p < 0.0001$). Treatment with ginkgo also decreased the state of anxiety ($p < 0.0001$) and anxious behavior ($p < 0.01$).

Side effects
None mentioned in paper.

Author's comments
The subjectively experienced improvement in the target symptoms of chronic

cerebrovascular insufficiency (CCVI) was clearly evident after patients had been treated with *Ginkgo biloba* extract for about two weeks. According to objective psychological tests, *Ginkgo biloba* also brings about an appreciable improvement in memory, logical thinking, and vigilance.

Reviewer's comments
Well-conducted crossover study in CCVI patients. Improvement was seen in symptoms including tinnitus, anxiety, attention, higher functions, and memory. The study was not randomized, and the blinding was not adequately described. (Translation reviewed) (1, 6)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Cerebrovascular insufficiency and depressive symptoms**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Halama P (1990). Treatment with *Ginkgo biloba* in patients with cerebrovascular insufficiency and refractory depressive symptoms: Results of a placebo-controlled, randomized double-blind pilot study. *Therapiewoche* 40 (51/52): 3760-3765.

Trial design
Parallel. Patients continued their existing antidepressant medication.

Study duration	2 months
Dose	3 (80 mg extract) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described

No. of subjects enrolled	20
No. of subjects completed	20
Sex	Male and female
Age	55-85 years

Inclusion criteria
Diagnosis of depression in mild to moderate cerebro-organic disturbances, with at least three months' unsuccessful treatment with antidepressants.

Exclusion criteria
Alcoholism or other addictions; concomitant treatment not dose-stable; concomitant diseases which must be expected to get worse during the period of the study; and pregnancy.

End points
Treatment was monitored using the Zung Self-Rating Depression Scale (SRDS), late auditory-evoked potentials (LAEP), and several psychometric tests, including short screening test for cerebral insufficiency (CI test); self-assessment method for the objective measurement of mild cerebral insufficiency (CI scale); the short test of general intelligence (Kurztest für Allgemeine Intelligenz [KAI]); subjective assessment of depression; and subjective assessment of the ability to concentrate. Patients were assessed at baseline and at four and eight weeks.

Results
The Zung SRDS index decreased by 5.3 points in the active medication group in the eight-week period, whereas there was an increase of 5.2 points in the placebo group. Mean latency time of P300 in the active group was reduced significantly in the eight-week period ($p = 0.048$) and increased in the placebo group. Psychometric findings showed clear differences in favor of the ginkgo group. Severity of depression improved in three patients in the ginkgo group, remained unchanged in four, and got worse in three patients. In the placebo group, no patients improved their depression, five remained the same, and five got worse. The ability to concentrate, assessed subjectively, also improved after eight weeks of treatment with ginkgo.

Side effects
No adverse drug effects occurred during treatment.

Author's comments
Because of the small number of cases and the differing baseline situations of the groups, this must be regarded as a pilot study and used as a basis for investigations in a larger group of patients.

Reviewer's comments
In this small study in depressed cerebrovascular insufficiency patients,

there are patterns of improvement in latency of evoked potential reaction times and symptoms of depression. Neither the randomization nor the blinding processes were adequately described. (Translation reviewed) (1, 5)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Peripheral vascular disease**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Blume J, Kieser M, Holscher U (1996). Placebo-controlled double-blind study on the efficacy of *Ginkgo biloba* special extract EGb 761 in the maximum-level trained patients with intermittent claudication. *Zeitschrift fur Gefasskrankheiten/Journal for Vascular Diseases* 25 (3): 265-274.

Trial design
Parallel. Pretrial two-week run-in phase with placebo.

Study duration	6 months
Dose	1(40 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	60
No. of subjects completed	54
Sex	Male and female
Age	47-82 years

Inclusion criteria
Patients with peripheral arterial occlusive disease of the lower extremities, Fontaine stage IIb, intermittent claudication for over six months, no improve-

ment in walking performance in spite of consistent walking three to four times per week. Pain-free walking distance had to be below 150 meters and within 30 percent of initial value at the end of the placebo run-in phase.

Exclusion criteria
Patients less than 18 years of age; cardiac infarction during the preceding six months; New York Heart Association stage III or IV cardiac insufficiency; severe circulatory hypertension; severe renal insufficiency; severe functional hepatic disorders; respiratory insufficiency as a limiting factor of the walking distance; restricted walking due to an orthopedic disorder; venous insufficiency from stage II (Basel classification); badly manageable diabetes mellitus; malabsorption; anemia; hematocrit above 48 percent; fibrinogen over 500 mg/dl; regular intake of platelet aggregation inhibitors, anti-inflammatory agents, or analgesics; pregnancy; or expected insufficient compliance.

End points
The main outcome measure was the difference in walking distance from the start of therapy and after 8, 16, and 24 weeks. Secondary parameters were the corresponding differences for the maximum walking distance, the relative increase in pain-free walking distance, the Doppler index, and the subjective evaluation of the patients.

Results
At the start of the therapy, the treatment group had a pain-free walking distance of 96 m and a maximum walking distance of 126 m. In the ginkgo group, there was a continuous improvement in pain-free walking distance compared to placebo at 8, 16, and 24 weeks ($p < 0.0001$, $p < 0.0003$, $p < 0.0001$, respectively). There was a 20 percent clinically relevant difference between the two groups. Maximum total walking distance values also increased significantly in the treatment group at 8, 16, and 24 weeks (22 m, 32 m, 50.5 m, respectively) compared to the placebo group (0 m, 7.5 m, 15.5 m, respectively) ($p < 0.005$ for between group comparison). The Doppler index remained unchanged in both groups. The results of the subjective assessment survey indicated that the treatment group felt that they had improved significantly, while the placebo group did not.

Side effects
Two ginkgo patients had gastric pains and nausea which disappeared spontaneously during continued administration of the extract.

Authors' comments
The present study confirmed the clinical efficacy of *Ginkgo biloba* special extract EGb 761 previously documented in other clinical trials involving patients with intermittent claudication and also demonstrated the additive use-

fulness of such a therapy in patients who had already reached their maximum physical capacity through previous exercise.

Reviewer's comments
This is an excellent study with clear, unequivocal results. (Translation reviewed) (5, 6)

Clinical Study: Rökan®

Extract name	EGb 761
Manufacturer	Intersan GmbH, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Peripheral vascular disease**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Bauer U (1984). 6-month double-blind randomized clinical trial of *Ginkgo biloba* extract versus placebo in two parallel groups in patients suffering from peripheral arterial insufficiency. *Arzneimittel-Forschung/Drug Research* 34 (6): 716-720.

Trial design
Parallel. Pretrial washout period of six weeks with placebo.

Study duration	6 months
Dose	1 (40 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	80
No. of subjects completed	79
Sex	Male and female
Age	Mean: 60.9 years

Inclusion criteria
Outpatients suffering from obliterative arterial disease of the lower limbs, Fontaine's stage IIb, with accompanying stenosis of the superficial femoral artery, with or without stenosis of other arteries, predominantly on one side, and lasting for more than a year; pain-free walking distance below 150 meters and within 30 percent of initial value at the end of the placebo run-in phase.

Exclusion criteria
Uncooperative patients; patients taking disallowed medication; other stages of Fontaine's classification; concomitant diseases such as pathology of the veins, anemia, noncompensated cardiac insufficiency, recent myocardial infarction, uncontrolled hypertension, other causes of walking impairment, poorly controlled diabetes, significant kidney or hepatic insufficiency, and treatment with anticoagulant drugs during the past six months.

End points
Examinations were performed at the beginning of the washout phase, before treatment, and after 6, 12, and 24 weeks. Efficacy was evaluated according to the following parameters: subjective assessment of pain using a visual analog scale; assessment of walking distance before onset of pain and total walking distance; Doppler pulse volume recording and ankle pressure measurements; trophicity; venous occlusion plethysmography values at rest and after application of a cuff for three minutes; blood pressure; and heart rate.

Results
After 24 weeks, decreases in subjective estimates of pain were almost four times as great for the ginkgo group compared to placebo ($p < 0.001$). There was a statistically significant improvement in the distance the ginkgo group was able to walk without pain ($p < 0.05$) as well as for total distance the patients were able to walk ($p < 0.001$) compared with placebo. Blood flow in the affected side increased significantly in the ginkgo group ($p < 0.01$) and only slightly in the placebo group. Doppler measurements showed no change in the ratio of ankle to arm pressure in either group.

Side effects
Nausea and blood in urine occurred in one patient in the ginkgo group who also had bladder cancer.

Author's comments
This trial demonstrates the beneficial effect of ginkgo extract on walking tolerance, together with an improvement of the limb perfusion. At the end of this six-month trial, this improvement is not only statistically significant, but also clinically relevant.

Reviewer's comments
This is an excellent early study showing ginkgo improving walking distance in this condition. However, the randomization process was not adequately described. (3, 6)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Ipsen, France (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Peripheral vascular disease**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Thomson GJL, Vohra RK, Carr MH, Walker MG (1990). A clinical trial of *Ginkgo biloba* extract in patients with intermittent claudication. *International Angiology* 9 (2): 75-78.

Trial design
Parallel. Pretrial washout period of six weeks with placebo.

Study duration	6 months
Dose	3 tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	49
No. of subjects completed	37
Sex	Not given
Age	Not given

Inclusion criteria
Patients with Fontaine stage II peripheral vascular disease affecting the iliac or femoral arteries and involving predominantly one leg.

Exclusion criteria
Claudication distance of greater than 300 meters, alternating side of pain, poorly controlled diabetes, and significant concomitant illness. Improvement by 30 percent or more during pretrial washout. Smoking more than five cigarettes per day.

End points
Doppler pressures at the ankles were measured at the beginning of the washout phase, before treatment, and at weeks 6, 12, and 25. Ankle/brachial (A/B) pressure ratio, walking distance to claudication, changes in pressures in response to exercise, and recovery time were measured using a treadmill. Patients assessed pain using a 10 cm analog scale.

Results
Pain scores were significantly improved after 24 weeks in patients receiving ginkgo ($p < 0.05$), but not in those receiving placebo. Claudication distance (distance before onset of painful walking) increased for both groups but was significant only for the ginkgo group. Comparison of the actual distance walked at 24 weeks showed no significant difference between the two groups. There was no difference in A/B ratio, resting ankle pressure, ankle pressure immediately after exercise, or recovery times.

Side effects
No major side effects in either group.

Authors' comments
Ginkgo biloba extract is a safe and effective method of improving walking distance and reducing pain severity in patients with intermittent claudication, although Doppler studies have failed to suggest any gross improvement in the perfusion of the ischemic leg. A six-month course of EGb 761 results in symptomatic improvement in Fontaine stage II peripheral vascular disease.

Reviewer's comments
This is a positive trial with clear findings, but neither the randomization nor the blinding were adequately described. (1, 6)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Peripheral vascular disease**

Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Peters H, Kieser M, Holscher U (1998). Demonstration of the efficacy of *Ginkgo biloba* special extract EGb 761 on the intermittent claudication: A placebo-controlled, double-blind multicenter trial. *Zeitschrift fur Gefasskrankheiten/Journal for Vascular Diseases* 27 (2): 106-110.

Trial design
Parallel. Pretrial washout period of two weeks with placebo.

Study duration	6 months
Dose	1(40 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	111
No. of subjects completed	109
Sex	Male and female
Age	60-67 years (mean: 63)

Inclusion criteria
Patients with peripheral arterial occlusive disease of the lower extremities, Fontaine stage IIb, intermittent claudication for over six months, no improvement in walking performance in spite of consistent walking three to four times per week. Pain-free walking distance had to be below 150 meters and within 30 percent of initial value at the end of the placebo run-in phase.

Exclusion criteria
Patients with neuropathies; Raynaud's disease; severe restrictions in cardiac, liver, and kidney functions; restrictions in walking ability due to respiratory insufficiency or orthopedic condition; poorly managed diabetes mellitus; pathologically changed hemorheology; and regular intake of platelet aggregation inhibitors, anti-inflammatory agents, or analgesics.

End points
Main outcome was the difference in pain-free walking distance between the

start of therapy and after 8, 16, and 24 weeks. The absolute walking distance was determined and the subjective assessment of the patients was documented using a visual analog scale. Doppler pressure measurements were performed bilaterally over the posterior tibial arteries and the brachial arteries prior to inclusion, at baseline, and at 24 weeks.

Results
Pain-free walking increased continuously with treatment from 108 to 153 m after 24 weeks. Pain-free walking distance in the EGb 761 group was significantly greater than placebo at 8, 16, and 24 weeks ($p = 0.014$, $p = 0.006$, and $p = 0.012$, respectively). Total walking distance also improved under therapy with ginkgo extract compared to placebo ($p = 0.021$ after 16 weeks, and $p = 0.030$ after 24 weeks). Subjective assessment of therapy by patients showed an improvement in both groups. The Doppler quotients remained the same in both groups.

Side effects
No adverse reactions were recorded for EGb 761.

Authors' comments
This study confirms the clinical efficacy of EGb 761 in patients with peripheral arterial occlusive disease Fontaine stage IIb, with very good tolerance.

Reviewer's comments
This is a sound replication of previous trial from this group (Blume, Kieser, and Holscher, 1996). The placebo effect was larger in this study, but it did not affect the positive outcome. However, neither the randomization nor the blinding were adequately described. (1, 6)

Clinical Study: Rökan®

Extract name	EGb761
Manufacturer	Intersan GmbH, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Peripheral vascular disease**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Schweizer J, Hautmann C (1999). Comparison of two dosages of *Ginkgo biloba* extract Egb 761 in patients with peripheral arterial occlusive disease

Fontaine's stage IIb. *Arzneimittel-Forschung/Drug Research* 49 (11): 900-904.

Trial design
Parallel. Dose comparison with pretrial washout period of two to four weeks.

Study duration	6 months
Dose	120 mg or 240 mg daily (both in split doses)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	77
No. of subjects completed	74
Sex	Male and female
Age	55-71 years

Inclusion criteria
Patients with peripheral arterial occlusive disease (pAOD) Fontaine's stage IIb with occlusion of the superficial femoral artery on one leg and without occlusion of the deep femoral artery, for which there were no other therapeutic options. The pain-free walking distance, evaluated on a treadmill, had to be <200 meters and the maximum walking distance between 100 and 300 meters. The difference between the walking distances at the end of the wash-out period and at week 0 (start of treatment) had to be <25 percent. Pain associated with pAOD had to be unilateral, had to occur regularly, and the patients had to be able to describe pain precisely.

Exclusion criteria
Patients with severe kidney of hepatic insufficiency (creatinine > 140 µmol/l; serum glutamic pyruvic transaminase [SGPT] > 40U/l), gastrointestinal disturbances, malabsorption, diabetes, noncompensated cardiac insufficiency, myocardial infarction within the preceding six months, poorly controlled hypertension, hypertension below 100 mmHg systolic blood pressure, or other causes of walking impairment. Patients with coronary heart disease could be included if the disease was not a limiting factor for the walking distance.

End points
Patients were assessed at inclusion, at the beginning of treatment, and at week 6, 12, 18, and 24 for pain-free walking distances and the maximum walking distance on a treadmill. Bilateral Doppler pressure measurements were carried out above the posterior artery, the dorsal foot artery, and the brachial artery, and comparisons were made with the arm. Pain was rated subjectively by the patients.

Results
The pain-free walking distance improved in both groups. There was a mean increase of 61 meters in the group of patients who received 120 mg *Ginkgo biloba* extract daily and a statistically significant higher ($p = 0.0253$) mean increase of 107 meters in the group of patients who were treated with the higher dose of 240 mg. The maximum walking distance also increased in both groups, with the higher dose significantly superior at weeks 8 and 24 (both $p = 0.01$). There were no significant differences in Doppler pressure measurements between the two groups.

Side effects
One patient developed a rash and the association to the drug was rated as possible by an investigator.

Authors' comments
The clear-cut positive and statistically significant effects of the daily administration of 240 mg *Ginkgo biloba* extract compared 120 mg on the pain-free walking distance and the maximum walking distance in patients with pAOD demonstrated the substantial therapeutic benefit of the higher dose.

Reviewer's comments
This is another positive trial complementing previous trials. However, neither the randomization nor the blinding were adequately described. (1, 6)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Tinnitus** (ringing in the ears)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Morgenstern C (1997). *Ginkgo biloba* extract EGb 761 in the treatment of tinnitus aurium. *Fortschritte der Medizin* 115: 7-11.

Trial design
Parallel. Two-week pretrial run-in phase with placebo.

Study duration	3 months
Dose	3 × 1 tablet (each tablet contains 40 mg extract) daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	99
No. of subjects completed	78
Sex	Male and female
Age	Mean: 45.5 years

Inclusion criteria
Patients with normal hearing capacity, at least three adjacent frequencies in the audiogram, experiencing a tonally defined and maskable tinnitus for at least two months previously, able to reliably reproduce and describe noises in the ears, and over 18 years of age.

Exclusion criteria
Patients hearing objectively audible noises; diseases of the middle ear; nonreleasable stapedial reflex; reproducibility of otoacoustic emissions <85 percent at the initial medical examination; absolute latency period <0.5 ms in waves I through V in recordings of brainstem potential; severe organic diseases; alcohol or drug abuse; and pregnancy. Patients whose tinnitus decreased between the time of the first examination and the start of therapy two weeks later were excluded from the trial.

End points
Target parameter was a change in tinnitus sound volume in the more severely affected ear at the start of the study. As secondary parameters, the reproducibility of the click-evoked otoacoustic emissions as well as their response, the intensity of tinnitus, loss in hearing, and the subjective impression of the patient in the context of improvement or aggravation were recorded. Measurements were taken before the pretrial phase, at the beginning of treatment, and on weeks 4, 8, and 12.

Results
From the eighth week of treatment on, a clear drop in sound volume was recorded in the ginkgo group which was statistically significant after ten weeks ($p = 0.015$). The values in the placebo group did not change significantly. Recording of the otoacoustic emissions showed no changes in either group. In both groups, patients were of the opinion that their tinnitus had improved. No changes were found in either group in the measurement of hearing loss.

Side effects
No adverse drug reactions were reported by patients in either group.

Author's comments
For the long-term therapy to be expected in the case of tinnitus, the *Ginkgo biloba* extract EGb 761 is a suitable substance due to a positive influence on tinnitus sound volume and also due to its high tolerance level.

Reviewer's comments
This is a model study in conduct and reporting with clear and important clinical benefit in this unpleasant condition. (5, 6)

Clinical Study: EGb 761®

Extract name	EGb 761
Manufacturer	Intersan GmbH, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Sudden hearing loss**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Burschka MA, Hassan HAH, Reineke T, van Bebber L, Caird DM, Mösges R (2001). Effect of treatment with *Ginkgo biloba* extract EGb 761 (oral) on unilateral idiopathic sudden hearing loss in a prospective randomized double-blind study of 106 outpatients. *European Archives of Oto-Rhino-Laryngology* 258 (5): 213-219.

Trial design
Parallel. Dose comparison. Patients were given either 12 mg EGb 761 (L) or 120 mg EGb 761 (H) twice daily (24 or 240 mg daily).

Study duration	2 months
Dose	2 (12 or 120 mg) tablets daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	106
No. of subjects completed	78
Sex	Male and female
Age	Mean: 44 years

Inclusion criteria
Patients with acute unilateral idopathic sudden sensorineural hearing loss (ISSHL) of at least 15 dB at one frequency (250, 500, 1000, 2000, or 3000 Hz). The hearing loss had to have happened within ten days of the initial hospital visit.

Exclusion criteria
Patients were excluded if in the affected ear they experienced conductive deafness; signs of inflammation; injury; suspected retrocochlear dysacousis, Ménière's disease; hearing loss greater than 75 dB. Patients with the following conditions were also excluded: severe hepatic or renal insufficiency or cardiovascular diseases; severe gastrointestinal disturbances or malabsorption syndrome; noncontrollable diabetes; breast-feeding women; women of childbearing age taking no contraception; suspected alcoholics; or patients taking disallowed concomitant medication (diuretics, aminoglycoside antibiotics, vasoactive medication, tranquilizers, CNS-stimulating drugs, antihistamines, calcium antagonists, nitrates, beta-blockers, anticoagulants, and platelet aggregation inhibitors).

End points
Patients were examined by their ear-nose-throat (ENT) specialist and given routine blood tests at baseline and on days 3, 4, 14, 28, 42, and 56. The main end point was the recovery (in dB) of the auditory threshold, averaged over the individual affected frequencies, from the baseline measurement to the final measurement at the end of treatment.

Results
A large majority of patients in both treatment groups recovered fully by the end of the trial. Overall there were no statistically or medically significant differences between the two groups. After reanalyzing the data, 13 subjects

were found to be in violation of the inclusion criteria. With these 13 subjects excluded from the analysis, risk of failing to improve measurably was lower in the high-dose group, and patients in that group had a greater chance of becoming "healed." This advantage surfaced after one week of treatment, and the high-dose group showed faster recovery in the low-tone area. This high-dose advantage in recovery occurred almost exclusively in those patients without tinnitus.

Side effects
Nine adverse effects occurred in eight patients: nausea and gastrointestinal discomfort (H: 2, L: 1), headache (H: 1), tinnitus (L: 2), and two patients in the L group reported severe effects (myocardial inflammation and severe vertigo, neither associated with the treatment).

Authors' comments
EGb 761 (oral) appears to speed up and improve the recovery of those patients with uncomplicated ISSHL who have a good chance of recovering completely. The results of this study are exploratory rather than conclusive, however, largely because the recovery rate under the low-dosage treatment had been underestimated in planning the study.

Reviewer's comments
The results need to be verified with a placebo-controlled trial. (5, 6)

Clinical Study: Tebonin® forte

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Protection against hypoxia**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Schaffler K, Reeh PW (1985). Double-blind study on the protective effect against hypoxia of a standardized *Ginkgo-biloba* preparation following repeated administration to normal subjects. *Arzneimittel-Forschung/Drug Research* 35 (2): 1283-1286.

Trial design
Crossover. Two 14-day study phases were separated by a one-week washout period.

Study duration	2 weeks
Dose	2 ml extract twice daily (equivalent to 40 drops twice daily, or 160 mg extract daily)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	8
No. of subjects completed	8
Sex	Male
Age	Mean: 27.3 years

Inclusion criteria
Healthy young male subjects.

Exclusion criteria
None mentioned.

End points
After 14 days of administration, subjects' performance in terms of oculomotor (and complex choice reactions were evaluated with the aid of a computer-assisted oculodynamic test during three exposures to hypoxia (10.5 percent oxygen, balanced nitrogen). Concomitantly, simple cardiorespiratory parameters were recorded.

Results
The main oculomotor parameters showed an insignificant trend toward improved performance after administration of ginkgo compared to placebo. After repeated exposure to hypoxia (in the third session), the ocular adaptation time was shortened following administration of the drug ($p < 0.01$). The number of correct answers on the operational tests tended to be increased with medication, and the complex choice reaction time was slightly reduced. However, upon repeated exposure to hypoxia (second and third tests), the choice reaction time was significantly ($p < 0.05$ and $p < 0.01$, respectively) shorter with the ginkgo than with placebo.

Side effects
None mentioned in paper.

Authors' comments
The overall conclusion to be drawn is that ginkgo enhances the resistance of healthy subjects to certain consequences of repeated respiratory hypoxia. These findings are interpreted as indicative of a protective action against hypoxia relevant to the treatment of cerebrovascular insufficiency.

Reviewer's comments
This is an interesting study showing the ability of ginkgo to protect against hypoxia-induced slowing of choice reaction time and saccadic eye movements. However, the randomization and blinding were not adequately described, and the data were not described sufficiently to allow for alternative analyses or replication. (1, 5)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Ipsen, France (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Antioxidant effects; postoperative oxidative stress**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Pietri S, Seguin J, d'Argigny P, Drieu K, Culcasi M (1997). *Ginkgo biloba* extract (EGb 761) pretreatment limits free radical-induced oxidative stress in-patients undergoing coronary bypass surgery. *Cardiovascular Drugs and Therapy* 11 (2): 121-131.

Trial design
Parallel. Patients were treated for five days preceding aortic valve replacement surgery.

Study duration	5 days
Dose	160 mg twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes

Drug comparison	No
Site description	Single center
No. of subjects enrolled	20
No. of subjects completed	15
Sex	Male and female
Age	43-79 years (mean: 63)

Inclusion criteria
Patients undergoing aortic value replacement in nonurgent open-heart surgery.

Exclusion criteria
Patients could have no recent (<one month) myocardial infarction, no severe cardiac or renal failure, no severe hypertension, and no anti-ischemic, anti-inflammatory, vasoactive, or antioxidant medications for at least five days before surgery.

End points
Plasma samples were obtained from the peripheral circulation and the coronary sinus at crucial stages of the operation: before incision, during ischemia, and within the first 30 minutes after unclamping.

Results
Upon aortic unclamping, EGb 761 inhibited the transcardiac release of thiobarbituric acid reactive species ($p < 0.05$) and attenuated the early (five to ten minute) decrease in dimethylsulfoxide/ascorbyl free radical levels ($p < 0.05$). EGb 761 also significantly reduced the more delayed leakage of myoglobin ($p = 0.007$) and had an almost significant effect on ventricular myosin leakage ($p = 0.053$, six days postoperatively). The clinical outcome of recovery of treated patients was improved, but not significantly, compared with untreated patients.

Side effects
None mentioned by authors.

Authors' comments
The results demonstrate the usefulness of adjuvant Egb 761 therapy in limiting oxidative stress in cardiovascular surgery.

Reviewer's comments
This is an important, well-conducted study showing the utility of ginkgo in coronary artery bypass-elective patients. Ginkgo significantly limited oxidative stress and improved recovery of patients, though the sample size was too small for this to reach significance. Also, the randomization and blinding were not described adequately. (1, 5)

Clinical Study: Ginkgold®

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Electrophysiological effects** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Itil T, Martorano D (1995). Natural substances in psychiatry (*Ginkgo biloba* in dementia). *Psychopharmacology Bulletin* 31 (1): 147-158.

Trial design
Crossover.

Study duration	3 hours
Dose	40 mg, 120 mg, or 240 mg extract
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Ginkgo Power™, Super Ginkgo™
Site description	Single center
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male
Age	18-65 years (mean: 32.2)

Inclusion criteria
Healthy.

Exclusion criteria
None mentioned.

End points
Computer electroencephalographic (CEEG: Pharmaco-EEG/dynamic brain

mapping) data were collected before, as well as one and three hours after, administration of ginkgo.

Results
After one hour, a statistical difference in CEEG effects occurred in the Ginkgold groups versus the Ginkgo Power group. Ginkgold increased alpha activity in all brain areas. Super Ginkgo had only a mild increase in alpha activity at one hour but showed greater activity than Ginkgold at three hours. Ginkgo Power showed a minimal increase in alpha activity limited to the anterior brain region.

Side effects
No major side effects.

Authors' comments
Data suggest that the only ginkgo extract which has potent alpha-enhancing effects and could be classified as a cognitive activator was Ginkgold (EGb 761). The central nervous system (CNS) effects of Ginkgold were similar to other psychoactive compounds classified as cognitive activators. In further CEEG studies, the CNS effects of three doses of Ginkgold could be differentiated from placebo, and the effects of the higher doses (120 and 240 mg) could be discriminated from the lowest dose (40 mg).

Reviewer's comments
This is a well-conducted pilot study suggesting differing EEG effects of three gingko preparations, with EGb 761 appearing best. The description of the methodology was sparse, and the blinding process was not described at all. The study was not randomized. (1, 6)

Clinical Study: Tanakan®

Extract name	EGb 761
Manufacturer	Ipsen, France (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Electrophysiological effects** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Luthringer R, d'Arbigny P, Macher JP (1995). *Ginkgo biloba* extract (EGb 761), EEG and event-related potentials mapping profile. In *Advances in*

Ginkgo biloba *Extract Research,* Volume 4: *Effects of* Ginkgo biloba *Extract (EGb 761) on Aging and Age-Related Disorders.* Eds. Y Christen, Y Courtois, M-T Droy-Lefaix. Paris: Elsevier, pp. 107-118.

Trial design
Two-part study. Part I compared the effects of single doses of 80 and 160 mg of ginkgo extract versus placebo in a double-blinded design. Part II investigated the effects of five days of treatment with 160 mg extract per day in a single-blinded design. A one-day washout period separated the treatment days in part 1 and preceded treatment in part 2.

Study duration	2 × 1-day treatments (part I), and 1 × 5-day period (part II)
Dose	Part I: 80 mg and 160 mg ginkgo extract; Part II: 160 mg ginkgo extract daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double/single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	15
No. of subjects completed	15
Sex	Not given
Age	Mean: 30 years

Inclusion criteria
Healthy young volunteers were included in this trial.

Exclusion criteria
Psychotropic drug intake was not allowed for two weeks prior to the study. Subjects were not allowed to smoke or to drink coffee, tea, or alcohol in the hours preceding the measurements.

End points
Electroencephalography (EEG) and event-related potentials (ERP) mapping data were collected prior to drug administration and 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours after drug administration. Auditory P300 was recorded, as was contingent negative variation (CNV).

Results
After single doses of either 80 or 160 mg ginkgo extract, the alpha-1 band was significantly increased compared to placebo in terms of both absolute and relative power. For the alpha-2 band the increase was significant at the beginning and end of the recordings. After five days of treatment with ginkgo extract, the alpha increase was still present. A marked beta increase also occurred. Theta values were decreased significantly at 1.5 and 2 hours. ERP were only slightly modified in amplitude. However, there was a significant decrease in P300 latency after both single-dose and five-day administration ($p < 0.05$).

Side effects
None mentioned in the paper.

Authors' comments
These EEG data confirm that EGb 761 extract has a nootropic profile with obvious improvements of the vigilance level, concomitant with beneficial effects on some cognitive skills, such as memory. Furthermore, the fact that additional effects, such as the beta increase, occurred after five days of treatment may suggest other therapeutic indications of EGb 761, for example antistress effects after long-term treatment.

Reviewer's comments
This is a well-conducted trial indicating that ginkgo has nootropic or cognition-enhancing action on EEG and evoked potentials. The study participants did not appear to be randomized, and the blinding process was not described. (1, 6)

Clinical Study: Tebonin®

Extract name	EGb 761
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Electrophysiological effects** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**MOA**

Bibliographic reference
Kunkel H (1993). EEG profile of three different extractions of *Ginkgo biloba. Neuropsychobiology* 27 (1): 40-45.

Trial design
Crossover. Two-part study. Part I: three doses (40, 80, and 160 mg) of EGb 761. Part II: 80 mg each of EGb 761 and two fractions (fraction 1: flavonoid concentrate and ginkgolides; fraction 2: flavonoid concentrate). Subjects for the two parts of the study were different; 12 subjects participated in each study part. Medication was administered for three days prior to recording sessions.

Study duration	6 tests; 3 days of treatment preceded each test
Dose	Part I: 40, 80, and 160 mg EGb 761 extract; Part II: EGb 761, subfraction 1 and 2 (all 80 mg)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male
Age	Part I: 24-29 years (median: 26) Part II: 25-29 years (median: 27)

Inclusion criteria
Normal, healthy males with a typical high-alpha EEG (defined as alpha activity during 70 percent of recording period and a frequency between 9 and 11 Hz).

Exclusion criteria
None mentioned.

End points
Five 15-minute electroencephalography measurements (EEG) were obtained at hourly intervals on test days. Vigilance was examined using the critical-flicker fusion frequency (CFF) and a speeded arithmetic test (Pauli test). In addition, emotional changes were assessed with a mood-adjective checklist.

Results
Both experiments revealed a number of effects on various EEG parameters. However, the topographical distribution of effects was completely different in the two experiments. Part I: there was no clear dose-response relationship for any of the parameters. Part II: statistically marked EEG effects were observed for the extract and its two subfractions; however, there was no predictable relationship. In both studies, no drug effects were found for the CFF or speeded arithmetic test. The mood-adjective checklist did not show any consistent mood changes under any of the dosages.

Side effects
None of the subjects reported any side effects.

Author's comments
No clear EEG profile of an extract of *Ginkgo biloba* and its subfractions could be delineated through the two experiments of the present study.

Reviewer's comments
This is a carefully conducted trial showing the effect of ginkgo on EEG and differential effects for different preparations. No profile emerged, though; thus, there are central effects but they are not easily clarified by EEG. The randomization process was not described. (3, 5)

Product Profile: Ginkai™

Manufacturer	**Lichtwer Pharma AG, Germany (Indena S.p.A., Italy)**
U.S. distributor	**Lichtwer Pharma U.S., Inc.**
Botanical ingredient	**Ginkgo leaf extract**
Extract name	**LI 1370 (GinkgoSelect™)**
Quantity	50 mg
Processing	Plant to extract ratio 50:1
Standardization	25% (12.5 mg) flavone glycosides, 6% (3 mg) terpenoids (ginkgolides, bilobalide)
Formulation	Tablet

Recommended dose: Take one tablet, three times daily with cool liquid. Results observed after six weeks of usage.

DSHEA structure/function: Clinically proven to improve memory and concentration.

Cautions: If pregnant, nursing a baby, or administering to children, seek the advice of a health professional before using this product.

Other ingredients: Lactose, microcrystalline cellulose, citric acid, magnesium silicate, hydroxy propylmethyl cellulose, magnesium stearate, silicum dioxide, castor oil, stearic acid.

Comments: Sold as Ginkyo® and Kaveri® in Europe.

Source(s) of information: Product package; product information on Internet (<www.lichtwer.com/ginkai/ginkai_prod_info.html>, accessed on 1/25/02; information is currently available at <www.lichtwer.com/product_ginkai.html>); Ginkyo® product information (Lichtwer Pharma GmbH, 1996); information provided by Indena USA, Inc.

Product Profile: Ginkgo Biloba-24%

Manufacturer	**Enzymatic Therapy® (Indena S.p.A., Italy)**
U.S. distributor	**Enzymatic Therapy®**
Botanical ingredient	**Ginkgo leaf extract**
Extract name	**GinkgoSelect™**
Quantity	40 mg
Processing	Plant to extract ratio 50:1
Standardization	24% flavone glycosides, 6% terpene lactones, and 2% bilobalide
Formulation	Capsule

Recommended dose: One capsule three times daily.

DSHEA structure/function: Dietary supplement for improved short-term memory.

Other ingredients: Cellulose, gelatin, magnesium stearate, titanium dioxide.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Product Profile: GB24™

Manufacturer	**Thorne Research (Indena S.p.A., Italy)**
U.S. distributor	**Thorne Research**
Botanical ingredient	**Ginkgo leaf extract**
Extract name	**GinkgoSelect™**

Quantity	40 mg
Processing	Plant to extract ratio 50:1
Standardization	24% ginkgo heterosides
Formulation	Capsule

Recommended dose: None given.

Cautions: If pregnant, consult a health care practitioner before using this or any other product.

Other ingredients: Cellulose capsule. May contain one or more of the following hypoallergenic ingredients to fill space: magnesium citrate, silicon dioxide.

Comments: This product is available only through pharmacies and health care practitioners.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Product Profile: Ginkgo Biloba

Manufacturer	**Swanson Health Products (Indena S.p.A., Italy)**
U.S. distributor	**Swanson Health Products**
Botanical ingredient	**Ginkgo leaf extract**
Extract name	**GinkgoSelect®**
Quantity	60 mg
Processing	Plant to extract ratio 50:1
Standardization	24% flavone glycosides and 6% terpene lactones
Formulation	Capsule

Recommended dose: Take one capsule with water during the morning and evening meals.

Cautions: Consult a health care provider before use if taking a blood-thinning medication.

Other ingredients: Microcrystalline cellulose (plant fiber), gelatin.

Comments: Also distributed by Doctor's A-Z™.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Clinical Study: LI 1370

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Age-related cognitive impairment**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Bruchert E, Heinrich SE, Ruf-Kohler P (1991). Wirksamkeit von LI 1370 bei alteren patienten mit hirnleistungsschwache. *Munchener Medizinische Wochenschrift* 133 (Suppl 1): S9-S14.

Trial design
Parallel. Pretrial washout period of 14 days.

Study duration	3 months
Dose	1 (50 mg) tablet 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	33 general practices
No. of subjects enrolled	303
No. of subjects completed	209
Sex	Male and female
Age	45-80 years (mean: 69)

Inclusion criteria
Elderly outpatients with cerebral insufficiency or impaired cerebral function, with at least one symptom from each of four typical symptom groups.

Exclusion criteria
Patients with pronounced stenoses of the supraaortal vessels; severe internal diseases such as advanced heart or kidney failure, cirrhosis of the liver, or poorly controlled mellitus or hypertension; suspect abuse of alcohol, narcotics, or prescription drugs; and treatment with nootropic, psychotropic, or vasoactive drugs during, or in the 14 days prior to, the trial.

End points
Patients were tested for symptoms of cerebral insufficiency and asked to perform a connect-the-numbers test at admission and after 6 and 12 weeks of therapy. Both physicians and patients judged effectiveness.

Results
Statistically significant improvements were demonstrated after six weeks of therapy on 3 out of 11 typical symptoms, and after 12 weeks of therapy on 8 out of 11. Forgetfulness, depression, and headache were improved after six weeks. In addition, memory gaps, concentration, fatigue, lack of drive, and tinnitus were improved after 12 weeks. In the treatment group the time period for the figure connection test was improved by 25 percent in the ginkgo group and 14 percent in the placebo group ($p < 0.01$). Both the doctors' and the patients' judgment concerning the efficacy showed highly significant differences between the two groups, with over 50 percent giving positive assessment to ginkgo.

Side effects
Minor adverse events (the principal one being stomachache), most mentioned twice as often in the placebo group.

Authors' comments
In this trial, the parameter with the greatest statistical significance in the comparison of ginkgo and placebo was the overall integrative assessment by physician and patient. Psychometric methods are highly valued today due to their objectivity in follow-up observations of patients with impaired cerebral function. They are less significant in general practice, however, and should be viewed on the scale of the results reported here.

Reviewer's comments
Excellent, very large trial showing clear and highly believable improvements in cognitive functions, symptoms, and clinician ratings. However, the study groups were not randomized and the blinding was not adequately described. (Translation reviewed) (1, 5)

Clinical Study: Kaveri®

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Age-related cognitive impairment**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Vesper J, Hansgen KD (1994). Efficacy of *Ginkgo biloba* in 90 outpatients with cerebral insufficiency caused by old age. *Phytomedicine* 1: 9-16.

Trial design
Parallel.

Study duration	3 months
Dose	1 (50 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	11 practices
No. of subjects enrolled	90
No. of subjects completed	86
Sex	Male and female
Age	55-80 years (mean: 62.7)

Inclusion criteria
Elderly outpatients with cerebral insufficiency according to ICD-290.x., premorbid IQ of at least 80 (Mehrfachwahl-Worschatz-Intelligenztest [MWT-B]), affected by distinct subjective troubles (>19 points on the cerebral insufficiency [CI]-scale), and did not exhibit any pseudodementias (dementia-pseudodementia differentiation [DPD] value > 2). The use of nootropic agents, psychopharmaceuticals, vasoactive, or psychotropic substances was prohibited three weeks before and during the trial.

Exclusion criteria
Patients with cerebral/myocardial infarction in the previous six months, serious cardiac or renal insufficiency, other serious internal diseases requiring medical treatment, cardiac arrhythmia, stenoses of the supraaortic vessels, psychoses, epilepsy, cerebral tumors, abuse of alcohol, drugs, and medical remedies, and other diseases generally accepted as exclusion criteria.

End points
Medical checks were performed at the beginning of the study and after 6 and 12 weeks of treatment. The test parameters were long-term and short-term memory, concentration power, maximum stress, mental flexibility, family problems, and general satisfaction with life. Psychometric tests were: Mini

Mental Status according to Folstein; multiple verbal comprehension test version B (the MWT-B); dementia/pseudodementia differentiation sheet; and the brief form of Hachinski's ischaemia scale (K-HIS).

Results
Significant improvement in performance was seen with LI 1370 compared to placebo, particularly between the sixth and twelfth week of treatment. Particular improvement was seen in short-term memory and concentration. Improvement was observed in the patients' attention in tasks requiring quick orientation and readaptation, and consistent attentiveness level maintained over a longer period of time (long-term stress). The length of time with optimum attention was increased. There were also positive changes of the patients' subjective performance (reduction of troubles, reduction of behavioral abnormalities, and assessment of behavior by others).

Side effects
No side effects were observed.

Authors' comments
This study was the first to prove the clinical efficacy of *Ginkgo biloba* special extract in the treatment of cerebral insufficiency in a larger group of patients with the help of computer diagnostics. Due to the established favorable benefit/risk profile of LI 1370, it is among the remedies which are particularly recommended in the treatment of cerebral insufficiency.

Reviewer's comments
This is a well-conducted and written up trial with a medium sample size ($n = 90$) that shows clear benefits of ginkgo on computerized cognitive tests and symptoms. (5, 5)

Clinical Study: LI 1370

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Age-related cognitive impairment**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Hofferberth B (1991). *Ginkgo biloba* special extract in patients with organic brain syndrome. *Munchener Medizinische Wochenschrift* 133 (Suppl. 1): S30-S33.

Trial design
Parallel. Pretrial washout period of 14 days.

Study duration	6 weeks
Dose	1 (50 mg) tablet 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 neurological ward
No. of subjects enrolled	50
No. of subjects completed	50
Sex	Male and female
Age	57-76 years (mean: 65)

Inclusion criteria
Inpatients with organic brain syndrome.

Exclusion criteria
None mentioned.

End points
Measurements were made before the trial and after three and six weeks of therapy. The Vienna determination instrument and the digit connection test were used as psychometric methods. Saccadic eye movements, EEG analysis, and measurement of evoked potentials served as neurophysiologic methods.

Results
For all five target criteria there was improvement in the ginkgo group compared to placebo, which was evident at three weeks ($p < 0.001$). Eleven typical symptoms assessed by the physician showed good improvement in 19 of 25 in the ginkgo group and 11 of 25 in the placebo group.

Side effects
None discussed.

Author's comments
The results show that therapy with the *Ginkgo biloba* special extract LI 1370

in patients with cerebro-organic syndrome contributes to an increased cerebral capacity.

Reviewer's comments
This is the fourth study on ginkgo from these researchers showing dramatic, widespread, and large benefits in a small sample. Dramatic improvements were seen in all measures, from tests of performance to P300 evoked potentials and saccadic eye movements. It is hard to understand, however, why such widespread, highly consistent effects should occur in a relatively small sample. The study was not randomized, the blinding was inadequately described, and the data were not described in sufficient detail to permit alternative analysis. (Translation reviewed) (1, 5)

Clinical Study: LI 1370

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Age-related cognitive impairment**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Schulz H, Jobert M, Breuel HP (1991). Wirkung von spezialextrakt LI 1370 auf das EEG alterer patienten im schlafentzugsmodell. *Munchener Medizinische Wochenschrift* 133 (Suppl. 1): S26-S29.

Trial design
Parallel.

Study duration	2 months
Dose	1 (50 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	16

No. of subjects completed	15
Sex	Male and female
Age	Mean: 64.9 years

Inclusion criteria
Subjects age 55 to 75 years with age-dependent symptoms of forgetfulness; decreasing alertness and insufficient concentration; impairment of brain function based on assertion by subjects and according to the MWT (multiple choice vocabulary), and ZVT-G (number association) tests; and physically healthy (with allowance for age).

Exclusion criteria
Subjects with alcohol and/or drug abuse; intake of other medications which were not allowed in the study; known hypersensitivity to ginkgo extracts; participation in other clinical trials within the past 30 days; and incapacity to cooperate in the trial.

End points
EEG recordings (15 minutes duration) were taken twice: between 7:30 and 8 p.m. and between 4 and 4:30 a.m. after a sleepless night. The tests were conducted on the first and last day of the study. Sleepiness symptoms were documented hourly with a questionnaire.

Results
Ginkgo biloba extract LI 1370 did not cause changes in EEG activity in the evening but did cause changes in the early morning after a sleepless night. The output of the theta band decreased, whereas the alpha slow-wave index on average increased in the treatment group compared to the placebo group. There was no difference in the degree of tiredness.

Side effects
Not discussed.

Authors' comments
Ginkgo biloba extract LI 1370 does not cause a general change in EEG activity but does cause changes that are situation and stimulus dependent. This is corroborated by the selective influence on the EEG under sleep deprivation conditions compared to control measurements of the previous evening.

Reviewer's comments
This is an interesting pilot study suggesting ginkgo may help pharmaco-EEG in impaired elderly in sleep deprivation model. The study was flawed by the lack of details on randomization and blinding, the small sample size, the lack of description of withdrawal/dropouts, and inadequately applied/described statistical methods. (Translation reviewed) (0, 4)

Clinical Study: LI 1370

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Cognitive functioning** after brain aneurysm operation
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Maier-Hauff K (1991). LI 1370 after cerebral aneurysm operation; efficacy in outpatients with disorders of cerebral functional capacity. *Munchener Medizinische Wochenschrift* 133 (Suppl. 1): S34-S37.

Trial design
Parallel.

Study duration	3 months
Dose	1 (50 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	50
No. of subjects completed	42
Sex	Male and female
Age	21-63 years (mean: 48)

Inclusion criteria
Patients who had subarachnoidal hemorrhage and subsequent aneurysm operation in the previous 7 to 42 months.

Exclusion criteria
No psychoactive drugs or nootropics were allowed for two weeks before, as well as during, the study.

End points
Neuropsychological tests were carried out before the study as well as at the

end of the sixth and twelfth weeks. Tests included the Zimmermann test battery for attentiveness and assessment of short-term memory on verbal and nonverbal levels.

Results
After 12 weeks of treatment there was a statistically significant improvement in reaction time to stimuli in comparison to baseline as well as placebo (both $p < 0.01$). The number of errors was reduced compared to baseline ($p < 0.001$) and placebo ($p < 0.01$). Short-term verbal memory also improved compared to baseline ($p < 0.001$) and placebo ($p < 0.05$). There was no significant change to nonverbal memory which was already in the normal range.

Side effects
One report of nausea and stomach pains.

Author's comments
In summary the trial showed that cognitive disorders in patients with subarachnoidal hemorrhage and subsequent aneurysm operation can be favorably influenced with *Ginkgo biloba* extract LI 1370. Significant improvements were shown in the field of attention and verbal short-term memory. These results argue in favor of early initiation of therapy in order to improve cognitive deficits in performance after aneurysm operation.

Reviewer's comments
Well-conducted study showing cognitive improvements in patients recovering from cerebral aneurysms. Study received a Level II due to the statistical methods being inadequately described/applied and an inadequate description of data, thus preventing replication or alternative analysis. (Translation reviewed) (5, 4)

Clinical Study: LI 1370

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Cognitive functioning** in normal volunteers
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Rigney U, Kimber S, Hindmarch I (1999). The effects of acute doses of stan-

dardized *Ginkgo biloba* extract on memory and psychomotor performance in volunteers. *Phytotherapy Research* 13 (5): 408-415.

Trial design
Dose comparison in five-way crossover design: 150 mg (50 mg three times daily); 300 mg (100 mg three times daily); 120 mg (1 dose); 240 mg (1 dose); or placebo. Each treatment was taken for two days and separated by a minimum five-day washout period.

Study duration	2 days
Dose	(3 × 50 mg) or (3 × 100 mg) or (1 × 120 mg) or (1 × 240 mg) extract per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	36
No. of subjects completed	31
Sex	Male and female
Age	30-59 years (mean: 43.6)

Inclusion criteria
Good physical condition and mental health and free from concomitant medication.

Exclusion criteria
None mentioned.

End points
A psychometric test battery was administered predose and at regular intervals until 11 hours postdose. Working memory was assessed using immediate word recall and Sternberg's short-term memory scanning task (STM). Long-term memory was assessed using delayed word recall. Other measures included Stroop color task (SCT), critical flicker fusion, choice reaction time, digit symbol substitution task (DSST), line analog rating scales for subjective sedation (LARS), Leeds sleep evaluation questionnaire (LSEQ), and continuous activity monitoring using an actigraphy during the two-day treatment period.

Results
Reaction times in the Sternberg STM were significantly faster under the influence of LI 1370 for all doses except 150 mg on day 2 of treatment, while reaction times with 120 mg and 300 mg were faster on both days of treatment. This effect was most evident for the group receiving 120 mg and older in age (50 to 59 years). An insignificant trend toward increased immediate word recall was seen only with the 120 mg dose. Other treatment effects were not significantly different from placebo.

Side effects
None mentioned.

Authors' comments
The results show that the effects of LI 1370 extract on aspects of cognition in normal healthy volunteers are more pronounced for memory, particularly working memory, than for arousal or selective attention. These effects may be dose dependent, though not in a linear dose-related manner. The once per day dose of 120 mg produced the most evident effect of the doses examined. The cognitive-enhancing effects are more likely to be apparent in individuals aged 50 to 59 than those aged 30 to 49 years.

Reviewer's comments
This is a well-controlled and well-powered trial with five-way crossover design and frequent assessments with a wide range of tests. Authors did not state method to blind five differing dosing regimens, however. The dose relationship of response on Sternberg test is also hard to understand. In addition, the authors should have explained their rationale between different dosing conditions and regimen and addressed the difference between 120 mg in one dose and 50 mg three times a day. (2, 6)

Clinical Study: LI 1370

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Tinnitus** (ringing in the ears)
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Drew S, Davies E (2001). Effectiveness of *Ginkgo biloba* in treating tinnitus: Double blind, placebo controlled trial. *British Medical Journal* 322 (7278): 1-6.

Trial design
Parallel. Of the participants, 956 were matched for sex, age (less than ten years difference), and tinnitus duration (489 pairs). Each pair was then given one random number corresponding to placebo treatment and one number corresponding to active treatment.

Study duration	3 months
Dose	1 (50 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Remote: via questionnaire
No. of subjects enrolled	1121
No. of subjects completed	909
Sex	Male and female
Age	Mean: 53 years

Inclusion criteria
Healthy volunteers between 18 and 70 years old with tinnitus.

Exclusion criteria
Patients who were pregnant or trying to become pregnant, had previously taken *Ginkgo biloba* extract, had tinnitus for less than 12 months, reported that their tinnitus had varied greatly in the six months before the screening questionnaire, had tried any treatment for tinnitus in the six months before the screening questionnaire (e.g., homeopathy, acupuncture, hypnotherapy, etc.), were not in generally good health, were taking antidepressants or anticoagulant drugs, or had abnormal blood pressure.

End points
The main outcome measure was the participants' assessment of tinnitus before, during, and after treatment with ginkgo (change in tinnitus). Measurement of tinnitus severity was the secondary outcome measure. In addition, subjects were asked questions about other symptoms of cerebral insufficiency besides tinnitus. These end points were measured by questionnaires completed four times: at the beginning of the study, four weeks after treatment start, at the end of the 12 weeks of treatment, and two weeks after treatment had ended.

Results
Only data from the matched pairs were reported, as the authors believed that the unmatched analysis did not provide any additional information. There were no significant differences in any of the end points for either group. After 12 weeks of treatment, 34 subjects out of 360 in the ginkgo group reported that their tinnitus was less troublesome, versus 35 out of 360 placebo subjects. However, 4.9 percent of the ginkgo group (n = 489) reported beneficial side effects (e.g., in general well-being, hearing better, improved circulation, etc.) versus only 2.2 percent of the placebo group (n = 489).

Side effects
Side effects were analyzed for the 489 matched pairs. The incidence of side effects was similar between the two groups (ginkgo: 10.4 percent, placebo: 11 percent), with the most common being gastrointestinal upset.

Authors' comments
Ginkgo biloba extract LI 1370 had no greater therapeutic effect than placebo in treating tinnitus. In addition, other symptoms of cerebral insufficiency were not significantly affected by the treatment.

Reviewer's comments
Clear and unequivocal negative results. (5, 6)

Clinical Study: LI 1370

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Microcirculation; retinal blood flow** in patients with fundus hypertonicus
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Koza KD, Ernst FD, Sporl E (1991). Retinal blood flow after *Ginkgo biloba* therapy in fundus hypertonicus. *Munchener Medizinische Wochenschrift* 133 (Suppl. 1): S47-S50.

Trial design
Parallel.

Study duration	6 weeks
Dose	1 (100 mg) tablet 3 times daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	24
No. of subjects completed	24
Sex	Male and female
Age	28-64 years (mean: 50)

Inclusion criteria
Hypertensive patients with fundus hypertonicus phase I according to Thiel.

Exclusion criteria
None mentioned.

End points
Measurements were taken one day before beginning medication and on the fourteenth and forty-second days of treatment. The following aspects of retinal microcirculation were determined: quadrant artery diameter, blood velocity and blood flow in that artery, arteriovenous transit time,diameter of all arteries, and blood flow through these arteries. Other hemorheologic parameters measured were hematocrit values, plasma viscosity, erythrocyte aggregation, and erythrocyte filtration time.

Results
After treatment with ginkgo, blood flow in the quadrant artery and the total blood flow improved significantly in comparison to placebo (both $p < 0.05$ on day 14 and $p < 0.01$ on day 42). The arteriovenous circulation time decreased significantly. Erythrocyte aggregation and erythrocyte filtration time showed a tendency to decrease, and plasma viscosity demonstrated a significant drop in comparison to placebo.

Side effects
None reported.

Authors' comments
In summary, after administration of *Ginkgo biloba* extract LI 1370 there is a substantial increase of the retinal circulation in phase I fundus hypertonicus (according to Thiel) in comparison with placebo. Because in advanced dia-

betic retinopathy, and in a large portion of venous occlusive diseases of the retina, arterial constriction and reduced fluidity of the blood can be of pathogenetic importance, it seems permissible to include LI 1370 in the treatment of these retinal diseases.

Reviewer's comments
Important study showing ginkgo improves retinal circulation—confirming one potential mechanism of action. The study shows that vascular effects of *Ginkgo biloba* extract may be important in its cognitive effects. The findings support the results of Jung and colleagues (1990). However, neither the randomization nor the blinding were adequately described. (Translation reviewed) (1, 5)

Clinical Study: Kaveri®

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Microcirculation and blood fluidity** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Jung F, Mrowietz C, Kiesewetter H, Wenzel E (1990). Effect of *Ginkgo biloba* on fluidity of blood and peripheral microcirculation in volunteers. *Arzneimittel-Forschung/Drug Research* 40 (1) 5: 589-593.

Trial design
Crossover. One-week washout period between each one-day study period.

Study duration	1 day
Dose	45 ml (0.25 g extract/100 g solution)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center

No. of subjects enrolled	10
No. of subjects completed	10
Sex	Male and female
Age	21-30 years

Inclusion criteria
Healthy volunteers with limited fluidity of blood (plasma viscosity > 1.29, erythrocyte (red blood cell) aggregation > 17.3, erythrocyte rigidity > 1.14, thrombocyte (platelet) aggregation > 40).

Exclusion criteria
Subjects with hypertension, diabetes mellitus, hyperuricemia, hyperlipoproteinemia, or adiposity.

End points
Before as well as one, two, and four hours after administration, the following blood parameters were examined: hematocrit, plasma viscosity, erythrocyte aggregation, erythrocyte rigidity, spontaneous thrombocyte aggregation, number of circulating thrombocyte aggregates, thrombocyte count, and leukocyte count. Peripheral microcirculation (mean erythrocyte velocity and erythrocyte column diameter in the nail fold) was measured before and every 30 minutes for four hours after administration.

Results
A significant decrease (15.6 percent, $p < 0.0001$) in erythrocyte aggregation was observed two hours after administration of ginkgo compared to baseline. Blood flow in nail fold capillaries increased significantly by about 57 percent ($p < 0.004$) one hour after administration of ginkgo. All other parameters, blood pressure, heart rate, hemocrit, plasma viscosity, erythrocyte rigidity, thrombocyte count, and leukocyte count, as well as thrombocyte aggregation and the number of circulating thrombocyte aggregates, remained unchanged.

Side effects
None reported.

Authors' comments
In conclusion, it can be said that after administration of 45 ml *Ginkgo biloba* solution, compared to placebo, an improvement in blood viscosity, as well as an increase in the erythrocyte flow in skin capillaries, was observed.

Reviewer's comments
This is an important study with clear findings illustrating one mechanism of action of ginkgo—decrease in erythrocyte aggregation plus 57 percent increase in blood flow in nail capillaries—clear and important findings for the

actions of ginkgo on blood motility. However, the study was only single-blind and the randomization process was not adequately described. (1, 6)

Clinical Study: LI 1370

Extract name	LI 1370
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Sleep quality** in healthy volunteers
Level of evidence	**I**
Therapeutic benefit	**MOA**

Bibliographic reference

Murray BJ, Cowen PJ, Sharpley AL (2001). The effect of Li 1370, extract of *Ginkgo biloba,* on REM sleep in humans. *Pharmacopsychiatry* 34 (4): 155-157.

Trial design

Crossover. Subjects were given either placebo or ginkgo two hours before going to bed. After a one-week washout period, subjects were given the opposite treatment. Normal sleeping and waking schedule was maintained throughout the study. Subjects were allowed to continue their normal caffeine intake, but they were asked to refrain from alcohol on the preceeding and study nights.

Study duration	1 night
Dose	240 mg
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Subjects' homes
No. of subjects enrolled	10
No. of subjects completed	10
Sex	Male and female
Age	18-48 years (mean: 35.9)

Inclusion criteria
Healthy volunteers with no current or past history of psychiatric or sleep disorder (determined by clinical interview).

Exclusion criteria
Subjects taking medication.

End points
On both study nights, sleep polysomnograms were recorded by the patients at home. REM sleep latency was calculated from these measurements. Also, after each study night, subjects were asked to rate how well they had slept.

Results
There were no significant differences between the two treatments for any sleep parameter. *Ginkgo biloba* extract did not have any shortening effect on REM sleep latency. Objective and subjective measures of sleep efficiency were also unaffected by ginkgo.

Side effects
None mentioned.

Authors' comments
The purpose of this study was to test the hypothesis that LI 1370 increases cholinergic activity as measured by its effect on latency to rapid eye movement sleep. As cholinergic effects on REM sleep can be affected by other factors such as noradrenaline or serotonin function, the results do not prove conclusively that LI 1370 does not promote cholinergic activity. The main findings are that even a reasonably high dose of *Ginkgo biloba* extract is well tolerated in healthy subjects and does not affect sleep more than placebo.

Reviewer's comments
Well-conducted trial but the statistical power was marginal. Although the power was adequate to detect a 30-minute reduction in REM latency, there is no basis to expect LI 1370 to have this magnitude of effect. (5, 5)

Product Profile: GK501™

Manufacturer	**Pharmaton S.A., Switzerland**
U.S. distributor	None
Botanical ingredient	**Ginkgo leaf extract**
Extract name	**GK501™**
Quantity	60 mg

Processing	No information
Standardization	24% flavone glycosides and 6% terpene lactones
Formulation	Capsule

Source(s) of information: Kennedy, Scholey, and Wesnes, 2000.

Clinical Study: GK501™

Extract name	GK501
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Cognitive functioning** in normal volunteers
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Kennedy DO, Scholey AB, Wesnes KA (2000). The dose-dependent cognitive effects of acute administration of *Ginkgo biloba* to healthy young volunteers. *Psychopharmacology* 151 (4): 416-423.

Trial design
Multidose, balanced, crossover (Latin-square design) trial comparing 120 mg, 240 mg, and 360 mg of GK501 extract to placebo. Study took place on five separate testing days, each separated by a seven-day washout period. No placebo or active medication was administered on the first study day, which was used to familiarize subjects with procedures.

Study duration	1 day
Dose	2, 4, or 6 (60 mg extract) capsules per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	20

No. of subjects completed	20
Sex	Male and female
Age	19-24 years (mean: 20)

Inclusion criteria
Healthy young volunteers who were taking no medication with the exception of oral contraception for female volunteers. Participants abstained from caffeine-containing products and alcohol on each study day.

Exclusion criteria
Volunteers who were heavy smokers (more than ten cigarettes per day).

End points
Cognitive performance was assessed using the Cognitive Drug Research (CDR) computerized test battery immediately prior to dosing, and at 1, 2.5, 4, and 6 hours after. Primary outcome measures were speed of attention, accuracy of attention, speed of memory, and quality of memory. Patients also completed the Bond-Lader visual analog scales (VAS) to analyze three mood factors: alertness, calmness, and contentedness.

Results
Compared with placebo, there was a dose-dependent improvement of the speed of attention factor following both 240 mg and 360 mg extract; this was evident after 2.5 hours ($p = 0.036$ and $p = 0.0001$, respectively), and still present after six hours ($p = 0.026$ and $p = 0.0004$, respectively). There was a trend toward improvement of speed of attention for the lowest dose of 120 mg. The other factor that showed a convincing pattern was quality of memory. Performance was significantly enhanced with 120 mg at one and four hours ($p = 0.033$ and $p = 0.02$, respectively), with trends toward significant enhancement for the 240 mg dose at the same time points. Changes in speed of memory and accuracy of attention did not follow a pattern. None of the three factors on the Bond-Lader VAS for mood showed a significant difference.

Side effects
None mentioned in paper.

Authors' comments
Acute administration of *Ginkgo biloba* is capable of producing a sustained improvement in attention in healthy young adults.

Reviewer's comments
This study shows clear, accurate, dose-dependent improvements to index combining speed scores on three tests of attention in healthy volunteers. (4, 6)

Clinical Study: GK501™, G115®, Ginkoba M/E™

Extract name	GK501, G115
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Cognitive functioning** in normal volunteers
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference

Scholey AB, Kennedy DO (2002). Acute, dose-dependent cognitive effects of *Ginkgo biloba, Panax ginseng* and their combination in healthy young volunteers: Differential interactions with cognitive demand. *Human Psychopharmacology* 17 (1): 35-44.

Trial design

Crossover. Three studies are reported here testing ginkgo, ginseng, and a combination of the two. All studies had a total of five test days. The first day was a training day in which subjects performed all tests but were not given any treatment. The following four test days, in which subjects were given one of four treatments, were separated by one-week washout periods. The dosing was as follows: Study I: 120, 240, or 360 mg ginkgo (GK501), or placebo; Study II: 200, 400, or 600 mg ginseng (G115), or placebo; Study III: 320, 640, or 960 mg ginkgo-ginseng combination (Ginkoba M/E), or placebo.

Study duration	1 day
Dose	120, 240, or 360 mg ginkgo; 200, 400, or 600 mg ginseng; or 320, 640, or 960 mg ginkgo plus ginseng
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	20, each
No. of subjects completed	Not given
Sex	Male and female
Age	Mean: approximately 20 years

Inclusion criteria
Healthy volunteers taking no medication, except for some females taking the contraceptive pill.

Exclusion criteria
Heavy smokers (more than 10 cigarettes per day).

End points
Five testing sessions took place on each day: predose (to establish baseline for that day), and 1, 2.5, 4, and 6 hours after taking that day's treatment. Cognitive ability was tested using serial arithmetic tasks, consisting of a modified computerized version of the serial sevens test and the serial threes task.

Results
Study I: Ginkgo significantly improved speed of responding on the serial threes task in a dose-dependent manner. Although ginkgo did not affect the speed of responding on the serial sevens task, the accuracy was significantly increased by all doses after 2.5 hours. Study II: Ginseng had no effect compared to placebo on the serial threes task. However, various doses of ginseng significantly slowed the speed of reaction, while some increased the accuracy, on the serial sevens task. Study III: Several significant and sustained improvements in performance occurred after taking the ginkgo-ginseng combination. On the serial threes task, the speed of responding was significantly increased with 320 mg dose at four hours, compared to placebo ($p < 0.05$). Accuracy was also significantly increased for 640 mg at 2.5 hours ($p < 0.05$) and for 960 mg at all test times (all $p < 0.05$). On the serial sevens test, speed of responding significantly increased for the 320 mg dose at all test times (all $p < 0.01$). Speed of responding also increased for the 640 mg dose after four hours ($p < 0.01$). Accuracy was significantly improved for all doses after 2.5 and 6 hours, and the 640 mg dose also made fewer errors at the four-hour test session.

Side effects
None mentioned.

Authors' comments
Each of the three treatments under investigation significantly affected performance on computerized serial subtractions in a dose-, time-, and task-specific manner. The effects of single doses of ginkgo and ginseng were reasonably consistent with previous findings. The most striking (and unexpected) result, however, was a marked and sustained improvement in serial sevens performance following the ginkgo-ginseng combination. It would appear that the comprehensive improvements in performance associated with the ginkgo-ginseng combination represents a synergistic behavioral effect of the two extracts interacting with cognitive demand.

Reviewer's comments
Clear evidence of acute beneficial effects of GK501 on cognitive function. (4, 6)

Product Profile: Ginkgoforce

Manufacturer	**Bioforce AG, Switzerland**
U.S. distributor	**Bioforce USA**
Botanical ingredient	**Ginkgo leaf extract**
Extract name	None given
Quantity	50 g fresh plant (16.4 g dried plant) per 100 g tincture
Processing	Plant to extract ratio 1:9, 63% alcohol
Standardization	No information
Formulation	Liquid

Recommended dose: Take 15 to 20 drops in a small amount of water three times daily.

DSHEA structure/function: Benefits memory, mental clarity, and alertness.

Comments: Sold as Geriaforce in Europe.

Source(s) of information: Information provided by distributor.

Clinical Study: Geriaforce

Extract name	None given
Manufacturer	Bioforce AG, Switzerland
Indication	**Age-related memory impairment**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Degenring FH, Brautigam MRH (1999). Geriaforce for the treatment of age-induced memory disorders—A placebo-controlled double-blind study with two dosages. Schweizerische *Zeitschrift fur GanzheitsMedizin* 11 (5): 252-257.

Trial design
Parallel. Two different doses compared to placebo. Trial preceded by a four-week washout period.

Study duration	6 months
Dose	3 (20 or 40 drops) doses daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	22 general practices
No. of subjects enrolled	241
No. of subjects completed	197
Sex	Male and female
Age	55-85 years (mean: 69)

Inclusion criteria
Patients with age-induced memory disorders determined by their score on the Mini-Mental State Examination.

Exclusion criteria
Exclusion criteria were dementia, depression, loss of memory for a known cause that needed other treatment, psychoses and secondary cerebral insufficiency as the result of intoxication or metabolic disorders (including liver and renal failure, diabetes mellitus, diseases of the gastrointestinal tract, heart failure, malignant diseases, as well as abuse of alcohol and medicaments), concomitant anticholinergic medication, and prior treatment with *Ginkgo biloba* in the past 3 months.

End points
Assessment was based on objective psychometric tests: the extended mental control test (EMCT) measuring attention and concentration; the Rey test parts I and II, for measuring short- and long-term memory and learning ability; and the Benton test for measuring visual short-term memory. In addition, subjective impressions of memory and concentration were recorded by the patients. Tests were administered at baseline and after 12 and 24 weeks of treatment.

Results
A marked improvement was noted in all three groups on all psychometric tests after six months due to a learning effect. Only the Benton test for visual short-term memory showed significant improvement compared to placebo ($p = 0.0076$) for the lower dose of Geriaforce. There was a 14.2 percent improvement over baseline. The higher dose of Geriaforce also caused more improvement compared to baseline (10 percent) than the placebo compared to baseline (6.1 percent). In the EMCT and Rey tests I and II, there

were no statistically significant differences between groups. There was also no significant difference in the improvement of memory and concentration according to the subjective assessment of the patients.

Side effects
Tolerance was good in all three treatment groups. Mild symptoms included gastric symptoms, dizziness and stupor, headache, and tiredness.

Authors' comments
From the present results, it can be deduced that in patients with age-related disorders of memory and concentration the dosage corresponding to the commercial preparation (20 drops three times a day) is superior not only to the placebo but also to the double dose.

Reviewer's comments
Very large trial, but results were partially spoiled by not training subjects on tests prior to study, with the result that training effects appeared on all assessments. Nonetheless, on one of the tests (Benton Visual Retention Test), improvements were greater with ginkgo. The randomization of subjects was inadequately described. (3, 5)

Product Profile: Ginkoba M/E™

Manufacturer	**Pharmaton S.A., Switzerland**
U.S. distributor	**Pharmaton Natural Health Products**
Botanical ingredient	**Ginkgo leaf extract**
Extract name	**GK501™**
Quantity	60 mg
Processing	No information
Standardization	24% flavone glycosides and 6% terpene lactones
Formulation	Capsule
Botanical ingredient	**Ginseng root extract**
Extract name	**G115®**
Quantity	100 mg
Processing	No information
Standardization	4% ginsenosides

Recommended dose: One capsule with water twice daily. Optimal results have been shown after four weeks of continuous daily use. Ginkoba M/E works gradually over time and should be taken as part of an ongoing healthy regimen.

DSHEA structure/function: Promotes fast and accurate thinking, reduces mental fatigue, safely promoting blood circulation and oxygen supply to the brain.

Cautions: If taking a prescription medicine, such as an anticoagulant agent, are pregnant, or are lactating, please contact a doctor before taking this product. In case of accidental ingestion/overdose, seek the advice of a professional immediately.

Other ingredients: Mannitol, gelatin, silicon dioxide, magnesium stearate, titanium dioxide, synthetic iron oxides.

Comments: Sold as Gincosan® in Europe.

Source(s) of information: Product package (© Boehringer Ingelheim Pharmaceuticals, Inc. 2000); Wesnes et al., 1997.

Clinical Study: Gincosan®

Extract name	GK501 and G115
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Cognitive functioning** in healthy volunteers with neurasthenic complaints
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Wesnes KA, Faleni RA, Hefting NR, Hoogsteen G, Houben JJG, Jenkins E, Jonkman JHG, Leonard J, Petrini O, van Lier JJ (1997). The cognitive, subjective and physical effects of a *Ginkgo biloba/Panax ginseng* combination in healthy volunteers with neurasthenic complaints. *Psychopharmacology Bulletin* 33 (4): 677-683.

Trial design
Parallel. Compared three different doses of Ginkoba M/E to placebo.

Study duration	3 months
Dose	80 mg, 160 mg, or 320 mg Ginkoba M/E twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind

Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	64
No. of subjects completed	64
Sex	Male and female
Age	42-65 years (mean: 55)

Inclusion criteria
Subjects with neurasthenic complaints (fatigue, lack of motivation, feeling of inadequacy) identified using the SCL-90-R questionnaire and ICD-10 F48.0 diagnosing guidelines.

Exclusion criteria
Pregnancy or lactation; mental handicap; heavy smoking (more than15 cigarettes daily); alcohol abuse or drug addiction; participation in a drug study within 90 days; insulin-dependent diabetes or epilepsy; organic psychiatric disorders; regular use of neuroleptics, antidepressants, calcium antagonists, cinnarizine, or hydergine that could not be stopped seven days before the study; the use of ginseng preparations within six weeks of the start of the study and/or the use of *Ginkgo biloba* preparations within four weeks of the study; and the inability to perform the study pharmacodynamic tests adequately.

End points
Assessments were performed at baseline and on days 1, 30, and 90 one hour after the morning dose, one hour after the afternoon dose, and again five hours later. Assessments included the Cognitive Drug Research computerized assessment system, the Vienna determination unit, cycle ergometry, and various questionnaires.

Results
Significant improvements were seen one hour after the morning dosing with all doses on day 1 (80 mg, $p = 0.003$; 160 mg, $p = 0.033$; 320 mg, $p = 0.004$). Also, one hour after the morning dosing on day 90, the 320 mg dose significantly improved the quality of memory index compared to placebo ($p = 0.003$); however, the placebo group had improved so much that there was no significant difference between it and the two lowest doses. The opposite pattern appeared on the tests one hour after afternoon dosing. The 320 mg dose impaired the global index of memory on day 1 and day 90 ($p < 0.004$ and $p < 0.001$, respectively). Afternoon memory impairments appeared to be dose dependent. After morning exercise on day 90, all doses of Ginkoba M/E showed a greater reduction in heart rate from the prestudy level com-

pared to placebo; however, the effect was not clearly dose dependent and only the 80 mg dose was significantly different from placebo ($p = 0.03$). The mean score on neurasthenic-related questions (SCL-90-R symptom checklist) showed a decrease on days 30 and 90 compared with the pre-study score for all groups, with no significant differences between groups.

Side effects
The nine adverse events considered to be possibly related to the treatment were of mild intensity. Of those, four were considered to be probably related to the treatment and were either nausea or abdominal pain.

Authors' comments
This study found that a combination of ginkgo and ginseng has beneficial effects on cognitive function and other measures. The reversal of some of the cognitive effects hours later after an additional dose suggests that a longer in-between dosing interval may be appropriate.

Reviewer's comments
This trial showed significant benefit to quality of memory. Benefits began at day 30, but they appeared to reverse later on day 90. Neither randomization nor blinding were adequately described. (0, 6)

Clinical Study: Ginkoba M/E™

Extract name	GK501 and G115
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Cognitive functioning** in normal volunteers
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Wesnes K, Ward T, McGinty A, Petrini O (2000). The memory enhancing effects of a *Ginkgo biloba/Panax ginseng* combination in healthy middle-aged volunteers. *Psychopharmacology* 152 (4): 353-361.

Trial design
Parallel. Comparison of two dosing regimens: 160 mg twice daily or 320 mg once daily. Twelve-week study preceded by a two-week placebo washout phase, and followed by two weeks of no treatment.

Study duration	14 weeks
Dose	2 (160 mg) capsules daily, either together or 5 hours apart

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	7 health centers
No. of subjects enrolled	279
No. of subjects completed	256
Sex	Male and female
Age	38-66 years (mean: 56)

Inclusion criteria
Healthy middle-aged volunteers.

Exclusion criteria
Volunteers with signs or history of depression, evidence of dementia, clinically relevant abnormalities in medical history or examination, history of alcohol or drug abuse, heavy smokers (more than 10 cigarettes per day), history of food or drug allergies relevant to the study compound, clinically relevant deviation from normal of any finding during prestudy medical screening, unable to perform the cognitive tests, and taking a cognition-enhancing substance or medication which may have been stopped at some time during the active dosing phase.

End points
Assessment was conducted before pretrial washout, at baseline, and after 4, 8, 12, and 14 weeks. Volunteers performed a selection of tests of attention and memory from the Cognitive Drug Research computerized cognitive assessment system prior to morning dosing, and again at one, three, and six hours later. The volunteers also completed questionnaires about mood states, quality of life, and sleep quality.

Results
The ginkgo/ginseng combination significantly improved the quality of memory index by 7.5 percent. There was no difference between the two dosing regimens, nor in the successive weeks of testing. Memory enhancement was seen throughout the 12-week treatment and after the two-week final washout. There were no significant effects of Ginkoba M/E on the secondary vari-

ables: power of attention, continuity of attention, and the speed of memory process.

Side effects
Five volunteers suffered mild adverse events leading them to withdraw from the study.

Authors' comments
This study represents the first substantial demonstration of improvements to the memory of healthy middle-aged volunteers produced by a phytopharmaceutical.

Reviewer's comments
This is the largest properly controlled study of a phytopharmaceutical in normals ever conducted. No evidence of biphasic effect seen in previous study (Wesnes et al., 1997). The selective improvement of quality of memory confirmed in this study is a new phytopharmaceutical benchmark. The only deficit to the trial was an inadequate description of the randomization process. (3, 6)

Clinical Study: Ginkoba M/E™

Extract name	GK501 and G115
Manufacturer	Pharmaton
Indication	**Cognitive functioning** in normal volunteers
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Kennedy DO, Scholey AB, Wesnes KA (2001). Differential, dose dependent changes in cognitive performance following acute administration of a *Ginkgo biloba/Panax ginseng* combination to healthy young volunteers. *Nutritional Neuroscience* 4 (5): 399-412.

Trial design
Crossover. Subjects received 320, 640, and 960 mg Ginkoba M/E and matching placebo in order dictated by a Latin square. There was a washout period of seven days between each treatment.

Study duration	1 day
Dose	2, 4, or 6 (60 mg GK501 and 100 mg G115) capsules per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	20
No. of subjects completed	20
Sex	Male and female
Age	Mean: 20.6 years

Inclusion criteria
Healthy young volunteers who were taking no medication with the exception of oral contraception for female volunteers. Participants abstained from caffeine-containing products and alcohol on each study day.

Exclusion criteria
Volunteers who were heavy smokers (more than 10 cigarettes per day) or were taking herbal supplements.

End points
Cognitive performance was assessed using a computerized test battery immediately prior to dosing and at 1, 2.5, 4, and 6 hours after treatment. Primary outcome measures were quality of memory; working memory (subfactor) and secondary memory (subfactor) (derived from quality of memory); speed of memory; speed of attention; and accuracy of attention. Patients also completed the Bond-Lader visual analog scales to analyze three mood factors: alertness, calmness, and contentedness.

Results
Compared to placebo, quality of memory was significantly improved following treatment with 960 mg both one hour and six hours postdose ($p = 0.0009$ and $p = 0.002$, respectively). Further analysis revealed that this effect was differentially targeted at the secondary memory, which improved one, four, and six hours after dosing, rather than the working memory component, which was not different from placebo. There was no improvement in quality of memory following the 320 mg dose and only a trend toward improvement six hours after the 640 mg dose. Both 320 mg and 640 mg treatments produced trend improvements in secondary memory after six hours. No dose

produced significant differences in general speed of performance. Speed of attention, however, was significantly slowed for both the 320 mg and 640 mg doses four hours after treatment ($p = 0.01$ and $p = 0.05$, respectively), and again for 320 mg at six hours ($p = 0.0006$). The 960 mg dose saw no significant drop in performance for this factor. No dose produced a significant difference in performance on the accuracy of attention factor. There were also no significant differences on the Bond-Lader VAS.

Side effects
None mentioned.

Authors' comments
The results show improvements of mnemonic performance in healthy young participants within one hour of ingestion, and this offers support to the possibility that the ginkgo-ginseng combination may have some utility in combating cognitive deficits.

Reviewer's comments
Important replication of selective enhancement of quality of memory index with ginkgo-ginseng combination, this time in a third laboratory and in young, healthy volunteers. Trial dropouts were not described, but the authors assured that there were none (4, 6).

Ginseng

Other common names: **Asian ginseng; Chinese ginseng; Korean ginseng, *ren shen***
Latin name: ***Panax ginseng* C.A. Meyer** [Araliaceae]
Latin synonyms: ***Panax schinseng* T. Nees**
Plant part: **Root**

American Ginseng

Other common name: ***xi yang shen***
Latin name: ***Panax quinquefolius* L.** [Araliaceae]
Plant part: **Root**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Ginseng, or in Chinese, *ren shen,* has been translated roughly as "man-root," referring to the shape of the root. Only products of *Panax* species are properly labeled ginseng. However, the name has been used more loosely, and incorrectly, to include members of other genera, such as *Eleutherococcus senticosus* (Rupr. et Maxim) Maxim., given the nickname "Siberian ginseng." The genus *Panax* includes 11 species—the most commonly used is *Panax ginseng* C.A. Meyer, also known as Asian ginseng (Awang, 2003; Wen, 2001).

The root of Asian ginseng has been used in traditional Asian medicine for more than 2,000 years. Commercially supplied roots are graded according to their source, age, part of the root, and method of preparation (Bahrke and Morgan, 1994). The root can be used fresh, or prepared as "white" ginseng (peeled and dried) or "red" ginseng (steamed and dried). The fresh root is often sliced thinly and taken with or without honey, or it can be boiled in soup. White or red ginseng can be powdered, extracted, or made into a tea (Yun and Choi, 1998). The main active components of ginseng roots are glycosidal

GINSENG SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Asian Ginseng Products						
Ginsana®*	Pharmaton S.A., Switzerland/ Pharmaton Natural Health Products	Extract standardized to 4% ginsenosides (G115®)	2-6 (100 mg) capsules; 200-600 mg daily	Physical performance	7	Yes (I-1, II-2, III-1) Undetermined (III-1) No (II-2)
				Cognitive functioning	2	Yes (I-1, II-1)
				Vaccination potentiation	1	Yes (II-1)
				Bronchitis	2	Yes (II-1, III-1)
				Menopausal symptoms	1	Trend (II-1)
				General well-being	2	Yes (I-1) Undetermined (II-1)
Ginsana® Gold Blend	Pharmaton S.A., Switzerland/ Pharmaton Natural Health Products	Extract standardized to 4% ginsenosides (G115®) plus vitamins and minerals	1-2 (40 mg) capsules daily	General well-being	3	Yes (I-2, II-1)
				Physical performance	1	Yes (III-1)
				Age-related memory impairment	1	Yes (II-1)
				Geriatric rehabilitation	1	No (II-1)

Gerimax	Dansk Droge, Denmark/None	Extract standardized to 4% ginsenosides	100-400 mg daily	Cognitive functioning	1	Yes (II-1)
				Diabetes (NIDDM)	1	Yes (III-1)
American Ginseng Products						
American ginseng root	Chai-Na-Ta Corp., Canada/None	Ontario grown powdered root	1-9 g	Diabetes (NIDDM)	2	Trend (II-1, III-1)
				Postprandial glycemia	3	Undetermined (III-2) No (II-1)

*See the ginkgo profile for information on the combination product Ginkoba M/E™, which contains extracts of ginseng root (G115®) and ginkgo leaves (GK501™).

saponins known as ginsenosides. There are eight commonly measured ginsenosides, in addition to three malonylginsenosides. The heating process in the production of red ginseng converts the malonylginsenosides to their ginsenoside counterparts (Chuang et al., 1995) and also results in other chemical transformations.

American ginseng, *Panax quinquefolius* L., is native to eastern North America and cultivated both in North America and in Asia. American ginseng root can be distinguished from Asian ginseng by profiling the constituent ginsenosides (Dou, Hou, and Chen, 1998; Chuang et al., 1995).

Ginsana® is manufactured by Pharmaton S.A. in Switzerland, and is sold by Pharmaton Natural Health Products in the United States. Ginsana contains the ginseng root extract G115®, which is characterized as containing 4 percent ginsenosides. This standardized extract is also sold in combination with vitamins and minerals as Ginsana® Gold Blend in the United States and Gericomplex in Europe. Three similar products also produced by Pharmaton (Geriatric Pharmaton®, Gegorvit®, Pharmaton® Capsules) contained an additional ingredient, deanol (dimethylaminoethanol bitartrate), and were used in three of the reviewed clinical trials (Le Gal, Cathebras, and Struby, 1996; Neri et al., 1995; Pieralisi, Ripari, and Vecchiet, 1991).

Gerimax Ginseng Extract is manufactured by Dansk Droge in Denmark and is characterized as containing 4 percent ginsenosides. This product is not sold in the United States.

Powdered American ginseng root is manufactured by Chai-Na-Ta Corporation in British Columbia, Canada. However, this product has not been developed commercially and is not available on the market.

SUMMARY OF REVIEWED CLINICAL STUDIES

Ginseng has been described as an "adaptogen," a substance that corrects dysfunction in sick individuals and protects healthy individuals from stresses without producing unwanted side effects. The adaptogen concept originated from Soviet scientists in the late 1950s. The concept was translated recently into Western conventional medicine as a medicinal agent with a pharmacological profile of antioxidant and/or anticancer activity, immunomodulatory, and cholesterol-lowering properties, as well as having hypoglycemic and choleretic actions (Davydov and Krikorian, 2000). Adaptogens have also been

described as increasing nonspecific resistance to stress due to adverse physical, chemical, and/or biological factors (Bahrke and Morgan, 1994).

The trials reviewed in the book test ginseng for its effects on physical performance, well-being, cognitive performance, the immune system, and diabetes. Case reports indicate that the use of ginseng may reduce the risk of cancer.

Ginsana (G115)

Physical Performance

The five reviewed trials with Ginsana (G115) focus on physical fitness using the standard dose of 200 mg per day over a period of two to three months. Three studies reported positive results and two studies reported no benefit to fitness. The positive studies, including 28 to 30 male athletes each, reported an increase in fitness following nine weeks of treatment compared to placebo. The studies reported an increase in oxygen capacity during exercise, a decrease in maximum exercise heart rate, and a decrease in lactate levels following exercise. The most recent study was a good-quality placebo-controlled trial (Forgo and Schimert, 1985). Our reviewer, Keith Wesnes, observed that the results of this study showed great improvements in fitness and faster reaction times. The second study, of poor quality, compared the G115 extract (with 4 percent ginsenosides) to G115S (a special extract containing 7 percent ginsenosides) and found no difference in the effectiveness of the two products. The authors concluded that no advantage existed in increasing the ginsenoside concentration to greater than 4 percent (Forgo and Kirchdorfer, 1982). This study was rated as having poor quality because it lacked a placebo control and the study subjects were not randomized. The third study, a good-quality trial, contained three treatment groups: 200 mg G115S with 7 percent ginsenosides; 200 mg of the standard G115 plus 400 mg vitamin E; and placebo. Compared with placebo, similar increases in fitness were observed in both treatment groups (Forgo, 1983).

Two well-conducted trials on exercise capacity, conducted by a different research group, failed to find any benefit to exercise capacity with G115 after eight weeks of treatment. These trials used 19

healthy females and 31 healthy males, respectively, and a dose of 200 mg, or 200 or 400 mg extract per day, respectively (Engels, Said, and Wirth, 1996; Engels and Wirth, 1997). The contradictory data reported by these two research groups leave open the question of whether ginseng can enhance exercise capacity. It may be that larger sample sizes are needed to evaluate efficacy or that a difference exists between the effect of G115 on athletes, subjects in the positive studies, and normal healthy persons, included in the negative studies.

Two other studies reported an increase in the speed of reactions to light and sound following a dose of 200 mg G115 extract for three months. A placebo-controlled study with 120 members of a sports club reported increases in reaction times and pulmonary function, particularly in those above 40 years of age (Forgo, Kayasseh, and Staub, 1981). A smaller, poorly described study with 60 subjects reported faster responses, improved two-handed coordination, and increased recovery after exercise (Dörling, Kirchdorfer, and Ruckert, 1980).

Cognitive Functioning

Cognitive function was assessed in two trials. One placebo-controlled study with 32 healthy male students found improved mental arithmetic compared to placebo after three months of treatment with 200 mg extract per day (D'Angelo et al., 1986). A crossover trial with 20 young volunteers (mean age: 21 years) showed that single doses of 200, 400, or 600 mg improved the ability to retain information in short- and long-term memory, with the greatest benefit in quality of memory following a single dose of 400 mg. The study also reported a decrement in reaction times on attention tasks following a single dose of 200 or 600 mg but not 400 mg. The significance of the latter result is not fully understood by the researchers, who recommended further investigation (Kennedy, Scholey, and Wesnes, 2001).

Vaccination Potentiation

The clinical data suggest that G115 can protect against influenza and improve immune responses, including those in smokers with chronic bronchitis. In a large, placebo-controlled study investigating vaccination potentiation, 219 healthy subjects were vaccinated with a flu vaccine four weeks into a three-month treatment period with ei-

ther G115 (200 mg per day) or placebo. As a result, G115 reduced the incidence of influenza or common cold by about two-thirds compared to placebo. In addition to the reduction in colds, the treatment group also had increased antibody titers and increased natural killer cell activity compared to the placebo group (Scaglione et al., 1996).

Bronchitis

Two trials that studied the effect of G115 on subjects with bronchitis indicated an increase in immune response following a dose of 200 mg per day. A single-blind study of 40 smokers with chronic bronchitis reported increases in immune parameters, including alveolar macrophage phagocytosis and intracellular killing, after two months of treatment (Scaglione et al., 1994). An open study, with 44 subjects with symptoms of an acute attack of chronic bronchitis reported increased bacterial clearance in the group receiving G115 plus antibiotics for nine days compared to the group receiving only antibiotics (Scaglione, Weiser, and Alessandria, 2001).

Menopausal Symptoms

A well-conducted study examined the quality of life in 379 healthy, postmenopausal women. There was a trend toward symptomatic relief of menopausal symptoms, with the strongest evidence for reduction in depression. There was no change in physiological parameters or hot flashes (Wiklund et al., 1999).

General Well-Being

Ginseng had no effect on psychological outlook or mood in a placebo-controlled study with 83 young, healthy adults (average age: 26 years). Treatment groups were given either 200 or 400 mg of G115 per day for two months, and mood was assessed using a questionnaire regarding emotional states (Cardinal and Engels, 2001). A small pilot study assessing general quality of life via a questionnaire found improvements in social functioning and mental health in young adults following four weeks of treatment with 200 mg of G115 per day compared with placebo. However, these differences did not appear at the end of the eight-week trial (Ellis and Reddy, 2002).

Ginsana Gold Blend (G115 with Vitamins and Minerals)

We reviewed six trials on a mixture of G115 with vitamins and minerals. Three studies indicated benefits in quality of life indexes, particularly when they were poor to begin with. One study reported improvement in exercise capacity. Another indicated improvements in age-associated memory impairment. The final study did not indicate a benefit in geriatric rehabilitation.

General Well-Being

Three large, good-quality trials indicated a general improvement in quality of life. Quality of life was assessed from a questionnaire scoring general well-being, satisfaction with life, activity and energy levels, sexual activity, and ability to sleep. The largest trial, well-conducted and well-described, with 501 adults subject to increased physical and mental stress, compared one capsule of the ginseng mixture to vitamins and minerals alone. After three months, quality of life was improved in the ginseng group when compared to the baseline and to the control group (Marasco et al., 1996). Another excellent study with 390 healthy adults showed no overall increase in general well-being, according to a questionnaire, following ingestion of two capsules daily for three months. However, a subset of the subjects, with the lowest well-being scores at baseline, improved in vitality and mood compared with placebo. There were, however, general improvements in behavioral aspects, such as alertness, appetite, and relaxation, for the entire treatment group (Wiklund, Karlberg, and Lund, 1994). The third large trial with 219 subjects showed improved quality of life in people who had been suffering from functional fatigue for more than 15 years. Both treatment and placebo groups improved greatly, but even so a statistically significant improvement was observed with a dose of two capsules per day compared to placebo at the end of six weeks (Le Gal, Cathebras, and Struby, 1996).

Physical Performance

A placebo-controlled study with 47 healthy male sports teachers noted an increase in exercise capacity after six weeks of administration of two capsules of the G115 formula compared with placebo (Pieralisi, Ripari, and Vecchiet, 1991).

Age-Related Memory Impairment

Improvements in memory and life satisfaction were noted in a placebo-controlled trial of 60 elderly volunteers (mean age 60 years) with age-associated memory impairment. The subjects were assessed after nine months of treatment with two capsules daily (Neri et al., 1995).

Geriatric Rehabilitation

Another well-conducted trial studied 40 nondemented geriatric patients (mean age 78 years) admitted to the hospital for treatment of cardiovascular, pulmonary, or musculoskeletal diseases. Compared with placebo, there was no difference in quality of life, cognitive function, or length of hospital stay following treatment with two capsules daily for two months (Thommessen and Laake, 1996).

Gerimax

Cognitive Functioning

In a trial including 112 healthy subjects, ages 40 to 70 years old, reaction times and ability for abstract thinking increased after receiving 400 mg Gerimax Ginseng Extract for eight to nine weeks compared to no controls. However, no difference developed between the two groups in assessments of concentration or memory (Sorensen and Sonne, 1996).

Diabetes

A trial including 36 newly diagnosed patients with non-insulin-dependent diabetes mellitus (NIDDM) recorded increased psychomotor performance, mood, and vigor after two months of treatment compared to the baseline. A dose of 200 mg for two months reduced fasting blood glucose and glycosylated hemoglobin (HbA_{1c}) levels compared to placebo (Sotaniemi, Haapakoski, and Rautio, 1995). Neither the blinding nor the randomization were adequately described in this trial, which diminished its quality.

American Ginseng Root

Diabetes

Four pilot trials focused on the ability of American ginseng root powder to reduce the rise in blood sugar following administration of oral glucose. Vuksan, Sivenpiper, and colleagues (2000) reported in a small study including ten healthy subjects and nine type II diabetics that 3 g ginseng root powder administered 40 minutes before the glucose challenge caused significant reductions (approximately 20 percent of the area under the curve) in the resulting rise in blood sugar in both groups compared to placebo. For diabetics, the reduction in blood sugar also occurred when ginseng and glucose were taken at the same time.

Other studies by the same group reported that there was no significantly different response in healthy subjects when higher doses of 6 or 9 g were administered or when lower doses of 1 or 3 g were administered. In addition, similar reductions in blood glucose were recorded whether ginseng was taken 40, 80, or 120 minutes before challenge, but not later (Vuksan, Stavro, Sievenpiper, Koo et al., 2000; Vuksan et al., 2001). Further studies with a small group of 12 type II diabetics also reported no change with response regardless of whether doses of 3, 6, or 9 g were administered. In contrast to healthy subjects, glucose levels were reduced when ginseng was administered concurrently with the challenge, as well as 40, 80, or 120 minutes before challenge (Vuksan, Stavro, Sievenpiper, Beljan-Zdravkovic et al., 2000). A weakness of these studies is the small number of participants. The size of the groups in all studies ranged from 10 to 12.

Sievenpiper and colleagues (2003) recently reported a fifth study using 12 normal healthy subjects. A different batch of powdered American ginseng was used for this study. In contrast to previous studies, this study reported no reduction in plasma glucose when 6 g ginseng was given 40 minutes before the 75 g oral glucose test. The batch of powdered American ginseng used in this study contained approximately half the amount of the previous batch. The authors suggested that the quantity of total ginsenosides or differences in the profiles of the individual ginsenosides may account for the lack of activity.

SYSTEMATIC REVIEWS

A systematic review of double-blind, randomized, placebo-controlled clinical studies was conducted on all "ginsengs." The review included 16 trials: ten of which were conducted on *Panax ginseng;* one on *Panax quinguefolius* (American ginseng); three on *Eleutherococcus senticosus* (commonly referred to as "Siberian ginseng"); and two on materials simply described as "ginseng." The indications for the trials were physical performance, psychomotor performance and cognitive function, immunomodulation, diabetes mellitus, and herpes simplex type II infections. The authors found that the evidence for these conditions was not convincing (Vogler, Pittler, and Ernst, 1999). However, with multiple species and different preparations all lumped together, it would be difficult to reach any meaningful conclusions.

EPIDEMIOLOGICAL STUDIES

A cohort study that included 4,634 adults over 40 years old in a province in Korea reported evidence that *Panax ginseng* has a non-organ-specific preventive effect against cancer. Ginseng consumers had less than half the risk of cancer compared with nonconsumers (relative risk 0.40, 95 percent confidence interval). The risk decreased with an increase in the frequency of ginseng consumption when those who consumed ginseng less than three times per year were compared with those taking ginseng more than once a month (Yun and Choi, 1998). Two case-controlled studies, wherein newly diagnosed cancer patients admitted to the hospital were paired with patients admitted to the hospital for other reasons (905 pairs and 1,987 pairs, respectively), questioned subjects regarding their use of ginseng. Fewer of the cancer patients reported taking ginseng when compared to the controls. The authors thus reported a reduction in risk of cancer of about half (relative risk 0.56 and 0.50, respectively) (Yun and Choi, 1990, 1995). These three studies were reanalyzed in a recent publication. Taking into account results from the studies, there was a significant decrease in the proportion of cancer cases with increasing frequency of intake of ginseng. Red ginseng was profiled as

having the strongest anticancer activity in comparison with other ginseng preparations (Yun, Choi, and Yun, 2001).

ADVERSE REACTIONS OR SIDE EFFECTS

Ginseng was well tolerated in the reviewed studies. A systematic review of adverse effects and drug interactions was published for *Panax ginseng* (Coon and Ernst, 2002). The authors found that data from clinical trials suggest that the incidence of adverse events with ginseng (single ingredient) preparations is similar to that of placebo. The most commonly experienced events were headaches, sleep disorders, and gastrointestinal disorders. The review cited two case reports involving potential herb-drug interactions. One was a 64-year-old woman who was taking phenelzine along with triazolam and lorazepam and developed a headache and tremulousness upon adding ginseng to her regime. The second was a 47-year-old man with a mechanical heart valve taking warfarin, whose bleeding time decreased after supplementation with ginseng. The latter report was surprising since ginseng has been reported to have some platelet-inhibiting effects, and the opposite effect might be expected. The review also reported an open, nonrandomized clinical trial with 14 healthy volunteers that suggested that ginseng enhances the clearance rate of blood alcohol (Coon and Ernst, 2002).

The *British Herbal Compendium (BHC)* warns that extensive use of ginseng can lead to hypertension (Bradley, 1992). However, a placebo-controlled study including 26 subjects with mild or moderate hypertension (systolic blood pressure over 140 mmHg and diastolic blood pressure between 90 and 110 mmHg) reported opposite results. The participants were placed on a 24-hour blood pressure monitoring system. Administration of 4.5 g powdered red ginseng root (obtained from Korea) per day for eight weeks resulted in significant decreases in systolic blood pressure with only a tendency for diastolic blood pressure to decrease. The authors concluded that red ginseng might be a relatively safe medication to add to standard hypertensive therapy (Han et al., 1998).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

British Herbal Compendium
German Commission E
World Health Organization

Indications

The German Commission E, the *British Herbal Compendium (BHC),* and the World Health Organization (WHO) specify that the dried main and lateral root and root hairs of ginseng are indicated as a tonic, prophylactic, or restorative agent for invigoration and fortification in times of fatigue and debility, physical or mental exhaustion, stress, and for declining capacity for work and concentration (Blumenthal et al., 1998; Bradley, 1992; WHO, 1999). The Commission E and the WHO suggest that ginseng can be used during convalescence as well (Blumenthal et al., 1998; WHO, 1999). The *BHC* also states that ginseng can be used for inadequate resistance to infections and lists the following actions: adaptogenic, stimulant, and tonic (Bradley, 1992).

Doses

Dried root: 1 to 2 g daily (Blumenthal et al., 1998); 0.6 to 2 g daily, taken in the morning (Bradley, 1992); 0.5 to 2 g daily, taken in the morning (WHO, 1999); or equivalent preparations
Decoction: equivalent amounts to above (Bradley, 1992; WHO, 1999)

Treatment Period

Both the Commission E and the *BHC* suggest that ginseng be used for up to three months and that a repeated course is feasible (Blumenthal et al., 1998; Bradley, 1992). However, the *BHC* also states that

occasional use or courses of one month followed by a two-month interval are recommended (Bradley, 1992).

Contraindications

The Commission E and the WHO list no known contraindications (Blumenthal et al., 1998; WHO, 1999). The *BHC,* however, lists the following: pregnancy, acute illness, hypertension, and use of other stimulants (including significant consumption of caffeine-containing beverages) (Bradley, 1992).

Adverse Reactions

The Commission E states no known adverse reactions, and the WHO adds that there are none if ginseng is taken at the recommended dose (Blumenthal et al., 1998; WHO, 1999). The *BHC* warns that extensive use can lead to sleeplessness, hypertension, or other side effects (Bradley, 1992).

Precautions

The WHO advises that diabetic patients should consult a physician prior to taking ginseng root, since it may slightly reduce blood glucose levels (WHO, 1999).

Drug Interactions

The Commission E lists no known drug interactions, whereas the WHO states that two reports exist of an interaction between ginseng and phenelzine, a monoamine inhibitor (Blumenthal et al., 1998; WHO, 1999).

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DETAILS ON GINSENG PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication in accordance with the order in the Summary Table.

Index to Ginseng Products

Product Profile: Ginsana®

Manufacturer	**Pharmaton S.A., Switzerland**
U.S. distributor	**Pharmaton Natural Health Products**
Botanical ingredient	**Ginseng root extract**
Extract name	**G115®**
Quantity	100 mg extract (equivalent to 500 mg root)
Processing	No information
Standardization	4% ginsenosides
Formulation	Capsule

Recommended dose: Two capsules with water in the morning, or one capsule in the morning and one in the afternoon. Optimal results have been shown with four weeks continuous use, when taken as directed.

DSHEA structure/function: Enhances physical endurance; improves oxygen utilization; helps maintain natural energy and an overall feeling of healthy well-being.

Cautions: Consult a health care professional if taking a prescription medicine, pregnant, or nursing a baby. There have been rare reports of mild allergic skin reactions with the use of the extract in this product. In case of accidental ingestion/overdose, seek the advice or a health care professional immediately.

Other ingredients: Sunflower oil, gelatin, glycerin, lecithin, beeswax, chlorophyll.

Source(s) of information: Product package (© Boehringer Ingelheim Pharmaceuticals, Inc. 2000); Engels, Said, and Wirth, 1996; Forgo, Kayasseh, and Staub, 1981.

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	GPL Ginsana Products Ltd., Switzerland (Pharmaton S.A., Switzerland)
Indication	**Physical performance** in healthy athletes
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Forgo I, Schimert G (1985). The duration of effect of the standardized ginseng extract G115 in healthy competitive athletes. *Notabene Medici* 15 (9): 636-640.

Trial design
Parallel.

Study duration	9 weeks
Dose	2 (100 mg G115) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	28

No. of subjects completed	28
Sex	Male
Age	Mean: 24.5 years

Inclusion criteria
Healthy male athletes whose training program consisted of at least ten hours per week with their trainer.

Exclusion criteria
None mentioned.

End points
Performance capacity was measured before treatment, at the end of 9 weeks, and 1, 3, 7, and 11 weeks following the treatment. Oxygen uptake was measured at rest and during exercise with a cyclic ergometer. Pulmonary functions and heart rate were monitored, as well as reaction times to visual signals.

Results
Following nine weeks, the Ginsana group had an increase in maximum oxygen uptake (VO2 max.) of 17 percent and a lowering of the maximum exercise heart rate by 10 percent. The oxygen pulse, oxygen uptake divided by heart rate, increased by 26 percent. Serum lactate levels decreased by 40 percent. There was an increase in parameters of pulmonary function, i.e., forced expiratory one-second volume (FEV1) and forced vital capacity (FVC), as well as a shortening of reaction time to visual stimuli. These changes persisted for three weeks following treatment.

Side effects
None mentioned.

Authors' comments
It is concluded that the increased performance is based on far-reaching metabolic effects that are of importance from the clinical point of view. Particularly significant is the approximately 26 percent increase in oxygen transport capacity of the heart, which has a positive influence on the coronary reserve.

Reviewer's comments
This is a well-conducted study. The results showed very large improvements in fitness plus faster reaction times. However, the trial lacked an adequate description of randomization, and no mention was made of withdrawals or dropouts (translation reviewed). (2, 6)

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	GPL Ginsana Products Ltd., Switzerland (Pharmaton S.A., Switzerland)
Indication	**Physical performance** in athletes
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Forgo I, Kirchdorfer AM (1982). The effect of different ginsenoside concentrations on physical work capacity. *Notabene Medici* 12 (9): 721-727.

Trial design
Comparison of two standardized ginseng preparations: G115 containing 4 percent ginsenosides, and G115S containing 7 percent ginsenosides (200 mg daily). Subjects were instructed not to take any other pharmaceutical preparations during the trial period. Twenty subjects received G115 extract one summer, and ten received G115S the following summer.

Study duration	9 weeks
Dose	2 (100 mg) capsules daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	G115S
Site description	Not described
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male
Age	18-31 years (mean: 23.5)

Inclusion criteria
Top-class male athletes engaged in karate, wrestling, or boxing.

Exclusion criteria
None mentioned.

End points
Criteria measured were the maximum oxygen absorption capacity, lactate concentration in blood, and the heart rate during effort in an ergometry test.

Results
After nine weeks of treatment, oxygen capacity (VO2) increased 17 percent in subjects treated with G115 and by 20 percent in subjects treated with G115S. No statistical difference was found between the two groups. Lactic acid levels after ergometer effort were significantly lower in both groups at the end of the nine-week period. The differences between the groups were not statistically significant. Heart rate during effort improved significantly in both groups after nine weeks of treatment with no discernible differences between the two groups.

Side effects
No discernible side effects or intolerance reactions.

Authors' comments
Our clinical experimental results validate the view that there is no advantage in using ginseng extracts with a concentration of total ginsenosides greater than 4 percent.

Reviewer's comments
There was no placebo control and no difference between two very similar treatments. The results are consistent with other work from same lab (Forgo, Kayasseh, and Staub, 1981; Forgo, 1983; Forgo and Schimert, 1985) that fitness increases in athletes with ginseng, but these results are not scientific evidence on their own. The study subjects were not randomized (translation reviewed). (2, 5)

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	GPL Ginseng Products Ltd., Switzerland (Pharmaton S.A., Switzerland)
Indication	**Physical performance** in athletes
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Forgo I (1983). Effect of drugs on physical performance and hormone sys-

tem of sportsmen. *Münchener Medizinische Wochenschrift* 125 (38): 822-824.

Trial design
Parallel. Comparison of G115S (200 mg of 7 percent ginsenoside extract), Ginsana G115 plus vitamin E (200 mg 4 percent ginsenosides plus 400 mg vitamin E), and placebo in a three-arm study. Subjects were instructed to abstain from eating or drinking alcohol for two hours before tests and not to participate in heavy work/exercise for the preceding 24 hours.

Study duration	9 weeks
Dose	2 (100 mg G115 + 200 mg vitamin E) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	G115S
Site description	Not described
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male
Age	18-31 years (mean: 24.2)

Inclusion criteria
Top-class male athletes engaged in karate, wrestling, or boxing.

Exclusion criteria
Subjects were not allowed to take other pharmaceutical preparations during the trial.

End points
Aerobic capacity was measured using a cyclic ergometer. Heart rates were monitored. Serum lactate levels and hormone levels (testosterone and luteinizing hormone in plasma and cortisol in urine) were determined.

Results
Following nine weeks of treatment, oxygen capacity (VO2) increased from 4.0 to 4.3 liters/minute to 5.2 and 4.9 for the G115S and G115 + vitamin E groups, respectively. There was no change for the placebo group, with a sig-

nificant difference, $p < 0.01$. Lactate levels two minutes following exercise were significantly lower for both Ginsana groups. Heart rates were also lower for the Ginsana groups compared to placebo. There was no change in hormone levels.

Side effects
None mentioned.

Author's comments
The significantly increased oxygen absorption capacity and significantly reduced lactate levels in both Ginsana groups are indicative of greater fitness and a shorter recovery time. In addition, the decrease in heart rate attests to the improvement in physical work capacity.

Reviewer's comments
This is a well-reported study. The sample size is small (< 40) but adequate for this purpose (translation reviewed). (4, 6)

Clinical Study: G115®

Extract name	G115
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Physical performance** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Engels HJ, Said JM, Wirth JC (1996). Failure of chronic ginseng supplementation to affect work performance and energy metabolism in healthy adult females. *Nutrition Research* 16 (8): 1295-1305.

Trial design
Parallel.

Study duration	2 months
Dose	2 (100 mg) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	19
No. of subjects completed	19
Sex	Female
Age	21-35 years

Inclusion criteria
Healthy females maintaining normal diet and nonconsumption of other dietary supplements at least three to four weeks prior to initial pretest and throughout test period, maintaining regular physical activity habits throughout the study, and abstaining from food and caffeine products for at least three hours and from strenuous exertion for 24 hours prior to each laboratory testing session.

Exclusion criteria
Not mentioned.

End points
Test sessions were conducted before treatment and after eight weeks. Physical work capacity was measured while seated on a cycle ergometer. Volunteers cycled until voluntary exhaustion. Recovery oxygen uptake (VO2), respiratory exchange ratio (RER), minute ventilation (VE), heart rate, and blood lactic acid levels were measured at baseline rest, submaximal exercise, maximal exercise, and during postexercise recovery.

Results
Chronic ginseng supplementation had no effect on maximal work performance, resting, exercise, and recovery oxygen uptake, respiratory exchange ratio, minute ventilation, heart rate, and blood lactic acid levels. Habitual physical activity scores of study participants were found to be similar between the placebo and ginseng treatment groups at the beginning and end of the eight-week trial period.

Side effects
None reported.

Authors' comments
The present data in healthy adult females indicate that chronic dietary supplementation with a standardized extract of *Panax ginseng* C.A. Meyer does not result in an enhancement of work performance or a change in energy metabolism and improvement of the recovery response from maximal physical work.

Reviewer's comments
This well-conducted and well-reported study found no benefits in fitness of 19 normal, young, healthy females. The sample size may be inappropriate, but Forgo and Schimert (1985) found large effects among 28 athletes. In conclusion, either nonathletes will not benefit from ginseng, a larger sample is required, or there are problems with the following trials: Forgo, 1983; Forgo and Kirchdorfer, 1982; and Forgo and Schimert, 1985. (2, 5)

Clinical Study: G115®

Extract name	G115
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Physical performance** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Engels HJ, Wirth JC (1997). No ergogenic effects of ginseng (*Panax ginseng* C.A. Meyer) during graded maximal aerobic exercise. *Journal of the American Dietetic Association* 97 (10): 1110-1115.

Trial design
Parallel.

Study duration	2 months
Dose	200 or 400 mg G115 daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug Comparison	No
Site description	Single center
No. of subjects enrolled	36
No. of subjects completed	31
Sex	Male
Age	Mean (range for 3 groups): 23-27 years

Inclusion criteria
Healthy males maintaining a normal diet and nonconsumption of other dietary supplements at least three to four weeks prior to initial pretest and throughout test period, maintaining regular physical activity habits throughout the study, and abstaining from food and caffeine products for at least three hours, and from strenuous exertion for 24 hours, prior to each laboratory testing session.

Exclusion criteria
None mentioned.

End points
Participants were evaluated before and after eight weeks of treatment. Assessment of submaximal and maximal exercise responses were performed using a standard, graded maximal exercise protocol on a mechanically-braked cycle ergometer. Recovery oxygen uptake (VO2), respiratory exchange ratio (RER), minute ventilation (VE), heart rate, and blood lactic acid levels were measured, and the subjects rated perceived exertion.

Results
Supplementation with ginseng had no effect on the following physiologic and psychological parameters: oxygen consumption, respiratory exchange ratio, minute ventilation, blood lactic acid concentration, heart rate, and perceived exertion ($p > 0.05$).

Side effects
None mentioned.

Authors' comments
Our data in healthy men do not offer support for claims that *Panax ginseng* C.A. Meyer is an ergogenic aid to improve submaximal and maximal aerobic exercise performance.

Reviewer's comments
This well-conducted and reported trial showed no effects of ginseng on fitness in normal males. The data were not inconsistent with Forgo, Kayasseh, and Staub (1981) in which males (30 to 39 years) showed no benefits on fitness from ginseng. The randomization was not adequately described. (3, 5)

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	GPL Ginseng Products Ltd., Switzerland (Pharmaton S.A., Switzerland)
Indication	**Physical performance**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Forgo I, Kayasseh L, Staub JJ (1981). Effects of a standardized ginseng extract on general health, reaction capacity, pulmonary function and hormones. *Medizinische Welt* 32 (19): 751-756.

Trial design
Parallel. Each test group was divided into two age groups: 30 to 39 and 40 to 60 years old.

Study duration	3 months
Dose	2 (100 mg extract) capsules daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	120
No. of subjects completed	120
Sex	Male and female
Age	30-60 years

Inclusion criteria
Members of sports clubs.

Exclusion criteria
None mentioned.

End points
Visual and acoustic reactions were tested using the Vienna reaction unit. Subjects were tested before the study and after 3, 6, 9, and 12 weeks. Pul-

monary function was measured by a Sandoz analyzer before the trial and after 6 and 12 weeks. Luteinizing hormone, follicle stimulating hormone, estradiol (women), and testosterone (men) levels were determined before the study and after 12 weeks. Subjective variables were determined using a self-assessment questionnaire before the study as well as after 6 and 12 weeks.

Results
Reaction time and pulmonary function showed significant improvement in the Ginsana group, compared with the placebo group, in the 40- to 60-year-old men and women. Men and women ages 30 to 39 showed no significant change in reaction time, and men ages 30 to 39 showed no change in pulmonary function. In the self-evaluation (performance, mood, concentration) a clear improvement was evident in the subjects treated with Ginsana (men and women 40 to 60, $p = 0.001$, women 30 to 39, $p = 0.01$), with the exception of the men ages 30 to 39. No significant changes in hormone levels were observed.

Side effects
Not mentioned.

Authors' comments
The results obtained, particularly with regard to reaction, pulmonary function, self-assessment and compatibility have shown that Ginsana, a standardized ginseng extract, has a positive influence on the mental and physical functions investigated.

Reviewer's comments
Large well-conducted trial with clearly defined outcome measures and appropriately applied statistical methods. Older men and women showed improved reaction times with ginseng. All except males (30 to 39 years) showed enhanced pulmonary function. The study subjects were not randomized (translation reviewed). (2, 6)

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	GPL Ginseng Products Ltd., Switzerland (Pharmaton S.A., Switzerland)
Indication	**Physical performance**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Dörling E, Kirchdorfer AM, Ruckert KH (1980). Do ginsenosides influence the performance? Results of a double-blind study. *Notabene Medici* 10 (5): 241-246.

Trial design
Parallel.

Study duration	3 months
Dose	2 (100 mg extract) capsules daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Male and female
Age	22-80 years

Inclusion criteria
None mentioned.

Exclusion criteria
None mentioned.

End points
Subjects' response time to light and sound, assessment of the critical flicker fusion threshold, two-hand coordination, and the recovery quotient were measured. Each subject was questioned before commencement of the trial and after 2, 4, 6, 8, 10, and 12 weeks concerning general subjective physical condition, physical fitness, mental alertness, attitude to life/mood, concentration/memory, and sleep behavior.

Results
Reaction times to light and auditory stimuli improved in 81.6 percent of subjects in the Ginsana group, compared to 33.3 percent of subjects in the placebo group—a statistically significant difference. Improvement in critical flicker fusion thresholds was seen in 59.4 percent of Ginsana patients and 29.7 percent of placebo patients. Hand coordination in the Ginsana group

improved steadily from weeks 4 to 12, reaching 74.4 percent improvement at week 12. This was significantly different from the placebo group, in which improvement of coordination measured 16.6 percent. Recovery quotient for climbing exercise improved in 29 patients in the Ginsana group, and in 9 patients in the placebo group. After three months, recovery periods after exercise decreased in 97 percent of Ginsana patients and 33.3 percent of placebo patients. Results of self-assessments indicated that many Ginsana patients felt more fit after the trial, compared to only a few placebo patients.

Side effects
None mentioned.

Authors' comments
The test results indicate beneficial effects of several weeks of Ginsana treatment, especially on reaction time, two-hand coordination, recovery period, and recovery quotient. Questioning showed the results in the Ginsana group to be markedly superior to those of the placebo group, especially in the parameters of subjective physical condition, physical fitness, and sleep behavior.

Reviewer's comments
The trial was not well-reported, but it was run on a good sized sample. It was also placebo-controlled and double-blind. The data were favorable for reaction time, critical flicker fusion frequency and exercise capacity (translation reviewed). (2, 3)

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	GPL Ginsana Products Ltd., Switzerland (Pharmaton S.A., Switzerland)
Indication	**Cognitive functioning** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
D'Angelo L, Grimaldi R, Caravaggi M, Marcoli M, Perucca E, Lecchini S, Frigo GM, Crema A (1986). A double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. *Journal of Ethnopharmacology* 16 (1): 15-22.

Trial design
Parallel.

Study duration	3 months
Dose	2 (100 mg G115) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	32
No. of subjects completed	32
Sex	Male
Age	20-24 years

Inclusion criteria
Students in good physical condition.

Exclusion criteria
None mentioned.

End points
Patients were assessed before the trial and during the last week of treatment. Psychomotor assessments included a tapping test, simple and choice reaction time, cancellation test, digit symbol substitution test, mental arithmetic, and logical deduction. Blood tests were also preformed before the trial and in the last week. Subjects were asked to refrain from drinking caffeine or alcoholic beverages on assessment days.

Results
End performance of the G115 group was statistically superior to the placebo group only in mental arithmetic. Four other assessments showed an improvement over baseline for the G115 group compared to one assessment for the placebo group. However, no significant differences between G115 and placebo were found in other psychomotor tests.

Side effects
None reported.

Authors' comments
It is generally recognized in experimental and clinical studies that an improvement in psychomotor performance by pharmacological agents can be induced more easily when brain function is disturbed or impaired; therefore, the significant effect of G115 in these young, intellectually active volunteers appears remarkable.

Reviewer's comments
This study provides the first evidence of improved cognitive function in normal subjects with ginseng: one of eight tests showed significant improvement in the 12-week trial (mental arithmetic). However, no tests of memory were used. The randomization was inadequately described in this otherwise well-conducted trial. (3, 6)

Clinical Study: G115®

Extract name	G115
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Cognitive functioning** in healthy volunteers
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Kennedy DO, Scholey AB, Wesnes KA (2001). Dose dependent changes in cognitive performance and mood following acute administration of ginseng to healthy young volunteers. *Nutritional Neuroscience* 4: 295-310.

Trial design
Crossover. Subjects received 200, 400, and 600 mg of G115, as well as a matching placebo, in counterbalanced order, with a seven-day washout period between treatments.

Study duration	1 day
Dose	2, 4, or 6 (100 mg extract) capsules per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	20
No. of subjects completed	Not given
Sex	Male and female
Age	20-27 years (mean: 21.3)

Inclusion criteria
Healthy young volunteers taking no medication with the exception of oral contraception for female volunteers. Participants abstained from caffeine-containing products and alcohol on each study day.

Exclusion criteria
Heavy smokers (more than ten cigarettes per day).

End points
Cognitive performance was assessed using a computerized test battery immediately prior to dosing, and at 1, 2.5, 4, and 6 hours after. Primary outcome measures were quality of memory, speed of memory, speed of attention, and accuracy of attention. Secondary outcome measures of working memory (subfactor) and secondary memory (subfactor) were derived from quality of memory. Patients also completed the Bond-Lader Visual Analogue Scales (VAS) to analyze three mood factors: alertness, calmness and contentedness.

Results
For the "quality-of-memory" factor, 400 mg of ginseng saw improvements in the accuracy-of-memory task at 1, 2.5, 4, and 6 hours after dose (p = 0.0043, p = 0.026, p = 0.035, p = 0.002, respectively) in comparison with placebo. The 600 mg dose saw improvement at 2.5 hours after dosing (p = 0.02), but 200 mg saw no improvement. Only the 200 mg saw any difference in "speed of memory," which decreased four hours after dosing (p = 0.0045). Speed of performance on the attention tasks was reduced at four hours post dose for both 200 mg and 600 mg (p = 0.0001, p = 0.0019, respectively), as well as six hours post dose (p = 0.0006, p = 0.0003, respectively); 400 mg was not affected. For the secondary outcome measures, only the "secondary memory" subfactor reflected any differences from placebo: the 600 mg dose enhanced performance at 1, 2.5, and 4 hours after dosing (p = 0.046, p = 0.0034, p = 0.034, respectively); the 400 mg dose produced improvements at all time points (1, 2.5, 4, and 6 hours after dosing; p = 0.0022, p = 0.0027, p = 0.013, p = 0.0036, respectively); and the 200 mg dose caused a difference at four hours after dosing (p = 0.039). The 200 and 400 mg groups

also saw reductions on the "alert" factor of the Bond-Lader VAS six hours after dosing ($p = 0.001$, $p = 0.01$, respectively).

Side effects
None mentioned.

Authors' comments
The results of the current study show that ingestion of ginseng can affect cognitive performance in a time and dose-dependent manner. Moreover, these modulatory effects were caused by single doses of ginseng. Although this modulation was overwhelmingly beneficial for the middle dose (400 mg), there was evidence of cognitive and subjective mood costs associated with the other doses.

Reviewer's comments
This is a clear demonstration of acute cognitive effects of ginseng on young volunteers. Quality of memory is enhanced, but attention is disrupted. (4, 6)

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Vaccination potentiation**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Scaglione F, Cattaneo G, Alessandria M, Cogo R (1996). Efficacy and safety of the standardized ginseng extract G115 for potentiating vaccination against common cold and/or influenza syndrome. *Drugs Under Experimental and Clinical Research* 22 (2): 65-72.

Trial design
Parallel. Vaccination with Agrippal® influenza polyvalent vaccine (0.5 ml) took place four weeks after the start of administration of G115 or placebo.

Study duration	3 months
Dose	2 (100 mg G115) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind

Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	3 private practices
No. of subjects enrolled	227
No. of subjects completed	219
Sex	Male and female
Age	31-65 years (mean: 48)

Inclusion criteria
Over 18 years of age, recommended for influenza vaccination.

Exclusion criteria
Already vaccinated for influenza; already taking ginseng; with granulocytes <1,000 mm; hypersensitivity to ginseng; receiving any investigational agent or antineoplastic chemotherapy; with underlying terminal diseases (e.g., AIDS) or liver disease; pregnant or nursing women; and subjects with severe gastritis.

End points
Incidences of influenza/common cold were recorded at 2, 4, 8, 10, and 12 weeks. Natural killer activity (peripheral blood mononuclear cells) and antibody titers were measured before the trial and after 4, 8, and 12 weeks. Laboratory safety parameters were measured before the trial and after 12 weeks. Adverse events were recorded every two weeks after the trial.

Results
The frequency of influenza or common cold between weeks 4 and 12 was 42 cases in the placebo group and 15 cases in the G115 group, the difference being statistically highly significant ($p < 0.001$). Whereas antibody titers by week 8 rose to an average of 171 units in the placebo group, they rose to an average of 272 units in the G115 group ($p < 0.0001$). Natural killer activity levels at weeks 8 and 12 were nearly twice as high in the G115 group as compared to the placebo group ($p < 0.0001$).

Side effects
Of the eight adverse events reported for G115, four were insomnia, three were gastrointestinal, and one was anxiety.

Authors' comments
The results obtained from this study show that the standardized ginseng extract G115 Ginsana is able to improve the immune response in vivo in humans and can protect against influenza and the common cold.

Reviewer's comments
Well-conducted study showing that ginseng protects against influenza and improves immune response. The randomization was inadequately described. (3, 6)

Clinical Study: G115®

Extract name	G115
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Bronchitis**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Scaglione F, Cogo R, Cocuzza C, Arcidiancono M, Beretta A (1994). Immunomodulatory effect of *Panax ginseng* C.A. Meyer (G115) on alveolar macrophages from patients suffering with chronic bronchitis. *International Journal of Immunotherapy* 10 (1): 21-24.

Trial design
Parallel.

Study duration	2 months
Dose	1 (100 mg G115) capsule every 12 hours
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	40
No. of subjects completed	Not given
Sex	Male and female
Age	Not given

Inclusion criteria
Smokers (less than 20 cigarettes per day) who suffered from chronic bronchitis.

Exclusion criteria
Subjects who underwent vaccination within 20 days prior to the study, and those with suspected or known hypersensitivity toward the tested drug and/or its excipients. No treatment with corticosteroids or immunomodulatory agents was allowed during the study.

End points
Alveolar macrophages were collected by bronchoalveolar lavage before and after four and eight weeks of treatment. Macrophages were immediately assayed for phagocytic activity and killing power toward *Candida albicans.*

Results
The phagocytosis index and the phagocytosis fraction show an increase in the G115 group that was statistically significant at the end of the eighth week. Intracellular killing also showed a significant increase in the G115 group detectable at the end of the eighth week. No modification of these parameters was seen in the placebo group.

Side effects
The treatment was well-tolerated in all patients enrolled in the study.

Authors' comments
These results show that G115 extract is able to improve the immune response of alveolar macrophages in chronically compromised subjects. These findings suggest that substances such as G115 may play an important role in the prevention and therapy of respiratory disorders.

Reviewer's comments
This is an important pilot study showing that ginseng may protect by increasing immune response in smokers with chronic bronchitis. The study showed improvements under placebo that were not statistically evaluated, but may have been significant. Such findings stress the need for placebo-controlled trials in this field. However, the placebo effects do not affect the outcome of this study since the effect of G115 was far greater. This study needs replication: the randomization process was not described and blinding was only single. (0, 5)

Clinical Study: G115®

Extract name	G115
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Bronchitis**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Scaglione F, Weiser K, Alessandria M (2001). Effects of the standardized ginseng extract G115 in patients with chronic bronchitis: A non-blinded, randomized, comparative pilot study. *Clinical Drug Investigation* 21 (1): 41-45.

Trial design
Parallel. Patients received 875 mg amoxicillin and 125 mg clavulanic acid twice daily for nine days. They were then divided into two groups. Both groups continued with the antibacterial treatment, and one group also received G115, for an additional nine days.

Study duration	9 days
Dose	2 (100 mg G115) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Single center
No. of subjects enrolled	75
No. of subjects completed	44
Sex	Male and female
Age	Not given

Inclusion criteria
More than 18 years old with symptoms of acute bacterial attack of chronic bronchitis (ACB). Chronic bronchitis was defined as a productive cough present on most days of a minimum of three consecutive months over two or more successive years. ACB was defined as a rapid onset of cough with production of purulent sputum. In addition, the patients had to have one or more of the following: dyspnea, tachypnea, wheezing, fever (> 38°C), and be suitable for therapeutic treatment with amoxicillin and clavulanic acid.

Exclusion criteria
Concurrent pneumonia, systemic use of an anti-infective drug seven days prior to enrollment, systemic corticosteroid therapy (excluding inhaled or intranasal aerosolized corticosteroids), hypersensitivity to penicillins, a history of significant renal or hepatic impairment, or treatment with a drug within the last 30 days that had not received regulatory approval at the time of study entry. Immediate family of investigators and site personnel were also excluded.

End points
Each morning of the trial period, a sample of bronchial secretion was taken by protected expectoration. The sample was plated out and the bacterial count (colony forming units) was determined. Patients were considered cured and antibacterial therapy was stopped upon elimination of symptoms of infection.

Results
In the group receiving G115, bacterial clearance was significantly faster than those receiving antibacterials alone. Significant improvement in the G115 group was observed on days 4, 5, 6, and 7 ($p < 0.01$), whereas a borderline trend was observed on day 8 ($p = 0.055$). A significant decrease in time for clearance of infection was also observed.

Side effects
None mentioned.

Authors' comments
These results indicate a beneficial effect of G115 ginseng extract on the reduction of bacterial counts in the bronchial systems of patients with acute attacks of chronic bronchitis. Patients in whom the elimination of bacteria from the bronchial system is particularly difficult may benefit from the use of ginseng.

Reviewer's comments
An interesting, nonblinded pilot study showing ability of ginseng to speed recovery of patients treated with antibacterials. Lack of placebo control may present a problem, however, as an improvement in the placebo group was seen in a similar study (Scaglione et al., 1994). (3, 6)

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Menopausal symptoms**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Wiklund IK, Mattsson LA, Lindgran R, Limoni C (1999). Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: A double-blind, placebo-controlled trial. *International Journal of Clinical Pharmacology Research* 19 (3): 89-99.

Trial design
Parallel. Two-week run-in period before allocation to treatment groups.

Study duration	4 months
Dose	2 (100 mg G115) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	384
No. of subjects completed	379
Sex	Female
Age	45-65 years (mean: 53)

Inclusion criteria
Healthy postmenopausal women, ages 45 to 65 years, without hormone replacement therapy for the previous two months and with no bleeding during the previous six months, reporting at least six episodes of hot flashes during at least three days over the past seven days.

Exclusion criteria
Previous or concomitant serious or chronic medical conditions, uncontrolled hypertension (>160/95), psychiatric illness, taking concomitant medication such as tranquilizers, and those who were unable to understand and complete the questionnaires.

End points
Patients completed the following validated questionnaires at baseline and after 16 weeks of treatment to assess the effects of the extract on quality of life: Psychological General Well-Being (PGWB) index, Women's Health Questionnaire (WHQ), and Visual Analogue Scales (VAS).

Results
Ginseng treatment when compared with placebo showed only a tendency for a slightly better overall symptomatic relief according to the total score of the PGWB ($p < 0.1$). Analysis of PGWB subsets reported p values <0.05 for depression, well-being, and health subscales. No statistically significant effects were seen for the WHQ and the VAS of the physiological parameters, including vasomotor symptoms (hot flashes).

Side effects
Tolerability was rated as good or very good by more than 90 percent of subjects. Similar numbers of adverse events were seen in both the active and placebo groups. One patient on ginseng withdrew from the study due to a treatment-related adverse event (nausea).

Authors' comments
The data of the present study suggest that ginseng extract may offer effective relief in quality-of-life-related aspects in healthy postmenopausal women. The positive effects of ginseng on depression, well-being, and health deserve further attention.

Reviewer's comments
Well-conducted and well-presented study. The large sample validated instruments, yet results, while consistent and close to significant, were not robust. The effect on depression is interesting. The randomization was not adequately described. (3, 6)

Clinical Study: G115®

Extract name	G115
Manufacturer	Pharmaton, S.A., Switzerland
Indication	**Psychological well-being** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Cardinal BJ, Engels H-J (2001). Ginseng does not enhance psychological well-being in healthy young adults: Results of a double-blind, placebo-controlled, randomized clinical trial. *Journal of the American Dietetic Association* 101 (6): 655-660.

Trial design
Parallel. Patients received either 200 or 400 mg G115 per day, or placebo.

Study duration	2 months
Dose	200 or 400 mg daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind

Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Lab
No. of subjects enrolled	96
No. of subjects completed	83
Sex	Male and female
Age	21-31 (mean: 25.7)

Inclusion criteria
Healthy volunteers (determined by a medical history/health status questionnaire) who agreed to not change their physical activity level substantially, to maintain their usual diets, and to not take other dietary supplements during the study period.

Exclusion criteria
None mentioned.

End points
Subjects were assessed before the trial start (baseline) and at the end of the trial (between 56 to 60 days after starting supplementation). Three psychological variables were assessed: positive affect, negative aspect (both determined by the Positive Affect-Negative Affect Scale [PANAS]), and total mood disturbance (determined by the Profile of Mood States inventory [POMS]).

Results
No changes were observed in the assessed psychological variables for any of the treatments. Compared with published norms, subjects had normal psychological profiles both pre- and postintervention for positive affect, negative affect, and total mood disturbance.

Side effects
None mentioned.

Authors' comments
The present study offers no support for commercial manufacturers', distributors', and suppliers' claims that *Panax ginseng* C.A. Meyer enhances healthy, young adults' psychological well-being beyond "normal" levels. In our experiment, chronic ginseng supplementation—at both its clinically recommended level and twice that level—was no more effective in enhancing healthy, young adults' mental health than was a sugar pill.

Reviewer's comments
Although well conducted, this study is severely compromised by relying on

end points for which no previous history of sensitivity is presented. Further, having established that the study had adequate statistical power for one outcome, they raised the required significance level, but did not report final *p* values. Good trial methodology, but poor science. (5, 5)

Clinical Study: Ginsana®

Extract name	G115®
Manufacturer	Pharmaton S.A., Switzerland
Indication	**General well-being; quality of life**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Ellis JM, Reddy P (2002). Effects of *Panax ginseng* on quality of life. *The Annals of Pharmacotherapy* 36 (3): 375-379.

Trial design
Parallel. Subjects consumed no ginseng-containing products one week prior to the study. Treatment (ginseng or placebo) was taken with a full glass of water before 10 a.m.

Study duration	2 months
Dose	200 mg daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	30
No. of subjects completed	23
Sex	Male and female
Age	18-25 years (mean: 21.6)

Inclusion criteria
Volunteers at least 18 years old.

Exclusion criteria
Subjects taking anticoagulants; with previous adverse reaction to any ginseng extract (*Panax,* American, or Siberian) or lactose; with history of alcohol abuse; who were pregnant or planning on becoming pregnant; with a history of autoimmune, hepatic, or renal dysfunction; with a history of supraventricular or ventricular arrhythmias; or who did not provide informed consent.

End points
In order to assess health-related quality of life (HRQOL), subjects were given the Short Form-36 Health Survey version 2 (SF-36v2) at baseline and at weeks 4 and 8. This questionnaire assesses eight domains: mental health, physical functioning, social functioning, role limitation due to physical health, role limitations due to emotional problems, vitality, and general health perceptions.

Results
After four weeks of treatment, the ginseng group had significantly higher scores than the placebo group in social functioning ($p = 0.014$) and the mental component summary ($p = 0.019$). A trend toward a higher score in mental health ($p = 0.075$) was observed. These differences did not persist through the end of the eight-week trial. No significant differences in the other scored domains were found between groups at either 4 or 8 weeks after beginning treatment. Compared to the placebo group, the ginseng group was more likely to state that they thought they received ginseng and that they felt differently during the study ($p < 0.05$, $p = 0.03$, respectively).

Side effects
The incidence of side effects for ginkgo and placebo were similar (33 percent and 17 percent, respectively, $p < 0.40$). One report of each of the following adverse effects occurred in the ginseng group: nausea/vomiting, rebound irritability, insomnia, and headache.

Authors' comments
We found that *P. ginseng* 200 mg/day improved social functioning and mental component summary scores after four weeks of therapy, but these differences did not persist with continued use. Caution should be taken in interpretation because of the small sample size and the young population studied. Future studies should examine the effect of *P. ginseng* on HRQOL using a larger sample size, measure the effects at earlier time points, and investigate the effects of ginseng withdrawal.

Reviewer's comments
Sound study, even though the statistical power was marginal. The major flaw of the analysis was the substitution of data for dropouts. (5, 5)

Product Profile: Ginsana® Gold Blend

Manufacturer	**Pharmaton S.A., Switzerland**
U.S. distributor	**Pharmaton Natural Health Products**
Botanical ingredient	**Ginseng root extract**
Extract name	**G115®**
Quantity	40 mg
Processing	No information
Standardization	4% ginsenosides
Formulation	Gelcap

Recommended dose: Take two gelcaps with water in the morning or one gelcap in the morning and one in the afternoon. Effectiveness as early as four weeks of continuous uninterrupted use.

DSHEA structure/function: Clinically proven to increase vitality and reduce fatigue. Nourishes, fortifies, and revitalizes.

Cautions: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

Other ingredients: Vitamin A (beta carotene) 2,000 IU, vitamin C (ascorbic acid) 60 mg, vitamin D (cholecalciferol) 200 IU, vitamin E (dl-alpha tocopherol) 15 IU, thiamine (Vitamin B1) 1.2 mg, riboflavin (vitamin B2) 1.7 mg, niacin (vitamin B3) 15 mg, vitamin B6 (pyridoxine HCl) 2 mg, folic acid 200 mcg, vitamin B12 (cobalamin conc.) 1 mcg, calcium (calcium phosphate) 100 mg, iron (ferus sulfate) 9 mg, phosphorus 80 mg, magnesium 10 mg, zinc (zinc sulfate) 1 mg, copper (copper sulfate) 1 mg, manganese (manganese sulfate) 1 mg; microcrystalline cellulose, gelatin, hydrogenated corn syrup, providone, glycerin, croscarmellose sodium, magnesium stearate, colloidal silica, hydroxypropyl methylcellulose, ethylcellulose, titanium dioxide, dibutyl sebecate, stearic acid powder, polysorbate 80, FD&C yellow lake #6, FD&C red lake #40, vanillin powder, polyethylene glycol 8000, caramel color, FD&C blue lake #1.

Comments: Previously sold as Vitasana™. Sold as Gericomplex® and Pharmaton® Capsules in Europe.

Source(s) of information: Product package (© Boehringer Ingelheim Pharmaceuticals, Inc. 2001); Vitasana™ Supplement Facts (© Boehringer Ingelheim Pharmaceuticals, Inc. 1998); Engels, Said, and Wirth, 1996.

Clinical Study: Pharmaton® Capsules

Extract name	G115®
Manufacturer	Pharmaton S.A., Switzerland
Indication	**General well-being; physical or mental stress**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference

Marasco CA, Vargas RR, Villagomez SA, Infante BC (1996). Double-blind study of a multivitamin complex supplemented with ginseng extract. *Drugs Under Experimental and Clinical Research* 22 (6): 323-329.

Trial design

Parallel. Comparison of ginseng combined with multivitamins to multivitamins alone.

Study duration	3 months
Dose	One capsule (G115 + vitamins, minerals, trace elements, and lipotropic substances: inositol, choline, linoleic, and linolenic acid) daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Multivitamin capsules
Site description	Single center
No. of subjects enrolled	625
No. of subjects completed	501
Sex	Male and female
Age	18-65 years (mean: 37-39)

Inclusion criteria

Adults known to be subject to increased physical and mental stress and/or to present fatigue symptoms not related to any of the exclusion criteria.

Exclusion criteria
Pregnancy, interaction with other medication not normally allowed, or protocol violation.

End points
At each of the four monthly visits, quality of life (physical and sexual activity, well-being) was assessed by a standardized 11-item questionnaire validated by the Medical School of the National Autonomous University of Mexico. Pulse rate, arterial pressure and general clinical history were also assessed.

Results
Administration of either the Pharmaton complex or the multivitamins alone induced a significant increase in the quality-of-life index. However, improvement of 11.9 points for the Pharmaton Capsules was significantly superior to the 6.4 average increase with the multivitamin capsules. When indices at visit 4 were compared with visit 1, the Pharmaton group showed significant improvement in every one of the 11 questionnaire items ($p < 0.0001$), whereas the multivitamin group did not show significant improvement in any of these items. No differences were observed between the two groups' systolic blood pressure and heart rate, but the diastolic pressure at visit 4 was significantly lower for the Pharmaton group ($p < 0.01$). Significant increases in body weight were recorded in the multivitamin group.

Side effects
Adverse effects were minimal in both groups.

Authors' comments
This study demonstrated that Pharmaton Capsules were more effective than multivitamins alone in improving the quality of life in a population subjected to high levels of physical and mental stress.

Reviewer's comments
This is a well-conducted and well-designed large trial showing ginseng plus vitamins is better than vitamins alone in quality-of-life index. (4, 6)

Clinical Study: Gericomplex®

Extract name	G115®
Manufacturer	Pharmaton SA, Switzerland
Indication	**General well-being; quality of life** in healthy volunteers

Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Wiklund I, Karlberg J, Lund B (1994). A double-blind comparison of the effect on quality of life of a combination of vital substances including standardized ginseng G115 and placebo. *Current Therapeutic Research* 55 (1): 32-42.

Trial design
Parallel.

Study duration	3 months
Dose	2 (40 mg G115 + vitamins, minerals, and trace elements) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	417
No. of subjects completed	390
Sex	Male and female
Age	33-51 years (mean: 42.7)

Inclusion criteria
Healthy volunteers older than 25 years.

Exclusion criteria
Subjects with a systolic blood pressure greater than or equal to 200 mmHg or diastolic blood pressure greater than or equal to 100 mmHg were excluded. Other exclusion criteria were sensitivity to ginseng extracts, a history of alcohol or drug abuse, pregnancy or breastfeeding, inability or unwillingness to cooperate, and the use of concomitant medication (except short-term medication, for example, for headache or gastrointestinal discomfort).

End points
Quality of life was evaluated in two standard, self-administered questionnaires, the Psychological General Well-Being (PGWB) index and the Sleep Dysfunction scale. In addition, bipolar adjectives in Visual Analogue Scales

(VAS) were used to quantify changes in other behavioral aspects. Assessment was carried out at baseline and after 12 weeks of treatment.

Results
General well-being (PGWB index) improved significantly in both groups during the 12-week trial. No significant difference was observed between the two groups, either in the total score or in the dimensions. In terms of sleep, there was a similar slight improvement during the course of active treatment, but no statistical difference between the groups. On the VAS, subjects receiving ginseng showed significant improvement in alertness ($p = 0.05$), appetite ($p = 0.04$), relaxation ($p = 0.02$), and the overall score ($p = 0.03$). Among a subgroup of subjects with the 20 percent lowest scores at baseline, ginseng improved both vitality ($p = 0.03$) and depressed mood ($p = 0.05$). Benefits of ginseng therapy were more pronounced for the 20 percent of subjects who had the lowest quality-of-life rating for each measure.

Side effects
Nine subjects in the ginseng group and six subjects in the placebo group withdrew prematurely because of adverse effects that could be related to the medication.

Authors' comments
It was concluded that in healthy subjects the combination of vital substances including G115 offers significant advantages over placebo treatment in terms of improvement in self-assessed feelings of vitality, alertness, less time urgency (feeling more relaxed), and appetite. The beneficial effects appear to be more pronounced in those subjects who were at a disadvantage and worse off before the study started.

Reviewer's comments
Well-conducted, large, and well-reported study. (5, 6)

Clinical Study: Pharmaton® Capsules

Extract name	G115®
Manufacturer	Pharmaton S.A., Switzerland
Indication	**General well-being; functional fatigue**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Le Gal M, Cathebras P, Struby K (1996). Pharmaton Capsules in the treat-

ment of functional fatigue: A double-blind study versus placebo evaluated by a new methodology. *Phytotherapy Research* 10 (1): 49-53.

Trial design
Parallel.

Study duration	6 weeks
Dose	2 (40 mg G115 + vitamins, minerals, and deanol [dimethylaminoethanol bitartrate, 26 mg])
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	232
No. of subjects completed	219
Sex	Male and female
Age	25-60 years

Inclusion criteria
Patients included in the study were suffering from functional fatigue for at least 15 years.

Exclusion criteria
Excluded from the study were patients suffering from an acute or chronic disease (endocrine, neurological, infectious, malignant) that could have been responsible for the fatigue, liver disease, calcium lithiasis, or psychiatric illness, especially depression. Also excluded from the study were alcoholic patients and alcoholics undergoing detoxification therapy, patients being treated with psychotropic drugs, antibiotics, or antiasthenic preparations, including vitamins, trace elements and homeopathy, pregnant women or those likely to become pregnant, and women who had given birth less than three months before or who were still breast-feeding.

End points
Each patient was allowed to choose, from a preestablished list of 20 suggestions, the five items that best described his or her complaints. An individual fatigue score was calculated for each patient on the basis of the sum of the scores given by the patient for each of the five items selected (each item was

evaluated on a four-point scale). Assessment was carried out at baseline and on days 21 and 42.

Results
At the beginning of the study, 28 patients in the Pharmaton group and 29 patients taking placebo had signs or symptoms related to fatigue (the numbers of related signs/symptoms in each group were 46 and 52, respectively). Both groups had improved after 21 days, with 16 patients taking the active substance and 22 taking placebo having signs or symptoms associated with fatigue (number of associated symptoms in each group: 10 and 20, respectively). At the end of the study, both groups had improved even more. Only six patients in the Pharmaton group and 16 in the placebo group reported signs or symptoms associated with fatigue (the number of associated signs/symptoms in each group were 4 and 14, respectively). The difference between the groups was statistically significant ($p = 0.023$). The efficacy of Pharmaton Capsules was assessed as better than placebo by both the patients and the doctors.

Side effects
The most common unwanted effects were nausea and/or vomiting in six patients of the Pharmaton group and in one patient of the placebo group; sleep disorders in three patients of each group; abdominal pain in three patients of each group; bowel disorder in two Pharmaton patients; and headache in two placebo patients.

Authors' comments
The efficacy of Pharmaton Capsules on the complaints caused by a state of functional fatigue, after six weeks of treatment, has been proven by the results of this study.

Reviewer's comments
It is hard to judge the importance of active versus placebo after 42 days due to the large placebo effect. However, the final difference between groups was statistically significant. The blinding was not adequately described. (3, 5)

Clinical Study: Geriatric Pharmaton®

Extract name	G115®
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Physical performance** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Pieralisi G, Ripari P, Vecchiet L (1991). Effect of a standardized ginseng extract combined with dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements on physical performance during exercise. *Clinical Therapeutics* 13 (3): 373-382.

Trial design
Three phase trial. First two phases were crossover trials of six weeks each. Third phase was a single-blind placebo washout period of one week.

Study duration	6 weeks
Dose	2 (G115 + dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	50
No. of subjects completed	47
Sex	Male
Age	21-47 years (mean: 33)

Inclusion criteria
Healthy male sports teachers.

Exclusion criteria
None mentioned.

End points
Blood samples were taken for lab tests at the beginning of the study and at the end of each phase. An exercise test up to maximal load was performed on a treadmill with a seven-step protocol. Before and after each step, and three, six, and nine minutes after exercise, heart rate, oxygen consumption, ventilation, carbon dioxide production, the respiratory quotient, systolic and diastolic blood pressure, and plasma lactic acid levels were measured. At the end of each exercise test the total maximal work load and the maximal oxygen consumption were determined.

Results
The total work load and maximal exercise were significantly greater after ginseng consumption than after placebo. At the same work load, oxygen consumption, plasma lactate levels, ventilation, carbon dioxide production, and heart rate during exercise were significantly lower after the ginseng preparation than after placebo. The effects of ginseng were more pronounced in the subjects with maximal oxygen consumption less than 60 ml/kg per minute during exercise than in the subjects with levels of 60 ml/kg per minute or greater. The results indicate that the ginseng preparation increased the subjects' work capacity by improving muscular oxygenation.

Side effects
None reported.

Authors' comments
The results of this study showed that the administration of two capsules of a ginseng preparation per day for six weeks increased the subjects' work capacity, probably by improving muscular oxygen utilization.

Reviewer's comments
This is a good trial with interesting results. However, it did not adequately describe randomization and blinding, nor important aspects of the analysis of study results. (1, 5)

Clinical Study: Gegorvit® Pharmaton

Extract name	G115®
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Age-related memory impairment**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Neri M, Andermarcher E, Pradelli JM, Salvioli G (1995). Influence of a double blind pharmacological trial on two domains of well-being in subjects with age associated memory impairment. *Archives of Gerontology and Geriatrics* 21 (3): 241-252.

Trial design
Parallel. Fifteen-day run-in period before baseline evaluation and treatment phase.

Study duration	9 months
Dose	2 (G115 + dimethylaminoethanol bitartrate [deanol], minerals and vitamins) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	60
No. of subjects completed	Not given
Sex	Male and female
Age	51-65 years (mean: 60.7)

Inclusion criteria
Subjects with age-associated memory impairment (AAMI). Specifically, subjects older than 50 years with subjective memory disturbances exceeding the threshold value of a metamemory scale (De Vreese, forgetfulness scale threshold: 20) and memory deficit revealed by a paragraph recall test adjusted for age and education level (Babcock tale). Global cognitive deficit was ruled out by a score of at least 24 on the Mini Mental State Examination. A monotonic psychopathology rating scale (Scala di Valutazione del Benessere Affettiro [SVEBA]) graded and validated for the Italian population was applied to screen for clinically significant affective disorders.

Exclusion criteria
Medical or neurological disorders producing cognitive deterioration and current psychiatric diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised (DSM-III-R). Subjects on long-term medication.

End points
Testing performed before and after 15-day run-in period as well as at three-month intervals over nine months. Subjects were evaluated by the following tests: the Life Satisfaction in the Elderly Scale (LSES) evaluating eight categories of well-being; the Symptom Rating Scale (SRT), a checklist evaluating the frequency and intensity of depression, anxiety, somatisation, and inadequacy; and the Randt Memory Test, a battery of seven subtest scores to evaluate Acquisition-Recall (AR), Delayed Memory (DM), and the sum, indexed to age, yields the Memory Index (MI).

Results
At final evaluation, the SRT did not differ in the drug and placebo groups, whereas MI and LSES were significantly higher in the drug-treated group. Moreover, the negative correlation between the affective SRT and cognitive MI component of psychological well-being waned in the drug-treated group, but not in the placebo group. In the drug-treated group, a positive correlation emerged between the cognitive index and social contacts, mood, and self-concept factors of the LSES. Drug-treated subjects differed from controls in part by improved scores on objective cognitive tests, but even more so by modification of the correlations among indexes of psychological well-being and quality of life.

Side effects
None requiring withdrawal from study were reported.

Authors' comments
The effect of aging on cerebral function appears to be multidimensional in nature. Therefore a medication that is presumed to act on some of the mechanisms underlying AAMI meets the prerequisites as a candidate for drug therapy.

Reviewer's comments
Interesting, well-conducted study showing improved memory with treatment and a suggestion of enhanced quality of life. The trial lacked an adequate description of randomization and withdrawals or dropouts. (2, 6)

Clinical Study: Gericomplex®

Extract name	G115®
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Geriatric rehabilitation**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Thommessen B, Laake K (1996). No identifiable effect of ginseng (Gericomplex) as an adjuvant in the treatment of geriatric patients. *Aging* (Milan, Italy) 8 (6): 417-420.

Trial design
Parallel.

Study duration	2 months
Dose	2 (40 mg G115 + vitamins, minerals, and trace elements) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	60
No. of subjects completed	49
Sex	Male and female
Age	65-87 years (mean: 77.9)

Inclusion criteria
Patients admitted to a department of geriatric medicine for treatment and rehabilitation. Main diagnoses were cardiovascular, pulmonary, or musculoskeletal diseases, and depression/anxiety.

Exclusion criteria
Cognitive impairment Mini Mental State Examination (MMSE) score < 20, cancer, difficulties in swallowing, or in a terminal state of disease.

End points
Patients were assessed at baseline in the hospital and after eight weeks of treatment at home by the same physician. Activities of daily living (ADL) score was determined according to the Barthel ADL index. Cognitive function was assessed at baseline and after eight weeks using the MMSE, the Kendrick Object Learning test and the Trail-Making test. Somatic symptoms and symptoms of depression and anxiety were scored on a 23-question version of the Hopkins Symptom Checklist.

Results
Length of stay in hospital did not differ in the two groups. The groups also improved to the same degree on the various functional outcome measures, except for the Kendrick Object Learning test, on which the placebo group improved more markedly.

Side effects
None reported.

Authors' comments

We conclude that Gericomplex has no significant effect as an adjuvant in the rehabilitation of geriatric patients ages 65 years and older.

Reviewer's comments

A well-conducted and well-written study that failed to mention the randomization technique but nonetheless has a clear negative finding. (3, 6)

Product Profile: Gerimax Ginseng Extract

Manufacturer	**Dansk Droge, Denmark**
U.S. distributor	None
Botanical ingredient	**Ginseng root extract**
Extract name	None given
Quantity	100 mg
Processing	No information
Standardization	No information
Formulation	Tablet

Recommended dose: One tablet per day.

Comments: According to personal correspondence, Gerimax is a copy of the G115® extract (Pharmaton S.A.).

Source(s) of information: Sotaniemi, Haapakoshi, and Rautio, 1995; <www.nycomed. at/allgemein/detail_allgemein.php?produkt_id=21>.

Clinical Study: Gerimax Ginseng Extract

Extract name	None given
Manufacturer	Dansk Droge, Denmark
Indication	**Cognitive functioning** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference

Sorensen H, Sonne J (1996). A double-masked study of the effects of ginseng on cognitive functions. *Current Therapeutic Research* 57: 959-968.

Trial design
Parallel.

Study duration	8 to 9 weeks
Dose	400 mg ginseng extract
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	127
No. of subjects completed	112
Sex	Male and female
Age	42-61 years (mean: 51)

Inclusion criteria
Healthy subjects ages 40 to 70.

Exclusion criteria
Serious illness, diseases of the central nervous system, and abuse of alcohol or drugs. Patients taking psychoactive medication that might interact with ginseng were also excluded.

End points
Patients received a battery of cognitive tests at baseline and again at the end of the study. The battery consisted of psychomotor tests (Simple Auditive Reaction Times Test, Simple Visual Reaction Times Test, and Finger-Tapping Test), attention and concentration tests (D2 Test and Fluency Test), learning and memory tests (Selective Reminding Test, Logical Memory and Reproduction Test, and Rey-Oestrich Complex Figure Test), and abstraction tests (Wisconsin Card Sorting Test). A questionnaire was also provided at the end of the trial for the subjects to discusses changes during the treatment period in their general well-being, energy, memory, concentration, and speed.

Results
The ginseng group showed a tendency toward faster simple reactions (Simple Auditive Reaction Times Tests; especially the most rapid auditive reaction time) and significantly better abstract thinking (Wisconsin Card Sorting Test) than the controls. No other differences in test scores reached signifi-

cance. With regards to the questionnaire, both groups reported a small improvement in general well-being and energy, but this did not reach significance.

Side effects
No side effects were identified.

Authors' comments
The group that received ginseng for eight to nine weeks showed slightly faster reaction times than the placebo group. Similarly, the subjects who received ginseng performed significantly better on an abstraction test. These findings conform to the assumption that ginseng causes increased alertness and arousal.

Reviewer's comments
This is a well-conducted trial showing some benefit of ginseng on reaction times and executive function. The results are also suggestive of enhancement on the Selective Reminding Test, which is relevant to a similar finding in Kennedy, Scholey, and Wesnes (2001). (3, 5)

Clinical Study: Gerimax Ginseng Extract

Extract name	None given
Manufacturer	Dansk Droge, Denmark
Indication	**Diabetes (NIDDM)**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Sotaniemi EA, Haapakoski E, Rautio A (1995). Ginseng therapy in non-insulin-dependent diabetic patients. *Diabetics Care* 18 (10): 1373-1375.

Trial design
Parallel. Pretrial run-in period of eight weeks. Patients were instructed to follow a diet consisting of 20 percent protein, 50 percent carbohydrates, and 30 percent fat.

Study duration	2 months
Dose	100 or 200 mg ginseng daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No

Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	36
No. of subjects completed	36
Sex	Male and female
Age	48-61 years (mean: 58.7)

Inclusion criteria
Newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM) patients.

Exclusion criteria
None mentioned.

End points
Patients kept diaries to monitor their physical activity, and the change was compared to the pretrial period. Patients self-rated subjective tests of mood, well-being, and vigor. Psychoperformance and memory (Digit Span test) were also tested. Patients were interviewed with a questionnaire about their sleep, degree of fatigue, and lifestyle. The following were also measured to evaluate efficacy: blood glucose and insulin levels; serum lipids; glycated hemoglobin (HbA1c); serum aminoterminalpropeptide (PIIINP); and body weight.

Results
Both doses of ginseng improved psychomotor performance, mood, and vigor significantly, and the 200 mg dose also improved well-being and physical activity significantly, all compared to baseline. Sleep and memory did not change significantly. Body weight was reduced significantly by all three groups. Fasting blood glucose was improved by both the 100 mg and 200 mg dose compared to placebo. The 200 mg dose also reduced serum HbA_{1c} and PIIINP values. Ginseng did not change serum lipid values.

Side effects
No side effects associated with the treatment.

Authors' comments
Our study demonstrates that drugs that activate mood and psychophysical performance may improve glucose balance.

Reviewer's comments
This is an important study showing improved cognition and mood in non-

insulin-dependent diabetics plus a lowering of fasting blood glucose. Neither the blinding nor the randomization were adequately described. (1, 6)

Product Profile: American Ginseng

Manufacturer	**Chai-Na-Ta Corporation, Canada**
U.S. distributor	None
Botanical ingredient	**Ginseng, American root**
Extract name	N/A
Quantity	500 mg
Processing	3-year-old Ontario dried and ground ginseng root
Standardization	No information
Formulation	Capsule

Comments: Product is not yet available on the market.

Source(s) of information: Vuksan et al., 2001; information provided by manufacturer.

Clinical Study: American Ginseng

Extract name	N/A
Manufacturer	Chai-Na-Ta Corporation, Canada
Indication	**Diabetes (NIDDM)**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Vuksan V, Sievenpiper JL, Koo VYY, Francis T, Beljan-Zdravkovic U, Xu Z, Vidgen E (2000). American ginseng (*Panax quinquefolius* L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. *Archives of Internal Medicine* 160 (7): 1009-1013.

Trial design
Crossover. Ten nondiabetic (ND) and nine diabetic (D) subjects participated in the study. Participants received one of two treatments (placebo or 3 g ginseng) at 0 or 40 minutes before an oral glucose challenge. Subjects were required to fast overnight (10 to 12 hours) before testing. A minimum of one week separated each of the four test days.

Study duration	1 day
Dose	3 g powdered root
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	One hospital
No. of subjects enrolled	ND:10; D: 9
No. of subjects completed	ND:10; D: 9
Sex	Male and female
Age	Means: ND: 34 ± 7 years; D: 62 ± 7 years

Inclusion criteria
Nondiabetic subjects and subjects with reasonably well-controlled type 2 diabetes mellitus (current treatments included diet, sulfonylurea, and a combination of sulfonylurea and metformin; these treatments were maintained constant during the study).

Exclusion criteria
None mentioned.

End points
Thirty minutes before the beginning of each test, the subjects with type 2 diabetes mellitus took their regular medication. Capillary blood was then collected for both sets of subjects before the administration of treatment, and at 0, 15, 30, 45, 60, and 90 minutes after the start of a 25 g oral glucose challenge. The diabetic subjects were also tested again at 120 minutes after the glucose challenge. Blood glucose levels of samples were later calculated.

Results
In nondiabetic subjects, ginseng did not significantly lower incremental glycemia after the glucose challenge when the administration was at the time of the challenge. Incremental glycemia was significantly lowered compared with placebo at 45 and 60 minutes after the challenge when ginseng was administered 40 minutes before the challenge (both $p < 0.05$). In addition, when ginseng was administered before, the area under the blood glucose curve was significantly lower than with placebo ($p < 0.05$), with a reduction of 18 percent. In subjects with diabetes, incremental glycemia was significantly lowered compared with placebo at 45 and 60 minutes when ginseng was given with the challenge (both $p < 0.05$) and at 30 and 45 minutes

when ginseng was given 40 minutes before the challenge (both $p < 0.05$). The areas under the curve were also significantly lower for ginseng than placebo for both administration times (both $p < 0.05$), with reductions of 22 percent (with challenge) and 19 percent (40 minutes before).

Side effects
Mild insomnia was reported by one subject with diabetes after taking ginseng.

Authors' comments
To our knowledge, we are the first to demonstrate an effect of American ginseng on postprandial glycemia in humans. We noticed significant blood glucose-lowering action both in nondiabetic subjects and subjects with type 2 diabetes mellitus when ginseng was given 40 minutes prior to the test meal.

Reviewer's comments
Despite the limitations of sample size and scope, this study offers valuable information regarding the acute effects of American ginseng in both normoglycemic individuals and those with type 2 diabetes. The results suggest a possible effect in individuals with impaired glucose tolerance; however, the duration of the experiments (less than two hours) makes it impossible to comment on long-term clinical significance in the treatment of diabetes. (1, 5)

Clinical Study: American Ginseng

Extract name	N/A
Manufacturer	Chai-Na-Ta Corporation, Canada
Indication	**Diabetes (NIDDM)**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Vuksan V, Stavro MP, Sievenpiper JL, Beljan-Zdravkovic U, Leiter LA, Josse RG, Xu Z (2000). Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. *Diabetes Care* 23 (9): 1221-1226.

Trial design
Crossover. Participants received one of four treatments (placebo, 3 g, 6 g, or 9 g powdered ginseng) at 0, 40, 80, or 120 minutes before an oral glucose challenge. Subjects were required to fast overnight (10 to 12 hours) before testing. A minimum of three days separated each of the 16 test days.

Study duration	1 day
Dose	3, 6, or 9 g powdered root
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	One hospital
No. of subjects enrolled	10
No. of subjects completed	10
Sex	Male and female
Age	Mean: 63 ± 2 years.

Inclusion criteria
Subjects with type 2 diabetes mellitus (current treatments included diet, sulfonylurea, and a combination of sulfonylurea and metformin).

Exclusion criteria
None mentioned.

End points
Capillary blood was collected before the administration of treatment and at 0, 15, 30, 45, 60, 90, and 120 minutes after the start of a 25 g oral glucose challenge. Blood glucose levels of samples were later calculated.

Results
For all doses of American ginseng, a significant effect was observed on incremental glycemia at 30, 45, 60, 90, and 120 minutes ($p < 0.05$). Reductions in the areas under the blood glucose curve occurred for all doses (3 g: 19.7 percent; 6 g: 15.3 percent; 9 g: 15.9 percent) and were significant ($p < 0.05$). No differences were observed between the doses. The time of administration did not affect either incremental glycemia or the area under the blood glucose curve. However, for the area under the curve, there was a significant interaction between dose and time of administration ($p = 0.037$).

Side effects
None reported.

Authors' comments
Consistent with our previous study, the present findings demonstrated the efficacy of American ginseng in reducing postprandial glycemia in type 2 di-

abetes. The reductions, however, occurred independent of the dose used or the time of administration. Taken together, these data indicate that 3 g administered within two hours of the test may be sufficient to achieve reductions in postprandial glycemia in type 2 diabetic individuals.

Reviewer's comments
Despite the preliminary nature of the study, these results suggest a possible therapeutic benefit in patients with type 2 diabetes. Further investigations are needed in larger, longer-term trials with end points such as hemoglobin A_{1C}. (3, 5)

Clinical Study: American Ginseng

Extract name	N/A
Manufacturer	Chai-Na-Ta Corporation, Canada
Indication	**Postprandial glycemia** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Vuksan V, Stavro MP, Sievenpiper JL, Koo VYY, Wong E, Beljan-Zdravkovic U, Francis T, Jenkins AL, Leiter LA, Josse AB, et al. (2000). American ginseng improves glycemia in individuals with normal glucose tolerance: Effect of dose and time escalation. *Journal of the American College of Nutrition* 19 (6): 738-744.

Trial design
Crossover. Participants received one of four treatments (placebo, 3 g, 6 g, or 9 g powdered ginseng) at 40, 80, or 120 minutes before an oral glucose challenge. Subjects were required to fast overnight (10 to 12 hours) before testing. A minimum of three days separated each of the 12 test days.

Study duration	1 day
Dose	3, 6, or 9 g powdered root
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes

Drug comparison	No
Site description	One hospital
No. of subjects enrolled	10
No. of subjects completed	10
Sex	Male and female
Age	Mean: 41 ± 2 years

Inclusion criteria
Nondiabetic individuals.

Exclusion criteria
None mentioned.

End points
Capillary blood was collected before the administration of treatment and at 0, 15, 30, 45, 60, and 90 minutes after the start of a 25 g oral glucose challenge. Blood glucose levels of samples were later calculated.

Results
Independent of administration time, incremental glucose values for all doses of ginseng were significantly lower than placebo ($p < 0.05$) at 30, 45, and 60 minutes after the glucose challenge. Both 3 and 9 g of ginseng were significantly lower than placebo at 90 minutes ($p < 0.05$). At 45 minutes postchallenge, the incremental glucose concentration for 9 g was significantly lower than 3 g ginseng ($p < 0.05$). Reductions in the areas under the blood glucose curve for 3, 6, or 9 g ginseng were 26.6 percent, 29.3 percent, and 38.5 percent, respectively. No significant differences were found between the ginseng administration times.

Side effects
None reported.

Authors' comments
The results of this study coincided with our previous finding that 3 g of American ginseng (AG) consumed 40 minutes before a 25 g glucose challenge improves glucose tolerance in normoglycemic individuals. However, the current results contraindicated our study hypothesis, such that no further enhancement of glucose tolerance occurred with escalating AG doses above 3 g, and/or administering them earlier than 40 minutes before the glucose challenge.

Reviewer's comments
The study is limited by its small sample size, single-blinding, short duration of the experiments, and limited description of the inclusion and exclusion criteria. Although the results provide information on acute postprandial effects on individuals with normal glucose tolerance, conclusions cannot be made

regarding longer-term therapeutic effects on subjects with impaired glucose tolerance or diabetes. (1, 3)

Clinical Study: American Ginseng

Extract name	N/A
Manufacturer	Chai-Na-Ta Corporation, Canada
Indication	**Postprandial glycemia** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Vuksan V, Sievenpiper JL, Wong J, Xu Z, Beljan-Zdravkovic U, Arnason JT, Assinewe V, Starvro MP, Jenkins AL, Leiter LA, et al. (2001). American ginseng (*Panax quinquefolius* L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals. *American Journal of Clinical Nutrition* 73 (4): 753-758.

Trial design
Crossover. Participants received one of four treatments (placebo, 1 g, 2 g, or 3 g powdered ginseng) at 40, 20, 10, or 0 minutes before an oral glucose challenge. Subjects were required to fast overnight (10 to 12 hours) before testing. A minimum of three days separated each of the 16 test days.

Study duration	1 day
Dose	1, 2, or 3 g powdered root
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	One hospital
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male and female
Age	Mean: 42 years

Inclusion criteria
Healthy subjects without diabetes.

Exclusion criteria
None mentioned.

End points
Capillary blood was collected before the administration of treatment and at 0, 15, 30, 45, 60, and 90 minutes after the start of a 25 g oral glucose challenge. Blood glucose levels of samples were later calculated.

Results
The main effects of treatment and administration time were significant ($p < 0.05$) by way of two-way analysis of variance. Over the last 45 minutes of the test, glycemia was lower than placebo with all doses of ginseng ($p < 0.05$), but no significant differences were observed between doses. Reductions in the areas under the blood glucose curve for 1, 2, or 3 g ginseng were 14.4 percent, 10.6 percent, and 9.1 percent, respectively. In the last hour of the test, glycemia was significantly lower when ginseng was given 40 minutes before the glucose challenge than when it was given 20, 10, or 0 minutes before the challenge ($p < 0.05$).

Side effects
No adverse effects were reported.

Authors' comments
The American ginseng used in the present study reduced postprandial glycemia in healthy subjects without diabetes in a manner that was dependent on the time of administration but not the dose. An effect was seen only when administration was 40 minutes before the challenge, and doses within the range of 1 to 3 g were equally effective. This lack of a dose response suggests that the next step should be to study lower doses.

Reviewer's comments
This study suggests that lower doses (1 g) can still affect glucose tolerance, as compared to higher doses used in the investigators' previous studies. However, the conclusions that can be drawn from the study are limited, and no statements can be made regarding longer-term therapeutic effects. The study was limited by the small sample size, the short-term nature of the experiments, and the limited description of the inclusion and exclusion criteria. (1, 4)

Clinical Study: American Ginseng

Extract name	N/A
Manufacturer	Chai-Na-Ta Corporation, Canada
Indication	**Postpriandial glycemia** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference

Sievenpiper JL, Arnason JT, Leiter LA, Vuksan V (2003). Variable effects of American ginseng: A batch of American ginseng (*Panax quinquefolius* L.) with a depressed ginsenoside profile does not affect postprandial glycemia. *European Journal of Clinical Nutrition* 57 (2): 243-248.

Trial design

Crossover. Volunteers were given either ginseng or placebo on two test days, separated by at least three days. Treatment was given 40 minutes prior to the start of a 75 g oral glucose tolerance test. Subjects were asked to maintain the same exercise and dietary patterns the evening before each test and to consume at least 150 g of carbohydrates each day in the three days preceding the test.

Study duration	1 day
Dose	6 g powdered root
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	1 hospital
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male and female
Age	Mean: 31 ± 3 years

Inclusion criteria

Healthy volunteers.

Exclusion criteria
Younger than 18 years or older than 75 years; previous diagnosis of dysglycemia, kidney or liver disease, morbid obesity, or a major surgery in the last six months.

End points
A fasting blood sample was collected before the administration of treatment, and blood was again collected at 0, 15, 30, 45, 60, 90, and 120 minutes after the start of the 75 g oral glucose tolerance test. Blood glucose levels of samples were later calculated.

Results
American ginseng had no significant effects on incremental plasma glucose, incremental plasma insulin, or their areas under the curve (indices of insulin sensitivity) compared to placebo.

Side effects
No difference in side effects reported by the ginseng and placebo groups, which included: nausea, belching, bloating, headache, dizziness, lightheadedness, diarrhea, flatulence, polyuria, numbness, anxiety, insomnia, cramping, or thirst.

Authors' comments
The present study demonstrated a favorable safety profile for the present batch of American ginseng but a lack of effect in postprandial indices of glycemia and insulinemia. This lack of efficacy is in direct contrast to previous studies (Vuksan, Sievenpiper, et al., 2000; Vuksan, Stavro, Sievenpiper, Beljan-Zdravkovic, et al., 2000; Vuksan, Stavro, Sievenpiper, Koo., et al., 2000; Vuksan et al., 2001). The reasons for this difference are unknown but might be due to differences in composition between the batch of ginseng used in this study compared to the batch used in previous studies. Although the ginsenoside profile confirmed that the present batch was also *Panax quinquefolius* L., marked differences in ginsenosides were observed compared to the original batch.

Reviewer's comments
This study demonstrates the complex nature of herbs and the inherent difficulties in studying them in clinical trials. Differences in ginsenoside profiles between ginseng batches used in the different trials may have been the cause of the different results. It seems that we must further understand these active components before a specific preparation is studied in a larger, longer-term trial. (1, 5)

Marilyn Barrett, PhD
Editor

The Handbook of Clinically Tested Herbal Remedies
Volume 2

Pre-publication REVIEWS, COMMENTARIES, EVALUATIONS . . .

"*The Handbook of Clinically Tested Herbal Remedies* is an important addition to the modern clinical literature on herbs."

Adriane Fugh-Berman, MD
Associate Professor,
Department of Physiology
and Biophysics,
Georgetown University School
of Medicine

"This book is well written by experts in their respective fields and for the first time provides information on specific botanical products that relate to their therapeutic value. It should be of great interest to students and practitioners in any of the health sciences, to manufacturers of botanical products, to the lay public, to those in the media who can rely on information in this book to be authoritative, and to libraries."

Norman R. Farnsworth, PhD
UIC Distinguished Professor
and Research Professor
of Pharmacognosy, College of Pharmacy,
University of Illinois at Chicago

More pre-publication
REVIEWS, COMMENTARIES, EVALUATIONS . . .

"This book includes profiles on thirty-two individual herbal medicines and ten combination formulas. These profiles include descriptions of most of the major published clinical studies, which have been analyzed by a panel of authoritative reviewers. It is obvious that great care was taken to ensure completeness and accuracy of information, and the reviewers' comments regarding study quality are especially informative and helpful.

Clinicians searching for detailed and accurate information on herbal clinical trials will find much in this text that is useful. It is a significant achievement in the field of evidence-based analyses of herbal medicine. It should be of most help to clinicians or researchers who want specific details on herbal clinical studies that are not readily available, or who are interested in clinical-trial-quality assessments by authoritative reviewers."

Michael Rotblatt, MD, PharmD
Associate Clinical Professor of Medicine, UCLA; Co-author,
Evidence-Based Herbal Medicine

"The purpose of this book is to provide both consumers and health care providers with concise, evidence-based information on the most widely used herbs and herbal formulas tested in clinical trials. The focus is on what preparations have been studied in clinical trials and how good the evidence is as assessed by preset criteria applied by botanical experts.

The book is broken down into three parts. The first section is very informative and sets the stage nicely for a discussion of individual herbs. The second part describes the process of evidence gathering, sorting, grading, and peer review. Those readers familiar with the Natural Standard database of natural products will recognize the editor's use of 'levels of evidence' criteria as a useful tool to distill the information available from clinical trials. In the third part, the authors provide monographs on the various herbals listed alphabetically. These are concise and cover basic questions of whether the trial was randomized and whether the methods were clearly described. One unique feature is a detailed description of specific products used in clinical trials. These are very helpful to both clinicians interested in recommending specific products and to patients interested in finding these same products at their local health food stores.

This book provides valuable information to providers and patients looking to sort out which commonly used herbs are evidence-based and particularly which specific products they should be looking for."

Philippe O. Szapary, MD
Assistant Professor of Medicine,
Division of General Internal Medicine,
University of Pennsylvania School
of Medicine

NOTES FOR PROFESSIONAL LIBRARIANS AND LIBRARY USERS

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NOTE TO VOLUME 2

The criteria used to include products and clinical trials in this book are explained in Chapter 12. The guidelines used to evaluate the clinical trials listed in this book are provided in Chapter 13. Please refer to these chapters in Volume 1.

The Handbook of Clinically Tested Herbal Remedies

Volume 2

Haworth Series in Evidence-Based Phytotherapy
Marilyn Barrett, PhD
Editor

The Handbook of Clinically Tested Herbal Remedies edited by Marilyn Barrett

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The Handbook of Clinically Tested Herbal Remedies
Volume 2

Part III: Botanical Profiles—
Product and Clinical Trial Information
(Grape Seed–Valerian and Herbal Formulas)

Marilyn Barrett, PhD
Editor

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PART III: BOTANICAL PROFILES—PRODUCT AND CLINICAL TRIAL INFORMATION (Grape Seed–Valerian and Herbal Formulas)

ABOUT THE EDITOR

Marilyn Barrett, PhD, is founder and principal of Pharmacognosy Consulting, whose mission is to provide a scientific foundation for botanical medicine. She was awarded a PhD in pharmacognosy from the School of Pharmacy, University of London, UK, in 1985 and a BA in botany from the University of California, Berkeley, CA, in 1977.

Since 1994, Dr. Barrett has provided scientific information and technical expertise to manufacturers, associations, and government concerning medicinal plant products through her consulting business. She is a member of the United States Pharmacopeia Committee of Experts for Dietary Supplements Information, an external advisory board member for the University of California at Los Angeles Center for Dietary Supplements (an NIH-funded center) and a consultant to the Office of Dietary Supplements in preparation of their botanical fact sheets. Dr. Barrett served on a working group for the Institute of Medicine of the National Academy of Sciences Committee developing a Framework for Evaluating the Safety of Dietary Supplements. She is a member of the American Botanical Council Advisory Board, the American Herbal Pharmacopoeia and Therapeutic Compendium Technical Advisory Board, and the American Herbal Products Association's Scientific Advisory Board.

Dr. Barrett has published over 30 publications in peer-reviewed journals and a booklet titled *Reference on Evaluating Botanicals* for the Council for Responsible Nutrition, in 1998. More information is available on her Web site at <www.pharmacognosy.com>.

EDITOR'S NOTE

The purpose of this book is informational. It is not intended as a guide to self-medication or as a substitute for the advice of a health practitioner.

The production of this book was partially supported by a grant from The Haworth Press. No monetary assistance was provided by any manufacturer whose product is, or is not, included in the book.

This book is not meant to promote any product(s) in particular. The purpose of the book is to examine the scientific data supporting the efficacy of herbal preparations. As therapeutic equivalence of these products has not been proven, examining the clinical evidence cannot be done without profiling individual products.

Manufacturers who wish to submit their product(s) for inclusion in future editions of this book should contact the editor via e-mail at <marilyn@pharmacognosy.com> or via the Internet at <http://www.pharmacognosy.com>.

PART III: BOTANICAL PROFILES— PRODUCT AND CLINICAL TRIAL INFORMATION

(Grape Seed–Valerian and Herbal Formulas)

Grape Seed

Other common names: **European grape; wine grape**
Latin name: ***Vitis vinifera* L.** [Vitaceae]
Plant part: **Seed**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

The grape plant is a woody, perennial vine that produces fruit from which juice, raisins, and wine are produced. Pigments and tannins in grapes contribute to the color and taste of the fruit. The tannins are polymers of the polyphenols catechin and epicatechin. Other names for these polymers are procyanidins, leucoanthocyanins, procyanidolic oligomers, and oligomeric proanthocyanidins (OPCs). The strong antioxidant properties of the OPCs have sparked interest in their therapeutic use. OPCs are concentrated in the skins of red grapes, but are even more abundant in the seeds. A patented process has been developed that produces a highly concentrated extract of polyphenols from crushed grape seeds (Bombardelli and Morazzoni, 1995).

Endotelon® contains a grape seed extract (LeucoSelect®) that is a 100-fold concentrate standardized to 95 percent polyphenols (80 to 85 percent OPCs). Endotelon is manufactured by Sanofi-Synthelabo in France using the LeucoSelect extract produced by Indena S.p.A in Italy. The LeucoSelect extract is incorporated into products distributed in the United States by Thorne Research (O.P.C.-100) and Bluebonnet Nutrition Corporation (Grape Seed Extract).

LeucoSelect™-phytosome® is a proprietary formulation made by Indena S.p.A. in Italy that combines the LeucoSelect extract with soy phospholipids in a ratio of one to two. This combination is reported by Indena to improve the bioavailability of grape procyanidins.

Proclandiol is manufactured by Bruschettini s.r.l. in Italy and contains a fermented grape seed product for which we could find very little specification. This product is not available in the United States.

GRAPE SEED SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Endotelon®	Sanofi-Synthelabo, France (Indena S.p.A., Italy)/None	Grape seed extract containing 80 to 85% OPCs (LeucoSelect®)	150 mg daily; range 100 to 300 mg daily	Chronic venous insufficiency	3	Yes (II-2) Trend (II-1)
				Capillary fragility	3	Trend (III-1) Undetermined (III-2)
				Postoperative edema	1	Trend (III-1)
				Vision	1	Yes (II-1)
LeucoSelect™-phytosome®	Indena S.p.A., Italy/Indena USA Inc.	LeucoSelect™ extract plus phospholipids	600 mg daily	Antioxidant activity	1	MOA (III-1)
Procianidol	Bruschettini s.r.l., Italy	Fermented product	300 mg daily	Vision	1	Trend (II-1)

*Products sold in the United States that contain the Indena LeucoSelect® extract as a single ingredient are listed here. The extract in these products has been tested clinically, but the final formulation has not.

Product Name	Manufacturer
O.P.C.-100	Thorne Research
Grape Seed Extract	Bluebonnet Nutrition Corporation

SUMMARY OF REVIEWED CLINICAL STUDIES

Most of the clinical studies on grape seed preparations have focused on benefits to the circulatory system. The studies described in this section explore the possible benefit of grape seed preparations in treating venous insufficiency, capillary fragility, edema, and visual contrast sensitivity due to glare, as well as antioxidant properties.

The procyanidins in grape seed extracts are thought to help maintain normal blood capillary function through their antioxidant, free-radical scavenging activity. In addition, the procyanidins inhibit the enzymes involved in the degradation of collagen, elastin, and hyaluronic acid, the main structural components of the matrix that surrounds the capillaries. Capillaries are the small blood vessels that allow for the exchange of fluid, nutrients, and blood cells between the blood and surrounding tissues. An increase in the permeability of the capillaries leads to an increase in fluid and blood cells in the tissues surrounding the capillaries. This decrease in capillary resistance, also called capillary fragility, can cause bleeding under the skin (purpura) sometimes observed as pinpoint black and blue spots (Dartenuc, Marache, and Choussat, 1980).

Chronic venous insufficiency is a term applied to a syndrome resulting from insufficient circulation to the legs and feet. Symptoms can include edema, bluish discoloration of the skin, and ultimately ulcers. Treatment can include elastic support stockings, drugs, or surgery (Schulz, Hänsel, and Tyler, 2001).

The circulatory system supports vision through the capillaries that deliver blood to the retina of the eye. The effect of grape seed extracts on recovery of vision after exposure to strong light or glare has been tested in a few studies. The procyanidins are thought to assist in the regeneration of rhodopsin, a visual pigment depleted by glare (Corbe, Boissin, and Siou, 1988).

Endotelon

Chronic Venous Insufficiency

Three good-quality trials focused on the effect of Endotelon on venous insufficiency in the legs. A large, placebo-controlled study, including 357 subjects with venous insufficiency in the legs, reported

improvement in a clinical symptom composite score consisting of heaviness or fatigue, itching (paresthesia), nocturnal leg cramps, leg agitation, and subjective edema. A benefit compared to placebo was observed following administration of 300 mg per day for two months, and increased benefit when treatment was extended for three months (Henriet, 1988). A smaller study, with 50 participants, compared the effects of 150 mg Endotelon to 450 mg Diosmine (a semisynthetic bioflavonoid) for one month. Endotelon appeared to benefit patients sooner (at day 9 compared to day 14) and to be more effective than Diosmine (Delacroix, 1981). This study would have been strengthened by the addition of a placebo group. A placebo-controlled trial, also with 50 patients diagnosed with venous insufficiency, showed significant benefit compared to placebo following treatment with 150 mg per day for 45 days. The trial used thermography (the use of heat to assess circulation) and rheography (the use of electrical impedance to measure blood volume) measurements as end points. Both measurements indicated statistical improvements in arterial and venous tone with treatment compared to placebo (Paitel, 1981).

Capillary Fragility

Three poorly described, small, placebo-controlled trials explored the effect of Endotelon on vascular resistance. One trial included 25 subjects with either hypertension or diabetes, and used a dose of 150 mg per day for one to three months. It reported a trend toward increasing capillary resistance (from 14.6 to 18.0 cmHg as measured using a capillarodynamometer) with treatment and no change with placebo (Lagrue, Olivier-Martin, and Grillot, 1981). Another trial included 37 subjects with capillary fragility who were given a dose of 100 mg grape seed extract or placebo per day for 15 days. The Endotelon group showed greater improvement than the placebo group, as measured using an angiosterrometer. The fact that some subjects had normal capillary resistance to begin with, along with other inadequacies in the methodology, meant the possible benefit of treatment was not determined by this study (Dartenuc, Marache, and Choussat, 1980). The third trial included two sets of subjects: patients with venous insufficiency and healthy subjects who took aspirin to experimentally induce a reduction in capillary resistance. Both sets of participants were given either 150 mg Endotelon per day or placebo for one

month. The authors reported improvement in both sets of participants following treatment with Endotelon compared with placebo (Dubos, Durst, and Hugonot, 1980). However, the number of subjects was judged too small, 30 in total, by our reviewer, Dr. Mary Hardy, for such a complex four-part design.

Postoperative Edema

A rather unique study explored the effect of Endotelon on postoperative edema caused by face-lift operations. Treatment was 300 mg per day for five days before surgery and for five days after surgery. The postoperative edema resolved more quickly in the treatment group (11.4 days) compared with the placebo group (15.8 days), according to the subjective evaluation of the physician. The volume of the edema did not differ in the two groups (Baruch, 1984).

Vision

A trial with 95 subjects without any major retinal or ophthalmological pathology studied the effect of Endotelon on visual contrast sensitivity. The trial was designed to imitate exposure to glare from video display units or traffic headlights while driving. Subjects received either 200 mg per day or nothing for five weeks. Visual recovery from glare, both general retinal glare and night vision glare, as a function of time, was significantly better in the treatment group compared to the baseline and the control group (Corbe, Boissin, and Siou, 1988).

LeucoSelect-phytosome

Antioxidant Activity

A small, placebo-controlled trial including a total of 20 healthy young students measured antioxidant activity in the plasma following one dose of 300 mg of LeucoSelect-phytosome or placebo and again after five days of treatment. After one dose of grape seed extract, the antioxidant activity in the serum of subjects increased for a period of 30 minutes to three hours. No effect was observed following adminis-

tration of placebo. Similar results were obtained following five days of treatment (Nuttall et al., 1998).

Procianidol

Vision

The trial with 75 subjects using video display units for at least six hours daily were divided into three treatment groups. One group (50 subjects) received 100 mg Procianidol capsules three times daily. The second group (ten subjects) received 100 mg bilberry anthocyanosides three times daily. The third group (15 subjects) received placebo. Following two months of treatment, a statistically significant increase in contrast sensitivity was observed in all ten points of the contrast sensitivity curve in the Procianidol group, six points of the curve for the bilberry group, and two points of the curve for the placebo group. No change was observed in visual acuity or chromatic sense (Fusi et al., 1990). A criticism of the latter trial was the unequal distribution of subjects.

ADVERSE REACTIONS OR SIDE EFFECTS

The preceding trials did not find any serious adverse effects with any of the products. When mentioned, the side effects, which did not differ from placebo, were gastric discomfort, nausea, headaches, and dizziness.

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DETAILS ON GRAPE SEED PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Grape Seed Products

Product Profile: Endotelon®

Manufacturer	**Sanofi-Synthelabo, France (Indena S.p.A., Italy)**
U.S. distributor	**None**
Botanical ingredient	**Grape seed extract**
Extract name	**LeucoSelect™**
Quantity	50 mg
Processing	Plant to extract ratio 100:1.
Standardization	95% polyphenols (80-85% oligomeric proanthocyanidins)
Formulation	Tablet

Source(s) of information: Dartenuc, Marache, and Choussant, 1980; information provided by Indena USA, Inc.

Product Profile: Grape Seed Extract

Manufacturer	**Bluebonnet Nutrition Corporation (Indena S.p.A., Italy)**
U.S. distributor	**Bluebonnet Nutrition Corporation**
Botanical ingredient	**Grape seed extract**
Extract name	**LeucoSelect®**
Quantity	100 mg
Processing	Plant to extract ratio: 100:1
Standardization	Standardized to contain 80-85% oligomeric proanthocyanidins
Formulation	Capsule

Recommended dose: Take one capsule daily or as directed.

Other ingredients: Calcium phosphate, cellulose, silica, magnesium stearate.

Source(s) of information: Product label; information from Indena USA, Inc.

Product Profile: O.P.C.-100

Manufacturer	**Thorne Research (Indena S.p.A., Italy)**
U.S. distributor	**Thorne Research**
Botanical ingredient	**Grape seed extract**
Extract name	**LeucoSelect™**
Quantity	100 mg
Processing	Plant to extract ratio: 100:1
Standardization	95% oligomeric proanthocyanidins
Formulation	Capsule

Cautions: If pregnant, consult a health care practitioner before using this, or any other product.

Other ingredients: Cellulose capsule. May contain one or more of the following hypoallergenic ingredients to fill space: magnesium citrate, leucine, silicon dioxide.

Comments: This product is available only through pharmacies and health care practitioners. Also available in a 30 mg capsule (O.P.C.-30).

Source(s) of information: Product label; information from Indena USA, Inc.

Clinical Study: Endotelon®

Extract name	LeucoSelect™
Manufacturer	Sanofi Pharmaceuticals, France (Indena S.p.A., Italy)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Henriet JP (1988). Endotélon® dans les manifestations fonctionnelles de l'insuffisance veineuse périphérique: Etude EIVE [Endotelon® in the functional disorders caused by peripheral vascular insufficiency]. *Actualité Médicales Internationales—Angiologie* 5 (74): n.p.

Trial design
Parallel. Pretrial run-in with placebo lasting one month.

Study duration	3 months
Dose	3 (50 mg) pills twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	65 centers
No. of subjects enrolled	364
No. of subjects completed	357
Sex	Male and female
Age	18-63 years (mean: 37)

Inclusion criteria
Subjects between 18 and 60 years old with functional difficulties in their lower extremities, including a sensation of heaviness, tension, or pain diagnosable

as vascular symptoms which have been present for at least the last six months.

Exclusion criteria
Complications such as deep or superficial thrombosis, or vascular treatments during the six months before the study. Subjects with postphlebitis diseases, lymphatic anomalies, and evolving nutritional problems. Patients who resorted to analgesics or anti-inflammatories during the study were also excluded.

End points
Functional vascular symptoms were assessed at inclusion, at the beginning of therapy, and after one, two, and three months. These symptoms included heaviness or sensation of weight, tension, fatigue; paresthesia or prickling, itching, burning sensation, tingling; nocturnal leg cramps; leg agitation; and subjective edema. Edema was also measured quantitatively by water displacement.

Results
Improvement was observed in the clinical score of symptoms in the Endotelon group compared to placebo after 56 days of treatment, and the difference between the two groups increased after 84 days. The efficacy of Endotelon was more significant for those with initially higher symptom scores. Leg volumes did not change for either group.

Side effects
Gastric problems, nausea, headaches, and dizziness were reported in both groups.

Author's comments
The efficacy of Endotelon compared to placebo confirmed the usefulness of this drug therapy at the dosage of 300 mg per day against functional vascular-lymphatic insufficiency.

Reviewer's comments
Overall this was a good trial, with adequate blinding and randomization. The trial was large, had a long placebo washout period, and attempts were made to control circumstances for outcome measurement. The statistical methods were not adequately described or applied, however, and the data was not sufficiently summarized to allow for alternative analyses. (Translation reviewed) (5, 4)

Clinical Study: Endotelon®

Extract name	LeucoSelect™
Manufacturer	Sanofi Pharmaceuticals, France (Indena S.p.A., Italy)
Indication	**Chronic venous insufficiency; varicose veins**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Delacroix P (1981). Double-blind trial of Endotelon in chronic venous insufficiency. *Revue de Medecine* 27/28: 1793-1802.

Trial design
Parallel. Pretrial placebo period of one month followed by the treatment period of one month. Half of the subjects received Endotelon, and the other half received semisynthetic Diosmine (450 mg daily).

Study duration	1 month
Dose	3 (50 mg) gel caps daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Diosmine
Site description	Gynecology-obstetrics outpatient clinic
No. of subjects enrolled	50
No. of subjects completed	50
Sex	Female
Age	Mean: 34 ± 6 years

Inclusion criteria
Subjects between 20 and 60 years of age with functional symptoms of chronic venous insufficiency, or varicose veins due to pregnancy or oral contraceptives.

Exclusion criteria
Women in the first two months of pregnancy; with venous pathology in the lower limbs including arteriopathy, lymphadenitis, and painless varicose

veins; on low salt diets; or those taking diuretics, anti-inflammatories, or other therapies that might interfere with the trial. Also excluded were unstable, undisciplined, or neurotic patients.

End points
Patients were evaluated after the pretrial placebo period and after one month of treatment according to both functional and objective criteria. Functional criteria included pain typical of venous insufficiency including heaviness sensation in the legs, other pain, and swelling. Objective criteria included measurement of swelling via leg circumference and hypodermal lesions, including varicose veins and skin lesions due to hemorrhage.

Results
Both drugs were effective in treating peripheral venous insufficiency. Endotelon appeared more effective in treating functional parameters, since 65 percent of patients improved compared to 45 percent with Diosmine. Improvement was seen after nine days of treatment with Endotelon and after 14 days treatment with Diosmine. The therapeutic effect of Endotelon persisted 15 days after termination of treatment, whereas the effect persisted for only 10 days with Diosmine.

Side effects
Side effect were uncommon and never serious. Endotelon produced transient epigastric discomfort in some patients, and one case of nausea.

Author's comments
Compared with Diosmine, the therapeutic effect of Endotelon is more intense, more constant, and longer lasting, and can therefore be more readily utilized in the treatment of chronic venous insufficiency.

Reviewer's comments
This trial was well reported and conducted, except for the small number of subjects. The randomization and blinding were adequate and well described. (Translation reviewed) (5, 5)

Clinical Study: Endotelon®

Extract name	LeucoSelect™
Manufacturer	Laboratoires Labaz, France (Indena S.p.A., Italy)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Paitel D (1981). Rheographic and thermographic study of the effects on peripheral hemodynamics of an endotheoliotrophic, double blind versus placebo study. *Vie Medicale* 11: 776-783.

Trial design
Parallel.

Study duration	45 days
Dose	1 (50 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	50
No. of subjects completed	50
Sex	Male and female
Age	31-69 years (mean: 47)

Inclusion criteria
Patients with mild venous insufficiency, without significant reflux at the level of saphenous internal arch, or dilatation of the same vein. For patients affected by vascular sclerosis, the tests were performed on veins not previously treated.

Exclusion criteria
Younger than 20 or older than 70 years, use of vasculomotor therapies during the trials, or serious venous insufficiencies associated with important ostial insufficiency.

End points
Arterial and venous tone were measured using rheography (impedance plethysmography). Circulation was measured using thermography. Patients were examined before treatment and after 15, 30, and 45 days of treatment.

Results
Clinical, rheographic, and thermographic results all show a statistically significant difference in favor of Endotelon over placebo after one month of treatment. Of 25 patients treated with Endotelon, results are excellent in

seven cases, very good in 14 cases, good in two cases and acceptable in two cases. Of the 25 patients that received placebo, there were no excellent results, one very good result, two good results, seven acceptable results, and 15 cases of no results.

Side effects
None mentioned.

Author's comments
This study showed that Endotelon is effective in the treatment of peripheral vascular insufficiency.

Reviewer's comments
The end points of thermography/rheography measurements are not well validated in clinical literature. This trial was both double-blinded and randomized, but the data were not presented in sufficient detail to permit alternative analyses. (Translation reviewed) (5, 5)

Clinical Study: Endotelon®

Extract name	LeucoSelect®
Manufacturer	Laboratoires Labaz, France (Indena S.p.A., Italy)
Indication	**Capillary fragility** in hypertensive and diabetic patients
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Lagrue G, Olivier-Martin F, Grillot A (1981). A study of the effect of procyanidolic oligomers on capillary resistance in the hypertension and certain nephropathies. *La Semaine des Hopitaux Paris* 57 (33-36): 1399-1401.

Trial design
Parallel. Two-phase study: first an open trial and second a comparative double-blind trial. The latter is reported here.

Study duration	1 to 3 months
Dose	3 (50 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	25
No. of subjects completed	25
Sex	Male and female
Age	18-68 years (mean: 46.5)

Inclusion criteria
Hypertensive and diabetic patients with capillary resistance decidedly less than normal.

Exclusion criteria
Subjects receiving other vascular therapies.

End points
Capillary resistance was measured using a Lavollay's capillarodynamometer. Capillary resistance, renal functions, arterial pressure and drug tolerance were monitored before and after treatment.

Results
Capillary resistance increased significantly after treatment with Endotelon, from 14.6 cmHg to 18.0 cmHg ($p < 0.0005$). No significant change was observed in the placebo group. Endotelon was significantly more effective compared to placebo ($p < 0.01$).

Side effects
In the open trial segment, treatment was interrupted in four out of 28 cases because of secondary effects (pruriginous eruption, palpitations, elation, and insomnia).

Authors' comments
Considering the increase in capillary resistance caused by Endotelon compared to placebo, it appears to be an interesting drug for microcirculation disorders associated with capillary fragility.

Reviewer's comments
The end point of capillary fragility/resistance is not well connected to a clinical condition, i.e., capillary fragility/resistance is a secondary end point or intermediate end point, and the exact relationship to other diseases is not established. Although the study was double-blind and randomized, the randomization process was not adequately described, the study was too small, and the

statistical methods were not adequately described or applied. (Translation reviewed) (3, 2)

Clinical Study: Endotelon®

Extract name	LeucoSelect™
Manufacturer	Laboratoires Labaz, France (Indena S.p.A., Italy)
Indication	**Capillary fragility**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Dartenuc JY, Marache P, Choussat H (1980). Capillary resistance in geriatrics: Study of a microangioprotector = Endotelon. *Bordeaux Medical* 13: 903-907.

Trial design
Parallel. Two-part trial: open trial and a double-blind placebo-controlled trial. The second is reported here.

Study duration	15 days
Dose	2 (50 mg) tablets daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	37
No. of subjects completed	Not given
Sex	Male and female
Age	42-92 years (mean: 74.7)

Inclusion criteria
Hospitalized patients with capillary fragility with abnormal angiosterrometry (except eight patients that did not show more than five to ten petechias at –30 cmHg). Nine patients showed capillary fragility in the form of ecchymosis or petechias.

Exclusion criteria
Subjects taking therapies that were not related to the circulatory system.

End points
Capillary resistance was recorded using an angiosterrometer before treatment and at the end of the first and second treatments.

Results
Although cases of improvement were fewer than cases of no improvement, it is important to keep in mind that six patients had normal capillary resistance before treatment. Endotelon showed effectiveness in ten cases out of 21, whereas the placebo produced improvement in three patients out of 12. It appears that Endotelon is more effective against capillary fragility compared to placebo.

Side effects
None mentioned.

Authors' comments
The study showed that Endotelon is suitable in all clinical peripheral microangiopathy, all capillary permeability troubles, and in cases of capillary fragility revealed by angiosterrometric measures.

Reviewer's comments
It is not clear that the outcome measure used is clinically relevant. The variable dosage and variable length of trials (comparing both parts of trial) confound results. Variable tests were also performed on members of treatment groups. Although the study was double-blind, it was not randomized, the data were not summarized in sufficient detail, and the statistical methods were not adequately described or applied. (Translation reviewed) (2, 3)

Clinical Study: Endotelon®

Extract name	LeucoSelect™
Manufacturer	Laboratoires Labaz, France (Indena S.p.A., Italy)
Indication	**Capillary fragility** in patients with venous insufficiency and induced in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Dubos G, Durst G, Hugonot R (1980). Capillary resistance evolution, spontaneously or artificially lessened by action of a capillaro-toxic substance in aged people. *Extrait de Geriatrie* September: 302-305.

Trial design
Parallel. Two-part study: open and double-blind controlled. The second part is described here. Each part of the study included two different groups of subjects: one group had low initial low capillary resistance, and another group who initially had normal levels but took 1 g aspirin for 15 days before treatment to reduce capillary resistance.

Study duration	1 month
Dose	150 mg daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male and female
Age	Mean: 74 years

Inclusion criteria
Two groups of subjects: some with venous insufficiency and others who were healthy. Those with capillary fragility had an initial mean capillary resistance of 13.32 cmHg. Those with normal capillary resistance had an initial mean level of 25.21 cmHg.

Exclusion criteria
None mentioned.

End points
Capillary resistance was evaluated using Parrot's angiosterrometer before taking the product and at the end of each week during the month of treatment.

Results
The subjects with initially low capillary resistance improved significantly af-

ter 15 and 30 days of treatment ($p < 0.02$ and $p < 0.01$, respectively). No significant change was observed with placebo. Similarly, the group with aspirin-induced capillary fragility improved after 15 and 30 days (both $p < 0.001$), whereas no significant change occurred with placebo.

Side effects
Endotelon did not cause any clinical or biological tolerance problems.

Authors' comments
Administered at a dose of 150 mg per day, Endotelon was capable of restoring normal values in subjects affected by capillary fragility caused by multiple pathologies and was able to oppose the decrease in capillary resistance produced by aspirin.

Reviewer's comments
This is a very complicated trial for such small numbers, and I am not convinced of the direct clinical relevance of this outcome and of the process of artificially lessening capillary resistance with aspirin. This study was adequately randomized, although the blinding was not described in enough detail. The sample size was also small, and the statistical methods and data were not adequately described. (Translation reviewed) (3, 3)

Clinical Study: Endotelon®

Extract name	LeucoSelect™
Manufacturer	Laboratoires Labaz, France (Indena S.p.A., Italy)
Indication	**Postoperative edema**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Baruch J (1984). The effects of Endotelon on postoperative edema: Results of a double-blind study vs. placebo in thirty-two patients. *Annales de Chirurgie Plastique et Esthetique* 29 (4): 393-395.

Trial design
Parallel. Treatment was given five days before surgery and from the second day until the sixth day after surgery (a second five-day treatment period).

Study duration	10 days
Dose	2 (50 mg) tablets 3 times daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Cosmetic surgery practice
No. of subjects enrolled	33
No. of subjects completed	32
Sex	Female
Age	44-65 years (mean: 56.5)

Inclusion criteria
Women undergoing facelift surgery.

Exclusion criteria
Concurrent therapy.

End points
Three criteria were used to assess efficacy: the speed of edema disappearance expressed in days, the volume of edema assessed by the clinician, and a global clinical assessment. Patients were assessed on the second, fifth, and twelfth day postoperatively.

Results
The time until disappearance of edema after operation was 11.4 days for the treatment group and 15.8 days for the placebo group. This difference is statistically significant ($p = 0.01$). No significant difference in edema volume was observed between the two groups. However, global clinical evaluation on day 12 was in favor of the treatment group ($p = 0.04$).

Side effects
None observed.

Author's comments
The preventive effect of Endotelon on postoperative edema in face-lift surgery was demonstrated in this homogeneous group of patients.

Reviewer's comments
The primary outcome measure was not very objective, and this lack of an "objective" outcome limits the usefulness of this trial. Although the study was both

randomized and double-blind, neither process was adequately described. The length of the trial was also very short. (Translation reviewed) (1, 3)

Clinical Study: Endotelon®

Extract name	LeucoSelect™
Manufacturer	Sanofi Pharmaceuticals, France (Indena S.p.A., Italy)
Indication	**Vision**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Corbe C, Boissin JP, Siou A (1988). Chromatic sense and chorioretinal circulation: Study of the effect of O.P.C (Endotelon). *Journal Français d'Ophtalmologie* 11 (5): 453-460.

Trial design
Parallel. Half of the subjects received Endotelon treatment and the other half received no treatment. Evaluators were blind.

Study duration	5 weeks
Dose	2 (50 mg procyanidolic oligomers) tablets twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Single-Blind
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	2 centers
No. of subjects enrolled	100
No. of subjects completed	95
Sex	Male and female
Age	Mean: 37 years

Inclusion criteria
Adults whose work in front of video displays subjected them to frequent bright stimuli of long duration, and drivers subject to bright lights and repeated glare from headlights.

Exclusion criteria
Any major retinal or ophthalmological pathology. This included patients with retinal pathology from diabetes and hypertension, retinopathy and retinal detachment, glaucoma, myopia over six dioptric units, astigmatism over three units, and nystagmus.

End points
The evaluations included visual recovery after glare as a function of time (Comberg's nycometer), night morphoscopic vision threshold (Beyne's scoptometer), and ergovision tests. Examinations were completed before treatment and after five weeks.

Results
For subjects treated with Endotelon, the improvement in the visual performances after glare, as well as the rapidity of recovery from glare, was very significant compared to the results obtained by the control group. Visual adaptation to low luminance also improved under treatment. The ergovision tests support the above results.

Side effects
Gastric symptoms in one subject and dizziness in another with known hypertension.

Authors' comments
The efficacy of Endotelon and the observed good tolerance in the study allows the endorsement of this therapy for subjects having increased sensitivity to glare and a decrease in nocturnal vision, especially a lesser distinguishing ability in a weak luminance environment.

Reviewer's comments
This trial demonstrated a benefit for sensitivity to glare, but no conclusion can be made regarding any other ophthalmologic conditions. The study was not double-blind, and the data was not summarized in sufficient detail to permit replication. (Translation reviewed) (3, 5)

Product Profile: LeucoSelect™-phytosome®

Manufacturer	**Indena S.p.A., Italy**
U.S. distributor	**Indena USA, Inc.**
Botanical ingredient	**Grape seed phytosome**
Extract name	**LeucoSelect-phytosome**
Quantity	150 mg

Processing	1 part LeucoSelect® (extract of grape seeds) to 2 parts phosphatidylcholine. LeucoSelect plant/extract ratio 100:1
Standardization	No information
Formulation	Capsule

Other ingredients: Phosphatidylcholine from soybean

Source(s) of information: Nuttall et al., 1998; information provided by the distributor.

Clinical Study: LeucoSelect™-phytosome®

Extract name	LeucoSelect-phytosome
Manufacturer	Indena S.p.A, Italy
Indication	**Antioxidant activity** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Nuttall SL, Kendall MJ, Bombardelli E, Morazzoni P (1998). An evaluation of the antioxidant activity of a standardized grape seed extract, Leucoselect. *Journal of Clinical Pharmacy and Therapeutics* 23 (5): 385-389.

Trial design
Crossover study. Levels of antioxidant activity were measured after one dose and after five days of treatment. The experiment was repeated following at least a two-week washout period.

Study duration	5 days
Dose	2 (150 mg) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	20

No. of subjects completed	Not given
Sex	Male and female
Age	19-31 years (mean: 23)

Inclusion criteria
Healthy young students. All volunteers were nonsmokers, maintained a standardized dietary pattern throughout the study period, and did not take vitamin supplements.

Exclusion criteria
Major medical or surgical illness in the previous five years, hospital admissions, or current medications.

End points
A series of blood samples were taken before breakfast and following breakfast plus either placebo or active treatment over a period of six hours on days 1 and 5 of each treatment arm. Blood samples were assayed for antioxidant activity and levels of vitamins C and E.

Results
LeucoSelect had no effect on serum vitamins C and E levels, but increased serum total antioxidant activity (TAC). On day 1, TAC was significantly increased 30 minutes after drug treatment compared with baseline values, $p < 0.05$. TAC was further increased at 60 minutes postdose, and remained elevated more than three hours postdose ($p < 0.01$). On day 5, results showed similar increases in TAC at 30 and 60 minutes postdose compared with baseline levels ($p < 0.05$ and $p < 0.01$). No significant difference was observed between days 1 and 5. There was no significant change in serum TAC following administration of placebo on either test day.

Side effects
Not mentioned.

Authors' comments
LeucoSelect capsules increase serum antioxidant activity, but the longer-term clinical implications need to be assessed in further randomized clinical trials.

Reviewer's comments
Antioxidant activity is an intermediate outcome, not a clinical end point (for example, heart disease). This study was single-blind and not randomized, and the sample size was too small. (0, 5)

Product Profile: Procianidol

Manufacturer	**Bruschettini s.r.l., Italy**
U.S. distributor	None
Botanical ingredient	**Grape seed fermented product**
Extract name	N/A
Quantity	100 mg
Processing	No information
Standardization	No information
Formulation	Capsule

Source(s) of information: Fusi et al., 1990.

Clinical Study: Procianidol

Extract name	N/A
Manufacturer	Bruschettini s.r.l., Italy
Indication	**Vision**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Fusi L, Czimeg F, Pesce F, Germogli R, Boero A, Vanzetti M, and Gandiglio G (1990). Effects of procyanidolic olygomers from *Vitis vinifera* in subjects working at video-display units. *Annali di Ottalmologia e Clinica Oculistica* 116: 575-584.

Trial design
Parallel. Three-arm treatment: Group 1 included 50 subjects treated with procyanidolic oligomers; group 2 included ten subjects treated with bilberry anthocyanosides at a dose of 1 × 100 mg capsule three times daily; and group 3 included 15 subjects treated with placebo.

Study duration	2 months
Dose	1 (100 mg) capsule 3 times daily procyanidolic oligomers
Route of administration	Oral
Randomized	Yes
Randomization adequate	No

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Bilberry anthocyanosides
Site description	Not described
No. of subjects enrolled	75
No. of subjects completed	75
Sex	Male and female
Age	20-60 years (mean: 37.9)

Inclusion criteria
Employees using video displays for at least six hours daily, some with various ophthalmological abnormalities.

Exclusion criteria
None mentioned.

End points
A complete ophthalmological examination, orthotic, chromatic sense, determination of contrast sensitivity curve, and a computerized examination of visual field were conducted before and after treatment.

Results
At baseline, the mean curve of contrast sensitivity was below the normal range at most contrast values. After treatment, a statistically significant increase was observed at all ten points of the curve in the group treated with procyanidolic olygomers, at six points of the curve for the bilberry anthocyanoside group, and two points of the curve for the placebo group. The visual acuity and chromatic sense data showed no treatment related changes. An examination of the kinetic visual field did not reveal pathological alterations in any patient. Comparison of overall therapeutic efficacy ratings shows that favorable results were obtained significantly more frequently in both groups treated with active compounds than in the placebo-treated group.

Side effects
Gastric complaints, which did not differ between the 3 groups, were reported.

Authors' comments
Procyanidolic oligomers and bilberry anthocyanosides significantly improved contrast sensitivity and angular resolution power, which are both re-

duced as a result of the visual stress induced by working with video-display units.

Reviewer's comments
This study is adequately double-blinded, and although it is also randomized, the randomization process is not well described. The statistical methods are not adequately described or applied. An unequal division of groups is present, with no statistical difference between them. (Translation reviewed) (3, 4)

Grass Pollen

Rye pollen (*Secale cereale* L.) [Poaceae]
Timothy pollen (*Phleum pratense* L.) [Poaceae]
Corn pollen (*Zea mays* L.) [Poaceae]

PREPARATION USED IN REVIEWED CLINICAL STUDIES

Pollen is the male fertilizing element of flowering plants. It consists of fine yellow grains that are dispersed by the wind and also by insects such as honeybees. A mechanical method of harvesting pollen by puncturing the pollen husk and extracting the nutrients has produced a product that has been tested in numerous studies (Schulz, Hänsel, and Tyler, 2001).

Cernilton® is a standardized product prepared from a proprietary blend of selected pollens, identified by the company literature only as flower pollen. However, it is suggested by Schulz, Hänsel, and Tyler (2001) that Cernilton complies with the German Commission E monograph description of an extract of pollens from grass flowers, consisting of rye pollen (*Secale cereale* L.), timothy pollen (*Phleum pratense* L.), and corn pollen (*Zea mays* L.) (family Poaceae, formally Graminae). Cernilton contains two extracts: Cernitin™ T60™, a water-soluble pollen extract fraction; and Cernitin™ GBX™, a fat-soluble pollen extract fraction. Each capsule/tablet contains 60 mg T60 and 3 mg GBX. Cernilton is manufactured and distributed by A.B. Cernelle, Sweden, and Graminex LLC.

SUMMARY OF REVIEWED CLINICAL STUDIES

Cernilton was tested in clinical studies for treatment of symptomatic benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy and prostatic adenoma. BPH is a nonmalignant en-

GRASS POLLEN SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Cernilton®	A.B. Cernelle, Sweden (Graminex LLC)/Graminex LLC	Cernitin™ T60™ (water-soluble pollen extract fraction); Cernitin™ GBX™ (acetone-soluble pollen extract fraction)	3 to 6 capsules or tablets (containing 60 mg T60 and 3 mg GBX) daily	Benign prostatic hyperplasia	3	Yes (II-1) Trend (II-1) Undetermined (III-1)

largement of the prostate that is common in men over 40 years of age. Symptoms include hesitancy in initiating the urinary stream, a weak or intermittent stream, terminal dribbling of urine, increased urinary urgency and frequency (diuresis: increased formation and release of urine; and nocturia: frequent and/or excessive urination at night), and sensation of incomplete voiding.

The progressive symptoms of BPH have been categorized by Vahlensieck, Alken, and others. The Vahlensieck classification has four stages of symptoms. Stage I is characterized by no voiding difficulties, no residual urine, and a urine flow of more than 15 ml per second. Stage II is characterized by transient voiding difficulties and urine flow between 10 and 15 ml per second. Stage III is characterized by constant voiding dysfunction, urine flow less than 10 ml per second, residual urine greater than 50 ml, and a trabeculated (ridged) bladder. Stage IV is characterized by residual urine volume greater than 100 ml and bladder dilatation (Schulz, Hänsel, and Tyler, 2001). The Alken classification has three stages. Stages I to III are similar to Vahlensieck stages II through IV. Stage I is characterized by an increase in the frequency of urination, pollakiuria (abnormally frequent urination), nocturia, delayed onset of urination, and weak urinary stream. Stage II is characterized by the beginning of the decomposition of the bladder function accompanied by formation of residual urine and urge to urinate. Stage III is characterized by decomposition of the bladder, vesicular overflowing, continuous drip incontinence, and damage to the urinary system and kidneys due to regressive obstruction (Löbelenz, 1992).

Cernilton

Benign Prostatic Hyperplasia

We reviewed three studies, two of which were double-blind and placebo-controlled. The larger study included 96 men with Vahlensieck stage II or III, who were treated Cernilton (two capsules three times daily) or placebo for three months. Observations at 6 and 12 weeks revealed that symptoms of nocturia, diuresis, and sensation of residual urine were significantly improved compared to placebo. No difference in hesitancy, urgency, intermittency, terminal dribbling,

dysuria, peak urine flow, or voided volume was reported (Becker and Ebeling, 1988).

The second study included 53 men awaiting an operation to relieve urinary obstruction, who were given either two capsules twice daily or placebo for six months. The study reported a significant decrease in residual urine and a decrease in the diameter of the prostate with treatment compared to placebo. As with the previous study, flow rate and voided volume were not changed (Buck et al., 1990).

The third study, which included 89 men with BPH stages I and II (classification system not given), compared Cernilton to Tadenan (a product containing a *Pygeum africanum* extract that is also covered in this book). The Cernilton group received one to two tablets of Cernilton three times daily, and the Tadenan group received two tablets twice daily. After four months of treatment, a positive therapeutic response was reported for both treatments, with improved peak flow rate, decreased residual urine volume, decreased prostate volume, and improved obstructive and irritative symptom scores. Scores for the Cernilton group showed more improvement than scores for the Tadenan group, although statistical analysis was not conducted (Dutkiewicz, 1996). The lack of a placebo group limited the usefulness of this study.

According to our reviewer, Dr. Elliot Fagelman, the studies range from fair to good in quality and provide evidence that Cernilton may be beneficial in patients with BPH. However, no studies compared Cernilton with an alpha-adrenergic receptor blocker (e.g., prazosin, terazosin) or a five-alpha reductase inhibitor (e.g., finasteride), the two classes of drugs used in standard clinical practice.

SYSTEMATIC REVIEWS

Four controlled trials, published between 1981 and 1996 with a minimum of one month's duration, were included in a systematic review of Cernilton for the treatment of benign prostatic hyperplasia. The trials' durations were from three to six months, and included 444 men (163 in placebo-controlled trials and 281 in the comparison trials). The subjects received dosages ranging from three to six capsules daily. Three of these trials were reviewed previously (Becker and Ebeling, 1988; Buck et al., 1990; Dutkiewicz, 1996). The forth trial is a double-blind study that compared Cernilton with Paraprost (a mix-

ture of amino acids). In all studies, Cernilton performed better than the controls (placebo, Paraprost, and Tadenan) in terms of the self-reported improvement of symptoms. The frequency of urination was reduced by Cernilton compared with controls, whereas urinary flow measures were not significantly different. Postvoid residual urine volume was reduced modestly by Cernilton compared to placebo, and was similarly reduced by the other control agents. Cernilton's performance was similar to Paraprost and Tadenan with obstructive and irritative symptoms. Only one placebo-controlled study reported a significant reduction in prostate size with Cernilton. The authors of the review conclude, however, that because of the methodological shortcomings of the studies (such as short duration, small sample sizes, and unclear concealment of treatment allocation), Cernilton's efficacy in preventing complications of BPH is undetermined. The trials could not be combined in a meta-analysis due to the differences in reporting methods and control agents (MacDonald et al., 1999).

ADVERSE REACTIONS OR SIDE EFFECTS

Nausea was noted in one study we reviewed (Becker and Ebeling, 1988). A systematic review reported that Cernilton was well tolerated with no serious side effects (MacDonald et al., 1999). In an unpublished report including 1,798 patients treated with Cernilton N, 15 patients (0.8 percent) reported adverse effects, which included mostly gastrointestinal symptoms (indigestion, stomach pain, nausea, pressure sensation, and diarrhea) (Bach and Ebeling, n.d.).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

German Commission E

Indications

In 1994, the German Commission E recommended a grass pollen preparation for the treatment of benign prostatic hyperplasia (micturi-

tion difficulties associated with Alken stage I-II benign prostatic enlargement). The preparation is described as containing a complex extract of 92 percent rye pollen (*Secale cereale* L.), 5 percent timothy pollen (*Phleum pratense* L.), and 3 percent corn pollen (*Zea mays* L.). The herbs are extracted with a water and acetone mixture, yielding a product with an herb to extract ratio of 2.5:1 (Schulz, Hänsel, and Tyler, 2001).

Doses

Extract: 80 to 120 mg daily in two or three divided doses (Schulz, Hänsel, and Tyler, 2001).

Treatment Period

Treatment should last at least three months (Schulz, Hänsel, and Tyler, 2001).

Contraindications

None (Schulz, Hänsel, and Tyler, 2001)

Adverse Reactions

Adverse reactions include rare instances of gastrointestinal complaints or allergic skin reactions (Schulz, Hänsel, and Tyler, 2001).

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DETAILS ON GRASS POLLEN PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Cernilton®

Manufacturer	**AB Cernelle, Sweden**
U.S. distributor	**Graminex L.L.C.**
Botanical ingredient	**Flower pollen extract**
Extract name	**Cernitin™ T60™; Cernitin™ GBX™**
Quantity	60 mg Cernitin T60, 3 mg Cernitin GBX in one tablet
Processing	Cernitin T60 (water-soluble pollen extract concentrate) and Cernitin GBX (fat-soluble pollen extract concentrate), ratio of 20:1
Standardization	No information
Formulation	Tablet

Recommended dose: Four tablets daily as a dietary supplement with meals or a glass of water.

DSHEA-Structure/Function: Promotes a healthy prostate. Supplies vital nutrients to the body and cells (including all essential amino acids, unsaturated fatty acids, and enzymes). Improves absorption of vitamins, minerals, and trace elements from the food we eat. Enables better adaptation to stress, enhancing physical and mental capacity. Helps bioregulate organism functions such as immune system, lipid metabolism, blood cholesterol level, and function of prostate.

Other ingredients: Microcrystalline cellulose, silicon dioxide colloidal, and magnesium stearate.

Source(s) of information: Product label; product information pamphlet.

Clinical Study: Cernilton® N

Extract name	T60™; GBX™
Manufacturer	AB Cernelle, Sweden
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Becker H, Ebeling L (1988). Conservative therapy of benign prostate hyperplasia (BPH) with Cernilton: Results of a placebo-controlled, double blind study. *Urologe [B]* 28: 301-306.

Trial design
Parallel. Study was preceded by a washout phase.

Study duration	3 months
Dose	2 capsules 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	6 urology clinics
No. of subjects enrolled	103
No. of subjects completed	96
Sex	Male
Age	42-85 years

Inclusion criteria
Patients with benign prostatic hyperplasia (BPH) in stages II and III according to Vahlensieck.

Exclusion criteria
Suspicion of a prostate carcinoma; urinary retention of >150 ml; neuro-

genous bladder-emptying difficulties; acute and/or chronic prostatitis/prostatovesiculities; deformity or postoperative condition in the urogenital area with obstruction of the urethra; bladder calculus.

End points
The controlled parameters were micturition problems, urinary retention, palpation result, uroflow, and overall assessment of therapy by patient and doctor. Patients were examined before the trial and after 6 and 12 weeks.

Results
Observations at 6 and 12 weeks showed that all individual symptoms had higher improvement rates and/or positive responses under Cernilton compared to placebo. These differences were especially evident for nocturia, diuresis, and sensation of residual urine. Nocturia improved significantly in 68.8 percent of Cernilton patients and in 37.2 percent of placebo group (comparison $p < 0.005$). The average decrease in urinary retention during treatment was significantly different ($p = 0.006$). No difference was seen between the groups in terms of dysuria, urge, and discomfort. Patients and doctors rated the results of the treatment as very good and good with statistical significance, corresponding to the efficacy of treatment.

Side effects
Slight nausea in one patient taking Cernilton.

Authors' comments
The results of this study demonstrate the effectiveness of the pollen extract preparation for clinical symptoms, urodynamics, and overall opinion of BPH patients stages II and III. The pollen extract is salubrious, and makes long-term treatment with little risk of side effects possible. The use of Cernilton for the symptomatic treatment of BPH stages II and III is recommended.

Reviewer's comments
Overall this is a good study showing symptomatic improvement in those treated with Cernilton. However, 12 weeks is a relatively short duration of treatment. (Translation reviewed) (3, 6)

Clinical Study: Cernilton®

Extract name	T60™, GBX™
Manufacturer	AB Cernelle, Sweden
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Buck AC, Cox R, Rees R, Ebeling L, John A (1990). Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, Cernilton. *British Journal of Urology* 66 (4): 398-404.

Trial design
Parallel.

Study duration	6 months
Dose	2 capsules twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	60
No. of subjects completed	53
Sex	Male
Age	56-89 years (mean: 68.6)

Inclusion criteria
Patients awaiting operative treatment for outflow obstruction due to benign enlargement of the prostate.

Exclusion criteria
None mentioned.

End points
Objective criteria for the evaluation of outflow obstruction were urine flow rate, voided volume, residual urine, and prostate size. Subjective assessment was based on a modified Boyarsky scoring scale for symptoms of frequency, hesitancy, urgency, intermittency, incomplete emptying, terminal dribbling, and dysuria. Investigations were performed before the patients entered treatment, at three months, and at six months.

Results
A statically significant subjective improvement with Cernilton (69 percent of patients) was observed compared with placebo (30 percent) ($p < 0.009$). Residual urine volume decreased significantly in the patients receiving Cernilton compared with the placebo group, in whom it increased ($p <$

0.025). No statistical difference in the symptoms of diurnal frequency was observed between the two groups ($p = 0.66$). Sixty percent of patients on Cernilton were improved or symptom free of nocturia compared with 30 percent of patients on placebo ($p < 0.063$). On Cernilton, 57 percent of patients showed improvement in bladder emptying, compared to 10 percent on placebo ($p < 0.004$). No significant differences between the two groups were found in hesitancy, urgency, intermittency, terminal dribbling, dysuria, peak urine flow rate, or voided volume.

Side effects
No adverse side effects.

Authors' comments
The precise mode of action of Cernilton in benign prostatic hyperplasia is not known. However, this study has shown distinct subjective and objective improvement with a positive response in the Cernilton group. Cernilton may prove to be a useful agent in alleviating the early symptoms of outflow tract obstruction due to BPH.

Reviewer's comments
This study is limited by the small number of patients and lack of randomization (however, the groups were similar at baseline). Overall a symptomatic benefit was seen in those on Cernilton. A decrease in residual urine was statistically significant, but may not be clinically significant. (3, 4)

Clinical Study: Cernilton®

Extract name	T60™; GBX™
Manufacturer	AB Cernelle, Sweden
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Dutkiewicz S (1996). Usefulness of Cernilton in the treatment of benign prostatic hyperplasia. *International Urology and Nephrology* 28 (1): 49-53.

Trial design
Parallel. For the first two weeks of the trial, the Cernilton group received two tablets three times daily; for the remainder of the trial, patients received one tablet three times daily. Patients in the control (Tadenan) group received two tablets twice daily.

Study duration	4 months
Dose	1 to 2 tablets 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Tadenan
Site description	Not described
No. of subjects enrolled	89
No. of subjects completed	89
Sex	Male
Age	50-68 years

Inclusion criteria
Patients with clinical stages I and II benign prostate hyperplasia, with a short history of symptoms no longer than a few weeks in duration (classification system not given).

Exclusion criteria
Patients with complete urine retention.

End points
Subjective assessment was made using a symptom score system and objective evaluation by physical examination, uroflowmetry, and ultrasound examination of residual urine and prostate size.

Results
The therapeutic response was positive in 40 (78 percent) and 21 (55 percent) patients in the Cernilton and Tadenan groups, respectively. Peak flow rate improved by 19.5 percent in the Cernilton group, and by 10.8 percent in the Tadenan group. Residual urine volume improved by 47.8 percent and by 21.6 percent in the Cernilton and Tadenan groups, respectively. Prostate volume also improved by 5.15 percent (Cernilton) and by 0.45 percent (Tadenan). Obstructive symptom scores improved by 62.75 percent in the Cernilton group and by 45.8 percent in the Tadenan group. Irritative symptoms improved in the Cernilton group by 68.4 percent and by 40 percent in the Tadenan group.

Side effects
No adverse reactions were seen.

Author's comments
In BPH, the decongestive effect of Cernilton leads to a lasting improvement of voiding difficulties. The residual urine volume decreases significantly. In comparison to *Pygeum africanum* extract (Tadenan), Cernilton proved much more effective.

Reviewer's comments
This study compares Cernilton with Tadenan. Although a benefit was observed in the patients treated with Cernilton, a poor study design and lack of a placebo group limit the usefulness of the study. The treatment was also given for a short duration. (1, 3)

Green Tea

Latin name: ***Camellia sinensis* (L.) Kuntze** [Theaceae]
Latin synonyms: ***Thea sinensis* L.**
Plant part: **Leaf**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Chinese legend has it that tea was discovered in 2700 B.C. when a gust of wind blew some tea leaves into a kettle of boiling water. A competing legend advanced by the British East India Company claims tea originated in India and not China (Gutman and Ryu, 1996).

Green tea and black tea are both derived from the young shoots (the first two or three leaves plus the growing bud) of *Camellia sinensis* (L.) Kuntze. The teas are differentiated by their method of processing. Heating the freshly picked leaves shortly after harvest produces green tea. This process inactivates enzymes (polyphenol oxidases) that form the dark pigments associated with black tea. The heated leaves are then rolled to squeeze the juices to the surface of the leaf and dried using hot air. Black teas are produced by a natural enzymatic fermentation of the leaves that occurs after harvest (Gutman and Ryu, 1996).

A cup of green tea usually contains 300 to 400 mg polyphenols. Polyphenols are a large class of mildly acidic compounds with antioxidant properties. Polyphenols can be divided into many subclasses, including catechins, an example of which is epigallocatechin gallate (EGCG) (Gutman and Ryu, 1996).

Two studies were conducted on a product defined as US Tea Associations regular tea freeze-dried solids and called "Lipton® Research Blend." The tea was prepared by Thomas J. Lipton Co., of Englewood Cliffs, New Jersey, which is now part of Unilever Bestfoods, North America. The rest of the studies were conducted on extracts of tea leaves with concentrated amounts of polyphenols.

GREEN TEA SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Exolise™	Arktopharma Laboratoires Pharmaceutiques, France/Health from the Sun/ Arkopharma	Aqueous ethanolic dry extract standardized to 25% catechins, expressed as EGCG	1 capsule 3 times daily (375 mg catechins, 150 mg caffeine)	Weight loss	1	MOA (III-1)
Lipton® Research Blend	Thomas J Lipton Co. (Unilever Bestfoods, North America)/none	Tea solids	3 g tea solids (900 ml/day)	Cardio-vascular risk factors	1	MOA (III-1)
			2 g tea solids (300 ml/day)	Antioxidant activity	1	MOA (III-1)
Tegreen 97® (US), Xin Nao Jian (China)	Pharmanex LLC/Pharmanex Natural Healthcare	Extract containing 97% polyphenols	600 mg extract per day	Hemato-poietic effects of cancer therapy	1	Undetermined (III-1)
				Renal insuf-ficiency	1	Undetermined (III-1)
Polyphenon E®	Mitsui Nohrin Co., Ltd., Japan/None	Polyphenol extract	600 mg extract per day	Cardio-vascular risk factors	1	Undetermined (III-1)

Editor's note: Exolise was taken off the market while this book was in press.

Exolise™, which is manufactured by Arktopharma Laboratoires Pharmaceutiques in France and distributed by Health from the Sun/Arkopharma, Stamford, Connecticut, contains an 80 percent ethanolic dry extract standardized to 25 percent catechins, expressed as EGCG. The amount used in the weight-loss study was specifically characterized as three capsules per day containing a total of 375 mg catechin (270 mg of which as epigallocatechin) and 150 mg caffeine.

Tegreen®, produced by Pharmanex LLC, a wholly owned subsidiary of Nu Skin Enterprises, Inc., Provo, Utah, is characterized as containing 97 percent polyphenols.

Polyphenon E®, produced by Mitsui Nohrin Co. Ltd., Tokyo, Japan, is characterized simply as a polyphenol extract. This product is not available commercially in the United States.

SUMMARY OF REVIEWED CLINICAL STUDIES

Studies of green tea as tea solids or extracts have been conducted exploring its use in weight loss and as an antioxidant useful in reducing cardiovascular risk factors, in alleviating the adverse effects of renal insufficiency, and in reducing the negative effects of cancer therapy on blood cells. On balance, green tea extracts and green tea have positive effects on metabolism and antioxidant activity. However, the impact of these effects on health outcomes remains to be determined.

Exolise

Weight Loss

A study exploring green tea's effect on weight loss was conducted using Exolise, one capsule three times daily. This mechanistic study showed an increase in energy expenditure over a 24-hour period with Exolise compared to placebo. The energy expenditure was 4 percent above the stimulatory effects produced by equivalent amounts of caffeine found in Exolise (Dulloo et al., 1999). Although this carefully controlled study demonstrated thermogenic activity and promotion of the oxidation of fat, the results were of questionable significance for clinical weight management. A follow-up study with moderately obese subjects did report weight loss as a result of treatment. How-

ever that study did not include a control group, and thus did not qualify for review in this book (Chantre and Lairon, 2002).

Lipton Green Tea, Research Blend

Cardiovascular Risk Factors/Antioxidant Activity

Potential antioxidant activity was explored in two studies comparing green and black teas. In a study with 45 participants, the daily consumption of six cups of green or black tea (Lipton tea solids, 0.5 g in 150 ml water) over a four-week period did not lead to any effect on serum lipid concentrations, resistance of low-density-lipoprotein-cholesterol (LDL) to oxidation, or to markers of oxidative damage to lipids. However, consumption of green tea led to a slight increase in total antioxidant activity in plasma (van het Hof et al., 1997). The other study included 21 adults who received six different treatments on six different days with at least two days in between treatments. The administration of a single dose of 2 g of green or black tea solids (Lipton) in 300 ml water led to a significant increase in plasma catechin levels and in plasma antioxidant activity one hour later. The rise in total catechins was greater with green tea than black tea, as expected based on the higher content of catechins in green tea compared to black tea. The addition of milk to either green or black tea did not affect results (Leenen et al., 2000). These studies were both rated as low in quality due to a lack of blinding and poor descriptions of the randomization process.

Tegreen

Hematopoietic Effects of Cancer Therapy

A study examined the potential protective effect of a green tea polyphenol extract (Xin Nao Jian) on the damage to the development and formation of blood cells due to cancer radiation therapy or chemotherapy. Sixty cancer inpatients with a normal blood cell profile undergoing their first treatment were included in the study. They were given 200 mg of extract three times daily, another herbal formula for improving blood quality (Sha Gan Chun), or no additional treatment for one month. Total white blood cell counts improved in the green tea group but declined in the Sha Gan Chun group after five weeks

and in the control group after three weeks. No significant changes were observed in hemoglobin levels or platelet counts in any group (Walsh, 1997a). Our reviewer, Dr. David Heber, commented that the effects of green tea on lymphocyte stabilization and immune function deserve further study. This study was limited by inadequately described statistical methods and a small sample size.

Renal Insufficiency

In another study, Tegreen was given in the same dose (200 mg three times daily) to patients with chronic renal insufficiency for three months. Renal function (as measured by blood urea nitrogen) was improved, erythrocyte superoxide dismutase activity was significantly increased, and plasma lipid peroxide levels were significantly decreased. The author of the study commented that the benefits of Tegreen to this population were due to its antioxidant activity and free radical scavenging activity (Walsh, 1997b). Although it had some serious methodological flaws, this study remains a good guide for future studies.

Polyphenon E

Cardiovascular Risk Factors

A small study using a green tea concentrate, Polyphenon E, measured the effect of 300 mg extract twice daily, the equivalent of seven to eight cups of tea, on markers of antioxidant activity in the blood compared to untreated controls. After one week, plasma catechin levels were measurable, whereas they were not detectable at baseline. No effect was reported on the concentration of plasma lipids or on lipid peroxides compared to baseline. However, an increase in resistance to oxidation of LDL-cholesterol was measured ex vivo (Miura et al., 2000). The study was weak due to the small sample size and the lack of blinding and randomization of patient populations.

EPIDEMIOLOGICAL STUDIES

Many of the studies on green tea are epidemiological: population studies and statistical comparisons of the health status and subsequent disease history of large groups of people who customarily drink several cups of green tea daily in comparison with other groups who do not.

A meta-analysis of 17 epidemiological studies explored the possible relationship between black and green tea consumption and cardiovascular disease. Although the study-specific effect estimates for heart attack and coronary heart disease were too heterogeneous to summarize, the relative risk for heart attack was estimated to decrease by 11 percent with consumption of three cups of tea per day (Peters, Poole, and Arab, 2001). The study did not distinguish, however, between the various types of tea, methods of preparation, or the strength of the tea.

A recent study with 13,916 healthy Japanese workers concluded that consumption of green tea was associated with lower serum total cholesterol. There appeared to be an inverse dose relationship with increasing quantities of green tea consumption correlating with decreasing levels of total cholesterol. This inverse relationship appeared to level off with consumption of more than ten cups per day. Consumption of green tea was unrelated to serum levels of high-density lipoprotein cholesterol or serum triglycerides. (Tokunaga et al., 2002).

The authors of a review of epidemiological studies on tea drinking and cancer concluded that there was no evidence of a protective role against cancer in general. However, when the studies were broken down to specific body sites, the authors reported that the results suggest a protective effect from green tea consumption on the development of colon cancer. The authors indicated that benefits are likely restricted to high consumption of tea in high-risk populations. The range and crude categorization of tea consumption, as well as the choice of control groups and inadequate control for confounding variables, limited this review (Kohlmeier et al., 1997).

A population-based, case-controlled study was conducted in China with 1,324 women, wherein women diagnosed with lung cancer were matched by age with women in the general population. Information was obtained from both groups regarding their tea drinking

habits. The researchers found that consumption of green tea was associated with a reduced risk of lung cancer. Among nonsmoking women, regular consumption of green tea (501 to 1,500 grams per year) over a five-year period was associated with a reduced risk of lung cancer (odds ratio 0.65). The risks decreased with increasing consumption of green tea (over 1,500 grams per year; odds ratio 0.46). However, there was no reduced risk in women who smoked (Zhong et al., 2001).

A hospital-based, epidemiological research program in Japan that followed a total of 1,160 new surgical cases of female invasive breast cancer reported a decreased risk for recurrence with consumption of three or more cups of green tea per day (odds ratio 0.69). The decreased risk was significant for those with stage I cancer (odds ratio 0.43), and strongest for those who consumed three to five cups per day (odds ratio 0.37). Those with stage II cancer exhibited a nonsignificant trend toward reduced cancer recurrence, whereas no benefit was observed for those with more advanced stages of cancer (Inoue et al., 2001).

A population-based, case-controlled study conducted in China, with 133 patients with stomach cancer, 166 with chronic gastritis, and 433 healthy controls, reported an inverse association between green tea drinking and risk of both stomach cancer and chronic gastritis (odds ratios 0.52 and 0.49, respectively, with more than 21 cups per week). The possible benefit increased with larger amounts of tea and additional years of tea drinking (Setiawan et al., 2001). In contrast, a prospective study that followed 38,540 Japanese men and women in Hiroshima and Nagasaki for 13 to 14 years found no correlation between green tea consumption and the incidence of an array of solid cancers or hematopoietic cancers (lymphoma, multiple myeloma, and leukemia) (Nagano et al., 2001).

ADVERSE REACTIONS OR SIDE EFFECTS

No side effects were reported in the individual trials discussed earlier. The caffeine contained in green tea may have a stimulant effect, especially for those who choose to drink large quantities.

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DETAILS ON GREEN TEA PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Green Tea Products

Product Profile: Exolise™

Manufacturer	**Arkopharma Laboratoires Pharmaceutiques, France**
U.S. distributor	**Health from the Sun/Arkopharma**
Botanical ingredient	**Green tea leaf extract**
Extract name	**AR25**
Quantity	375 mg
Processing	Alcohol extraction from dry leaves of unfermented *Camellia sinensis*
Standardization	Standardized to 25% catechins
Formulation	Capsule

Recommended dose: Take two capsules with breakfast and two capsules with lunch with a glass of water.

DSHEA structure/function: Helps maintain a healthy body weight.

Other ingredients: Cellulose derivative (capsule shell), vegetal magnesium stearate, silicon dioxide.

Source(s) of information: Product package; Dulloo et al., 1999.

Clinical Study: Exolise™

Extract name	AR25
Manufacturer	Arkopharma Laboratoires Pharmaceutiques, France
Indication	**Weight loss; thermogenic effect** (energy expenditure)
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, Chantre P, Vandermander J (1999). Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *American Journal of Clinical Nutrition* 70 (6): 1040-1045.

Trial design
Parallel. Each subject spent 24 hours in the respiratory chamber on three separate occasions (each separated by five to ten days) and was randomly assigned to receive one of the following three treatments at breakfast, lunch, and dinner: green tea extract (containing 50 mg caffeine and 90 mg epigallocatechin), 50 mg caffeine, or placebo.

Study duration	3 days
Dose	2 capsules green tea extract (50 mg caffeine and 90 mg epigallocatechin per dose) 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Caffeine
Site description	Single center

No. of subjects enrolled	10
No. of subjects completed	10
Sex	Male
Age	Mean: 25 ± 1 years

Inclusion criteria
Healthy young men with body composition ranging from lean to mildly obese (8 to 30 percent body fat), consumption of a typical Western diet with fat contributing 35 to 40 percent of dietary energy intake, and estimated intake of methylxanthines (mostly caffeine-containing beverages) ranging from 100 to 200 mg/day.

Exclusion criteria
Smokers, competitive athletes, and persons who engaged in intense physical activities or who had a history of weight loss.

End points
Energy expenditure (EE), respiratory quotient (RQ), and urinary excretion of nitrogen and catecholamines were measured for each 24-hour stay in the respiratory chamber.

Results
Relative to placebo, treatment with the green tea extract resulted in a significant increase in 24-hour EE (4 percent, $p < 0.01$) and a significant decrease in 24-hour RQ (from 0.88 to 0.85, $p < .001$) without any change in urinary nitrogen. Twenty-four-hour urinary norepinephrine excretion was higher during treatment with green tea extract than with the placebo (40 percent, $p < 0.05$). Treatment with caffeine in amounts equivalent to those found in the green tea extract had no effect on EE and RQ nor on urinary nitrogen or catecholamines. With green tea extract, fat oxidation was significantly higher ($p < 0.001$) and carbohydrate oxidation was significantly lower ($p < 0.01$) than with placebo.

Side effects
None reported.

Authors' comments
Green tea has thermogenic properties, and promotes fat oxidation beyond that explained by its caffeine content per se. The green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis.

Reviewer's comments
This was a mechanistic study showing green tea to have thermogenic and fat-oxidation-promoting activity; however, its role in weight loss is undeter-

mined. Neither the randomization nor the double-blinding were adequately described. (1, 6)

Product Profile: Lipton Research Blend

Manufacturer	**Thomas J. Lipton Co.** (now Unilever Bestfoods, North America)
U.S. distributor	None
Botanical ingredient	**Green tea leaf extract**
Extract name	None given
Quantity	No information
Processing	Lyophilized (freeze-dried) tea solids
Standardization	No information
Formulation	Tea solids

Source(s) of information: Leenen et al., 2000.

Clinical Study: Lipton Research Blend

Extract name	None given
Manufacturer	Thomas J. Lipton Co.
Indication	**Cardiovascular risk factors** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
van het Hof KH, de Boer HSM, Wiseman SA, Lien N, Westrate JA, Tijburg LBM (1997). Consumption of green or black tea does not increase resistance of low-density lipoprotein to oxidation in humans. *American Journal of Clinical Nutrition* 66 (5): 1125-1132.

Trial design
Parallel. After a two-week pretrial period in which all subjects consumed 900 ml (6 cups) of water per day, they were divided into three groups and given 900 ml (6 cups) of either water, green tea, or black tea (0.5 g black tea extract per cup) daily.

Study duration	1 month
Dose	6 (0.5 g tea extract in 150 ml) cups daily

Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Single center
No. of subjects enrolled	48
No. of subjects completed	45
Sex	Male and female
Age	20-61 years

Inclusion criteria
Ages 18 to 65 years, healthy, nonsmoking, not using vitamin C, vitamin E, carotenoid, selenium, or zinc supplements or consuming a medically prescribed or weight-loss diet, and a stable weight for at least one month before the start of the study.

Exclusion criteria
Pregnant or lactating women.

End points
Blood samples were obtained before and after experimental period. Serum lipid concentrations, plasma and low-density lipoprotein (LDL) antioxidant status, resistance of LDL to oxidation, and plasma malondialdehyde and LDL-hydroperoxide concentrations were measured.

Results
Consumption of green or black tea did not affect serum lipid concentrations, resistance of LDL to oxidation ex vivo, or markers of oxidative damage to lipids in vivo. However, consumption of green tea slightly increased total antioxidant activity of plasma.

Side effects
None mentioned.

Authors' comments
Daily consumption of 900 ml (six cups) green or black tea per day for four weeks had no effect on serum lipid concentrations or resistance of LDL to oxidation ex vivo. Future research should focus on mechanisms by which tea flavonoids may reduce the risk of cardiovascular disease other than by increasing the intrinsic antioxidant status of LDL.

Reviewer's comments
Although this study gave negative results, the sample size was small, and the subjects were not randomized or blinded. (1, 5)

Clinical Study: Lipton® Research Blend

Extract name	None given
Manufacturer	Thomas J. Lipton Co.
Indication	**Antioxidant activity** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Leenen R, Roodenburg AJC, Tijburg LBM, Wiseman SA (2000). A single dose of tea with or without milk increases plasma antioxidant activity in humans. *European Journal of Clinical Nutrition* 54 (1): 87-92.

Trial design
Crossover. Each subject received six treatments on six different days with at least two days in between. After an overnight fast, volunteers were given a single dose of black tea, green tea, or water, with or without milk.

Study duration	1 day
Dose	2 g tea solids in 300 ml water (equivalent to 3 cups of tea)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Black tea
Site description	Single center
No. of subjects enrolled	24
No. of subjects completed	21
Sex	Male and female
Age	18-65 years

Inclusion criteria
Between 18 and 70 years old, healthy, nonsmokers. Subjects did not use any medicines, a medically prescribed diet, a weight-loss regime, or supplements containing vitamin C, vitamin E, carotenoids, calcium, or iron, and had a stable body weight for at least one month before the start of the study.

Exclusion criteria
Pregnant or lactating women.

End points
Blood samples were obtained at baseline and at 30, 60, 90, and 120 minutes after tea drinking. Plasma was analyzed for total catechins and antioxidant activity, using the ferric reducing ability of plasma (FRAP) assay.

Results
Consumption of black tea resulted in a significant increase in plasma antioxidant activity, which reached maximal levels at about 60 minutes ($p < 0.001$ tea versus water). A larger increase was observed after consumption of green tea ($p < 0.05$ green versus black). As anticipated from the higher catechin concentration in green tea, the rise in plasma total catechins was significantly higher after consumption of green tea when compared to black tea ($p < 0.001$). Addition of milk to black or green tea did not affect the observed increases in plasma antioxidant activity.

Side effects
None mentioned.

Authors' comments
Consumption of a single dose of black or green tea induces a significant rise in plasma antioxidant activity in vivo. Addition of milk to tea does not abolish this increase. Whether the observed increases in plasma antioxidant activity after a single dose of tea prevent in vivo oxidative damage remains to be established.

Reviewer's comments
This study shows that a single dose of black or green tea increases antioxidant activity in plasma. The study was not blinded, and the randomization was not adequately described. (1, 6)

Product Profile: Tegreen 97®

Manufacturer	**Pharmanex LLC**
U.S. distributor	**Pharmanex Natural Healthcare**

Botanical ingredient	**Green tea leaf extract**
Extract name	**Tegreen 97**
Quantity	250 mg
Processing	Plant/extract ratio 20:1
Standardization	97% green tea polyphenols
Formulation	Capsule

Recommended dose: Take one capsule daily with food and drink. Take consistently for best results.

DSHEA structure/function: Supports the antioxidant defense system in the presence of pollution, stress, and toxins.

Cautions: If pregnant or nursing, or taking a prescription medication, consult a physician before using this product.

Other ingredients: Millet, gelatin, magnesium silicate, silicon dioxide.

Source(s) of information: Product package.

Clinical Study: Xin Nao Jian (Tegreen 97®)

Extract name	Tea polyphenol
Manufacturer	Pharmanex LLC
Indication	**Hematopoietic effects** of cancer therapy
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Walsh B (1997). Scientific report: The protective effect of "Xin Nao Jian" capsule on the hemogram of cancer patients undergoing radiotherapy and chemotherapy. Pharmanex Inc. Confidential Report #PN0411.

Trial design
Parallel. The study began with the first day of radiotherapy or chemotherapy. Patients were divided randomly into three groups and given either Xin Nao Jian, Sha Gan Chun (a traditional Chinese medicine used to improve blood quality; 100 mg three times daily), or no additional therapy.

Study duration	1 month
Dose	200 mg tea polyphenol three times daily
Route of administration	Oral
Randomized	Yes

Randomization adequate	Yes
Blinding	Not described
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Sha Gan Chun
Site description	Multicenter
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Not given
Age	Not given

Inclusion criteria
Cancer inpatients with a normal hemogram undergoing the first course of radiotherapy and chemotherapy.

Exclusion criteria
None mentioned.

End points
After the beginning of treatment, patient blood samples were taken every week. Hemoglobin content was determined, along with platelet and white blood cell levels.

Results
Total white blood cell counts improved in the Xin Nao Jian group, but significantly declined in the Sha Gan Chun group after five weeks ($p < 0.05$) and in the control group after three weeks ($p < 0.001$). No significant changes in hemoglobin or blood platelet levels were observed.

Side effects
Three cases of nausea and loss of appetite were reported in the Xin Nao Jian group. However, the other groups reported these effects as well.

Author's comments
It can be seen that Xin Nao Jian has a protective effect on the hemogram of patients undergoing radiotherapy and chemotherapy, especially a definite effect on the stabilization of the number of total leucocytes.

Reviewer's comments
This study had several flaws: inadequately described statistical methods and data, and it was nonblinded. However, the stabilization of lymphocytes and the effects on immune function deserve further study. (2, 3)

Clinical Study: Tegreen 97®

Extract name	Tea polyphenol
Manufacturer	Pharmanex LLC
Indication	**Renal insufficiency**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Walsh B (1997). Scientific report: Observation of the anti-free-radical effect in the treatment of chronic renal insufficiency using tea polyphenol. Pharmanex Inc. Confidential Report #PN0409.

Trial design
Parallel. Both groups adopted a low-protein, low-salt diet, and routine therapy. In addition, the treatment group was given capsules with tea polyphenols.

Study duration	3 months
Dose	2 (100 mg) capsules three times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Male and female
Age	19-59 years (mean: 36.7)

Inclusion criteria
Patients with chronic renal insufficiency.

Exclusion criteria
None mentioned.

End points
Measurement of the content of blood plasma lipid peroxide (LPO), erythro-

cyte superoxide dismutase (SOD) activity, blood urea nitrogen (BUN), serum creatine (SCr), and clinical symptoms.

Results
Erythrocyte SOD was significantly increased ($p < 0.05$), and the plasma LPO was significantly decreased ($p < 0.01$) in the treatment group relative to the control group. Renal function was improved in the treatment group relative to the control group as assessed by BUN ($p < 0.01$) and SCr ($p < 0.05$).

Side effects
None mentioned.

Author's comments
Tea polyphenol is able to clear free radicals and prohibit lipid peroxidation. It can also mobilize and activate the endogenous antioxidant system of the body, raise the activity of SOD and other enzymes, cause the reduction of blood plasma LPO levels, and therefore produce body-protecting effects.

Reviewer's comments
Although serious flaws are present in the study design and description of results, this heterogeneous group of renal failure patients claimed to have improvement in renal function: BUN decreased from 21 to 11 in treatment group; serum creatinine decreased from 405 to 275; and positive effects on plasma SOD and lipid peroxide were observed. This is a good guide for future study. (0, 0)

Product Profile: Polyphenon E®

Manufacturer	**Mitsui Nohrin Co., Ltd., Japan**
U.S. distributor	None
Botanical ingredient	**Green tea leaf extract**
Extract name	None given
Quantity	No information
Processing	No information
Standardization	No information

Source(s) of information: Miura et al., 2000.

Clinical Study: Polyphenon E®

Extract name	Not given
Manufacturer	Mitsui Nohrin Co., Ltd., Japan

Indication	**Cardiovascular risk factors** in normal volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Miura Y, Chiba T, Miura S, Tomita I, Umegaki K, Ikeda M, Tomita T (2000). Green tea polyphenols (flavan 3-ols) prevent oxidative modification of low density lipoproteins: An ex vivo study in humans. *Journal of Nutritional Biochemistry* 11 (4): 216-222.

Trial design
Parallel. All subjects had a strict dietary regimen, including drinks. After a one-week baseline period, they were divided into control and tea groups.

Study duration	1 week
Dose	300 mg tea extract twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Single center
No. of subjects enrolled	22
No. of subjects completed	22
Sex	Male
Age	22-32 years (mean: 24.5)

Inclusion criteria
Normolipidemic, smokers or nonsmokers, who did not take any medications or special dietary additives.

Exclusion criteria
Medication, vitamin supplements, or special dietary additives. Additional consumption of green or black teas, fruit juice, or vegetable juice was not allowed during the pretrial and trial periods.

End points
Fasting blood samples were drawn before the pretrial baseline period, after the pretrial period, and after one week of treatment. Plasma catechin levels

were measured as well as plasma lipids, antioxidative vitamins, and thiobarbituric acid-reactive substances.

Results
Plasma catechin (epigallocatchin-gallate) concentration at the end of the experiment was 56 nmol/l on average (56 percent in free form) after one week ingestion of tea, whereas none was detected beforehand. Plasma concentration of lipids, ascorbate, alpha-tocopherol, and lipid peroxides did not change before and after the experiment in either group, but beta-carotene was higher in the tea group ($p < 0.01$ by paired Student's t-test). Low-density lipoprotein (LDL) oxidation lag time was prolonged by 13.7 minutes in the tea group, whereas such a change was not observed in the control group ($p < 0.05$).

Side effects
None mentioned.

Authors' comments
These results suggest that daily consumption of seven to eight cups (approximately 100 ml each cup) of green tea may increase resistance of LDL to in vivo oxidation, leading to a reduction in the risk of cardiovascular diseases.

Reviewer's comments
This is a carefully controlled and well-reported study. However, it was not randomized and the blinding was not described. (0, 6)

Hawthorn

Other common names: **English hawthorn; May tree; white thorn**
Latin name: ***Crataegus laevigata* (Poir.) DC.** and ***C. monogyna* Jacq.** as well as other species [Rosaceae]
Latin synonyms: ***Crataegus oxyacantha* L. = *C. laevigata***
Plant parts: **Leaf, flower**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Hawthorn, a tall shrub that grows throughout Europe, was first documented as having medical use in the first century A.D., but the plant's use as a heart medicine can only be traced back to the 1600s. The two primary species are *Crataegus laevigata* (Poir.) DC. and *C. monogyna* Jacq. However, other species have been used medicinally, and to make matters more complex, the two primary species are known to hybridize (Upton, Graff, Williamson, et al., 1999). Therapeutic efficacy has been documented most reliably for the leaves and flowers. The dried, berrylike fruits have also been used, either alone or in combination with the leaves and flowers. The main constituents of hawthorn are identified as procyanidins, flavonoids, triterpenoids, catechins, aromatic carboxylic acids, and amino and purine derivatives. For quality control purposes, the flavonoid content and/or the oligomeric procyanidin content are determined. The leaves and flowers contain approximately 1 percent flavonoids and 1 to 3 percent oligomeric procyanidins (Schulz, Hänsel, and Tyler, 2001).

HeartCare™ contains 80 mg WS 1442, a hydroalcoholic extract of hawthorn leaves and flowers (5:1) standardized to 18.75 percent oligomeric procyanidins. This product is made by Dr. Willmar Schwabe GmbH & Co. in Germany, and is distributed in the United States by Nature's Way Products, Inc. WS 1442 is sold in Europe in a product named Crataegutt®.

HAWTHORN SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
HeartCare™ (US); Crataegutt® (EU)	Dr. Willmar Schwabe GmbH & Co., Germany/ Nature's Way Products, Inc.	Hydroalcoholic extract of leaves and flowers (WS 1442)	160 or 180 mg daily	Chronic heart failure	6	Yes (II-1, III-1) Trend (I-1) Undetermined (III-3)
Faros® 300 (EU)	Lichtwer Pharma AG, Germany/ None	Hydroalcoholic extract of leaves and flowers (LI 132)	300, 600, or 900 mg daily	Chronic heart failure	4	Yes (II-1) Trend (I-1, II-2)

Faros® 300 is manufactured by Lichtwer Pharma AG in Germany and contains a hydroalcoholic extract of leaves and flowers (LI 132). Tablets or capsules containing 50, 200, and 300 mg hawthorn extract have been used in clinical studies. Faros 300 is not sold in the United States.

SUMMARY OF REVIEWED CLINICAL STUDIES

Hawthorn has been studied for its clinical use in the treatment of early stage heart failure, which is also called cardiac insufficiency. Heart failure is defined as the inadequate supply of oxygen and nutrients to the body as the result of heart disease. Animal studies indicate that hawthorn preparations increase the contraction of the heart muscle, increase the integrity of the blood vessel wall, and improve the flow of blood to the heart without changing heart rate or aggregation of red blood cells (Loew, 1997).

The New York Heart Association (NYHA) has classified heart failure in four stages. Patients with Class I heart failure have cardiac disease but are able to conduct ordinary physical activity without limitation. Class II is defined as a slight limitation of ordinary physical activity due to fatigue, palpitation, dyspnea, or anginal pain. Class III is defined as marked limitation of physical activity even on light exertion. Patients with Class IV heart failure are unable to carry on any physical activity without discomfort—they may experience symptoms of congestive heart failure even at rest (Cochran Foundation, 1997). Many of the clinical studies using hawthorn have been conducted on patients with Class II disease.

HeartCare

Chronic Heart Failure

Five placebo-controlled studies evaluated the effectiveness of WS 1442 in the treatment of stable chronic heart failure classified as NYHA Class II. An additional study evaluated patients with NYHA Class III.

Two of the studies with patients classified as NYHA Class II were rated as good quality. The largest good-quality study included 129

patients treated with either 160 mg extract or placebo daily for two months. As a result of treatment, there was a statistically significant increase in cardiac performance compared to placebo, as measured by blood pressure and heart rate at rest and after exercise. Clinical symptoms such as restricted physical performance, shortness of breath, and edema around the ankles were improved (Weikl et al., 1996). Another good-quality, but smaller, study with only 39 subjects showed a trend toward improvement in exercise tolerance following three months of treatment with 80 mg three times daily. A decrease in a measurement combining heart rate and blood pressure was observed in the hawthorn group but not in the placebo group (Zapfe, 2001). According to our reviewer, Dr. Mary Hardy, an increase in the study size may have strengthened the results.

Three other studies, with small groups of patients (30 to 58) classified as having NYHA Class II, were rated poorly due to methodological flaws. A crossover study that used a dose of 180 mg per day for six weeks reported that the patients' exercise-induced rise in systolic blood pressure and heart rate was reduced compared to placebo. In addition, a decrease in blood pressure at the end of the recovery period was observed compared to baseline and placebo (O'Conolly et al., 1986). An eight-week parallel study found that a measure of blood pressure and heart rate during exercise decreased continuously after four and eight weeks of treatment compared to baseline. This measure was also statistically below that from the placebo group. In addition, a greater decrease in subjective complaints was observed in the treatment group compared to the placebo group (Leuchtgens, 1993). Another study reported a significant increase in exercise tolerance compared to the placebo group following treatment with 180 mg per day for three weeks. The treatment group's ischemic reaction to exercise also decreased as measured by electrocardiogram. This study found no difference in blood pressure or heart rate (Hanack and Brückel, 1983).

A three-arm trial with 197 subjects with NYHA Class III heart failure assessed the ability of WS 1442 to increase exercise capacity and decrease symptoms. Either 900 or 1,800 mg WS 1442 daily, or placebo, was given in addition to preexisting diuretic therapy (50 mg triamterene and 25 mg hydrochlorothiazide). After four months of treatment, maximum tolerated workload during exercise with the 1,800 mg dose increased significantly compared to the 900 mg dose

and to placebo. Subjective heart failure symptoms were significantly reduced by both doses compared to placebo (Tauchert, 2002).

Faros 300

Chronic Heart Failure

Four trials were reviewed that evaluate the use of Litchwer's extract LI 132 for patients with NYHA Class II heart failure. The trials used a dose ranging from 100 to 300 mg three times daily for a period of one to two months. The largest trial, which was rated as being of good quality, included 124 subjects, and compared the effectiveness of LI 132 (300 mg three times daily) with captopril (12.5 mg three times daily). Captopril is an ACE (angiotension converting enzyme) inhibitor that lowers blood pressure in hypertensive individuals and reduces peripheral resistance of blood vessels. In this trial, both LI 132 and captropril equally improved exercise capacity and decreased a measured product of heart rate and blood pressure after two months of treatment (Tauchert, Ploch, and Hübner, 1994).

Three smaller trials, with about 70 subjects each, were placebo-controlled. One of them, using a dose of 200 mg three times daily for two months, reported a statistical improvement in exercise capacity and a decrease in the measured product of heart rate and blood pressure compared to placebo (Schmidt et al., 1994). Another trial, using a dose of 300 mg three times daily, showed only a trend toward an increase in exercise capacity, but reported a significant increase both in exercise time taken to reach anaerobic metabolism and in oxygen absorbed by the lungs both during exercise and afterward (Forster et al., 1994). The final study used a smaller dose (100 mg three times daily) for short period of time (only one month) and showed statistically insignificant increases in exercise capacity compared with placebo (Bodigheimer and Chase, 1994).

POSTMARKETING SURVEILLANCE STUDIES

A study including 940 medical practioners and 3,664 patients diagnosed with cardiac insufficiency NYHA Class I or Class II documented a therapeutic benefit in 1,476 patients given hawthorn and no

other medication to treat their disease. Patients were evaluated after four and eight weeks of treatment, consisting of Faros 300 in a dose of 300 mg three times daily. At the end of the surveillance period, the average cardiac insufficiency symptom score was reduced from 6.9 to 1.7 points out of nine total. Work tolerance, as measured using bike ergometry, was increased, and a measurement of heart rate and blood pressure associated with exercise was reduced. In a subset of patients with borderline hypertension, reductions were observed in systolic and diastolic blood pressure. In patients with tachycardia, a reduction in heart rate and incidence of arrhythmias was reported (Schmidt et al., 1998).

ADVERSE REACTIONS OR SIDE EFFECTS

No significant side effects were reported in the trials reviewed in this section. In a surveillance study with 3,664 patients diagnosed with NYHA Class I or Class II heart failure, 48 of the patients (1.3 percent) reported 72 adverse reactions. The majority of these reactions were gastrointestinal complaints (24 cases), palpitations (10), vertigo (7), headache (7), and flushing (3). The treatment was Faros 300 taken in a dose of 300 mg three times daily (Schmidt et al., 1998).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

American Herbal Pharmacopoeia
European Scientific Cooperative on Phytotherapy
German Commission E

Indications

The German Commission E has approved the dried flowering twig tips (leaf with flower) for decreasing cardiac output as described in functional Stage II of heart disease as described by the New York Heart Association (Blumenthal et al., 1998). The European Scientific

Cooperative on Phytotherapy (ESCOP) also lists this treatment, but specifies that the preparation used be a hydroalcoholic extract. ESCOP also suggests hawthorn leaf and flowers for nervous heart complaints and support of cardiac and circulatory functions when prepared as tea or other preparations (not as a hydroalcoholic extract) (ESCOP, 1999).

The *American Herbal Pharmacopoeia (AHP)* lists hawthorn leaf and flowers for the treatment of Class I and II cardiac insufficiency, hypertonic heart with and without signs of coronary insufficiencies, myocardial insufficiencies, arrhythmia, cerebral insufficiency, mild hypertension, and patients with a history of myocardial infarction. It is also distinguished as having the ability to potentiate the effects of cardiac glycosides. The actions listed by the *AHP* include: increases coronary and myocardial perfusion, lowers peripheral resistance, and has economizing action with respect to oxygen and energy consumption; it is positively inotropic, positively dromotropic, negatively chronotropic, and negatively bathmotropic; and hawthorn is considered to be an antiarrhythmic, an antioxidant, a diuretic, a hypocholesterolemic, a hypotensive, and a sedative (Upton, Graff, Williamson, et al., 1999). The *AHP* has also published a monograph on hawthorn berry with similar indications (Upton, Graff, Bencie, et al., 1999).

Doses

Powder: 200 to 500 mg (Upton, Graff, Williamson, et al., 1999); 2 to 5 g daily (ESCOP, 1999)

Infusion: one cup morning and evening; at beginning of therapy, three cups daily (Upton, Graff, Williamson et al., 1999); 1 to 1.5 g of comminuted drug as an infusion three to four times daily (ESCOP, 1999)

Tincture: 20 drops two to three times daily (Upton, Graff, Williamson, et al., 1999; ESCOP, 1999)

Extract: 160 to 900 mg , extract (ethanol 45 percent v/v or methanol 70 percent v/v with a drug-extract ratio of 4 to 7:1), corresponding to 30 to 168.7 mg procyanidins, calculated as epicatechin, or 3.5 to 19.8 mg flavonoids, calculated in accordance with the *German Pharmacopoeia (DAB 10),* in two or three individual doses (Blumenthal et al., 1998; ESCOP, 1999; Upton, Graff, Williamson et al., 1999)

Fluid extract (as defined by the *French Codex IX*): 0.5 to 2.0 g daily, 60 to 120 drops three times daily (ESCOP, 1999)
Dry extract (as defined by *Belgium Farm V*): 50 to 300 mg dry extract three times daily (ESCOP, 1999)
Glycerol macerate: 50 drops three times daily (ESCOP, 1999)

Treatment Period

The Commission E suggests a treatment period of six weeks minimum, whereas ESCOP gives no restrictions (Blumenthal et al., 1998; ESCOP, 1999).

Contraindications

None of the pharmacopoeias list any contraindications (Blumenthal et al., 1998; ESCOP, 1999; Upton, Graff, Williamson, et al., 1999).

Adverse Reactions

The Commission E and ESCOP list no known adverse reactions (Blumenthal et al., 1998; ESCOP, 1999). The *AHP,* however, mentions that adverse reactions are minimal, but that some patients have reported gastrointestinal disorders, palpitations, headaches, and dizziness (Upton, Graff, Williamson, et al., 1999).

Precautions

The Commission E and ESCOP suggest that a physician must be consulted in cases where symptoms continue unchanged for longer than six weeks or in case of swelling of the legs. Medical diagnosis is necessary when pains occur in the region of the heart, spreading out to the arms, upper abdomen or the area around the neck, or in cases of respiratory distress (dyspnea) (Blumenthal et al., 1998; ESCOP, 1999). The *AHP* also advises that patients with cardiovascular disease should inform their primary health care provider if they are using hawthorn preparations (Upton, Graff, Williamson, et al., 1999).

Drug Interactions

Both the Commission E and ESCOP list no known drug interactions (Blumenthal et al., 1998; ESCOP, 1999). However, the *AHP* states that hawthorn potentiates the effects of cardiac glycosides as well as barbiturate-induced sleeping times. One particular hawthorn product, Esbericard® (Schaper & Brümmer GmbH & Co., KG, Germany), has reportedly augmented the coronary artery dilating effect brought on by caffeine, adenosine, epinephrine, theophylline, sodium nitrate, and papaverine. Hawthorn has also been found to work synergistically with garlic to protect against enzymatic changes caused by isoprenaline-induced myocardial necroses in rats (Upton, Graff, Williamson, et al., 1999).

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DETAILS ON HAWTHORN PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Hawthorn Products

Product Profile: HeartCare™

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	**Nature's Way Products, Inc.**
Botanical ingredient	**Hawthorn leaves and flowers extract**
Extract name	**WS 1442**
Quantity	80 mg
Processing (m/m)	Plant to extract ratio 5:1, 45% ethanol
Standardization	18.75% oligomeric procyanidins
Formulation	Tablet

Recommended dose: One tablet twice daily with water. For intensive use take up to two tablets three times daily. Best results are obtained with continual use.

DSHEA structure/function: Improves blood and nutrient flow to the heart muscle. Supports efficient heart muscle metabolism by improving its oxygen and energy utilization.

Other ingredients: Cellulose, maltodextrin, modified cellulose gum, stearic acid, modified cellulose, silica, titanium dioxide, riboflavin, glycerine, carmine.

Comments: WS 1442 has been sold in Europe as Crataegutt®, Crataegutt® forte, and Crataegutt® novo.

Source(s) of information: Product label (©2000 R/O Nature's Way Products, Inc.); Weikl et al., 1996; information provided by distributor.

Clinical Study: Crataegutt®

Extract name	WS 1442
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Chronic heart failure (NYHA II)**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Weikl A, Assmus KD, Neukum-Schmidt A, Schmitz J, Zapfe G, Noh HS, Siegrist J (1996). *Crataegus* special extract WS 1442: Objective proof of efficacy in patients with cardiac insufficiency (NYHA II). *Fortscritte der Medizin* 114 (24): 291-296. (Reported in *The Quarterly Review of Natural Medicine* Fall 1997: 201-209.)

Trial design
Parallel. Pretrial placebo run-in phase of two weeks.

Study duration	2 months
Dose	1 (80 mg extract) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	5 centers
No. of subjects enrolled	136
No. of subjects completed	129

Sex	Male and female
Age	Mean: 65.4 years

Inclusion criteria
Cardiac insufficiency Stage II according to the NYHA; ages 40 to 80 years; at least two symptoms of "cardiac findings" (nocturia, ankle edema, congestion of the cervical veins, incipient enlargement of the left ventricle, dyspnea under exertion and restricted "loadability"); change in blood pressure × rate, product (PRP) difference (50 watt [W] exertion versus rest) at the end of the run-in phase <15 percent. All nonpermissible concomitant medication was stopped at the start of the placebo run-in phase.

Exclusion criteria
Severe cerebral degeneration, severe organic or mental disease, decompensated cardiac insufficiency, arterial hypertension, ventricular arrhythmias, myocardial infarction during the preceding six months, unstable angina pectoris, stenosis of the aortal valves, hypertrophic obstructive cardiomyopathia, pregnancy/lactation, degenerative changes in the joints, insufficient cooperation during the run-in phase, participation in another clinical trial at the same time or during the preceding four weeks. Cardiac glycosides were not allowed, and concomitant medications, specifically calcium antagonists and ACE inhibitors, were only maintained at an unchanged doses for long-term therapy lasting at least six months.

End points
The change in pressure rate/product difference (systolic blood pressure times heart rate divided by 100 (PRP), exercise exertion of 50 W versus rest) between the beginning and the end of therapy was the primary target parameter. The secondary parameter was "life quality" as assessed by patients.

Results
From the pressure rate/product differences recorded, a clear improvement in cardiac performance was demonstrated in the Hawthorn group (p = 0.018), whereas a progressive aggravation occurred in the placebo group. The difference between therapy groups was significant statistically. The positive results were confirmed by a statistically clear improvement in major symptoms such as restricted physical performance, shortness of breath (dyspnea), and edema around the ankles. Active treatment in comparison with placebo resulted in an improvement in the quality of life for the patients, including a better sense of mental well-being.

Side effects
Nine adverse events were reported (six in placebo and three in the Hawthorn group) that were transitory, mild or medium in intensity, and not attributed to the treatment.

Authors' comments
This clinical trial confirmed the results of preceding studies, which have shown the *Crataegus* special extract WS 1442 to be an effective and low-risk treatment for patients with cardiac insufficiency NYHA Stage II.

Reviewer's comments
This evaluation is based on a published translation, therefore, some details may not be accurate. The trial was fairly well-designed and reported. However, the randomization method is not described adequately enough to assess. Further, no statistics were performed on the groups at the onset of the study. (Translation reviewed) (3, 6)

Clinical Study: WS 1442

Extract name	WS 1442
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Chronic heart failure (NYHA II)**
Level of evidence	**I**
Therapeutic benefit	**Trend**

Bibliographic reference
Zapfe G (2001). Clinical efficacy of *Crataegus* extract WS 1442 in congestive heart failure NYHA class II. *Phytomedicine 8* (4): 262-266.

Trial design
Parallel. Pretrial washout period of up to seven days.

Study duration	3 months
Dose	1 (80 mg) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	40
No. of subjects completed	39

Sex	Male and female
Age	Mean: 62 ± 11 years

Inclusion criteria
Patients ages 40 to 80 years with congestive heart failure NYHA II.

Exclusion criteria
Patients were excluded if they had severe cerebral deterioration, severe organic or mental disease (e.g., addiction), decompensated heart disease, pregnancy or lactation, severe blood pressure elevation (diastolic >120 mmHg), ventricular arrhythmia (greater than Lown Class III), cardiac infarction within the last six months, unstable angina pectoris, participation in other clinical trials simultaneously or within the last four weeks, degenerative joint disease or other disorder that limits ergometric investigation from the outset.

End points
The primary outcome variable was exercise tolerance (watts times minutes) calculated from the results of bicycle tests carried out at the start and end of the treatment. The secondary outcome was the double product (pressure-rate product: heart rate x systolic blood pressure times 10–2) calculated at rest and after two minutes of 50 watt (W) workload in the bicycle test.

Results
After treatment with WS 1442, patients experienced an improvement in exercise tolerance of an average of 66.3 W times minutes, whereas the placebo group experienced a decrease of 105.3 W times minutes. The difference between the groups is borderline significant ($p = 0.06$). In the hawthorn group, the double product declined by 26.8 percent (14.4 mmHg/s). In the placebo group, this parameter did not change markedly.

Side effects
None observed.

Author's comments
Crataegus extract WS 1442 is a safe and effective alternative for the treatment of patients suffering from mild heart failure corresponding to NYNA Class II.

Reviewer's comments
This is a well-done study with adequately described randomization and blinding. The outcome measures were clearly defined, the data were summarized in sufficient detail, and the statistical methods were adequately described and applied (intention-to-treat analysis). Unfortunately, the results were not clinically significant. A larger sample size would possibly strengthen the results. (5, 6)

Clinical Study: Crataegutt® novo

Extract name	WS 1442
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Chronic heart failure (NYHA I and II)**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
O'Conolly VM, Jansen W, Bernhöft G, Bartsch G (1986). Treatment of decreasing cardiac performance (NYHA Stages I to II) in advanced age with standardized *Crataegus* extract. *Fortschritte der Medizin* 104 (42): 805-808.

Trial design
Crossover. A two-week washout phase preceded the study composed of alternating six-week periods.

Study duration	6 weeks
Dose	1 (60 mg extract) tablet 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Geriatric hospital
No. of subjects enrolled	34
No. of subjects completed	32
Sex	Male and female
Age	62-84 years

Inclusion criteria
Patients in a geriatric hospital diagnosed with decreasing cardiac performance associated with heart failure of NYHA Classes I to II, present for at least two years. Cardioactive medication and psychopharmaceutical drugs (including neuroleptics) were discontinued at the start of the washout phase.

Exclusion criteria
Patients with an electrocardiogram ST wave segment depression below 0.1 mV, cor pulmonale, cardiac rhythm disturbances, arthritic alterations pre-

venting the performance of an exercise-tolerance test, and cerebrovascular insufficiency with distinct loss of mental performance (IQ < 90).

End points
Patients were assessed at baseline, 6 weeks, and 12 weeks. Patients were evaluated before and after exercise (two minutes at 25 W, and if possible at 50 W). Treatment effect was evaluated by the doctor on the basis of general state of health. Patients also assessed the changes in their general well-being. Two scales were also used to ascertain the psychologically relevant symptoms that accompany the onset of heart failure: Nurses' Observation Scale for Inpatient Evaluation (NOSIE) and Brief Psychiatric Rating Scale.

Results
Following treatment with hawthorn, patients' exercise-induced rise in systolic blood pressure and heart rate was reduced. There was a significant difference from placebo ($p < 0.0001$ for both). Hawthorn treatment also caused a decrease in blood pressure at the end of the recovery period compared to baseline and placebo. A decrease in the number of prematurely terminated exercise sessions served as evidence of an increased tolerance to loading. The success of the medication was associated with an improvement in the patients' well-being, including psychological parameters.

Side effects
None observed.

Authors' comments
The results of this study confirm that Crataegutt novo is therapeutically effective in incipient loss of cardiac performance (NYHA Grades I to II). The therapeutic efficacy, combined with its absence of contraindications and its good tolerability, all serve to justify the use of Crataegutt novo in elderly patients.

Reviewer's comments
This study was not randomized, and the blinding process was not described. The study lacked documentation for study designs and methods, but it was evaluated in translation, which may not be complete or accurate. (Translation reviewed) (1, 3)

Clinical study: Crataegutt® forte

Extract name	WS 1442
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany

Indication	**Chronic heart failure (NYHA II)**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Leuchtgens H (1993). *Crataegus* special extract WS 1442 in cardiac insufficiency NYHA II. *Fortschritte der Medizin* 111 (20-21): 352-354.

Trial design
Parallel.

Study duration	2 months
Dose	1 (80 mg) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male and female
Age	Mean: 65.5 ± 6 years

Inclusion criteria
Patients with cardiac insufficiency in Class II according to the NYHA, age between 50 and 70 years, with no complaints at rest and under mild physical exercise, but dyspnea and tiredness under increasing physical exertion.

Exclusion criteria
Exclusion criteria were cardiac arrhythmia greater than Lown Class III, electrocardiogram (ECG)-recorded ST segment depression at rest > 0.1 mV, degenerative conditions of the joints or other disease that would restrict exercise on an ergometric bicycle, and decompensated cardiac insufficiency or myocardial infarction up to six months previously.

End points
The major parameters were the change in the pressure times rate product (PRP = product of systolic blood pressure and heart rate divided by 100) under standardized exercise on a bicycle ergometer, as well as a questionnaire on subjective improvement of complaints (B-L-Total Score). Exercise toler-

ance, change in heart rate and change in arterial blood pressure were accepted as secondary parameters. Patients were examined prior to therapy and then after four and eight weeks.

Results
In both of the principal target variables, the differences in favor of the WS 1442 group were statistically significant after eight weeks of therapy. The PRP with exercise decreased continuously after four and eight weeks of treatment compared to baseline, and was statistically below that of the placebo group. Individual progression confirmed improvement in 13/15 WS 1442 patients, and in 3/15 placebo patients. In the hawthorn group, the B-L-Total Score decreased more than with placebo. In the secondary variables, the heart rate decreased in the hawthorn group whereas the increased values remained approximately the same in the placebo group. The systolic and diastolic blood pressures dropped slightly to about the same extent in both groups.

Side effects
Adverse events were not recorded.

Author's comments
The increase in well-being and the reduction of complaints could be demonstrated in the WS 1442-treated group of patients. This study confirms the therapeutic efficacy and good tolerance of Crataegutt forte, and justifies its application in patients suffering from NYHA Class II cardiac insufficiency.

Reviewer's comments
Significant methodological flaws as well as a poor description of methods make it hard to evaluate these results. Neither the randomization nor the blinding processs are well described, and the sample size is small. (1, 4)

Clinical Study: Crataegutt® novo

Extract name	WS 1442
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Chronic heart failure (NYHA I and II)**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Hanack T, Brückel MH (1983). The treatment of mild stable forms of angina pectoris using Crataegutt novo. *Therapiewoche* 33: 4331-4333.

Trial design
Parallel. Pretrial placebo washout period of eight days.

Study duration	3 weeks
Dose	1 (60 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	60
No. of subjects completed	58
Sex	Male and female
Age	Mean: 55 years

Inclusion criteria
Patients suffering from coronary disease New York Health Association (NYHA) Class I and II. Additional medication for circulatory and cardiac complaints was not allowed.

Exclusion criteria
Patients were excluded if they had instable angina pectoris, hypopotassemia, manifest cardiac insufficiency, essential hypertension according to WHO Grades II and III, and hyperlipoproteinemia (> 400 mg% cholesterol). Patients were also excluded if, after the first ergometric exertion after the washout period, they had an increase in pectoralgia, dysrhythmia, dyspnoea, or attainment of the submaximum heart rate.

End points
Patients' tolerance to ergometric loading was assessed using the bicycle ergometer before and after the trial. Typical changes in ECG under exertion were also evaluated to objectivize myocardial ischemia and to assess Crataegutt novo's therapeutic efficacy. Clinical and chemical parameters (blood count, blood sugar level, cholesterol, triglycerides, uric acid, serum creatinine, iron [including total iron-binding capacity], potassium, and magnesium) were also measured at the start and end of the trial.

Results
After treatment with Crataegutt novo, patients were able to increase (by 25 percent) tolerance to ergometric load by 100 watt times minute, whereas patients treated with placebo could not increase their tolerance. This difference

was statistically significant ($p < 0.08$). After 21 days of treatment, 18 patients in the hawthorn group had a marked reverse in their ischemic reaction in ECG under load, but only six patients in the placebo had the same reaction. No significant difference was found between the two groups in terms of the pulse rate, blood pressure, or the clinical and chemical parameters.

Side effects
None mentioned.

Authors' comments
Our examinations have confirmed that Crataegutt novo is suitable for the effective and side-effect-free treatment of stable forms of angina pectoris in NYHA Classes I and II.

Reviewer's comments
Workload was increased, but other parameters were unchanged. The lack of evidence of therapeutic efficacy may be due to the short trial length. The randomization and blinding were not adequately described. However, the outcome measures were clearly defined, the sample size was appropriate, and the data were summarized in sufficient detail. (Translation reviewed) (1, 5)

Clinical Study: WS 1442

Extract name	WS 1442
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Chronic heart failure (NYHA III)**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Tauchert M (2002). Efficacy and safety of *Crataegus* extract WS 1442 in comparison with placebo in patients with chronic stable New York Heart Association class-III heart failure. *American Heart Journal* 143 (5): 910-915.

Trial design
Parallel. Patients underwent a four-week, single-blind, placebo washout period before being randomized to receive either 900 or 1,800 mg WS 1442, or placebo, daily. Throughout the washout and trial period, all patients were also taking their preexisting diuretic therapy daily: triamterene (50 mg) and hydrochlorothiazide (25 mg).

Study duration	4 months
Dose	900 or 1,800 mg daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	232
No. of subjects completed	197
Sex	Male and female
Age	Mean: 67.6 ± 9.4 years

Inclusion criteria
Patients at least 40 years old with chronic congestive heart failure (NYHA Class III) known for at least six months, who had not been treated with a diuretic and/or a low dose of an angiotensin-converting enzyme (ACE) inhibitor, and with an exercise capacity of ≤ 75 watts (W) as assessed by seated bicycle ergometry.

Exclusion criteria
Major exclusion criteria consisted of: NYHA Classes I, II, or IV; treatment with digitalis within the previous six months; exercise capacity of > 75 W for two minutes at the test during run-in; unstable angina or myocardial infarction within the previous six months; atrial fibrillation or ventricular arrhythmia ≥ Lown Class III; cardiac valvular disease or hypertrophic cardiomyopathy; significant hypertension or hypotension (< 60 mmHg or ≥ 105 mmHg diastolic or < 90 mmHg or > 175 mmHg systolic); electrolyte disturbances, hyperuricemia, hypovolemia; impaired renal function (creatinine > 1.8 mg/dl) or hepatic function; obstructive airways disease; hypersensitivity to study drug; pregnancy, unreliable contraception, or breast-feeding mothers; and participation in another clinical trial within the previous six weeks. The following medications were prohibited during the study: ACE inhibitors, digitalis, antiarrhythmics, sympathomimetics, vasodilators, and diuretics other than triamterene/hydrochlorothiazide.

End points
The maximal workload tolerated was tested by symptom-limited bicycle exercise tests. The tests were carried out in a sitting position at the same time of day. The initial workload was 25 W, with the workload increasing by 25 W every two minutes. This test, as well as safety laboratory tests, was carried out at the beginning and end of the washout period, and after 8 and 16

weeks of treatment. Also measured at these tests were: blood pressure after each exercise stage, intensity of effort-induced dyspnea, and any ST-segment depression and arrhythmia. Subjective symptoms were also recorded every four weeks during the treatment phase.

Results
The increase in maximal workload tolerated at the end of the study in subjects in the 1,800 mg WS 1442 group was statistically significant compared with the placebo group. The high-dose group also improved more than the lower dose group (900 mg WS 1442). The subjective symptoms scores for the typical heart failure symptoms for those taking active treatment were lower than the scores for the placebo group, and these differences were statistically significant.

Side effects
Significantly fewer side effects occurred in the groups taking hawthorn compared with placebo. Overall, the group taking 1,800 mg WS 1442 experienced fewer side effects, particularly with respect to vertigo and dizziness. Tolerability was rated best by both the patients and the investigators for the 1,800 mg group.

Author's comments
The study confirms that treatment with WS 1442 is capable of improving the exercise capacity of patients with heart failure, including patients with an advanced state of the disease (NYHA Class III). This was demonstrated not only by the statistically significant improvement in the maximal workload tolerated by the 1,800 mg dose of WS 1442 versus placebo, but also by the fact that the efficacy of WS 1442 was dose dependent.

Reviewer's comments
The low score on the Jadad scale likely reflects problems with the report rather than problems with the conducted trial. Again, it is unfortunate that an objective medical measure was not included. (1, 6)

Product Profile: Faros® 300

Manufacturer	**Lichtwer Pharma AG, Germany**
U.S. distributor	None
Botanical ingredient	**Hawthorn leaf and flower extract**
Extract name	**LI 132**
Quantity	No information
Processing	No information
Standardization	No information
Formulation	Tablet

Source(s) of information: Bödigheimer and Chase, 1994; Hawthorn Leaf with Flower, *American Herbal Pharmacopoeia,* February 1999.

Clinical Study: Faros® 300

Extract name	LI 132
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Chronic heart failure (NYHA II)**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Tauchert M, Ploch M, Hübner WD (1994). Efficacy of hawthorn extract LI 132 in comparison with captopril: Multicenter double-blind study on 132 patients with cardiac insufficiency of NYHA grade II. *Münchener Medizinische Wochenschrift* 136 (Suppl. 1): 27-33.

Trial design
Parallel. Pretrial placebo run-in phase of one week. The dosages for the trial were as follows: patients took either one 300 mg hawthorn extract or one 6.25 mg captopril on day 0; two 300 mg hawthorn or two 6.25 mg captopril from days 1 through 3; three 300 mg hawthorn or three 6.25 mg captopril from days 4 through 6; and then took three 300 mg hawthorn or three 12.5 mg captopril for the rest of the trial.

Study duration	2 months
Dose	1 (300 mg extract) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Captopril
Site description	14 test centers
No. of subjects enrolled	132
No. of subjects completed	124

Sex	Male and female
Age	Mean: 62.5 ± 6 years

Inclusion criteria
Patients from 50 to 70 years of age with stable cardiac insufficiency of NYHA Class II, with work tolerance in standardized bicycle ergometry less than 100 W.

Exclusion criteria
Patients with cardiac insufficiency of NYHA Class III and IV, unstable angina pectoris, myocardial infarction during the previous six months, atrial fibrillation, ventricular extrasystoles of Lown Class IV, second-degree and third-degree AV block, bundle-branch block, hyperthyroidism, hypothyroidism, anemia, hypertension with blood pressures of more than 165/95 mmHg, more than 25 percent overweight, obstructive ventilation disorders, and physical infirmities such that exhaustive exercise in bicycle ergometry would have been ruled out. Further contraindications were hypersensitivity to captopril, angioneurotic edema, and severe kidney and liver disease. Medication with cardioprotective preparations before or during the trial were not generally permitted, except for diuretics that had been taken at a constant dose for at least four weeks before and were continued throughout the trial.

End points
Patients were monitored at inclusion and after 14, 28, and 56 days. The primary end point was symptom-limited ergometric exercise. Secondary criteria for the study were blood pressure, heart rate, and pressure-rate product (each measured both at rest and under maximum exertion), analysis of the resting ECG, assessment of the decrease in physical performance, exhaustion, susceptibility to fatigue, exertional dyspnea and edema, and general final judgments of efficacy and tolerance by the doctor and the patient.

Results
Both treatment groups showed statistically significant increases in work tolerance over the course of treatment. The pressure-rate product decreased in both groups, and the frequency and severity of symptoms decreased by about 50 percent in both groups. No significant differences were found for any of the target parameters between the two treatments. Judgment of efficacy by doctors slightly favored the captopril group at day 28, but reported better efficacy for the *Crataegus* group on day 56.

Side effects
No serious side effects were reported in the hawthorn group (two patients reported gastrointestinal symptoms and one reported cardiac pains).

Authors' comments
Apart from termination of treatment because of an adverse effect in one

case during treatment with captopril, the study gave substantially equivalent results for the principal and secondary criteria under treatment with both hawthorn and captopril.

Reviewer's comments
This was a very well-conducted study with a pharmaceutical comparison. The study was adequately powered to show moderate difference in efficacy, and both the randomization and blinding processes were well described. However, a sufficient description of data was lacking, as means and standard deviations were not reported. (Translation reviewed) (5, 5)

Clinical Study: Faros® 300

Extract name	LI 132
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Chronic heart failure (NYHA II)**
Level of evidence	**I**
Therapeutic benefit	**Trend**

Bibliographic reference
Schmidt U, Kuhn U, Ploch M, Hübner WD (1994). Efficacy of the hawthorn *(Crataegus)* preparation LI 132 in 78 patients with chronic congestive heart failure defined as NYHA functional class II. *Phytomedicine* 1 (1): 17-24.

Trial design
Parallel. Pretrial washout period of one week.

Study duration	2 months
Dose	200 mg 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	10 centers
No. of subjects enrolled	78
No. of subjects completed	70
Sex	Male and female
Age	Mean: 60 ± 6.9 years

Inclusion criteria
Patients with stable chronic heart failure defined as NYHA Class II, between the ages of 45 and 73, and initial maximum cardiac capacity measured by way of bicycle ergometry below 100 watts.

Exclusion criteria
Patients affected by chronic heart failure defined as NYHA Class III and IV, with cardiac angina at rest, cardiac infarction in the preceding three months, atrial fibrillation, ventricular extrasystoles of Class IV according to Lown, second- and third-degree atrioventricular block, more than 20 percent overweight, obstructive respiratory tract diseases, bodily defects that did not allow for the patients to be tested on the ergometer bicycle, pregnant or nursing women, and those addicted to alcohol or medical drugs.

End points
The primary target was the maximum working capacity measured using a bicycle ergometer (three minutes in 25 W increments). As secondary target criteria, the clinical symptoms, patients' subjective feelings of health, blood pressure, heart rate, and pressure/rate product at rest and under load were used.

Results
After 56 days of treatment, the median values obtained for the working capacity of the patients treated with hawthorn increased by 28 W, whereas the increase in the placebo group was as little as 5 watts. The difference was statistically significant ($p < 0.001$). A significant reduction of the systolic blood pressure, of the heart rate, and of the pressure/rate product was observed for the patients treated with hawthorn compared to the patients treated with the placebo preparation. The clinical symptoms were also found to have improved significantly.

Side effects
None observed.

Authors' comments
No improvement was observed in the working capacity of subjects with exercise levels below 75 W, whereas a distinct improvement was observed for those with exercise levels of 100 and 125 W. From this we can conclude that patients who are exposed to physical load corresponding to 100 to 125 W will benefit from hawthorn, if the drug is administered in adequate doses.

Reviewer's comments
This is a well-conducted trial. Unfortunately, the primary end point was work capacity, and I am unsure of the clinical significance regarding the prognosis. Obviously, some of the secondary end points are not inappropriate, but I

wish the authors had looked at anginal episodes, episodes of excitational angina, or another clinically relevant end point. (5, 5)

Clinical Study: Faros® 300

Extract name	LI 132
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Chronic heart failure (NYHA II)**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Forster A, Forster K, Buhring M, Wolfstadter HD (1994). *Crataegus* for moderately reduced left ventricular ejection fraction: Ergospirometric monitoring study on 72 patients in a double-blind comparison with placebo. *Münchener Medizinische Wochenschrift* 136 (Suppl. 1): 21-26.

Trial design
Parallel. Pretrial washout period of seven days.

Study duration	2 months
Dose	1 (300 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Cardiology outpatient center
No. of subjects enrolled	72
No. of subjects completed	69
Sex	Male and female
Age	31-79 years (mean: 51)

Inclusion criteria
Cardiology outpatients with diagnoses of cardiac insufficiency NYHA Class II with earlier diagnosis of postmyocarditic state, coronary heart disease, hypertensive heart disease, or other similar diagnosis.

Exclusion criteria
Cardiac insufficiency of NYHA Classes III and IV, myocardial infarction during the previous three months, arrhythmias such as atrial fibrillation, ventricular extrasystoles of Lown Class IV, and second-degree and third-degree AV block, more than 20 percent overweight, obstructive ventilation disorders, and physical infirmities such that a meaningful ergospirometric test would have been impossible. Patients could not use cardioactive preparations (except stabilized diuretic therapy) for eight days before the trial start and during the trial itself.

End points
Clinical examination and ergospirometric tests were carried out at the beginning of the study and after eight weeks of treatment. Running averages of the following parameters were obtained under resting conditions, under maximum efforts, and at the time of reaching the anaerobic threshold: maximum oxygen uptake, oxygen uptake at the time of reaching the anaerobic threshold, output achieved, heart rate, time taken to reach anaerobic threshold, oxygen pulse, respiratory equivalent for oxygen, and continuous effort endurance time. Patients were also questioned about their well-being after four and eight weeks of treatment.

Results
After treatment for eight weeks, statistically different improvements in subjective well-being were reported by 86 percent of patients in the hawthorn group and by 47 percent in the placebo group ($p < 0.01$). Exercise capacity increased more in the hawthorn group than in the placebo group, but not significantly. The quantity of oxygen absorbed by the lungs increased in the treated group compared to placebo, both at the exercise peak and afterward ($p < 0.05$ for both). For significantly more patients in the hawthorn group, the exercise time taken to reach the point of anaerobic metabolism increased ($p < 0.05$). An average increase of 30 seconds was observed for patients of the *Crataegus* group, whereas the time for the placebo group did not change. No significant differences were found between the two groups in terms of the control parameters of blood pressure, heart rate, oxygen pulse, and respiratory equivalent.

Side effects
No significant side effects were observed.

Authors' comments
A cardiac effect of hawthorn extract was demonstrated both in the ergospirometric parameters and in a distinct improvement of subjective symptoms. In view of its positive effects, hawthorn extract LI 132 can be recommended for the treatment of milder disturbances of cardiac function.

Reviewer's comments
This was a fairly well-designed and well-run study, with the randomization and double-blinding processes described adequately. It is not clear, however, that a 30 second increase in exercise time represents a clinically significant outcome. The changes in symptoms were reported as categorical. In addition, the subjective variable of well-being is not as reliable a measure, and the sample size was too small for a mild to moderate effect. (Translation reviewed) (5, 5)

Clinical Study: Faros® 300

Extract name	LI 132
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Chronic heart failure (NYHA II)**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Bödigheimer K, Chase D (1994). Efficacy of hawthorn extract in a daily dose of 3 x 100 mg: Multicenter double-blind study in 85 patients with NYHA stage II heart failure. *Münchener Medizinische Wochenschrift* 136 (Suppl. 1): 7-11.

Trial design
Parallel. Pretrial washout period of seven days.

Study duration	1 month
Dose	2 (50 mg) tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	85
No. of subjects completed	73
Sex	Male and female
Age	40-80 years (mean 61.5)

Inclusion criteria
Patients ages 40 to 80 years with stable NYHA Class II heart failure.

Exclusion criteria
Patients with NYHA Classes III and IV heart failure, coronary heart disease with angina pectoris, myocardial infarction less than three months before the start of the study, atrial fibrillation, ventricular extrasystoles (Lown Class IV), AV block Grade 2 or 3, hypertension requiring treatment, more than 20 percent overweight, pregnancy, obstructive airways diseases and physical infirmities that prevented the patient from being fully tested by bicycle ergometry. The use of cardiac substances, especially cardiac glycosides, ACE inhibitors, sympathicomimetics, antiarrhythmics, vasodilators, beta-blockers, calcium-channel blockers, and long-acting nitrates was not permitted during the study. The use of diuretics was allowed if they had been given in a constant dose for at least four weeks before the start of the study and this dosage was continued throughout the study.

End points
Exercise tolerance during bicycle ergometric testing was measured to a maximum watt level that a patient could sustain for at least two minutes, applied in 25 W increments. Heart rate, blood pressure, ECG course, and clinical symptoms were recorded. In addition, clinical findings (neck-vein distension, third/fourth heart sounds, rales and edema, blood pressure, and heart rate at rest) were recorded, as well as the global assessment by the doctor and the patient. Patients were assessed at inclusion, after the seven-day washout period, and after 14 and 28 days of treatment.

Results
Exercise tolerance in the active treatment group increased by 13 W, whereas the placebo group had an increase of 3 W. Heart rate, systolic blood pressure, and the two multiplied together decreased more markedly in the hawthorn group than in the placebo group—at rest and at maximal loading. However, none of the differences between the groups were statistically significant. In the final evaluation of the treatment outcome by the doctor and patient, hawthorn formulation received a more favorable assessment than the placebo treatment.

Side effects
Two cases of nonspecific side effects, including migraine, gastrointestinal complaints and palpitations, occurred in each group.

Authors' comments
Other studies using larger doses and longer durations reported significant effects of hawthorn on cardiac function. The fact that merely trends toward improvements were observed in the present study therefore suggests that neither the dose used here nor the treatment period was sufficient. It may be

that a dose of almost 1 g of extract should be recommended for *Crataegus* preparations, with minimum treatment periods of six to eight weeks.

Reviewer's comments
This was a well-done trial that was double-blind and randomized, but the results were not clinically significant. Also, no means or standard deviations were reported. The trial length was minimal, but adequate. (5, 6)

Horse Chestnut

Latin name: ***Aesculus hippocastanum* L.** [Hippocastanaceae]
Plant part: **Seed**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Native to the Near East, the horse chestnut tree was brought to northern Europe in the sixteenth century. As early as the 1800s, horse chestnut seed extracts were used therapeutically in France. Although preparations of other parts of the tree have been used medicinally, only the efficacy of the dried seeds has been proven. Powdered dried seeds contain 3 to 5 percent saponins, and powdered hydroalcoholic extracts of the seeds contain 16 to 20 percent triterpene glycosides (a class of saponins), calculated as aescin (escin). Aescin, itself a mixture of several glycosides derived from two triterpenoid aglycones, is believed to be the main active constituent of horse chestnut seed extract (Schulz, Hänsel, and Tyler, 2001).

Venastat™ contains the horse chestnut seed extract HCE 50 and is manufactured by Pharmaton S.A., in Switzerland and distributed in the United States by Pharmaton Natural Health Products. HCE 50 is characterized as containing 16 percent triterpene glycosides calculated as aescin. Each 300 mg capsule contains 50 mg aescin. Venastat is sold in Europe as Venostasin® retard.

Venaforce™ is manufactured in Switzerland by Bioforce AG, and is distributed in the United States by Bioforce USA. Venaforce contains horse chestnut seed extract (5 to 6.1:1, 60 percent ethanol m/m), and 76.5 mg tablets are standardized to contain 20 mg aescin. Venaforce is sold as Aesculaforce in Europe.

One trial used a generic horse chestnut seed extract with a plant/extract ratio of 5:1. Each capsule contained 369 to 412 mg standardized extract containing 75 mg triterpene glycosides calculated as aescin.

HORSE CHESTNUT SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Venastat™ (US); Venostasin® retard (EU)	Pharmaton, S.A., Switzerland/ Pharmaton Natural Health Products	Extract (HCE 50) contains 16% aescin	2 (300 mg extract) capsules daily (100 mg aescin)	Chronic venous insufficiency	12	Yes (II-4, III-3) Trend (II-1) No (II-1) Undetermined (III-1) MOA (II-1, III-1)
Venaforce™ (US); Aesculaforce (EU)	Bioforce AG, Switzerland/ Bioforce USA	Hydro-alcoholic extract	378-540 mg (120 mg aescin) daily	Chronic venous insufficiency	1	Yes (II-1)
Generic	None	Extract ratio of 5:1	2 capsules (150 mg aescin) daily	Chronic venous insufficiency	1	Yes (II-1)
Escin gel	Madaus AG, Germany/None	2% aescin	10 g gel	Hematoma	1	Undetermined (II-1)

Escin gel is a topical formulation of horse chestnut seed extract standardized to contain 2 percent aescin that is manufactured by Madaus AG of Germany. Escin gel, which is not available in the United States, is available in Europe as Reparil gel.

SUMMARY OF REVIEWED CLINICAL STUDIES

Horse chestnut has been used traditionally as an herbal remedy for chronic venous insufficiency, and numerous clinical trials support that use. Chronic venous insufficiency (CVI) is characterized by chronic inadequate drainage of venous blood and venous hypertension, which results in leg edema, dermatosclerosis (hardening of the skin), and feelings of pain, fatigue, and tenseness in the lower extremities. As a result, patients often require hospitalization and surgery, for instance, for symptomatic varicose veins. Pharmacological therapies and/or leg compression with specialized stockings or surgery are the treatment options (Pittler and Ernst, 2002).

CVI is divided into three stages according to the degree of severity. The symptoms of Grade I, according to Widmer and Marshall, are dilation of the veins of the feet and a tendency for edema. Grade II is defined by additional symptoms, including pigmentation of the skin, hypertrophy of the skin corneal layer, and hardening of the skin. Grade III is characterized by leg ulcers, either healed (IIIa) or unhealed (IIIb). In the early stages of CVI (Grade I), the veins have not suffered any permanent damage, and pharmacological therapy may reduce the leakage of fluid from the veins. At the later stages of CVI (Grades II and III), the disease process involves the larger veins, and ultimately the damage to the veins is irreversible (Ottillinger and Greeske, 2001). Studies reviewed here included patients with CVI Grades I or II. One study, on a generic product, included patients with CVI Grade II according to Hach. Although we found no information on this scale the description of symptoms were similar to Grade II according to Widmer and Marshall. They were obstructive edema, possible tropic skin changes, and venous capacity and/or venous return outside normal limits (Diehm et al, 1992).

Venastat

Chronic Venous Insufficiency

Twelve reviewed trials conducted with Venastat (Venostasin) measured symptoms related to CVI. All trials reported some benefit in clinical symptoms with a dose of 600 mg extract (100 mg aescin) per day, although the quality of some trials was better than others.

Three small, well-conducted, placebo-controlled studies reported significant decreases in leg/foot volume, circumference, edema, and pain in patients with CVI given 300 mg extract twice daily compared to placebo. The first study included 39 subjects with CVI Grades I or II who were treated for one month. The volume of the foot and the distal shank, and the circumference of the ankle and calf, all significantly decreased with horse chestnut compared to placebo. Neither group had a change in venous capacity (Rudofsky et al., 1986). In the second study, 28 outpatients with CVI (grade not given) were treated for 20 days, and a reduction in leg circumference compared to placebo was noted (Pilz, 1990). In the third study, 30 subjects (CVI grade not given) were treated for two months. After both one and two months, a reduction in edema, pain, and symptoms such as heaviness, pins and needles, restlessness, and nocturnal cramps was observed compared to placebo. After two months, significant differences in the circumferences of the ankle and leg in the Venostasin group were observed compared to placebo (Cloarec, 1993).

Another trial, including 74 subjects with CVI, measured the effect of treatment for two months with either 600 mg extract or placebo on edema provoked by sitting on an exercise bicycle with legs dangling in the air. As a result of treatment, provoked increases in leg volume and leg circumference were significantly reduced (Lohr et al., 1986). A group of 20 women with pregnancy-related edema or CVI Grade I were treated with 600 mg per day or placebo in a crossover study of two weeks duration for each treatment phase. Treatment with Venastat led to a significant reduction in leg volume and circumference (Steiner and Hillemanns, 1986).

A large, good-quality trial included 240 subjects (CVI Grade I) and compared Venastat (600 mg per day) with compression stockings and placebo. Following three months of treatment there was a significant decrease in leg volume and edema with both treatments com-

pared to placebo (Diehm et al., 1996). Another study of similar design included 355 patients with advanced CVI of Grades II or IIIa. In this study, both active therapies produced a reduction in lower leg volume, but the decrease was much larger for the group with compression stockings. Compression treatment was the only treatment that performed significantly better than placebo. A subgroup analysis determined that Venostasin was more effective in subjects with CVI Grade II than those with Grade IIIa. Compression, on the other hand, was more effective for those with the higher grade (Diehm and Schmidt, 2000). Ottillinger and Greeske (2001) compared these two trials and concluded that the lower CVI grades were suitable for therapy with horse chestnut, but that those with higher grades were better off with compression therapy.

A good-quality study with 30 subjects with CVI compared Venostasin to another edema-protective agent. Venostasin, 600 mg per day for one month, reduced an increase in ankle circumference caused by standing for 15 minutes when compared to baseline. The effectiveness of Venostasin was greater than the control agent (Erdlen, 1989). Although the control agent was not identified in the translation we reviewed, Pittler and Ernst (2002) identified the agent as rutoside (oxerutin) in their review. Oxerutin (*O*-beta-hydroxyethyl-rutosides) is a semisynthetic derivative of plant constituents that has been used as an alternative to horse chestnut preparations. It is used as a comparative agent in the following three studies.

A study included 137 postmenopausal women with CVI Grade II who were given one of three treatments for three months. The study compared a horse chestnut extract (thought to be Venostasin, 600 mg per day) to oxerutin (1,000 mg per day) and to oxerutin (1,000 mg per day for four weeks followed by 500 mg per day). Oxerutin at 1,000 mg per day was significantly more effective at reducing leg volume than horse chestnut extract. The constant 1,000 mg dose was better than the 1,000 to 500 mg stepped treatment (Rehn et al., 1996). Two other studies compared Venostasin to oxerutin, but are not reviewed in detail due to a lack of translation into English. They found the effectiveness of Venostasin (50 mg or 150 mg aescin per day, respectively) greater than or equal to oxerutin (500 or 2000 mg per day, respectively) (Kalbfleisch and Pfalzgraf, 1989; Erler, 1991).

A study using 19 normal volunteers explored the effectiveness of Venostasin in preventing the edema caused by a 14-hour airline

flight. Participants took 600 mg or placebo daily for ten days prior to the flight. The control group showed a steady and significant increase in the circumference of the ankle and foot. This swelling was significantly reduced by treatment with Venostasin (Marshall and Dormady, 1987).

A crossover mechanistic study explored the effect of Venostasin on the development of edema through measuring the quantity of fluid flowing from blood capillaries into the surrounding tissue (transcapillary filtration coefficient). The study included 22 women with CVI grades I to III who were given a single dose of 600 mg or placebo on test days. Measurements before and after dosing revealed a reduction in the transcapillary filtration coefficient of 22 percent in the Venostasin group compared to baseline (Pauschinger, 1987).

Another mechanistic study explored the effect of Venostasin on levels of serum proteoglycan hydrolases. Proteoglycan hydrolases cause the degradation of proteoglycans, a part of the capillary endothelium and a main component of the extravascular matrix. This matrix is thought to play a role in capillary permeability and fragility. Treatment of 15 patients with varicose veins with 900 mg Venostasin per day for 12 days resulted in a significant reduction in the activities of three glycosaminoglycan hydrolases. Thus, treatment with Venostasin may shift the equilibrium of degradation and synthesis of proteoglycans toward synthesis, thereby preventing vascular leakage (Kreysel, Nissen, and Enghofer, 1983).

Venaforce

Chronic Venous Insufficiency

Venaforce was reported to statistically reduce ankle edema, but not subjective symptoms of heaviness, pain, burning, itching, or pins and needles in the legs. This placebo-controlled study included 52 subjects with CVI Grades I or II. Treatment consisted of six tablets, containing 120 mg aescin, per day for six weeks (Shah, Bommer, and Degenring, 1997).

Generic

Chronic Venous Insufficiency

A well-conducted, placebo-controlled trial with 39 patients with CVI (Stage II according to Hach) reported a statistical reduction in mean leg volume after six weeks of treatment, both before and after edema provocation, compared to placebo. Treatment was an unbranded extract delivering 150 mg aescin per day (Diehm et al., 1992).

Escin Gel

Hematoma

Escin gel containing 2 percent aescin was compared to placebo in an experimentally induced hematoma model. Hematomas are swellings filled with blood that can form as the result of physical trauma to the body, causing damage to blood vessels beneath the skin. In this study, hematomas were induced in 70 healthy volunteers by subcutaneous injection of 2 ml of the subjects' own blood. Treatment with 10 g of gel or placebo followed within five minutes. Sensitivity measurements were taken from one to nine hours after treatment. As a result, the Escin gel statistically reduced pain at all time points compared to placebo (Calabrese and Preston, 1993). Our reviewer, Dr. Mary Hardy, criticized the model because the subcutaneous injection of blood does not produce all of the parameters as a bruise or hematoma acquired through trauma. Thus, she rated the possible benefit as undetermined.

SYSTEMATIC REVIEWS

A systematic review of double-blind, randomized, controlled trials was conducted on oral horse chestnut seed extract preparations for symptomatic treatment of CVI. Thirteen studies fulfilled the inclusion criteria, of which eight were placebo-controlled and five were controlled with a reference substance (oxerutin) or compression. The authors found that the use of horse chestnut was associated with a decrease in lower leg volume and a reduction in leg circumference at the

calf and ankle. Symptoms such as leg pain, pruritus, and a feeling of fatigue and tenseness were reduced. The authors concluded that horse chestnut seed extract is superior to placebo and as effective as reference medications in alleviating the objective signs and symptoms of CVI (Pittler and Ernst, 1998). In a subsequent review conducted by the same authors, using the "Cochrane Library" format, several placebo-controlled trials were considered adequate to enter into meta-analysis. Leg pain, as assessed in six placebo-controlled trials using visual analog scales and four-point scales, was significantly reduced in comparison to placebo. An analysis of four trials (n = 239) that used water displacement to measure leg volume determined a significant reduction in favor of horse chestnut extract compared with placebo (weighted mean difference 58.6 ml [95 percent CI 24.9-92.2]). A meta-analysis of three trials found that treatment reduced the circumference at the ankle (weighted mean difference 4.7 mm [95 percent CI 1.13-8.28]) as well as at the calf (weighted mean difference 3.5 mm [95 percent CI 0.58-6.45]) compared to placebo (Pittler and Ernst, 2002).

ADVERSE REACTIONS OR SIDE EFFECTS

The trials reviewed in this section rarely reported minimal adverse events that did not differ significantly from placebo. Eight of the 13 studies included in a systematic review reported symptoms of adverse reactions, including gastrointestinal tract symptoms, dizziness, nausea, headache, and pruritus. The frequency of adverse event reports ranged from 0.9 percent to 3.0 percent. In three studies the adverse events were not different from those reported by the placebo group (Pittler and Ernst, 1998). An observational study involving more than 5,000 patients with CVI receiving various therapies reported the incidence of adverse reaction with horse chestnut to be 0.6 percent. Gastrointestinal symptoms and calf spasm were reported most frequently (Greeske and Pohlmann, 1996).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

German Commission E
European Scientific Cooperative on Phytotherapy

Indications

The German Commission E recommends a dry extract manufactured from horse chestnut seed for the treatment of complaints found in pathological conditions of the veins of the legs (chronic venous insufficiency), for example, pains and a sensation of heaviness in the legs, nocturnal systremma (cramps in the calves), pruritus, and swelling of the legs (Blumenthal et al., 1998). The European Scientific Cooperative on Phytotherapy (ESCOP) also suggests horse chestnut for the treatment of chronic venous insufficiency, as well as for varicosis (ESCOP, 1999).

Doses

Dry extract of the seed adjusted to 16 to 20 percent triterpene glycosides (calculated as aescin [escin]): 100 mg aescin corresponding to 250 to 312.5 mg extract two times per day in a delayed release form (Blumenthal et al., 1998)

Hydroalcoholic extract containing 50 to 150 mg of triterpene glycosides (calculated as aescin) usually in divided doses (ESCOP, 1999)

Treatment Period

ESCOP lists no restriction for treatment period length (ESCOP, 1999).

Contraindications

The Commission E and ESCOP list no known contraindications (Blumenthal et al., 1998; ESCOP, 1999).

Adverse Reactions

The Commission E and ESCOP state that pruritis, nausea, and gastric complaints may occur in isolated cases after oral intake (Blumenthal et al., 1998; ESCOP, 1999).

Precautions

The Commission E lists no precautions; however, ESCOP does not recommend horse chestnut for children (Blumenthal et al., 1998; ESCOP, 1999).

Drug Interactions

The Commission E and ESCOP list no known drug interactions (Blumenthal et al., 1998; ESCOP, 1999).

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DETAILS ON HORSE CHESTNUT PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Horse Chestnut Products

Product Profile: Venastat™

Manufacturer	**Pharmaton S.A., Switzerland**
U.S. distributor	**Pharmaton Natural Health Products**
Botanical ingredient	**Horse chestnut seed extract**
Extract name	**HCE 50**
Quantity	300 mg
Processing	No information
Standardization	16% triterpene glycosides calculated as aescin
Formulation	Capsule, sustained release

Recommended dose: Adults: one capsule every 12 hours, or two a day, swallowed whole with water. Effectiveness is reached after four to six weeks of continuous use.

DSHEA structure/function: Helps maintain leg vein circulation. Helps protect against leg swelling. Clinically shown to be a safe and beneficial way to supplement your diet for optimal leg vein health.

Cautions: Consult a health care professional if you are taking a prescription medicine, are pregnant or nursing a baby. Discontinue use and see a physician if gastric irritation, nausea, or rapid heartbeat occurs. In case of accidental ingestion/overdose, seek the advice of a health care professional immediately.

Other ingredients: Dextrin, gelatin, copolyvidone, talc, polymethacrylic acid deratives, titanium dioxide, dibutyl phthalate, synthetic iron oxides.

Comments: Sold in Europe as Venostasin® retard (Klinge Pharma GmbH, Munich, Germany)

Source(s) of information: Product package (© Boehringer Ingelheim Pharmaceuticals, Inc., 1999).

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Rudofsky G, Neiss A, Otto K, Seibel K (1986). Demonstration of the antioedematous effect and the clinical efficacy of horse-chestnut extract in a double-blind study. *Phelebologie und Proktologie* 15: 47-54.

Trial design
Parallel.

Study duration	1 month
Dose	1 (300 mg extract, 50 mg of triterpene glycosides) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes

Drug comparison	No
Site description	Not described
No. of subjects enrolled	40
No. of subjects completed	39
Sex	Male and female
Age	Mean: 39.4 ± 9.2 years

Inclusion criteria
Patients with chronic venous insufficiency, Grades I or II, with at least two of the clinical signs, such as varicosis, cutaneous induration, hyperpigmentation, atrophie blanche, and two subjective symptoms such as sense of heaviness, pain, pruritus, sense of fullness and congestion in the legs and cramps in calves. Medication with vasoactive substances, diuretics, and "other venous therapeutics" was stopped four weeks before the study began.

Exclusion criteria
Patients who are pregnant, immobilized, with acute thrombophlebitis, nephritic syndrome heart failure, associated edema, and high-grade CVI.

End points
Volumetric measurements of volume of foot and distal shank using a water plethysmograph and circumference of ankle and calf were taken in the morning and evening. Venous capacity, assessment of pretibial impression and assessment of subjective symptoms were taken at the start of the study and after 14 and 28 days of therapy.

Results
The volume of the foot and distal shank decreased in the morning and evening during four weeks of treatment with horse chestnut. In contrast, an increase in both volumes at both measuring times was observed with the placebo group. The differences are statistically significant ($p < 0.001$, both measurements, 28 days). Neither Venostasin nor placebo had any influence on the venous capacity. A test for tibial edema revealed a significantly better response to treatment with Venostasin retard after 14 days ($p = 0.023$) and 28 days ($p = 0.003$) compared with placebo. Significant differences were also observed between Venostasin and placebo groups in circumference of ankle ($p < 0.01$) and in circumference of the calf ($p < 0.05$) after 28 days. For all subjective symptoms included in the evaluation, Venostasin was statistically and significantly better than placebo ($p < 0.05$), with the exception of "cramps in the calves."

Side effects
None observed.

Authors' comments
Based on the results of the study it is concluded that horse chestnut extract can exert an antiedematous effect.

Reviewer's comments
The very complete list of outcome measures makes this study more interesting and convincing clinically. The data were only reported in graphs, not in table form, making numbers difficult to determine. Also, no standard deviations were included. This trial had a well-described blinding procedure although the randomization was not adequately described. (Translation reviewed) (2, 5)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Pilz E (1990). Edema associated with venous illness. *Die Medizinische Welt* 41: 1143-1144.

Trial design
Parallel. Pretrial washout period of one week.

Study duration	20 days
Dose	1 (300 mg extract, 50 mg of triterpene glycosides) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	30

No. of subjects completed	28
Sex	Male and female
Age	27-60 years (mean: 46)

Inclusion criteria
Outpatients with symptoms of chronic venous insufficiency (CVI) associated with peripheral venous edema, and subjective symptoms including heaviness and/or exhaustion, feeling of tension, burning sensations, itching, calf cramps, restless legs, swelling of the legs and/or the feet, discoloration, tissue hardening, and eczema.

Exclusion criteria
Patients younger than 20 and older than 70; with fewer than two symptoms of CVI; with ulcus cruris, cardiac, hepatic, nephrotic, and lymphatic edema; leg pains other than that listed; nerve root irritation; and inflamed or degenerated joints. Patients for whom compression was indispensable were also excluded. The following medications were not allowed during the trial: cardiac glycosides, diuretics, nonsteroidal anti-inflammatories, or corticosteroids.

End points
The main clinical variables were leg circumference measurements (smallest distance between the ankle and thigh, distance from heel to small of back, and largest circumference of the thigh) which were measured at room temperature.

Results
The Venostasin group had larger decreases in leg circumference measurements than the placebo. In particular, a statistically significant reduction was observed in the distance from the heel to the small of the back in the Venostasin group compared with the placebo group ($p < 0.05$).

Side effects
None observed.

Author's comments
Even with a relatively small number of patients, 20 days therapy with Venostasin led to significant reductions in circumferences of edematous feet compared to placebo treatment.

Reviewer's comments
This trial had an excellent description of randomization and double-blinding. It did not receive a Level I rating due to the small sample size and the lack of a detailed explanation of the results (no standard deviations were provided). (Translation reviewed) (5, 5)

Clinical Study: Venostasin®

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Cloarec M (1993). Study on the effect of a new vasoprotective Venostasin administered over a period of 2 months in chronic venous insufficiency of the lower limbs. Controlled double blind study in randomized parallel groups versus placebo. Unpublished report.

Trial design
Parallel. Pretrial washout period of one month, followed by a one-month period with placebo, followed by two months treatment with drug or placebo

Study duration	2 months
Dose	1 (300 mg extract, 50 mg of triterpene glycosides) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	One hospital
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male and female
Age	23-69 years (mean: 46)

Inclusion criteria
Patients ages 20 to 70 years, ambulatory, with functional symptoms due to chronic venous insufficiency and impression edema on at least one leg, with at least two of the following symptoms exceeding Degree 5 on the visual analog scale: pain, heaviness, paresthesia or formication, restlessness, or nocturnal cramps.

Exclusion criteria
Patients with systolic pressure ankle/arm > 0.9; supporting bandage; acute or precedent (<1 month) thrombophlebitis; leg ulcer of venous origin; cardiac, renal, hepatic, or orthopedic edema; underwent sclerotherapy or surgery of the veins during the past six months; pregnant or lactating; having irregular menstrual cycle; severe hepatic, renal, or cardiovascular diseases; participating in another study; unable or unwilling to follow study instructions; or taking analgesics, diuretics or anti-inflammatory steroids.

End points
Patients were examined before pretrial placebo, before beginning treatment, and after 30 and 60 days. Measurements were taken of the circumference of the lower limb (ankle/calf), and by plethysmography. Pain and functional symptoms were evaluated by visual analog scale. Global assessments were made by patients and physicians.

Results
After 30 and 60 days of treatment there was a significant decrease in the size of edema in the Venostasin group compared to the placebo group ($p < 0.001$). After 60 days of treatment, the leg and ankle circumference in the Venostasin group decreased significantly compared to the placebo group ($p = 0.03$). A significant decrease in intensity of pain was observed after 30 and 60 days of treatment compared to placebo ($p < 0.001$). Functional symptoms of heaviness, paresthesia ("pins and needles"), and/or formication ("ants"), as well as restlessness and/or nocturnal cramps all decreased after 30 and 60 days of treatment ($p < 0.001$, 60 days compared with the placebo group). Plethysmography results showed a significant difference from placebo after 30 days ($p = 0.03$) and 60 days ($p = 0.001$) of treatment. Global judgments by both patients and physicians were positive.

Side effects
No difference in tolerance from placebo.

Author's comments
This study demonstrated that Venostasin improves in a statistically significant way the clinical symptoms and the values of occlusion plethysmography in patients with chronic venous insufficiency over a period of two months compared to placebo.

Reviewer's comments
The one-month washout followed by two-month treatment was very good. Also, an intention-to-treat analysis is a more rigorous evaluation for efficacy that eliminates bias due to poorly performing patients that are removed from therapy. Giving more attention to the reporting method of randomization would have increased the quality of this study. A significantly larger sample

size would have allowed better assessment of efficacy. (Translation reviewed) (3, 5)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Lohr E, Garanin G, Jesau P, Fischer H (1986). Anti-oedema treatment in chronic venous insufficiency with tendency to oedema. *Münchener Medizinische Wochenschrift* 128 (34): 579-581.

Trial design
Parallel. Pretrial washout period of 12 days.

Study duration	2 months
Dose	1 (300 mg extract, 50 mg of triterpene glycosides) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	80
No. of subjects completed	74
Sex	Male and female
Age	Mean: 53.8 ± 13.1 years

Inclusion criteria
Chronic venous insufficiency. No further details were included in the translation.

Exclusion criteria
Not included in the translation.

End points
Variables included leg volume measurement and three circumference measurements (fibula circumference, ankle circumference, and heel above the instep), in each case both before and after edema provocation, as well as an evaluation of the subjective symptoms. Edema was provoked by sitting on an exercise bicycle for 20 minutes with legs hanging loose and motionless. Patients were evaluated before and after the eight-week treatment period.

Results
The increase in leg volume observed under edema provocation fell in the Venostasin group during the eight-week treatment period from 32 ml to 28 ml on average, but increased in the placebo group from 27 ml to 31 ml on average. The leg circumference measurements confirmed the leg volume results. Edema was comparatively reduced both before ($p < 0.01$) and after provocation ($p < 0.001$) when measuring the heel above the instep. Subjective symptoms, such as "feeling of tension in the legs," "itching," and "degree of impression of edema," were altered significantly by Venostasin compared to placebo.

Side effects
No statistical difference from placebo.

Authors' comments
The horse chestnut seed extract treatment was proved statistically to be effective, and is tolerated just as well as placebo.

Reviewer's comments
Provoked edema is less clinically relevant than standard measurements; thus, the edema-reducing and edema-protecting effects are not very useful measurements. This trial was both randomized and double-blind, but the processes were not well described. The trial also lacked adequate inclusion/exclusion criteria, statistical methods, and a sufficient summary of the data (no standard deviations were provided). (Translation reviewed) (1, 3)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)

Indication	**Chronic venous insufficiency**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference

Steiner M, Hillemanns HG (1986). Investigation of the oedema-protective action of a venous therapeutic agent. *Münchener Medizinische Wochenscrift* 31: 551-552.

Trial design

Crossover study. Five-day washout phase followed by two treatment phases of 14 days duration.

Study duration	2 weeks
Dose	1 (300 mg extract, 50 mg aescin) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	20
No. of subjects completed	Not given
Sex	Female
Age	20-40 years

Inclusion criteria

Ambulant patients with pregnancy-related varicosis, or varicosis with chronic venous insufficiency Grade I.

Exclusion criteria

Subjects in the last three months of pregnancy, and those with Grades II and III chronic venous insufficiency.

End points

The main clinical variable was leg volume measured with a water plethysmometer. In addition, leg circumference was measured at three places: smallest ankle circumference, circumference of the heel above the instep, and circumference above the middle of the calf. Measurements were taken

before the start of the first treatment phase and at the end of the first and second treatment phases.

Results
Water plethysmometric measurements showed that treatment with horse chestnut lead to a reduction in leg volume of 114 ml in phase I and a reduction of 126.2 ml at the end of the treatment phase II. The volume values did not change under placebo treatment in treatment phase I and increased by 128.6 ml at the end of phase II after prior horse chestnut treatment in phase I. The difference between the two treatments was statistically significant ($p = 0.0009$). Circumference measurements also showed a statistically significantly reduction for all three measurement under horse chestnut therapy (heel value: $p < 0.001$, ankle value: $p < 0.001$, and calf value: $p < 0.05$).

Side effects
No difference between the two groups.

Authors' comments
In the present case, Venostasin retard was shown to have an edema-protective and edema-curative effect. It is also well tolerated.

Reviewer's comments
Although this trial was randomized and double-blind, neither process was described adequately. The data was not summarized in sufficient detail to allow for replication, and the sample size was too small. In addition, mixing pregnant and nonpregnant patients may not produce equivalent pathophysiological results. (Translation reviewed) (0, 4)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference: Diehm C, Trampisch HJ, Lange S, Schmidt C (1996). Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. *The Lancet* 347 (8997): 292-294.

Trial design
Parallel. Pretrial run-in phase with placebo for two weeks. Patients were then randomized to receive compression, horse chestnut extract, or placebo. Those allocated to receive compression received a diuretic once daily to ensure the best possible fit with a Class II compression stocking. The trial is considered partially blinded because those with stockings knew which treatment they were receiving.

Study duration	3 months
Dose	1 (50 mg aescin) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Partial
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Leg compression stockings
Site description	Single center
No. of subjects enrolled	262
No. of subjects completed	240
Sex	Male and female
Age	Mean: 52 years

Inclusion criteria
Subjects ages 18 years or older with substantial lower leg edema due to chronic venous insufficiency (confirmed by medical history, clinical findings and venous Doppler and/or duplex sonography).

Exclusion criteria
Patients who had received venotherapeutic drugs within the past six weeks before the run-in phase.

End points
Water displacement plethysmometry was used to measure the lower leg volume of the more severely affected limb at baseline and after 4, 8, and 12 weeks of therapy.

Results
Lower leg volume of the more severely affected limb decreased on average by 43.8 ml with horse chestnut seed extract (HCSE) and 46.7 ml with compression therapy, whereas it increased by 9.8 ml with placebo for the intent-to-treat group. Significant edema reductions were achieved by HCSE (p =

0.005) and compression ($p = 0.002$) compared to placebo, and the two therapies were shown to be equivalent ($p = 0.001$).

Side effects
No serious treatment related events were reported.

Authors' comments
These results indicate that compression stocking therapy and Venostasin therapy are alternate therapies for the effective treatment of patients with edema resulting from chronic venous insufficiency.

Reviewer's comments
This trial was actually relatively well constructed and conducted. Its value is probably greater than its Jadad score (the study could not be double-blinded due to the use of compression stockings, and the randomization was not described adequately). The trial had a good sample size, and used and described appropriate statistical methods (intention-to-treat analysis). (1, 6)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Diehm C, Schmidt C (2000). Venostasin retard gegen Plazebo und Kompression bei Patienten mit CVI II/IIIA. Final Study Report. Klinge Pharma GmbH, Munich, Germany. (Reported in Ottillinger B, Greeske K [2001]. Rational therapy of chronic venous insufficiency—Changes and limits of the therapeutic use of horse-chestnut seeds extract. *BioMed Central Cardiovascular Disorders* I: 5, <http://www.biomedcentral.com/1471-2261/1/5>.)

Trial design
Parallel. The trial was preceded by a two-week washout period with placebo. Subjects were randomized to receive either horse chestnut, placebo, or compression therapy. The allocation of the horse chestnut and placebo was double-blind, but the compression therapy was open. There was also a two-week follow-up period after treatment was finished.

Study duration	4 months
Dose	50 mg aescin daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind/open
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	355
No. of subjects completed	Not given
Sex	Not given
Age	Not given

Inclusion criteria
Patients with chronic venous insufficiency Grade II and Grade IIIa.

Exclusion criteria
Patients were excluded if they had received therapy with vein drugs during the six weeks prior to the study start, and patients with edemas of non-venous origin.

End points
The primary end point was the reduction of lower leg volume at the end of the study compared to baseline. Lower leg volume was determined by plethysmometry at baseline and at weeks 4, 8, 12, and 16, and twice during the follow-up period. Secondary end points included a subjective symptom score (including the following symptoms: heaviness, distension, distension pain, feeling of swelling, tiredness in the leg, itching, leg cramps, paresthesia, plantar burning, and unspecific subjective complaints) and a rating of quality of life (determined using the Fragebogen zur Lebensqualität bei Venenerkrankungen [FLQA]).

Results
The compression treatment was significantly better than placebo ($p < 0.001$), but horse chestnut was not. Mean reductions in leg volume for the compression, horse chestnut, and placebo groups were 89, 18, and 2 ml, respectively. The subjective symptom score evaluation rated horse chestnut better than compression therapy, but the difference was not statistically significant. Horse chestnut also showed more favorable results compared with compression therapy in the quality of life parameters. After a subgroup analysis, subjects with CVI Grade II were found to respond better to horse

chestnut than those with Grade IIIa. Compression, in contrast, was better for the higher CVI grade.

Side effects
The incidence of side effects was similar in all groups. The horse chestnut group experienced more gastrointestinal adverse effects, and constipation and dry mouth occurred only in this group (two and three cases, respectively).

Authors' comments
In the early stages of CVI, when the veins and their wall structures have not yet suffered any permanent damage, pharmacological methods (such as horse chestnut seed extract) may be sufficient to affect the disease process. Horse chestnut seed extract may still close the endothelial gaps in the later stages of CVI and thus reduce edema to some extent. At this time, however, the disease process has already caused irreversible damage in the larger veins.

Reviewer's comments
This trial had a good experimental design comparing horse chestnut to a placebo control and conventional therapy (stocking). (2, 6)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Erdlen F (1989). Clinical efficacy of Venostasin retard demonstrated in a double-blind trial. *Die Medizinische Welt* 40: 994-996.

Trial design
Parallel. Pretrial run-in period with placebo for one week. Translation does not give the name of the comparison agent.

Study duration	1 month
Dose	1 (300 mg extract, 50 mg of triperpene glycosides) capsule twice daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Another edema-protective agent
Site description	Single center
No. of subjects enrolled	30
No. of subjects completed	Not given
Sex	Male and female
Age	Mean: 54 ± 12 years

Inclusion criteria

Outpatients, over 18 years of age, suffering from varicosis and chronic venous insufficiency combined with peripheral venous edema.

Exclusion criteria

Patients suffering from cardiogenic or hepatogenic edemas, disturbances of renal function, or hepatic disease; patients receiving vasoactive medication or requiring compression treatment during study; patients with a history of allergic reactions to any of the constituents. In addition, primary lymphatic edema, ulcus cruris or administration of cardiac glycosides, methyl xanthine preparations or nonsteroidal antirheumatic agents were not allowed.

End points

At the beginning of the treatment period, as well as after two and four weeks of therapy, leg circumference was measured before and after edema provocation (standing for 15 minutes).

Results

In both the Venostasin group and comparison drug group, the ankle circumference decreased between the beginning and end of therapy by an average of 0.4 cm. The edema protective effect was 0.2 cm for Venostasin and –0.1 cm for the comparison group. The negative value suggests a greater increase in the leg circumference.

Side effects

Both preparations were well tolerated.

Author's comments
Venostasin retard is effective as another antiedematous and edema-protective agent, and is slightly superior to the comparison preparation.

Reviewer's comments
Edema provocation was standing for 15 minutes, a clinically relevant challenge. Venostasin had activity comparable to the comparison agent, which unfortunately was not identified in the translation (the Cochrain review by Pittler and Ernst [2002] identifies the agent as rutoside [*The Cochraine Library* 2: 1-17]). There was a problem with the randomization, since one of the groups had many more women than men. The trial lacked a description of withdrawals and dropouts, the sample size was small, and the statistical methods were not adequately described or applied. (Translation reviewed) (4, 4)

Clinical Study: Venostasin®

Extract name	HCE50
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Chronic venous insufficiency**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Rehn D, Unkauf M, Klein P, Jost V, Lücker PW (1996). Comparative clinical efficacy and tolerability of oxerutins and horse chestnut extract in patients with chronic venous insufficiency. *Arzneimittel-Forschung/Drug Research* 46 (5): 483-487.

Trial design
Parallel. Pretrial placebo run-in of one week. Patients were given one of three treatments for 12 weeks: horse chestnut extract, oxerutins (1,000 mg/day), or oxerutins (1,000 mg/day loading dose for four weeks, followed by 500 mg/day maintenance dose). A six-week follow-up period followed the trial end.

Study duration	3 months
Dose	600 mg per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind

Blinding adequate	No
Placebo	No
Drug comparison	No
Drug name	Oxerutins (Venoruton®)
Site description	12 centers
No. of subjects enrolled	155
No. of subjects completed	137
Sex	Female
Age	Mean: 60.1 ± 8.6 years

Inclusion criteria
Postmenopausal females with a maximum age of 70 years; uni- or bilateral chronic venous insufficiency (CVI) Grade II; corona phlebectatica paraplantaris, clinical persistent edema, low-grade skin alterations (e.g., hypo- or hyperpigmentation athrophie blanche, but without severe dermatosclerosis); have had a doppler sonography and a phlebological status in the past six months.

Exclusion criteria
Leg edema not due to venous diseases of the legs; older than 70 years; women with childbearing potential; decompensated cardiac insufficiency; current acute phlebitis or thrombosis; renal insufficiency; liver disease; and other relevant diseases, e.g., diabetes mellitus, etc. Pretreatment that could influence the results of the study, e.g., regular compression therapy within the last 4 weeks, treatment with other venous drugs for the last six weeks, use of laxatives with influence on fluid or electrolyte balance within the last eight days, treatment with theophylline, diuretics, cardiac glycosides angiotension converting enzyme inhibitors or calcium antagonists within the last eight days, and changes in the postmenopausal hormone replacement therapy within the last two months. These treatments, including compression therapy, were not allowed as concomitant therapy. Patients who participated in other clinical trials within 30 previous days were also excluded.

End points
The volume of the more affected leg was assessed by water displacement at baseline and at weeks 4, 8, and 12. At each visit, the volume was assessed twice. Subjective symptoms (tired, heavy legs, sensations of tension, and tingling sensation) were also evaluated at each visit using a 10 cm visual analogue scale.

Results
After 12 weeks of treatment, oxyrutins (1,000 mg/day) proved to be equivalent or better at reducing leg volume compared to oxerutin (1,000 then 500 mg/day) and horse chestnut. Mean leg volume was reduced by 57.9 ml, 40.2

ml, and 28.2 ml, respectively. In addition, 74.6 percent, 64.9 percent, and 57.6 percent of the respective groups were responders to therapy (had a leg volume reduction in week 12). The difference between the oxerutins (1,000 mg/day) and the horse chestnut group was statistically significant ($p = 0.0238$). Mean VAS values of tired, heavy legs were also reduced from baseline for all three treatments at the end of the treatment phase.

Side effects
Nine patients taking oxerutins and two patients taking horse chestnut reported adverse reactions. The reported symptoms were gastrointestinal complaints, headaches, and dizziness of transitory nature.

Authors' comments
In general, both tested drugs are able to achieve a mean leg volume reduction of about 100 ml after 12 weeks treatment in responding patients. This is a therapeutically relevant amount of edema reduction and comparable to values reported or calculated for compression therapy.

Reviewer's comments
The lack of placebo control and the use of an active control of unknown efficacy (i.e., not a standard drug or a "proven" herbal) made the interpretation of significance difficult. (1, 6)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency; Edema** due to long-distance flights
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Marshall M, Dormady JA (1987). Oedema of long distant flights. *Phlebology* 2: 123-124.

Trial design
Parallel. Medication was given ten days prior to a 14-hour flight and continued until landing in destination.

Study duration	11 days
Dose	1 (300 mg extract containing 50 mg of triterpene glycosides) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Flight
No. of subjects enrolled	19
No. of subjects completed	19
Sex	Not given
Age	Not given

Inclusion criteria
Phlebologists undergoing a 14-hour flight from Europe to Kyoto, with no past history of venous disease or chronic leg edema.

Exclusion criteria
None mentioned.

End points
Max circumference of the foot around the heel and the smallest circumference around the ankle were measured half an hour after departure on aircraft as well as three hours and 14 hours later.

Results
A steady and significant increase in both the ankle and heel size measurements was observed in the subjects receiving placebo over the 14-hour flight. The swelling in the lower legs was approximately equivalent to 60 ml. Subjects receiving Venostasin ($p < 0.05$) had significantly less swelling in the heel and ankles after 14 hours. There was no significant difference after only three hours of flight.

Side effects
None mentioned.

Authors' comments
Swelling in the lower legs of normal subjects exposed to a 14-hour flight was

completely prevented by Venostasin at the level of the ankle and very much reduced at the level of the heel.

Reviewer's comments
The outcome measures were appropriate to the clinical condition. The sample size was too small, but it is otherwise a generally well-conducted trial. I am concerned that the authors did not report their subjective data. The interpretation of this trial was limited by the poor methodology, since neither the blinding nor the randomization were described adequately. The treatment length was good, but it might be unrealistic—most patients will not take therapy for ten days prior to their flight. (1, 5)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Germany)
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**MOA**

Bibliographic reference
Pauschinger K (1987). Clinico-experimental investigations of the effect of horse-chestnut extract on the transcapillary filtration and the intravasal volume in patients with chronic venous insufficiency. *Phlebology and Proctology* 2: 57-61. (Previously published in Bisler H, Pfeifer R, Kluken N, Pauschinger P [1986]. *Deutsche Medizinische Wochenschrift* 111: 1321-1329.)

Trial design
Crossover. The two test days were separated by an interval of two weeks. All venous agents that were being taken were discontinued during the preliminary phase of the study.

Study duration	1 day
Dose	2 (300 mg) capsules
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	24
No. of subjects completed	22
Sex	Female
Age	Not given

Inclusion criteria
Females suffering from Grades I to III suprafascial chronic venous insufficiency of the lower extremities according to Widmer.

Exclusion criteria
The presence of occlusive arterial disease.

End points
The development of edema was monitored through measuring the quantity of fluid flowing from blood capillaries into the surrounding tissue. The transcapillary filtration coefficient and the intravasal volume on the shank was determined four times: before patients took the treatment and three times after taking the treatment at 35-minute intervals.

Results
Compared with baseline, the capillary filtration coefficient (CFC) remained constant when patients were given placebo. When given horse chestnut, the CFC was reduced by 22 percent, which was significantly lower when compared to baseline ($p = 0.006$). The intravasal volume of patients given placebo and horse chestnut decreased compared to baseline, with no significant difference found between groups ($p = 0.24$).

Side effects
None mentioned.

Author's comments
The results of the study allow one to conclude that horse chestnut extract inhibits development of edema in chronic venous insufficiency of the lower extremities.

Reviewer's comments
This is a single-dose study with an intermediate outcome (capillary filtration rate) that is not as effective in showing benefit as a clinical outcome measure. The data were not described in sufficient detail since no standard deviations were given, and no test of the effect of treatment order was conducted. The sample size was small and the randomization process was not adequately described. (Translation reviewed) (3, 4)

Clinical Study: Venostasin® retard

Extract name	HCE 50
Manufacturer	Klinge Pharma GmbH, Germany (Pharmaton S.A., Switzerland)
Indication	**Chronic venous insufficiency; varicosis** (varicose veins)
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference

Kreysel HW, Nissen HP, Enghofer E (1983). A possible role of lysosomal enzymes in the pathogenesis of varicosis and the reduction in their serum activity by venostasin. *VASA* 12 (4): 377-382.

Trial design

Crossover. Study in four phases: pretrial run-in period of three days without any medication, followed by three days of placebo treatment, 12 days of active therapy following, and then another three days of placebo.

Study duration	12 days
Dose	1 (300 mg extract containing 50 mg of triperpene glycosides) capsule 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Hospital
No. of subjects enrolled	15
No. of subjects completed	Not given
Sex	Male and female
Age	Mean: 40 years

Inclusion criteria

Patients with varicosis of the internal saphenous vein, Stages II and III, who were in hospital due to dermatological disorders.

Exclusion criteria
Patients with atherosclerosis, diabetes involving vascular complications, or hepatitis.

End points
Blood was drawn three days after entry, then on days 1 and 3 (first placebo phase), 5, 10, 15 (interval of active treatment), and again on day 18 (end of second placebo phase) for enzyme assays such as β-glucuronidase, β-*N*-acetylglucosaminidase and arylsulphatase.

Results
Treatment of varicose patients with an extract of horse chestnut for 12 days led to a significant reduction in the activities of three glycosaminoglycan hydrolases. At the end of treatment, serum activities were lowered by 29.1 percent ($p < 0.01$) for β-*N*-acetylglucosaminidase, 25.7 percent ($p < 0.01$) for β-glucuronidase, and 28.7 percent ($p < 0.01$) for arysulphatase. A further three days of control treatment caused only a slight and insignificant rise in the enzymes' activities, thus hinting at an effect that outlasts drug ingestion.

Side effects
None mentioned.

Authors' comments
Since the reductions in all three glycosaminoglycan hydrolases were of the same order of magnitude, Venostasin may act through a protective effect on the site of enzymatic release: the lysosomal membrane. The reduction in enzyme activity might be of clinical importance in reducing proteoglycan breakdown, and hence affecting capillary permeability and fragility. Long-term therapy with Venostasin could have an influence on the collagen content and architecture of the varicose vein, thus normalizing its elastic and contractile properties.

Reviewer's comments
It is not clear that the enzyme assays used as end points in this study are clinically relevant as they are not directly connected with the end points of the disease process. In addition, the trial was not randomized, and the blinding process was not described adequately. (0, 5)

Product Profile: Venaforce™

Manufacturer	**Bioforce AG, Switzerland**
U.S. distributor	**Bioforce USA**
Botanical ingredient	**Horse chestnut seed extract**

Extract name	None given
Quantity	76.5 mg
Processing	Plant to extract ratio 5.0-6.1:1, 60% (m/m) ethanol
Standardization	20 mg aescin
Formulation	Tablet (enteric coated)

Recommended dose: Adults take three tablets in morning, two tablets in evening, with meals, for the first week; thereafter, take two tablets in morning, one in evening.

DSHEA structure/function: Promotes integrity of veins, healthy circulation, stamina of legs.

Other ingredients: Microcrystalline cellulose, potato starch, silicea, polysaccaride of soy, methacrylic copolymer, colloidal silicon dioxide, triethyl citrate.

Comments: Sold as Aesculaforce in Europe.

Source(s) of information: Product package; information provided by distributor; Shah, Bommer, and Degenring, 1997.

Clinical Study: Aesculaforce

Extract name	None given
Manufacturer	Bioforce AG, Switzerland
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Shah D, Bommer S, Degenring FH (1997). Aesculaforce in chronic venous insufficiency. *Schweizerische Zeitschrift für GanzheitsMedizin* 9 (2): 86-91.

Trial design
Parallel.

Study duration	6 weeks
Dose	2 tablets (63-90 mg extract containing 20 mg aescin) 3 times daily
Route of administration	Oral
Randomized	Yes

Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	3 centers
No. of subjects enrolled	60
No. of subjects completed	52
Sex	Male and female
Age	Mean: 55 ± 12 years

Inclusion criteria
Subjects with a minimum age of 18 years, Widmer Stages I or II chronic venous insufficiency, with an admission summed score (edema, skin pigmentation, and eczema) and a symptoms summed score (sensation of heaviness or tension, pain, burning sensation, itching, and paresthesias affecting the legs) of at least 6.

Exclusion criteria
None mentioned.

End points
Patients were examined upon admission and after two and six weeks of treatment. The primary target parameter was the circumference of the leg measured just above the ankle. The second parameter was the summed score of subjective symptoms in the legs (sensation of heaviness or tension, pain, burning, itching, and paresthesias [pins and needles] affecting the legs). Plethysmography was also used to determine the venous refilling rate, caused by patients dangling legs after elevation at a 45 degree angle to empty them of blood.

Results
A statistically significant difference was observed in terms of the time course of the reduction in ankle edema ($p < 0.05$) that favored the test substance over the placebo. With respect to improvement in the subjective symptoms, only a small, statistically nonsignificant difference favoring the test substance was found. Photoplethysmographic measurement of the calf refilling favored the Aesculaforce tablets compared to placebo ($p = 0.0308$).

Side effects
Gastric complaints in one patient given test substance and two patients given placebo.

Authors' comments
The effectiveness of Aesculaforce was confirmed by the reduction or elimination of ankle edema and increase in venous capacity.

Reviewer's comments
The outcome measures were clear, and the sample size was appropriate. However, the data did not include standard deviations. The randomization was not adequately described. (3, 5)

Product Profile: Horse Chestnut (Generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Horse chestnut seed extract**
Extract name	None given
Quantity	No information
Processing	Plant to extract ratio 5:1
Standardization	No information

Source(s) of information: Diehm et al., 1992.

Clinical Study: Horse Chestnut (Generic)

Extract name	Not given
Manufacturer	None
Indication	**Chronic venous insufficiency**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Diehm C, Vollbrecht D, Amendt K, Comberg HU (1992). Medical edema protection—clinical benefit in patients with chronic deep vein incompetence. *VASA* 21 (2): 188-192.

Trial design
Parallel. Pretrial period of one week with placebo.

Study duration	6 weeks
Dose	Approximately 780 mg dry extract containing 150 mg aescin daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	40
No. of subjects completed	39
Sex	Male and female
Age	Mean: 51 ± 11 years

Inclusion criteria
Patients between ages 25 and 65 who were not liable to compression with chronic venous insufficiency of Stage 2 according to Hach, and venous flow impairment, obstructive edema, possible trophic skin changes, and venous capacity and/or venous return outside normal limits (venous capacity 3 to 6 ml per 100 ml tissue, venous return 27 ml/100 ml per minute).

Exclusion criteria
Patients younger than 25 or older than 65, primary venous insufficiency liable to compression, acute venous inflammation and/or acute thrombosis, venous ulcerations, edema due to cardiac insufficiency, renal functional disturbances or hepatic disorders, primary lymphatic edema, reflux in the region of the thigh, Hach Stage 3, diabetes for more than ten years, neuropathies, concurrent treatment with other venous agents/venous diuretics, cardiac glycosides, nonsteroidal antirheumatic agents, intolerance to horse chestnut seed extract, and pregnancy.

End points
Subjective symptoms such as feeling of heaviness/tenseness (both during day and night), leg fatigue, itching, and paresthesias, and the circumference of calves and ankles before and after edema provocation were measured at the end of the run-in phase and after each week during therapy. Leg volume (by hydroplethysmography before and after edema provocation) and venous occlusion (by plethysmography) were measured after two, four, and six weeks of therapy. Venous Doppler sonograms and phlebodynamometric measurements were taken at the beginning and end of treatment.

Results
After six weeks of therapy the mean leg volume in the horse chestnut group was statistically less than that of the placebo group ($p < 0.01$). The results

were similar after edema provocation ($p < 0.01$). Additional measurements of leg circumference confirmed the results from hydroplethysmography (leg volume). Horse chestnut seed extract was also markedly more effective in alleviating subjective complaints than placebo.

Side effects
Both extract and placebo were well tolerated.

Authors' comments
Treatment with an edema protective agent of the horse chestnut type is a useful adjunct to compression therapy.

Reviewer's comments
This was a well-conducted trial, but the randomization and blinding could have been better explained. The sample size was appropriate, the inclusion/exclusion criteria were adequate, and the statistical methods were applied and described well. (5, 6)

Product Profile: Escin gel

Manufacturer	**Madaus AG, Germany**
U.S. distributor	None
Botanical ingredient	**Horse chestnut seed extract**
Extract name	None given
Quantity	No information
Processing	Extract incorporated into gel
Standardization	2% aescin
Formulation	Gel

Other ingredients: Lavender oil, orange flower oil, polyacrilic acid (Carbopol 940), polyethelyne glycol-6 caprylic/capric acid glycerides (Softigen 767), edetic acid disodium salt, trometamol, 2-propanol, water.

Source(s) of information: Calabrese and Preston, 1993; information provided by manufacturer.

Clinical Study: Escin gel

Extract name	Not given
Manufacturer	Madaus AG, Germany

Indication	**Hematoma** (induced)
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Calabrese C, Preston P (1993). Report of the results of a double-blind, randomized, single-dose trial of a topical 2% escin gel versus placebo in the acute treatment of experimentally induced hematoma in volunteers. *Planta Medica* 59 (5): 394-397.

Trial design
Parallel. Experimental hematoma was induced by the subcutaneous injection of 2 ml of the subject's own blood.

Study duration	1 day
Dose	10 g gel (2% aescin)
Route of administration	Topical
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	71
No. of subjects completed	70
Sex	Male and female
Age	21-47 years

Inclusion criteria
Healthy and normal weight patients between the ages of 18 and 50.

Exclusion criteria
Patients who were pregnant, with coagulation disorders, with allergy to aescin or allergic diathesis, or having significant current skin disorders. Use of nonsteroidal anti-inflammatory drugs, analgesics, or psychotropic agents in the week before the trial, and consumption of alcohol in the 24 hours before trial, were also excluded.

End points
Tonometric sensitivity measurements were taken at 1, 2.5, 4, 5.5, 7, and 9 hours after treatment.

Results
After hematoma induction and treatment, the aescin group responded with the first report of pain at higher mean adjusted tonometric pressure measurements (i.e., less tenderness) than did the placebo group at every time point ($p < 0.001$). The group treated with aescin had a significantly higher mean area under the curve (AUC) than placebo ($p < 0.001$), indicating less pain and a smaller difference from baseline.

Side effects
None mentioned.

Authors' comments
The results indicate efficacy of the 2 percent aescin gel in reducing tenderness in the injection hematoma model.

Reviewer's comments
This trial is technically well- and fairly rigorously done, but the underlying method is flawed: injected blood is not equal to a bruise or a hematoma acquired through trauma. It is not clear that this model is effective for the clinical parameter being tested. In addition, the randomization process was not described adequately. (3, 4)

Kava

Other Common Names: **Kava kava, kava peper, awa, yangona**
Latin Name: ***Piper methysticum* G. Forst.** [Piperaceae]
Plant Part: **Root**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

A water extract of ground kava root (actually a rhizome or underground stem) has been used traditionally in the Pacific islands in religious ceremonies and at social events. Modern commercial preparations are usually made by extraction with ethanol or acetone. Pharmacological studies have profiled the constituent kavapyrones, also known as kavalactones, which are thought to be responsible for the anxiety-relieving effect of kava (Schulz, Hänsel, and Tyler, 2001).

Laitan®, produced by Dr. Willmar Schwabe GmbH & Co., Karlsruhe, Germany, contains an extract (WS 1490) prepared with acetone and standardized to 70 percent kavalactones.

Two studies used aqueous extracts prepared by soaking either 30 g root in 500 ml water or 200 g root in 1,000 ml water.

Kavatrol™, produced by Natrol, Inc., is sold in capsules containing 200 mg root extract including 60 mg kavalactones (30 percent) and 50 mg dried plant material each of hops (*Humulus lupulus* L.) flowers, passionflower (*Passiflora incarnata* L.) aerial parts (aboveground parts), schizandra [*Schisandra chinensis* (Turcz.) Baill.] fruits, and chamomile (*Matricaria recutita* L.) flowers.

SUMMARY OF REVIEWED CLINICAL STUDIES

Kava is used traditionally to make a ceremonial beverage. It has been tested clinically most often for its use to treat anxiety. Anxiety is

KAVA SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Single Ingredient Products						
Laitan® (EU)	Dr. Willmar Schwabe GmbH & Co., Germany/ None	Acetone extract containing 70% kavalactones (WS 1490)	100 mg 3 times daily	Anxiety	5	Yes (I-3, II-1, III-1)
				Sleep quality	1	Undetermined (III-1)
				Cognitive functioning	1	Undetermined (II-1)
Generic	None/None	Aqueous extract	30-100 g root	Cognitive functioning	2	Undetermined (III-2)
Combination Product						
Kavatrol™	Natrol, Inc./ Natrol, Inc.	Extract containing 30% kavalactones; dried hops flowers, passionflower aerial parts, schizandra fruits, and chamomile flowers	2 (200 mg) 2 times daily	Anxiety	1	Trend (II-1)

a vague, unpleasant emotional state with qualities of apprehension, dread, stress, and uneasiness. The presence and severity of characteristic anxiety symptoms are often measured using the Hamilton Anxiety Rating Scale (HAM-A), a standard and well-established clinician rated scale with 14 items. The total item score is the "gold-standard" measure used to establish and compare the efficacy of new treatments for general anxiety disorder. Benzodiazepines are commonly used to treat anxiety, but are associated with adverse effects such as dependence, sedation, and memory impairment (Hardman et al., 1996).

Ten controlled trials on the use of kava were reviewed. Six studies were conducted on anxiety. Five of these studies, which used the product Laitan, were well-designed studies that reported significant effects. The sixth study, which used the product Kavatrol, showed a trend toward efficacy. The other four studies on cognitive functioning and sleep were poorly designed, and although kava had no obvious effect on cognitive performance, any definite conclusion would be premature.

Laitan (WS 1490)

Seven trials with Laitan are reviewed here, the majority (five) being for relief from anxiety. One study explored the effect on sleep, and another showed that kava, unlike oxazepam, did not slow reaction times. The usual dose was 100 mg extract (WS 1490) three times daily, or a total of 210 mg kavalactones per day.

Anxiety

A well-conducted, placebo-controlled trial included 52 adults with a HAM-A anxiety score greater than 18 who were given 100 mg extract three times daily or placebo for one month. A significant reduction in anxiety scores was observed in the treatment group compared to the placebo group after one week, and this difference increased over four weeks. The average HAM-A score in the kava group dropped from 25.6 at baseline to 12.6 at the end of the month. The score remained practically unchanged in the placebo group (24.5 to 21.0) (Lehmann, Kinzler, and Friedemann, 1996).

Another study with 73 adults with anxiety as defined by DSM-III-R and a HAM-A score of at least 19 compared the effects of 300 mg

extract per day to placebo in a 25-week treatment period. A significant improvement was observed in the treatment group compared with the placebo group after eight weeks, with the improvement increasing over time. The baseline HAM-A total score in the kava group of 30.7 dropped to 9.7 by the end of the study. The placebo group scores also fell, but to a lesser extent, from 31.4 to 15.2 (Volz and Kieser, 1997). The quality of this study was reduced by the lack of detail in descriptions of both the randomization and blinding processes.

A good-quality, placebo-controlled study was conducted with 40 peri- and postmenopausal women with a HAM-A score of at least 18. Treatment was 300 mg extract per day for two months. There was a significant reduction in anxiety compared with placebo after one week that increased after four and eight weeks. In the kava group, the baseline HAM-A score of 31.1 was reduced to 5.5 after eight weeks. The placebo group score dropped from 30.2 to 22.5 after eight weeks (Warnecke, 1991).

A study investigated the efficacy of WS 1490 in patients treated previously with benzodiazepines for at least two weeks, with the purpose of assessing the potential of the extract to replace benzodiazepines in the treatment of anxiety. The placebo-controlled study included 37 subjects with anxiety according to DSM-III-R and a maximum HAM-A rating of 14 points. During the first two weeks of the trial, the benzodiazepines were tapered off and the dose of kava was increased. For the next three weeks patients received only kava, 300 mg extract per day, or placebo. At the end of five weeks, the kava group had a decrease in HAM-A scores of 7.5 points compared with a one point increase for placebo group. The kava group also had fewer benzodiazepine withdrawal symptoms (Malsch and Kieser, 2001).

A good-quality drug comparison trial with 164 participants with a HAM-A score of more than 18 compared the effects of Laitan (300 mg per day) with oxazepam (5 mg three times daily) and bromazepam (3 mg three times daily). The study reported that all three treatment groups showed a continuous reduction of anxiety from the first through the sixth week, with no significant difference between them (Woelk et al., 1993).

Sleep Quality

A small pilot study with 12 healthy subjects explored the effect of either 150 mg or 300 mg WS 1490, compared with placebo baselines, on sleep polysomnographic electroencephalograph (EEG) patterns. With both doses, the amount of sleep spindles (an EEG pattern) and the percentage of deep sleep increased, whereas REM sleep did not change. The time to fall asleep and the waking stage tended to decrease. There was a suggestion that the higher dose of kava produced more effects on sleep than the lower dose (Emser and Bartylla, 1991). The increase in sleep-spindle density is a typical effect of an anxiolytic. However kava did not cause a suppression of deep sleep and REM sleep, which is a typical effect of benzodiazepine and barbiturate sleep medications. However, poor study design and minimal details in the report led the reviewers to rate this study as having undetermined benefit.

Cognitive Functioning

A crossover-design pilot study with 12 healthy young men explored the effects of kava extract WS 1490 on memory performance as measured with a continuous word recognition task. The continuum of processes between stimulus and response was measured by recording event-related brain potentials (ERPs), scalp-recorded electrical potentials generated by neural activity associated with specific sensory, cognitive, and motor processes. A relatively high dose of kava, 200 mg three times daily for five days, was compared with placebo and oxazepam (15 mg the day before testing and 75 mg on the morning of testing). A significant slowing of reaction time and reduction in the number of correct responses were seen following administration of oxazepam. In contrast, a statistically insignificant trend toward improvement was observed following administration of kava compared to placebo. The results of the ERPs showed a similar pattern (Munte et al., 1993). Due to the use of relatively nonstandard techniques and lack of an a priori hypothesis, our reviewers, Drs. Lynn Shinto and Barry Oken, deemed the therapeutic benefit from kava as inconclusive.

Generic Extract

Cognitive Functioning

The effects of kava on cognitive function were tested in two poor-quality trials that used aqueous extracts of the root. The first study compared the effects of two different doses of kava to controls who consumed no kava in open-label experiments on 27 healthy college students. The lower dose was an aqueous extract prepared from 30 g root, and the second dose varied with the weight of the subject (1 g per kg body weight, or 70 g for a 150 lb person). After a single administration, neither kava dose altered the speed of activation of verbal information in long-term memory or alertness (Russell, Bakker, and Singh, 1987). The second study used a slightly higher dose of kava, equivalent to 100 g root. In this placebo-controlled study with 24 subjects, one dose of kava produced feelings of intoxication, body sway, and a trend toward reduced cognitive performance (Prescott et al., 1993).

Kavatrol

Anxiety

A kava product that also contains small amounts of four other botanicals, Kavatrol, was tested for its effect on anxiety in 60 subjects. A dose of two (200 mg) capsules were given twice daily, the equivalent of 800 mg extract per day, or 240 mg kavalactones. Subjects evaluated their own degree of stress in a Daily Stress Inventory and a State-Trait Anxiety Inventory. According to the authors, the study indicated that kava reduced the stress associated with the daily hassles of life (Singh et al., 1998). However, our reviewers deemed the study to be flawed due to a lack of description of the type of anxiety, coupled with the fact that no assessment of the anxiety state was made by a physician.

SYSTEMATIC REVIEWS

Pittler and Ernst (2000) conducted a systematic review of seven double-blind, randomized, placebo-controlled trials of oral kava ex-

tract for the treatment of anxiety. The superiority of kava extract (mostly WS 1490) over placebo was suggested by all seven trials. A meta-analysis of three of the trials suggests a significant difference in the reduction of the total score on the Hamilton Rating Scale for anxiety by approximately ten points in favor of kava. The studies lasted from 4 to 24 weeks, and the kava extract treatments ranged in kavalactone content from 60 to 240 mg per day.

ADVERSE REACTIONS OR SIDE EFFECTS

Recently, kava products have been taken off the market in several countries due to concerns over possible liver toxicity. However, in the reviewed clinical studies, side effects reported for kava preparations were similar to those reported for placebos. Four of the reviewed studies (three with WS 1490 and one on a generic product) listed side effects that included gastric pressure, tiredness, and nausea (Volz and Kieser, 1997; Warnecke, 1991; Woelk et al., 1993; Prescott et al., 1993). Two postmarketing surveillance studies were undertaken, each involving more than 3,000 patients. The first study, in which patients were given a daily dose equivalent to 120 to 240 mg kavapyrones, reported adverse events in 2.3 percent of patients. The second study, in which patients were given a daily dose equivalent to 105 mg kavapyrones reported adverse events in 1.5 percent of patients. The adverse events reported most frequently were gastrointestinal complaints, allergic skin reactions, headache, and photosensitivity (Pittler and Ernst, 2000).

A systematic survey of the physical health of a case-controlled population study of Aborigines in Australia reported that heavy use of kava, more than 310 g root per week, caused (directly or indirectly) malnutrition, weight loss, liver and kidney dysfunction, a skin rash, red eyes, and shortness of breath. Very heavy use, more than 440 g root per week, was associated with increased plasma levels of gamma-glutamyl transferase, an indication of liver dysfunction (Mathews et al., 1988). Chronic heavy traditional use is reported to cause a particular scaly skin eruption (ichthyosiform eruption), which is reversible with discontinued use (Norton and Ruze, 1994). A study concluded that the dermopathy was not caused by niacin deficiency after heavy

kava users were randomized to receive either 100 mg oral nicotinamide or placebo daily for three weeks (Ruze, 1990).

Kava may interact with alcohol, creating greater cognitive impairment than the alcohol alone, although the type of kava preparation may be important in this interaction. Forty men and women participated in a randomized, placebo-controlled, comparative study wherein participants received placebo, kava (1 g powdered root per kg body weight), alcohol (0.75 g per kg body weight), or kava plus alcohol. A battery of tests given 30, 60, and 90 minutes after consuming the beverage revealed that kava alone had no effect on subjective measures of sedation, cognition, coordination, intoxication, and willingness to drive. In contrast, subjects receiving alcohol, with blood levels beyond 0.05 percent, had marked changes in all measures. The combination of kava plus alcohol produced a significantly larger decrement in an attention performance test than alcohol alone (Foo and Lemon, 1997). In contrast, a similar study with 20 subjects that used kava extract WS 1490 (300 mg per day for eight days) and similar blood alcohol levels found no negative multiplicative effects in a battery of performance tests (Herberg, 1993).

Recently, a number of case reports of severe liver damage have been reported subsequent to taking kava preparations. In the majority of cases, various underlying diseases were present, or additional medication was being taken that is known to have hepatotoxic effects. It may be that this toxicity is idiosyncratic and not predictable. In any case, it needs to be further investigated (Loew, 2002). A study comparing the relative incidence of hepatoxicity of kava preparations with that of other anxiolytics (bromazepam, diazepam, oxazepam) found a comparable rate of toxicity (Schulze, Meng, and Siegers, 2001). However, several European governmental bodies have concluded that kava has a negative risk/benefit ratio based upon the available data on hepatotoxicity and the lack of data supporting efficacy. Following this conclusion, kava sales have been restricted in Germany, Switzerland, Canada, Australia, and France (Centers for Disease Control, 2003). The U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA CFSAN) issued a warning in March 2002, citing that "although liver damage appears to be rare, FDA believes consumers should be informed of this potential risk" and that "persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, should

consult a physician before using kava-containing supplements" (FDA CFSAN, 2002).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

German Commission E

Indications

The dried rhizome (underground stem) is approved by the German Commission E for conditions of nervous anxiety, stress, and restlessness (Blumenthal et al., 1998).

Doses

Root and preparations equivalent to 60 to120 mg kavalactones per day (Blumenthal et al., 1998).

Treatment Period

The Commission E suggests that treatment not last more than three months without medical advice (Blumenthal et al., 1998).

Contraindications

The Commission E lists the following contraindications: pregnancy, nursing, and endogenous depression (Blumenthal et al., 1998).

Adverse Reactions

According to the Commission E, extended continuous intake can cause a temporary yellow discoloration of skin, hair, and nails. In this case, further application of this drug must be discontinued. In rare cases, allergic skin reactions can occur. Also, accommodative distur-

bances, such as enlargement of the pupils and problems with oculomotor equilibrium, have been described (Blumenthal et al., 1998).

Precautions

The Commission E warns that even when administered within its prescribed dosages, this herb may adversely affect motor reflexes and judgment necessary for driving and/or operating heavy machinery (Blumenthal et al., 1998).

Drug Interactions

The Commission E states that potentiation of effectiveness is possible for substances acting on the central nervous system, such as alcohol, barbiturates, and psychopharmacological agents (Blumenthal et al., 1998).

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DETAILS ON KAVA PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Kava Products

Product Profile: Laitan®

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	None
Botanical ingredient	**Kava root extract**
Extract name	**WS 1490**
Quantity	100 mg
Processing	No information
Standardization	70% kavalactones
Formulation	Capsule

Source(s) of information: Lehmann, Kinzler, and Friedemann, 1996.

Clinical Study: Laitan®

Extract name	WS 1490
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Anxiety**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference

Lehmann E, Kinzler E, Friedemann J (1996). Efficacy of a special kava extract *(Piper methysticum)* in patients with states of anxiety, tension and excitedness of non-mental origin—A double-blind placebo-controlled study of four weeks. *Phytomedicine* 3 (2): 113-119. (Also published in Kinzler E, Kromer J, Lehmann E [1991] *Arzneimittel-Forschung/Drug Research* 41 [1]: 584-588.)

Trial design

Parallel. A washout period of at least five half-lives of the medication was required before admittance to the study.

Study duration	1 month
Dose	1 (100 mg extract) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	58
No. of subjects completed	52
Sex	Male and female
Age	31-55 years

Inclusion criteria

Total score of greater than 18 points on the Hamilton Anxiety Scale (HAM-A); age between 18 and 60 years.

Exclusion criteria
Suicidal tendencies; endogenous depression; organic psychoses; psychoses of the schizophrenic group; psychopathies; dementia syndrome; diseases of the kidneys, liver, lungs, heart, cardiovascular system, as well as neoplasia; pregnancy; and medications interfering with the effectiveness evaluation, and those not included as comedications (including medications such as psychotonics, neuroleptics, antidepressants, tranquilizers, and beta-blockers).

End points
Subjects were evaluated at the beginning of the study as well as after 7, 14, and 28 days using the HAM-A, the self-assessment Adjectives Check List (EWL), the Clinical Global Impression Scale (CGI), and Fischer's Somatic or Adverse Experiences Checklist (FSUCL).

Results
The HAM-A overall score of anxiety symptomatology was significantly reduced in the kava group compared to placebo after one week of treatment ($p < 0.02$). This difference between the two groups increased over four weeks. In the kava group, the average HAM-A score of 25.6 at baseline dropped to 12.6 at the end of the month. The score remained practically unchanged in the placebo group (24.5 to 21.0, respectively). The anxiety/depression subscale of the EWL dropped significantly compared to placebo ($p < 0.05$). The other subscales showed no changes. The CGI rating decreased compared to placebo. No undesirable events were documented by FSUCL.

Side effects
None documented.

Authors' comments
WS 1490 is suitable for general practitioners to use in treating states of anxiety, tension, and excitedness.

Reviewers' comments
Well-designed, randomized, double-blind, placebo-controlled trial on reducing anxiety. To improve the study even more, a comparison to a conventional treatment group (e.g., benzodiazepine) would help in the evaluation of recommending kava as an alternative treatment. A longer trial would also allow for the better characterization of adverse events. (5, 6)

Clinical Study: Laitan®

Extract name	WS 1490
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany

Indication	**Anxiety**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Volz HP, Kieser M (1997). Kava-kava extract WS 1490 versus placebo in anxiety disorders—A randomized placebo-controlled 25-week outpatient trial. *Pharmacopsychiatry* 30 (1): 1-5.

Trial design
Parallel. Pretrial single-blind washout period with placebo of one week. After the 24-week randomized treatment period there was again a one-week washout period.

Study duration	24 weeks
Dose	1 (100 mg extract) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	10 general practices
No. of subjects enrolled	101
No. of subjects completed	73
Sex	Male and female
Age	Mean: 53.9 ± 16.3 years

Inclusion criteria
Patients suffering from anxiety and tension of nonpsychotic origin, with one of the following DSM-III-R diagnostic criteria: agoraphobia, specific phobia, social phobia, generalized anxiety disorder, or adjustment disorder with anxiety. In the Mehrfachwahl-Wortschatz test (multiple-choice vocabulary test) version B (MWT-B), a maximum of 13 mistakes were allowed. On the Hamilton Anxiety Scale (HAM-A) a score of at least 19 was required.

Exclusion criteria
Comedication with psychoactive compounds; hypotension (blood pressure lower than 90/60 mmHg); cerebellar ataxia; sleep apnea syndrome; a history or presence of substance abuse; clinically relevant cardiovascular, renal, hepatic, or respiratory diseases; and malignancies. Patients with an increase or decrease of more than six points on the HAMA at the end of the

one-week, single-blind, placebo washout period preceding the trial were also excluded.

End points
Evaluations were performed at the beginning of the placebo washout period, at weeks 0, 12, and 24, and after the final placebo washout period. The outcome criteria were the HAM-A, self-report symptom inventory (SCL-90-R), Clinical Global Impression (CGI), subjective well-being scale (Befindlichkeits-Scala, Bf-S) and registration of adverse events in a questionnaire. Additional HAMA ratings and adverse checks were carried out at weeks 4, 8, 16, and 20.

Results
A significant superiority of kava was observed in the HAM-A scores compared to placebo starting from week 8 ($p < 0.02$) that later increased (weeks 16, 20, 24; $p < 0.001$). HAMA values in the kava group fell from 30.7 at baseline to 9.7 after 24 weeks. The HAMA values for the placebo group fell from 31.4 to 15.2, respectively. WS 1490 was also found to be superior with respect to the secondary outcome variables: HAMA subscores somatic and psychic anxiety, CGI, SCL-90-R, and Bf-S.

Side effects
Nine patients in placebo group reported 15 adverse events; five patients in the kava group reported six events (stomach upset in two cases that may have been related to kava).

Authors' comments
The results support WS 1490 as a treatment alternative to tricyclic antidepressants and benzodiazepines in anxiety disorders, with proven long-term efficacy and none of the tolerance problems associated with those drugs.

Reviewers' comments
Overall, this is a well-designed study evaluating the effects of kava for patients suffering from anxiety (as determined by DSM-III-R diagnostic criteria). The study reports a significant reduction in anxiety (measured by HAM-A) starting from week 8 of treatment and continuing until week 24. HAM-A scores from week 25 (one-week posttreatment washout) were not included. Randomization and blinding procedures were not described adequately. (1, 6)

Clinical Study: Laitan®

Extract name	WS 1490
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany

Indication	**Anxiety in menopausal women**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Warnecke G (1991). Psychosomatic disorders in the female climacterium, clinical efficacy and tolerance of Kava extract WS 1490. *Fortschritte der Medizin* 109 (4): 119-122. (Similar 12-week study published in Warnecke G, Pfaender H, Gerster G, Gracza E [1990]. Efficacy of an extract of kava root in patients with climacteric syndrome. *Zeitschrift für Phytotherapie* 11: 81-86.)

Trial design
Parallel. Pretrial washout period of one week (or at least five to six times the half-life of any prohibited medication) in which patients received placebo.

Study duration	2 months
Dose	1 (100 mg extract) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Female
Age	Not given

Inclusion criteria
Women ages 45 to 60 years with menopausal symptoms, presence of psychoautonomic syndromes (anxiety, conditions of restlessness and sleep disturbances) and psychosomatic disturbances that manifested themselves as gynecological disorders, and Hamilton Anxiety Score (HAM-A) > 18.

Exclusion criteria
Constitutional hypotension with blood pressure < 90/79 mmHg; suicidal tendencies; endogenic depression; organic psychoses; schizophrenia; psychopathies; dementia or lacking sufficient intelligence to fill out forms; severe conditions of the kidneys, liver, lungs, heart/circulation, and neoplasma; pregnancy; and long-term treatment with medications such as psychotonics, neuroleptics, antidepressants, tranquilizers, and hormone preparations.

End points
Overall score of anxiety symptomatology according to the HAM-A score, Depressive Status Inventory (DSI), subjective well-being (patient diary), severity of the disease with the Clinical Global Impression, and climacteric symptomatology (Kuppermann Index and Schneider Scale). Examinations were carried out before the trial and after one, four, and eight weeks.

Results
The overall HAM-A score of anxiety symptomatology revealed a significant difference in the kava group compared to the placebo group after one week of treatment ($p < 0.001$). By the fourth and eighth week the significance increased ($p < 0.0005$). In the kava group, the baseline score of 31.1 was reduced to 5.5 after eight weeks. The placebo group score dropped from 30.2 to 22.5. The DSI decreased significantly compared to the placebo in the fourth and eighth week, $p < 0.01$. Other parameters, such as subjective well-being and CGI, demonstrated a high level of efficacy for the kava extract.

Side effects
Six adverse events were reported in the placebo group, and four in the kava group. Patients reported restlessness, tremor, gastric pressure, and tiredness (events reported were similar between the two groups).

Author's comments
This study demonstrates a high level of efficacy of kava extract WS 1490 in neurovegetative and psychosomatic dysfunctions in menopause, associated with very good tolerance.

Reviewers' comments
Well-designed and well-reported trial on the efficacy of kava (WS 1490) in reducing both anxiety (significant decreases in HAMA scores) and severity of menopausal symptoms (Kuppermann Index). (Translation reviewed) (5, 6)

Clinical Study: Laitan® 50

Extract name	WS 1490
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Anxiety**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Malsch U, Kieser M (2001). Efficacy of kava-kava in the treatment of nonpsychotic anxiety, following pretreatment with benzodiazepines. *Psychopharmacology* 157 (3): 277-283.

Trial design
Parallel. Subjects had been taking benzodiazepines for at least two weeks prior to the trial start. During the first two weeks of the trial, the benzodiazepine treatment was tapered off at a steady rate. Simultaneously, during the first week of the study, the daily dose of the kava extract was increased from 50 mg to 300 mg. By weeks 3 through 5, subjects were only taking either 300 mg kava extract or placebo daily. A follow-up was conducted three weeks after the treatment phase.

Study duration	5 weeks
Dose	3 (50 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	One hospital
No. of subjects enrolled	40
No. of subjects completed	37
Sex	Male and female
Age	21-75 years (mean: 40)

Inclusion criteria
Subjects suffering from nonpsychotic nervous anxiety, restlessness, and tension that results in impairment of work performance, relationships, and normal social activities (diagnoses according to the DSM-III-R of agoraphobia, simple or social phobia, generalized anxiety disorders, or adaptation disturbances). Prior to inclusion into the study, subjects had to have been taking 14 days of uninterrupted treatment with benzodiazepines. Subjects also needed a medical indication for the change to a different anxiolytic drug and therefore a discontinuation of the benzodiazepine treatment. Subjects had to score a total of at least 12 points on the verbal multiple-choice intelligence test (MWT-B) and a score of at most 14 on the Hamilton Anxiety Scale (HAM-A).

Exclusion criteria
Subjects were excluded if they had other anxiety disorders and psychiatric

diseases, drug abuse or addiction, suicidal tendencies, severe physical illness, constitutional hypotension, ocular disorders, need of medical treatment that could interfere with the trial evaluation, or known lactose intolerance or allergies to kava extract. Pregnant or nursing mothers were also excluded.

End points
The primary end points were overall changes from baseline to the trial end in the HAM-A and the Befindlichkeits-Skala (Bf-S, subjective well-being scale), and the incidence of withdrawal symptoms from the cessation of benzodiazepine treatment. Secondary end points included the Erlangen Anxiety and Aggression Scale (EAAS) and the Clinical Global Impression Scale (CGI).

Results
After five weeks of treatment, the group taking kava extract saw a decrease in the HAM-A total score (median improvement: 7.5 points; 60 percent were responders). This was significantly different from placebo (HAM-A scores: $p < 0.05$; percent responders: $p < 0.013$). The kava group also showed significantly greater improvement on the Bf-S total score compared to placebo (median improvement: 18.5 and 3 points, respectively; $p < 0.01$). More subjects in the placebo group (52.6 percent) experienced withdrawal symptoms than in the kava group (40 percent), but this difference was not significant. On the EAAS, the kava group showed a reduction in the total score by 3.5 points, whereas the placebo group's total score was reduced by 0.5 points ($p = 0.02$). The kava group also improved more according to Items 1 and 2 of the CGI: perceived severity decreased for the kava but remained unchanged for placebo ($p = 0.01$); and subjects' overall condition was much improved for the kava group versus unchanged for the placebo ($p = 0.02$).

Side effects
No serious adverse events occurred during the trial. Five subjects in the kava group and ten in the placebo group experienced adverse events, all of which were related to the withdrawal of benzodiazepine. No differences were observed in laboratory tests at the beginning and end of the trial.

Authors' comments
This trial demonstrates that kava special extract WS 1490 is significantly more effective than placebo in the treatment of moderately severe anxiety disorders of nonpsychotic origin. Beyond confirming the anxiolytic effect of kava-kava special extract WS 1490, the results of the study also show that a further alleviation of many patients' anxiety could be produced despite long previous treatment with benzodiazepines.

Reviewers' comments
Although the sample size is small (40 subjects), this is a very well-designed study evaluating the effects of a well-studied standardized extract of kava

(WS 1490) in the treatment of moderately severe anxiety. The study demonstrated that subjects on long-term benzodiazapine therapy could be safely switched to kava by tapering subjects off preexisting benzodiazapines while tapering up the kava dose. There were no serious adverse events reported after five weeks of treatment. However this intervention period was not long enough to assess long-term treatment efficacy or the potential addictive properties of kava. (5, 5)

Clinical Study: Laitan®

Extract name	WS 1490
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Anxiety**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Woelk H, Kapoula O, Lehrl S, Schroter K, Weinholz P (1993). Treatment of patients suffering from anxiety. Double-blind study: Kava special extract versus benzodiazepines. *Zeitschrift für Allgemeinmedizin* 69: 271-277.

Trial design
Parallel. After a one-week washout period, patients were divided into three groups and received either kava, oxazepam (3 × 5 mg daily), or bromazepam (3 × 3 mg daily) for six weeks. In a subsequent 14-week open-study phase, all patients were treated with Kava (results of this phase are reported in another paper and not included here).

Study duration	6 weeks
Dose	3 (100 mg extract) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug names	Oxazepam and bromazepam
Site description	12 medical practices
No. of subjects enrolled	172

No. of subjects completed	164
Sex	Male and female
Age	Mean: 50 years

Inclusion criteria
Patients 18 to 65 years with conditions of anxiety, tension and agitation of nonpsychotic origin, a Hamilton Anxiety Scale (HAM-A) total score of more than 18, and Mehrfachwahl-Wortschatz-Intelligenztest (multiple-choice vocabulary intelligence test) IQ of at least 80.

Exclusion criteria
Patients lacking the mental or linguistic capacity to perform tests, or perform them with insufficient compliance; pregnant and nursing patients; patients with severe diseases of kidneys, liver, lung, heart and circulation, and neoplasia; myasthenia gravis; constitutional hypotension with RR values < 90/60 mmHg; cerebral ataxia; sleep apnea; lactose intolerance; psychoses and danger of suicide; acute intoxications with centrally sedating drugs or alcohol; known drug, alcohol, or medicament abuse; and treatment with therapeutics able to interfere with the assessment of efficacy, such as psychotonics, neuroleptics, antidepressants, or other plant-based anxiolytics.

End points
Anxiety was assessed using the HAM-A total score. Additional tests included: the physician's assessment of global therapeutic success (CGI); a self-assessment test; the KEPS (short test for evaluating personality); EAAS scale for anxiety, aggression and tension; and the EWL-60-S for recording patients' subjective feelings.

Results
In all three treatment groups, a continuous decrease of anxiety was found after the first week. No significant difference could be verified when comparing the HAM-A total score of kava to each of the other treatment groups during the six-week trial. A comparable action was measured by the EWL-60-S and EAAS.

Side effects
Adverse events related to medication were not collected. However, investigating physicians reported four cases of tiredness, one with mild reversible pruritis with Bromazepam; one patient with tiredness, pressure in head, vertigo, and unrest while taking oxazepam; and one case of gastric pressure and nocturnal nausea, as well as a lack of initiative and spasmodic state under stress.

Authors' comments
It can be concluded that the kava special extract WS 1490 is comparable to oxazepam or bromazepam with regard to anxiolytic effect. It should be in-

cluded as a possible therapy for anxiety, tension, and agitation of non-psychotic origin.

Reviewers' comments
Reasonably well-designed, randomized, double-blind trial showing kava comparable to oxazepam and bromazepam in reducing anxiety (measured by HAM-A). A comparison of all three therapies to a placebo group would increase the validity of the findings. (Translation reviewed) (5, 5)

Clinical Study: Laitan®

Extract name	WS 1490
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Sleep quality** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Emser W, Bartylla K (1991). Improvement in quality of sleep: Effect of kava extract WS 1490 on the sleep patterns in healthy people. *TW Neurologie Psychiatrie* 5: 636-642.

Trial design
Parallel. Dose comparison. Each group received placebo on days 1, 3, and 4, and kava (either 3 × 50 mg or 3 × 100 mg) on day 2.

Study duration	4 nights
Dose	3 (50 mg or 100 mg) capsules daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male and female
Age	20-31 years

Inclusion criteria
Healthy individuals.

Exclusion criteria
Patients with alcohol or medical abuse, pain, or suicidal tendencies.

End points
Primary objective: EEG sleeping patterns of the subjects. A long-time EEG system was used over the test period of four days and four nights. Enumeration of EEG sleep spindles during sleep Stage 2 was done visually. Subjects filled out a sleep questionnaire daily.

Results
EEG sleep spindle densities for 11 of the 12 subjects on the kava-extract night increased around 20 percent in comparison with the densities recorded for both placebo nights. The percentage of deep sleep (slow wave sleep) increased, and falling asleep latency was reduced compared to placebo. REM sleep did not change. The duration of sleep Stage 1 (falling asleep stage) as well as duration of the waking stage tended to decrease after higher doses of kava (3 × 100 mg). Sleep questionnaires were not always consistent with EEG measurements, but overall cited an improvement in deep sleep as well as an improvement in peace, calm, and well-being the morning after taking kava extract.

Side effects
None reported.

Authors' comments
The increase in sleep spindle density in sleep EEG measurements is a characteristic of conventional tranquilizers that is shared by the kava special extract WS 1490. Kava did not cause a suppression of deep sleep or REM sleep, which is typical of benzodiazepine-type and barbituate-type sleeping medications. The small number of subjects limits the statistical significance of the findings, but the study is useful in identifying trends.

Reviewers' comments
This is a small pilot trial using various polysomnographic EEG outcome measures, including spindles density, sleep latencies, sleep stages, and awakenings. Based on the polysomnographic data, the high-dose kava group showed a decrease in slow-wave sleep latency. Subjective sleep quality was assessed by questionnaire data, but not completely described in the study report. The subjective sleep latencies increased with drugs in contrast to the polysomnographic data; however, the subjects did report an improvement in deep sleep with drugs. Some of the study differences are hard to evaluate because the authors do not give variability measures. The data

suggest that the higher dose of kava produced more effects on sleep than the lower dose. (3, 4)

Clinical Study: WS 1490

Extract name	WS 1490
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Cognitive functioning** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Munte TF, Heinze HJ, Matzke M, Steitz J (1993). Effects of oxazepam and an extract of kava roots *(Piper methysticum)* on event-related potentials in a word recognition task. *Neuropsychobiology* 27 (1): 46-53. (Also published in Heinze HJ, Munthe TF, Steitz J, Matzke M [1994]. *Pharmacopsychiatry* 27 (6): 224-230.)

Trial design
Crossover study, Latin design. Experimental sessions were separated by 12 days. For five days prior to an experimental session, subjects took one capsule three times daily of one of three treatments: placebo; kava extract; or placebo on the first three days, then 15 mg oxazepam the day before testing, and 75 mg on the morning of testing.

Study duration	5 days
Dose	1 (200 mg) capsule 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Oxazepam
Site description	Single center
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male
Age	24-37 years

Inclusion criteria
Healthy subjects with normal vision or vision corrected to normal.

Exclusion criteria
Neurological conditions.

End points
Memory performance was evaluated with a continuous word-recognition task. Scalp-recorded electrical potentials or event-related brain potentials (ERPs), were also recorded.

Results
In the word-recognition test, a significant slowing of reaction time and a reduction in the number of correct responses was seen for oxazepam, whereas a nonsignificant increase in the number of correct responses was observed for kava. The results of the ERPs showed a similar pattern.

Side effects
None reported.

Authors' comments
The behavioral indices in the word-recognition test suggest enhanced memory performance under kava medication and a greatly impaired performance with oxazepam.

Reviewers' comments
Although oxazepam produced significant impairments on cognitive testing compared to placebo, no significant impairment was observed with kava. In addition to the cognitive testing, event-related potentials were recorded. Although the authors reported some differences, given their relatively nonstandard techniques and lack of a priori hypotheses, no definite effects of kava were observed. The strength of the study is reduced by the small sample size and the inadequate inclusion/exclusion criteria. Note: the dose in this study is twice that used in the anxiety study (Lehmann, Kinzler, and Friedemann, 1996). (3, 4)

Product Profile: Kava (Generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Kava root extract**
Extract name	None given
Quantity	No information

Processing	30 g kava root powder from Fiji was soaked in water, twice filtered through a piece of fine muslin cloth, and the residue discarded. The remaining liquid was adjusted to 250 ml by the addition of water.
Standardization	No information
Formulation	Liquid

Source(s) of information: Russell, Bakker, and Singh, 1987.

Clinical Study: Kava (Generic)

Extract name	None given
Manufacturer	None
Indication	**Cognitive functioning** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Russell PN, Bakker D, Singh NN (1987). The effects of kava on alerting and speed of access of information from long-term memory. *Bulletin of the Psychonomic Society* 25 (4): 236-237.

Trial design
In two experiments, a control group and either a low-dose kava group or a high-dose kava group were tested twice, two to six days apart. The control group consumed no kava prior to either session. The low-dose kava group consumed a 250 ml preparation made from 30 g of root. The high-dose kava group consumed 500 ml preparation made up to a strength of 1 g kava/kg body weight.

Study duration	2 testing sessions
Dose	250 ml (30 g root); 500 ml at a strength of 1g/kg body weight.
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No

Placebo	No
Drug comparison	No
Site description	Single center
No. of subjects enrolled	27
No. of subjects completed	27
Sex	Male and female
Age	18-22 years

Inclusion criteria
Caucasian undergraduates.

Exclusion criteria
None mentioned.

End points
Stimuli were presented to subjects. Reaction time and accuracy were recorded on two testing occasions (one at baseline and a second after two to six days).

Results
Kava produced no effect on the speed of activation of verbal information in long-term memory or on the rise or magnitude of the alerting function of a warning signal. Neither dose, one associated with traditional social use and one much greater, had an effect on reaction times or errors.

Side effects
None mentioned.

Authors' comments
It would be unwise to conclude from this study alone that kava has no effect on cognitive function. More research is needed. At this stage, however, kava appears preferable to alcohol as a beverage to be consumed on social occasions, at least in terms of its effects on human performance.

Reviewers' comments
This open-label pilot trial is not well designed. Instead of using a placebo, the "no kava" group did not consume anything before the cognitive performance test. Flaws also included a small sample size, inclusion criteria not well defined, no exclusion criteria, inadequately described statistical methods, and no randomization or blinding. (0, 2)

Product Profile: Kava (Generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Kava root extract**
Extract name	None given
Quantity	No information
Processing	200 g of commercially available Fijian powdered kava root, held inside a permeable nylon sack, was infused into 1,000 ml of water for 10 minutes while squeezing the sack repeatedly
Standardization	No information
Formulation	Liquid

Source(s) of information: Prescott et al., 1993.

Clinical Study: Kava (Generic)

Extract name	None given
Manufacturer	None
Indication	**Cognitive functioning** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Prescott J, Jamieson D, Emdur N, Duffield P (1993). Acute effects of kava on measures of cognitive performance, physiological function, and mood. *Drug and Alcohol Review* 12: 49-58.

Trial design
Subjects attended two sessions on consecutive days. The first session was without kava, and produced a baseline. On the second day, participants received either juice (1,000 ml) or kava (500 ml) plus juice (500 ml).

Study duration	2 sessions on successive days
Dose	500 ml water extract (100 g root)

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	University hospital
No. of subjects enrolled	24
No. of subjects completed	24
Sex	Male and female
Age	18-53 years (mean: 26.7)

Inclusion criteria
Subjects who were consumers of alcohol, but had never consumed kava.

Exclusion criteria
None mentioned.

End points
Subjects undertook tasks of acute cognitive functioning, including reaction time and tracking tasks, and a measure of body sway. Heart rate, respiration rate, and blood pressure were recorded. Subjects were also asked to rate their degree of intoxication and complete a stress/arousal checklist.

Results
Subjects taking kava reported low to moderate levels of intoxication that peaked one hour after consumption and declined thereafter. These levels were statistically significant compared to placebo ($p = 0.002$). Compared to placebo, the kava group had increased body sway ($p = 0.016$). Cognitive performance tasks showed slight impairment in complex tasks for the kava group, but no significant differences were found between the two groups.

Side effects
Three subjects reported nausea after consumption of kava.

Authors' comments
Overall, the effects of kava ingestion in naive volunteers were evident only in the sway test, and in subjective feelings of intoxication, with some trends in the complex cognitive tasks. The possibility that cognitive impairment may have been more evident with a larger sample size suggests that caution should be exercised in ingesting kava prior to tasks that are cognitively demanding.

Reviewers' comments
The methodology of this study has some serious flaws. The blinding of the kava drink was not well done. Kava taken as a drink can cause oral numbness—an effect that would have to be accounted for in the placebo drink; therefore, using only juice as placebo does not provide a proper placebo control. Randomization was done on an alternating basis, which presumably also limited blinding. The blinding of outcome assessments was never mentioned in this report. No exclusion criteria were mentioned. The trial did include some well-defined and appropriate objective outcome assessments, including: cognitive performance tasks; Sternberg memory scanning task; simple reaction time, choice reaction time, tracking, and divided attention; physiological recordings; respiratory and heart rate; blood pressure; and objective measures of body sway. Effects of kava were observed for self-rated intoxication and body sway. (1, 3)

Product Profile: Kavatrol™

Manufacturer	**Natrol, Inc.**
U.S. distributor	**Natrol, Inc.**
Botanical ingredient	**Kava root extract**
Extract name	None given
Quantity	200 mg
Processing	Plant/extract ratio 6:1, water-ethanol extraction
Standardization	30% kavalactones (including kawain, dihydrokawain, methysticin, dihydromethysticin
Botanical ingredient	**Schizandra fruit**
Extract name	N/A
Quantity	50 mg
Processing	No information
Standardization	No information
Botanical ingredient	**Hops flower**
Extract name	N/A
Quantity	50 mg
Processing	No information
Standardization	No information
Botanical ingredient	**Chamomile flower**
Extract name	N/A
Quantity	50 mg
Processing	No information

Standardization	No information
Botanical ingredient	**Passionflower aerial parts**
Extract name	N/A
Quantity	50 mg
Processing	No information
Standardization	No information
Formulation	Capsule

Recommended dose: Take two capsules 2 times per day, preferably before a meal or on an empty stomach.

DSHEA structure/function: Helps you relax naturally.

Cautions: Avoid using with alcohol or mixing with any prescription medication and/or OTC drugs. If pregnant or lactating, consult your physician prior to use. Do not use if diagnosed with liver disease. If any symptoms of jaundice (nausea, fever, dark urine, yellow eyes, etc.) occur, discontinue use and seek medical attention. Not recommended to exceed more than 4 capsules per day. Consult a physician if intending to use this product routinely.

Other ingredients: Magnesium stearate, silica, gelatin.

Comments: Also comes in tablet form.

Source(s) of information: Product label, product information (www.natrol.com/catalog); FAQ Kavatrol (www.natrol.com); information provided by distributor.

Clinical Study: Kavatrol™

Extract name	None given
Manufacturer	Natrol, Inc.
Indication	**Anxiety and stress**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference

Singh NN, Ellis CR, Best AM, Eakin K (1998). Randomized, double-blind, placebo-controlled study on the effectiveness and safety of Kavatrol in a non-clinical sample of adults with daily stress and anxiety. Unpublished manuscript.

Trial design
Parallel. Pretrial washout period of at least five half-life periods of participants' medications.

Study duration	1 month
Dose	2 (200 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	67
No. of subjects completed	60
Sex	Male and female
Age	Mean: 36.5 years

Inclusion criteria
State-Trait Anxiety Inventory (STAI) score of one standard deviation above the mean, ages between 18 and 60, and good physical health.

Exclusion criteria
Endogenous depression, mental conditions of organic origin, or psychoses; syndromes of the kidneys, liver, lungs, heart, cardiovascular system, as well as neoplasia, irrespective of its localization; pregnancy; on prescribed medications that may interact with the kavalactones or interfere with the assessment of efficacy and safety of Kavatrol (including neuroleptics, antidepressants, sedatives, anxiolytics, and beta-blockers).

End points
Efficacy measures included the Daily Stress Inventory (DSI) and STAI scores. Subjects completed the STAI and DSI once a week on the same day for four weeks. Safety and tolerance were also measured weekly using the Untoward Effects Checklist.

Results
The results showed that state anxiety of the subjects on Kavatrol decreased from baseline to week four, a statistically significant reduction compared to the placebo group, $p < 0.0001$. As expected, the levels of trait anxiety (trait anxiety is thought to be a relatively fixed attribute) for Kavatrol and placebo groups did not change.

Side effects
No serious or significant side effects.

Authors' comments
This is the first study to show that kava reduces the stress associated with the daily hassles of life. Findings confirm the belief that kava products may offer an alternative to benzodiazepines in the reduction of anxiety states in adults.

Reviewers' comments
It is not clear from the inclusion/exclusion criteria what type of anxiety is being evaluated—no physician assessment of anxiety state was made, and only a self-assessment based on STAI greater than 1 standard deviation above the mean was provided. Exclusions for prescription medications may affect study outcomes, but not other botanical use. No mention is made of alcohol or caffeine use in the study subjects. Data variability measures are not given, but type of analysis and data are described. (3, 5)

Lemon Balm

Other Common Names: **Balm, bee balm, Melissa balm**
Latin Name: ***Melissa officinalis* L.** [Lamiaceae]
Plant Part: **Leaf**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

The genesis of the lemon balm product Herpilyn®, indicated for the topical treatment of herpes infections, was the discovery of antiviral properties of the herb in a cell culture assay. The traditional use for lemon balm is reflected in the German Commission E's approval of oral preparations for nervous sleeping disorders and gastrointestinal complaints (Schulz, Hänsel, and Tyler, 2001).

A standardized preparation of lemon balm leaves is manufactured by Lomapharm, Rudolf Lohmann GmbH KG, Emmerthal, Germany. Lomaherpan® cream contains 1 percent of a dried aqueous extract called Lo-701 (ratio of leaf to extract 70:1). The product in the United States, distributed by Enzymatic Therapy under the name of Herpilyn®, contains the same lemon balm extract, Lo-701. In addition, it contains 1 percent allantoin, which is a monographed ingredient for over-the-counter (OTC) fever blister medications. The product tested in the two clinical trials reviewed here did not contain allantoin.

SUMMARY OF REVIEWED CLINICAL STUDIES

We reviewed two controlled clinical studies that examined the ability of Lomaherpan to reduce the symptoms of herpes simplex, a viral lesion that can occur on the lips of the mouths (cold sores), on the genitals (genital herpes), or on the skin. Herpes infections are characterized by local outbreaks with itching followed by blisters and

LEMON BALM SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Herpilyn® (US), Lomaherpan® (EU)	Lomapharm, Rudolf Lohmann GmbH KG/ Enzymatic Therapy	Cream containing 1% aqueous extract (Lo-701)	Apply 2-4 times daily	Herpes simplex	2	Trend (III-2)

inflammation, which usually heal in a few days, sometimes producing scabs in the process. Herpes is often treated with antiviral agents such as acyclovir, which, when given orally, can reduce virus shedding, symptoms, and time to healing. Such agents appear to have less benefit when given topically (Hardman et al., 1996).

Lomaherpan

Herpes simplex

A recent study included 66 adults with a history of recurrent herpes of the lips (orolabial herpes). The subjects were administered Lomaherpan or placebo cream (2 mm) four times daily at the first sign of an outbreak. Participants were monitored for five days following an outbreak, with symptoms on day 2 being the primary end point. The Lomaherpan cream produced a significant reduction in the symptom score compared with placebo on day 2. However, overall symptom scores for the five-day periods were not different for the two groups (Koytchev, Alken, and Dundarov, 1999). Our reviewer, Dr. Richard O'Connor, considered that the small improvement observed after two days might not be clinically relevant.

The second placebo-controlled, double-blind study examined a total of 116 outpatients, both children and adults, with herpes lesions on multiple sites, including the lips, skin, and genitals. Patients were instructed to apply cream two to four times daily to the affected site over a maximum of ten days (on average five) until the lesion was healed. A significant reduction in redness (rubor) and swelling was observed on day two, but no significant difference in symptoms of blisters, scabbing, erosion, pain, or course and extent of the lesions. However, a significant increase in healing time compared with placebo was seen in a subgroup of patients (67) with herpes on the lips of the mouth (Wolbling and Leonhardt, 1994). The evidence for benefit in this trial was weakened by poor methodological descriptions in the report.

ADVERSE REACTIONS OR SIDE EFFECTS

No adverse reactions due to treatment were reported in the reviewed studies, which included a total of 91 subjects in both treatment groups.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

German Commission E
European Scientific Cooperative on Phytotherapy

Indications

The German Commission E approved preparations of the fresh or dried leaf for nervous sleeping disorders and functional gastrointestinal complaints (Blumenthal et al., 1998). According to the European Scientific Cooperative on Phytotherapy (ESCOP) monograph, the dried leaves can be taken internally to treat tenseness, restlessness, and irritability, as well as the symptomatic treatment of digestive disorders, such as minor spasms. The dried leaves can be used externally to treat herpes labialis (cold sores) (ESCOP, 1996).

Doses

Tea: 1.5 to 4.5 g of herb per cup, several times daily as needed (Blumenthal et al., 1998); 2 to 3 g of the drug as an infusion, two to three times daily (ESCOP, 1996)
Tincture: 1:5 in 45 percent alcohol, 2 to 6 ml three times daily (ESCOP, 1996)
Topical application: cream containing 1 percent of a lyophilized aqueous extract (70:1), two to four times daily (ESCOP, 1996)

Treatment Period

ESCOP lists no restriction for oral administration. In topical application for herpes labialis, ESCOP suggests use from prodromal signs to a few days after the healing of lesions, or a maximum of 14 days (ESCOP, 1996).

Contraindications

The Commission E and ESCOP list no known contraindications (Blumenthal et al., 1998; ESCOP, 1996).

Adverse Reactions

The Commission E and ESCOP list no known adverse reactions (Blumenthal et al., 1998; ESCOP, 1996).

Precautions

ESCOP states there are no precautions (ESCOP, 1996).

Drug Interactions

According to the Commission E and ESCOP, there are no known drug interactions (Blumenthal et al., 1998; ESCOP, 1996).

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DETAILS ON LEMON BALM PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Herpilyn®

Manufacturer	**Lomapharm, Rudolf Lohmann GmbH KG, Germany**
U.S. distributor	**Enzymatic Therapy**
Botanical ingredient	**Lemon balm leaf extract**
Extract name	**Lo-701**
Quantity	No information
Processing	Plant to extract ratio 70:1
Standardization	No information
Formulation	Cream
Botanical ingredient	**Comfrey extract**
Extract name	None given
Quantity	No information
Processing	No information
Standardization	1% allantoin

Recommended dose: Apply at first sign of burning, tingling, or itching. If a cold sore has already developed, apply two to four times daily, or as often as needed.

DSHEA structure/function: OTC label indication: natural cold sore and fever blister medication.

Cautions: Avoid contact with eyes. If condition worsens or does not improve in 7 days, consult a physician.

Other ingredients: White soft paraffin, benzyl alcohol.

Comments: Sold as Lomaherpam® in Europe.

Source(s) of information: Product package; information provided by distributor; Koytchev, Alken, and Dundarov, 1999; correspondence with Enzymatic Therapy.

Clinical Study: Lomaherpan®

Extract name	Lo-701
Manufacturer	Lomapharm, Rudolf Lohmann GmbH, Germany
Indication	**Herpes simplex** (labialis)
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Koytchev R, Alken RG, Dundarov S (1999). Balm mint extract (Lo-701) for topical treatment of recurring herpes labialis. *Phytomedicine* 6 (4): 225-230.

Trial design
Parallel. Patients were instructed to start therapy no later than four hours after the onset of symptoms and to contact the physician within 24 hours for a visit.

Study duration	5 days
Dose	Cream (2 mm) applied 4 times daily
Route of administration	Topical
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	66
No. of subjects completed	66
Sex	Male and female
Age	18-65 years (mean: 43)

Inclusion criteria
Caucasian; history of recurrent herpes (at least four episodes per year); ex-

perienced in observing symptoms of itching, tingling, burning, and tautness; outbreaks typically localized to the lip margin or perioral skin; and previously diagnosed with recurrent herpes labialis.

Exclusion criteria
Concomitant local or systemic treatment with antiherpetic or antiviral agents, as well as immunosuppressive agents, were generally not allowed.

End points
During each herpetic episode there were four visits: on the first, second, third and fifth day after onset of symptoms. The primary target parameter was a combined symptom score of the values for complaints, size of affected area, and blisters at day 2 of therapy. The secondary target parameter was total score of herpetic symptoms over five days of therapy.

Results
A significant difference was observed in the values of the primary target parameter between groups on day 2, with a mean value of 4.03 in the Lo-701 group and 4.94 in the placebo group ($p = 0.042$). In the secondary target parameter (symptoms over five days of therapy), the verum group had a mean value lower than the placebo group, but not significantly ($p = 0.16$).

Side effects
None mentioned.

Authors' comments
As a whole, the results of the present trial obtained both for the primary and secondary target parameters were coherent and demonstrated the efficacy of Lomaherpan cream for the treatment of herpes simplex labialis.

Reviewer's comments
The primary end point (symptom score on day 2) was significantly better in the treatment group compared to placebo. The small difference between treatment arms, although statistically significant, may not be clinically relevant. None of the other parameters (five-day symptom score, global evaluation by either patient or investigator, or number of blisters) were statistically different. The results suggest integral efficacy, at best. Neither the blinding nor randomization were described in any detail. (1, 6)

Clinical Study: Lomaherpan®

Extract name	Lo-701
Manufacturer	Lomapharm, Rudolf Lohmann GmbH, Germany
Indication	**Herpes simplex**

Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference

Wolbling RH, Leonhardt K (1994). Local therapy of herpes simplex with dried extract from *Melissa officinalis. Phytomedicine* 1: 25-31. (Also published in Vogt HJ, Tausch I, Wolbling RH, Kaiser PM [1991]. *Der Allgemeinarzt 13* [11]: 832-841.)

Trial design

This paper reported both a phase I open-label controlled study and a phase II double blind study. The second study is reported here. Parallel. Patients were instructed to apply cream for five to ten days subject to the healing time of the lesion. Placebo was the same cream base as the active drug, but without the active ingredient of lemon balm.

Study duration	5-10 days
Dose	Apply cream 2-4 times daily for 5-10 days
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	2 dermatological centers
No. of subjects enrolled	116
No. of subjects completed	113
Sex	Male and female
Age	Mean: 33.2 ± 14.8 (placebo); 40.3 ± 14.8 (Lomaherpan)

Inclusion criteria

Children and adults with herpes simplex infection of the skin or transitional mucosa, with clinical symptoms lasting for not more than 72 hours before admission to the study.

Exclusion criteria

Known hypersensitivity to the ingredients of the drug or control preparation; concomitant treatment (internal or external) with another antiviral preparation; other treatment of viral infection; limited legal capacity.

End points
Clinical symptoms were documented after two days and upon termination of treatment (usually five days). Global evaluation was carried out by the physician and the patient on the patient's last visit. Scores ranged from 1 (very good) to 5 (very bad). The dimensions of the lesions were also recorded.

Results
The sites of lesions were similar for the two groups, including a total of 67 cases of lesions on the lips and ten cases of genital herpes. Compared to placebo, symptoms in the Lomaherpan group declined significantly after two days ($p = 0.0055$). After five days, 24 of 58 patients in the Lomaherpan group had no symptoms compared to 15 of 58 patients in the placebo group. Physicians assessed healing as "very good" in 25 cases in the Lomaherpan group and ten cases in the placebo group ($p = 0.031$). Patients assessed healing as "very good" in 24 cases in the Lomaherpan group, and 11 in the placebo ($p = 0.022$).

Side effects
No difference between the two groups.

Authors' comments
The effect of Lomaherpan cream in the topical treatment of herpes simplex infections of the skin and transitional mucosa is statistically significant. To be effective, the treatment must be started in the very early stages of the infection. The achieved acceleration of healing, particularly in the first two days of the treatment, adds corroborative evidence to this phenomenon.

Reviewer's comments
The results showed slight improvement on day 2 only for redness and swelling, but not on day 5. None of the other parameters (vesicle formation, scabbing, erosion, or pain) were different from placebo. The phase II study is described as randomized, but no details are given, and the ages of the two groups were significantly different. The blinding was also described poorly, and the data were not summarized in sufficient detail to permit alternative analysis. (1, 4)

Milk Thistle

Other common names: **Mary's thistle**
Latin name: ***Silybum marianum* (L.) Gaertn.** [Asteraceae]
Plant part: **Seed**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Milk thistle is native to southern Europe and northern Africa. The plant part that is used medicinally is the ripe fruit (seed) with the outer covering (pappus) removed. The seed contains about 2 to 3 percent of the active constituent silymarin, a mixture of four isomers: silybin (also spelled silybinin) (50 percent), isosilybinin, silydianin, and silychristin. Studies conducted on silymarin have shown that it promotes liver-tissue regeneration, and has antitoxic effects on the liver (Schulz, Hänsel, and Tyler, 2001).

Legalon® is manufactured in Germany by Madaus AG. Legalon contains a standardized extract of milk thistle seeds that is characterized as containing 80 percent silymarin (140 mg silymarin per 173 to 186.7 mg extract). Legalon was previously distributed in the United States by Nature's Way Products, Inc., under the name of Thisilyn®.

Silipide, produced by Inverni della Beffa in Italy, contains a milk thistle seed extract, IdB 1016, also known as Siliphos®, that is manufactured by Indena S.p.A. Siliphos is a complex of silybin combined with phosphatidylcholine containing 29.7 to 36.3 percent silybin. An initial pilot study was conducted on a product with a molar ratio of silybin to phosphatidylcholine of 1:1 (Buzzelli et. al., 1993). The current product is manufactured with a ratio of silybin to phosphatidylcholine of 1:2. Siliphos is sold in the United States under the

MILK THISTLE SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Legalon® (EU)	Madaus AG, Germany/None	Extract containing 80% silymarin	210-800 mg daily, usually in 3 doses	Alcoholic liver disease	10	Yes (III-1) Trend (I-1, II-1, III-2) Undetermined (III-3) No (I-2)
				Liver damage caused by toxins other than alcohol	2	Undetermined (III-2)
Silipide (EU)	Inverni della Beffa, Italy (Indena S.p.A., Italy)/None	Extract IdB 1060 (Siliphos®) complexed with phosphatidylcholine containing 29.7-36.3% silybin	240 or 480 mg daily	Chronic hepatitis	1	Yes (II-1)
				Viral hepatitis	1	Trend (II-1)
Silimarina® (Romania)	Biofarm, Romania/ None	Extract containing 5% silybin (said to be a copy of Legalon)	4.2 g (210 mg silybin) daily	Hepatitis or cirrhosis	1	Undetermined (II-1)
Generic	None/None	Silymarin	800 mg daily	Drug-induced liver damage	1	Trend (III-1)

*Products that contain the Indena S.p.A. Siliphos® extract as a single ingredient. The extract has been tested clinically but the following final formulations have not.

Product Name	Manufacturer	Product characteristics
Maximum Milk Thistle™	Natural Wellness	240 mg each capsule
Ultra thistle™	Natural Wellness	360 mg each capsule

names UltraThistle™ and Maximum Milk Thistle™ by Natural Wellness.

Silimarina® is manufactured in Romania by Biofarm. Each 700 mg tablet contains the equivalent of 35 mg silybin. The clinical study report claims that Silimarina is a copy of Legalon.

One trial was conducted on a product simply described as silymarin, using a dose of 800 mg daily. No further description was available.

SUMMARY OF REVIEWED CLINICAL STUDIES

Milk thistle preparations have been tested for their ability to treat symptoms of liver disease caused by alcohol, other toxins, or viral infections. The major liver diseases are hepatitis, cirrhosis, and dysfunctions related to bile secretion. Hepatitis is characterized as an inflammation of the liver that can be present with or without cirrhosis. Forms of viral hepatitis include hepatitis A, B, and C. Cirrhosis is a state in which the tissue in the liver breaks down, becoming fatty and fibrous. Liver disease can be acute (short term) or chronic (long term) leading to cirrhosis and eventually to liver failure (Morazzoni and Bombardelli, 1995; Habib, Bond, and Heuman, 2001).

The clinical symptoms of liver disease are jaundice (yellowing of the skin), enlarged liver, ascites (pooling of fluid in the abdominal cavity), and encephalopathy (breakdown of brain tissue leading to impaired consciousness). Liver disease is characterized by a buildup of liver enzymes in the blood. These enzymes include aspartate aminotransferase (AST, also known as glutamic oxalacetic transaminase or GOT), alanine aminotransferase (ALT, also know as glutamic pyruvate transaminase or GPT), gamma-glutamyl transferase (GGT), and alkaline phosphatase. Three laboratory parameters are used routinely to assess liver function: serum bilirubin, serum albumin, and plasma prothrombin time. The yellow coloring characteristic of jaundice is caused by a buildup of bilirubin in the blood. Bilirubin is a yellow pigment formed by the breakdown of red blood cells that is normally secreted by the liver in bile. Plasma prothrombin time (international normalized ratio [INR], a blood clotting index) is a useful indicator of liver function, since it is dependent upon blood clot-

ting factor VII, which is produced by the liver (Habib, Bond, and Heuman, 2001).

The presence and severity of cirrhosis has been graded using an index called the Child-Turcotte-Pugh (CTP) score. The CTP score is the sum of five parameter scores (prothrombin time, bilirubin, albumin, ascites, and encephalopathy). Lower CTP scores of relatively healthy subjects are classified as Child's Class A, moderate scores are classified as Child's Class B, and the high scores of subjects requiring liver transplants are classified as Child's Class C (Habib, Bond, and Heuman, 2001). Milk thistle has generally been used to treat those with cirrhosis categorized as Child's Class A.

Legalon

Twelve trials are reviewed that evaluate the potential benefit of Legalon on liver disease due to alcohol or other toxins. The usual dose was 420 mg silymarin, equivalent to 600 mg extract.

Alcoholic Liver Disease

The first trial included 36 adults with chronic alcoholic liver disease who were treated with 140 mg silymarin three times daily (420 mg per day) or placebo for six months. Significant improvement was reported for the silymarin group compared to baseline and to placebo. Serum bilirubin and liver enzymes AST and ALT were normalized, whereas GGT activity decreased (Feher et al., 1989).

In the second trial, 59 subjects with a history of alcoholism were treated with a lower dose of silymarin (140 mg twice daily, 280 mg per day) or placebo for 15 months. Those who ceased drinking had a significant fall in GGT, but more than half the subjects in both groups continued to drink. Overall there was no difference from placebo in mortality or laboratory tests (Bunout et al., 1992). Our reviewers, Drs. Karriem Ali and Richard Aranda, commented that there were some important differences existed in the two groups at the start of the study. GGT levels were different, indicating the silymarin group may have been heavier alcohol users. Differences in prothrombin time and total Child index indicated that the placebo group might have had more severe illness. They also commented that physicians conducting trials on alcoholic liver disease have a tendency to include the promotion of alcohol abstention in their protocol design. How-

ever, the deliberate alteration of alcohol consumption introduces a confounding variable that has the potential to affect agent pharmacokinetics, laboratory values, side effects, etc.

In a much shorter trial, 66 subjects with toxic liver damage, most often due to alcohol, were treated with 140 mg silymarin three times daily or placebo for one month. Elevated plasma transaminase levels (AST, ALT, and GGT) were significantly reduced in the silymarin group compared to the placebo group, and, in some cases, returning to normal values much sooner than in the placebo group (Fintelmann and Albert, 1980).

Another one-month study included 97 subjects with alcohol-induced slight acute and subacute liver disease with elevated serum transaminase levels (AST and ALT), despite the order to abstain from drinking alcohol. They were treated with 140 mg silymarin three times daily or placebo. As a result, a statistically significant reduction in ALT and AST levels was observed in the silymarin group in comparison to the placebo group. There was also a trend toward a reduction in bilirubin levels in the treatment group, although this change was not statistically significant (Salmi and Sarna, 1982).

A well-conducted trial with 81 subjects with alcoholic hepatitis, with or without cirrhosis, reported significant improvement after three months compared to baseline in liver biopsy histology scores and laboratory parameters in both the silymarin group (420 mg per day) and the placebo group. No significant difference was found between treatment groups. However, there were large statistical differences in both biopsy histology scores and serum transaminase levels between those who stopped drinking and those who continued to drink (Trinchet et al., 1989). Our reviewers commented that this finding illustrates the complication of promoting alcohol abstention as part of the study design.

A poor-quality trial, including 60 subjects with alcoholic cirrhosis, compared silymarin to a Hungarian hepatoprotective agent, Aica-P (4-amino-5-imidazol-carboxamid-phosphate) and placebo in a three-arm study lasting one month. Significant improvements were observed in both treatment groups (420 mg silymarin or 600 mg Aica-P per day) compared to placebo. Significant reductions in plasma transaminase levels (AST, ALT, and GGT) and bilirubin levels were observed in the silymarin group. Only AST and GGT were significantly reduced in the Aica-P group (Lang et al., 1990).

A well-conducted study included 125 alcoholics with cirrhosis of the liver who were asked to abstain from drinking alcohol. The subjects were given either 450 mg silymarin or placebo daily for two years. The study reported no difference in survival rate or disease state in alcoholics with cirrhosis given either treatment (Pares et al., 1998). Our reviewers pointed out that the majority of these patients were rated as having a disease severity of Child's Class B, but those rated as Child's Class A and C were also included. Disease severity may be an important variable to take into consideration in the efficacy of milk thistle.

The importance of disease severity was indicated in another good-quality trial that analyzed subgroups according to Child's Class. This study included 105 patients diagnosed as having alcoholic or non-alcoholic cirrhosis who were given either 420 mg silymarin per day or placebo and followed for two to six years (mean: 41 months). The four-year survival rate was significantly greater for the silymarin group compared to placebo, whereas the two-year survival rate showed only a trend toward benefit. When subgroups were analyzed, survival was significantly increased for those with alcoholic cirrhosis and those rated as Child's Class A. However, no statistical benefit was observed for those rated with more severe illness, Child's Classes B and C, or for those with nonalcoholic cirrhosis (Ferenci et al., 1989).

In another study, 138 patients with alcoholic or non-alcoholic cirrhosis were given either 420 silymarin mg per day or placebo for four years. The proportion of survivors was greater in the silymarin group compared to placebo, but not significantly. When patients were subdivided into cases of alcoholic and nonalcoholic cirrhosis, it was found that the survival rate was significantly improved for those with alcoholic cirrhosis. However, no significant increase in survival was seen for those with nonalcoholic cirrhosis taking silymarin (Benda et al., 1980).

Sixty non-insulin-dependent diabetics with alcoholic cirrhosis were given either silymarin (200 mg three times daily) or placebo for one year in addition to standard diabetic therapy. All subjects had given up alcohol for at least two years prior to the study. As a result of treatment with silymarin, there was a significant decrease in fasting blood glucose levels, mean daily blood glucose levels, glucosuria (glucose in urine), and glycosylated hemoglobin levels. In addition,

levels of malondialdehyde were reduced, indicating improvement in liver function (Velussi et al., 1997). A fault of this trial was that the control group did not receive a placebo, and as a result the trial was not blinded.

Liver Disease Caused by Hepatoxins Other Than Alcohol

Two studies examined the effect of silymarin (Legalon) on liver damage induced by toxins other than alcohol. In the first study, 49 workers with liver disease attributable to toluene and/or xylene exposure were treated with 420 mg silymarin or placebo for one month. At the end of that time, signs of clinical improvement as well as significant decreases in serum AST and ALT and an increase in platelet counts in the silymarin group were observed. These parameters remained unchanged or worsened in the control group (Szilard, Szentgyorgyi, and Demeter, 1988).

In another study, 14 subjects exposed to an organophosphate pesticide (malathion) were matched with ten volunteers not exposed to the pesticide. Both groups were given 420 mg silymarin per day for one month. In the group exposed to pesticides, levels of GGT, cholinesterase, and leucine aminopeptidase increased significantly with silymarin treatment, whereas plasma levels of lipids and trigylcerides decreased significantly compared to baseline. Similar changes, also statistically significant, but to a lesser extent, were observed in the control group, with the exception that no change was seen in cholinesterase levels. Since the pesticide is known to have anticholinesterase activity, the authors speculated that silymarin may be reversing or blocking that action. By inhibiting the anticholinesterase activity, silymarin may reduce the toxic effect of organophosphates (Boari et al., 1981). However, the conclusion was weakened by the poor quality of the trial, which lacked a placebo group.

Silipide

Two double-blind, placebo-controlled studies were conducted with Silipide, a milk thistle extract (silybin) combined with phosphatidylcholine.

Chronic Hepatitis

A well-conducted study with 65 subjects with chronic persistent hepatitis proven with a biopsy were treated for three months with placebo or 240 mg silybin per day. As a result, a statistically significant reduction in serum aminotransferases (AST and ALT) was observed in the treatment group compared to placebo (Marcelli et al., 1992).

Viral Hepatitis

In a short pilot study, 20 patients with active viral hepatitis due to hepatitis B and/or C were treated with either 480 mg silybin or placebo for one week. A significant decrease in serum aminotransferases (AST, ALT, and GGT) and bilirubin levels was observed in the treated group compared to the placebo group (Buzzelli et al., 1993).

Silimarina

Hepatitis or Cirrhosis

A study with 177 subjects included those with chronic persistent hepatitis, chronic active hepatitis, or cirrhosis. Subjects with the three disease types were randomized to receive either placebo or Silimarina (210 mg silybin) daily for 40 days. Clinical improvement was reported for all groups in comparison to placebo. However, laboratory tests as a whole failed to show any improvement (Tanasescu et al., 1988). The published report of this study did not include any details of the 25 symptoms that were said to be included in the clinical assessment. Therefore, no details of the potential clinical benefit were available. The dose was also about half that used in most other studies.

Generic

Drug-Induced Liver Damage

The ability of silymarin to prevent liver damage due to psychotropic drugs was examined in a trial with 60 subjects who had been treated with phenothiazines and/or butyrophenones for at least

five years. These subjects had AST and ALT activity more than twice the normal value. Half the participants suspended their intake of psychotropic drugs, and both groups were further divided into those who received silymarin, 800 mg per day, and those who received placebo. Serum levels of malondialdehyde (MDA) were used as indicators of oxidative liver damage, because MDA is an end product of the oxidation of polyunsaturated fatty acids. After three months, serum levels of MDA decreased significantly in subjects who suspended use of the psychotropic drugs. Little difference was observed between those subjects receiving silymarin and those receiving placebo. For those who continued to take the psychotropic drugs, a significant difference in MDA values was observed between those who also received silymarin and those who received placebo. The decrease in AST and ALT values was greatest for those who discontinued the use of psychotropic drugs, and there was little difference as to whether they received silymarin (Palasciano et al., 1994).

META-ANALYSES AND SYSTEMATIC REVIEWS

The Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services, sponsored a systematic review of milk thistle through one of its evidence-based practice centers (EPC) (Lawrence et al., 2000). A synopsis of this report was published in the American Journal of Medicine (Jacobs, et al., 2002). The evidence report summarized the effects of milk thistle on liver disease and cirrhosis, as well as clinical adverse effects. Sixteen prospective trials were included—14 were randomized, blinded, and placebo-controlled. Four trials reported outcomes for mortality among 433 participants with an overall odds ratio for mortality of 0.8, showing a slight benefit for those taking milk thistle. Three trials involving 237 participants assessed the physical appearance of the liver using biopsy specimens. Variable results were reported, with the highest quality trial reporting no effect, and two others reporting positive benefits. The majority of trials reported a greater reduction in ALT and AST levels with milk thistle compared to placebo (11 trials with 840 participants and 12 trials with 838 participants, respectively). Five studies assessed serum albumin levels (476 participants) reporting a greater reduction with milk thistle compared to placebo (0.06

g/dl). Six trials involving 496 participants reported changes in prothrombin times, with a two-second greater reduction with milk thistle compared with placebo. In general, meta-analysis showed positive, but small and insignificant effect sizes. The AHRQ study concluded that the clinical efficacy of milk thistle is not clearly established. Interpretation of the evidence was hampered by poor study methods and/or poor quality of the published reports. Available evidence was not sufficient to suggest whether milk thistle may be more effective for some liver diseases than others, or if effectiveness might be related to duration of treatment or the length or severity of the liver disease (Lawrence et al., 2000). Jacobs and co-workers (2002) were more blunt in their analysis. They concluded that milk thistle has no effect on mortality or improvements in liver histology or biochemical markers of liver function among patients with chronic liver disease. They found insufficient evidence to recommend milk thistle to patients for the treatment of liver disease (Jacobs, et al., 2002).

ADVERSE REACTIONS OR SIDE EFFECTS

No significant side effects were reported in the trials conducted with Legalon that we reviewed. Eight trials reported no side effects or adverse reactions, and four trials reported minor complaints that were not different from that of the placebo group. These included arthralgias, pruritis, headache, urticaria, constipation, dryness of the mouth, nausea, abdominal discomfort, and a mild laxative effect (Bunout et al, 1992; Pares, et al., 1998; Ferenci et al, 1989; Boari et al, 1981). One of the trials on silipide did not report any side effects, and the other reported side effects similar to those reported previously and no different from placebo (Marcelli et al., 1992).

The AHRQ review found that milk thistle was associated with few, generally minor adverse effects, although little evidence was present to demonstrate that these effects were indeed caused by milk thistle. For randomized trials reporting adverse effects, the incidence of adverse effects was similar to that of placebo groups. The most common side effects were gastrointestinal problems, skin reactions, and headache. An extended review of the literature found three case reports of anaphylaxis, but in only one case was this reaction possibly attributed to milk thistle (Lawrence et al., 2000).

A drug monitoring study observed 2,637 patients treated for eight weeks with Legalon. The majority of patients took one tablet three times daily and almost a third of the subjects took two tablets three times daily (each tablet containing 70 mg silymarin each). Twenty-one patients (0.8 percent) reported adverse reactions that included mild diarrhea, nausea, gastric intolerance, pruritis, rash, and headache (Albrecht et al., 1992).

The possible interaction between milk thistle and indinavir was evaluated in an open study with ten healthy volunteers. Indinavir is a common therapy for patients with human immunodeficiency virus (HIV). This study was conducted because milk thistle is commonly taken by patients with HIV for the treatment or prevention of liver disease caused by hepatitis or hepatotoxic drugs. Blood levels of indinavir were established following four doses of indinavir (800 mg every eight hours). Subjects then took 175 mg milk thistle extract (Thisilyn) (containing 153 mg silymarin) three times a day for three weeks. Then administration of indinavir was added to the milk thistle treatment, and the blood sampling was repeated in the same pattern as before. Measurements of indinavir blood levels were again repeated after an 11-day washout period. As a result, milk thistle did not significantly alter the indinavir blood levels. The authors concluded that milk thistle, in commonly administered dosages, should not interfere with indinavir therapy (Piscitelli et al., 2002).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

German Commission E

Indications

The German Commission E approves of preparations of the ripe seed of milk thistle for dyspeptic complaints. An extract of the seed, standardized to at least 70 percent silymarin (a composite of silibinin, silydianin, and silychristin), is approved for treatment of toxic liver

damage and for supportive treatment in chronic inflammatory liver disease and hepatic cirrhosis (Blumenthal et al., 1998).

Doses

Seed: 12 to 15 g daily (Blumenthal et al., 1998)
Extract: equivalent to 200 to 400 mg of silymarin, calculated as silibinin, daily (Blumenthal et al., 1998)

Contraindications

The Commission E lists no known contraindications (Blumenthal et al., 1998).

Adverse Reactions

The Commission E mentions that with the extract, a mild laxative effect has been observed in occasional instances (Blumenthal et al., 1998).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998).

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DETAILS ON MILK THISTLE PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Milk Thistle Products

Product Profile: Legalon®

Manufacturer	**Madaus AG, Germany**
U.S. distributor	None
Botanical ingredient	**Milk thistle seed extract**
Extract name	None given
Quantity	173-186.7 mg dry extract, equivalent to 140 mg silymarin
Processing	Plant to extract ratio 36-44:1, extracted with ethylacetate
Standardization	140 mg silymarin calculated as silibinin
Formulation	Capsule

Recommended dose: Take one capsule three times daily when starting treatment and also in serious cases. A maintenance dose of one

capsule three times daily is recommended. The capsules should be swallowed whole with a small amount of liquid.

DSHEA structure/function: German drug indications include toxic liver damage and supportive treatment in cases of chronic inflammatory liver diseases and hepatic cirrhosis.

Cautions: Should jaundice become apparent (pale to dark yellow coloration of the skin, yellow coloration of the whites of the eyes) a doctor should be consulted. There have been no adequate investigations of the use of this medicine in children. It should therefore not be used in children under 12 years of age. No results are available regarding the use of Legalon 140 during pregnancy or lactation. It should therefore be used only after consultation with your doctor. If symptoms persist for any length of time you should consult your doctor.

Other ingredients: Mannitol, sodium carboxymethyl starch, polysorbate 80, polyvidone, magnesium stearate, gelatin, titanium dioxide E171, ferric oxide E172, dodecyl sodium sulphate.

Source(s) of information: Product information page (www.madaus.de); information provided by Nature's Way Products, Inc.

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Alcoholic liver disease**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Feher J, Deak G, Muzes G, Lang I, Niederland V, Nekam K, Karteszl M (1989). The hepatoprotective effect of treatment with silymarin in patients with chronic alcoholic liver disease. *Orvosi Hetilap* 130 (51): 2723-2727.

Trial design
Parallel. Patients were encouraged to refrain from drinking alcohol.

Study duration	6 months
Dose	140 mg silymarin capsule 3 times daily
Route of administration	Oral
Randomized	Yes

Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	36
No. of subjects completed	36
Sex	Male and female
Age	Mean: 46 ± 7 years

Inclusion criteria
Patients with chronic alcoholic liver disease in whom daily average alcohol consumption exceeded 60 g (men) and 30 g (women). The duration of the chronic alcohol consumption was 8 ± 4 years.

Exclusion criteria
Symptoms or signs of encephalopathy, malnutrition, or other alcohol-associated disease, positive tests for viral and immunological markers, or previous corticosteroid or other immunosuppressive treatment.

End points
Patients were assessed at entry into the trial and after three and six months of treatment. Laboratory parameters included: serum aspartate aminotransferase (AST); alanine aminotransferase (ALT); gamma-glutamyl transferase (GGT); alkaline phosphatase and bilirubin; as well as procollagen III peptide levels. Liver biopsies were also obtained.

Results
During silymarin treatment, serum bilirubin, AST, and ALT values were normalized, and GGT activity and procollagen III peptide level decreased. The changes from baseline levels, as well as the difference between posttreatment values of the two groups were significant. In the placebo group only GGT values decreased significantly but to a lesser extent than that in the silymarin group. The histological alterations showed an improvement in the silymarin group and were unchanged in the placebo group.

Side effects
None noted.

Authors' comments
These results indicate that silymarin exerts hepatoprotective activity and is able to improve liver function.

Reviewers' comments
Alcohol consumption was not measured quantitatively, and this may confound the results. The deliberate alteration of alcohol consumption introduces a confounding covariable that has the potential to affect agent pharmacokinetics, laboratory values, experienced side effects, etc. Biopsies were performed only on select patients in each group, creating a potential selection bias. The treatment length was adequate for a study of histology and serum biochemistry changes. (Translation reviewed) (2, 4)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Alcoholic liver disease**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Bunout D, Hirsch S, Petermann M, Pia de la Maza M, Silva G, Kelly M, Ugarte G, Iturriaga H (1992). Effects of silymarin on alcoholic liver disease (a controlled trial). *Revista Médica de Chile* 120 (12): 1370-1375.

Trial design
Parallel.

Study duration	15 months
Dose	2 (140 mg silymarin) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	72
No. of subjects completed	59
Sex	Male and female
Age	Mean: 49.8 ± 2.4 years

Inclusion criteria
Patients having history of alcoholism (ingestion of at least 150 g/day alcohol or drinking attacks of more than three days at least once a month) and the presence of clinical signs (jaundice, ascites, edema, or encephalopathy) or lab values (total bilirubin more than 2 mg/dl, prothorombin time below 75 percent of control, or albumin below 3 mg/dl) indicating liver insufficiency.

Exclusion criteria
Patients with positive hepatitis B surface antigen, with renal or cardiac insufficiency, terminal liver damage.

End points
Patients were examined at least once a month for 15 months. Patients were asked about alcohol ingestion and possible adverse effects, and urine specimens were obtained. Hematocrit, albumin, creatinine, urea nitrogen, total bilirubin, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase (GGT), prothrombin time (PT percent), and glycemia were measured every three months. Composite Clinical and Laboratory Index (CCLI) scoring was calculated from clinical and laboratory data as an indication of disease severity and prognosis.

Results
Ten patients died during the study, five taking placebo and five taking silymarin. Those patients who died had higher clinical CCLI and total baseline CCLI than those who survived. Final laboratory values and their changes revealed no difference between the placebo and silymarin groups. Twenty-two patients on placebo (65 percent) and 14 on silymarin (58 percent) continued to drink. Those who abstained had a significant fall in GGT during follow-up. No other significant differences were observed between these two groups.

Side effects
Adverse events included pruritus, cephalea, constipation, dryness of the mouth, and abdominal pain with no difference between the placebo and silymarin groups.

Authors' comments
This study did not show a beneficial effect of the treatment with silymarin on the evolution and mortality of patients affected by alcohol-induced liver damage.

Reviewers' comments
In contrast to what is stated in the paper, significant differences were observed in the baseline GGT and PT percent values between the placebo group and silymarin group. The GGT difference shows that silymarin group subjects may have been heavier alcohol users. The differences in PT per-

cent and CCLI show that placebo group subjects may have had more severe illness. Altogether, this implies that randomization did not yield well-matched groups. Deliberate reduction in alcohol consumption introduces a confounding covariable that has the potential to affect agent pharmacokinetics, laboratory values, experienced side effects, etc. Abstention from alcohol was not consistent for all subjects. The exclusion criteria should have also included other causes of cirrhosis by serology, etc., as well as drug exclusions (e.g., D-penicillamine, colchicine). The sample size may have been appropriate. However, no power calculation was presented. The dose of 280 mg is one-third smaller than most other studies. The adverse incidence of pruritis could have been related to alcohol abstention. The trial length is adequate. (Translation reviewed) (3, 4)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Alcoholic or nonalcoholic liver disease**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Fintelmann V, Albert A (1980). The therapeutic activity of Legalon in toxic hepatic disorders demonstrated in a double blind trial. *Therapiewoche* 30 (35): 5589-5594.

Trial design
Parallel. Patients received a "uniform reducing diet" high in protein and low in carbohydrates and fat (1,000 calories/day).

Study duration	1 month
Dose	1 (140 mg silymarin) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Hospital

No. of subjects enrolled	70
No. of subjects completed	66
Sex	Male and female
Age	Not given

Inclusion criteria
Patients with clinical and serological diagnosis of toxic liver damage. The cause of toxic damage was not taken in account, but in most cases it was alcohol.

Exclusion criteria
None mentioned.

End points
Diagnosis of toxic liver damage was confirmed by liver biopsy. Laboratory parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma glutamyl transferase [GGT]) were determined on days 1, 3, 7, 10, 14, 21, and 28. At the start of the trial, and on days 14 and 28, additional parameters were determined: glutamate dehydrogenase, alkaline phosphatase, leucine aminopeptidase (LAP), cholinesterase, bilirubin, total proteins, electrophoresis, as well as sonographic assessment of the liver size and internal structure.

Results
The parameters AST ($p < 0.1$), ALT ($p < 0.05$) and GGT ($p < 0.05$) were reduced significantly in the silymarin group compared to the placebo group, sometimes returning to normal in a much shorter time than in the placebo group. The differences for glutamate dehydrogenase, LAP, and alkaline phosphatase were not statistically significant. The sonographic findings were not exact enough to be relevant to the outcome of the trial.

Side effects
None attributed to Legalon.

Authors' comments
Previously reported investigations and the outcome of the present trial justify the conclusion that the therapeutic activity of Legalon in toxic disorders of the liver has definitively been established.

Reviewers' comments
No baseline data was presented, the diagnostic criteria was not thoroughly discussed, and the "uniform reducing diet" is a confounding covariable. The grouping of all toxic liver disorders together may have obscured the potential to demonstrate the efficacy of Legalon in the treatment of any particular liver disorder. The sample size may have been appropriate. However, no power calculation was presented. (Translation reviewed) (3, 3)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Alcoholic liver disease**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Salmi HA, Sarna S (1982). Effect of silymarin on chemical, functional, and morphological alterations of the liver. *Scandinavian Journal of Gastroenterology* 17 (4): 517-521.

Trial design
Parallel. Patients were treated for the first week in the hospital and thereafter as outpatients.

Study duration	1 month
Dose	420 mg daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Military hospital
No. of subjects enrolled	106
No. of subjects completed	97
Sex	Male and female
Age	Mean: 37 ± 15.7 years

Inclusion criteria
Patients admitted to the hospital with an increase in the transaminase (serum aspartate aminotransferase [AST]; and serum alanine amino transferase [ALT]) levels of at least one month's duration, despite the order to abstain completely from alcohol. Patients had slight acute and subacute liver disease, mostly induced by alcohol abuse.

Exclusion criteria
None mentioned.

End points
Patients were examined before the trial, as well as after one, two, and three weeks. Laboratory tests included serum bilirubin, alkaline phosphatase, bromosulphalein (BSP), serum immunoglobulins, and blind liver biopsy.

Results
There was statistically a significantly greater decrease of ALT and AST in the treated group than in controls. Serum total and conjugated bilirubin decreased more in the treated group than in controls, but the differences were not statistically significant. BSP retention returned to normal significantly more often in the treated group. The mean percentage of decrease of BSP was also markedly higher in the treated group. Normalization of histological changes occurred significantly more often in the treated group than in controls.

Side effects
None reported.

Authors' comments
Silymarin appears to have a favorable effect on acute and subacute alcohol-induced liver disease of relatively slight degree. The results cannot be extrapolated to liver disease in general.

Reviewers' comments
The biopsy rate for the two groups was similar, but the reason for the low rate overall was not explained. The histological findings therefore may involve inadvertent selection bias. The trial may have been too short to allow resolution of a trend away from baseline. Transaminase levels remained very close, although the mean percentage decrease was reported to be significant. The deliberate promotion of abstention from alcohol consumption introduces a confounding covariable that has the potential to affect agent pharmacokinteics, laboratory values, experienced side effects, etc. At a minimum, a reevaluation should be conducted after a period of verifiable abstention to check baseline lab values. The sample size may have been adequate. However, no power calculation was presented. (1, 5)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Alcoholic hepatitis**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Trinchet JC, Coste T, Levy VG, Vivet F, Duchatelle V, Legendre C, Gotheil C, Beaugrand M (1989). Treatment of alcoholic hepatitis with silymarin: Comparative double-blind trial in 116 patients. *Gastroenterologie Clinique et Biologique* 13 (2): 120-124.

Trial design
Parallel.

Study duration	3 months
Dose	140 mg silymarin capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	116
No. of subjects completed	81
Sex	Male and female
Age	Mean 50.5 ± 10.5 years

Inclusion criteria
Patients with histologically proven alcoholic hepatitis confirmed by percutaneous liver biopsy, with or without cirrhosis.

Exclusion criteria
Patients with hepatic encephalopathy, diuretic-resistant ascites, or disorders of hemostasis contraindicating percutaneous liver biopsy, or hepatocellular carcinoma. The use of any other antihepatotoxic treatment or corticosteroid therapy was prohibited during the study.

End points
At the beginning and end of trial, the following lab parameters were measured: serum bilirubin, serum aspartateaminotransferase (AST) and gamma-glutamyl transpeptidase (GGT), PT, mean corpuscular volume (MCV) and serum albumin. A percutaneous liver biopsy was performed in all cases to determine the histological score at both times.

Results
Significant improvement in the score of alcoholic hepatitis and serum amino

transferase activity was noted in both groups during the trial, irrespective of treatment. At the end of the trial, 46 percent of patients had completely stopped drinking alcohol; these patients were equally distributed between the two groups. There were significant improvements in hepatitis scores, as well as in levels of serum AST ($p < 0.01$), GGT ($p < 0.0001$), and MCV ($p < 0.001$) in subjects who abstained compared to those who continued drinking.

Side effects
No side effects were noted.

Authors' comments
Silymarin treatment in patients with moderate alcoholic hepatitis, with or without cirrhosis, does not alter the biochemical or histological course of the disease.

Reviewers' comments
This is a well-conducted study. It illustrates the effect of promoting alcohol abstention as a confounding variable in protocol design. (Translation reviewed) (5, 6)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Alcoholic cirrhosis**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Lang I, Nekam K, Deak G, Muzes G, Gonzales-Cabello R, Gergely P, Csomos G, Feher J (1990). Immunomodulatory and hepatoprotective effects of in vivo treatment with free radical scavengers. *Italian Journal of Gastroenterology* 22 (5): 283-287.

Trial design
Parallel. Three treatment groups: Legalon; Aica-P (amino-imidazol-carboxamid-phosphate) 200 mg three times daily; and placebo three times daily. All groups were discouraged from consuming alcohol.

Study duration	1 month
Dose	1 (140 mg silymarin) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Aica-P
Site description	Not described
No. of subjects enrolled	60
No. of subjects completed	Not given
Sex	Male and female
Age	Mean: 44.7 years

Inclusion criteria
Patients with alcoholic cirrhosis. The mean daily alcohol consumption exceeded 60 g in men and 30 g in women. The duration of alcohol consumption was between 6 and 11 years. Histological diagnosis was micronodular.

Exclusion criteria
Patients with symptoms of vascular and/or perenchymal decompensation and those positive to hepatitis B surface antigen (HbsAg).

End points
Patients were seen once a week, and alcohol consumption was recorded. Routine laboratory parameters, including aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, and bilirubin, as well as cellular immunoreactivity, were determined before and after the treatment period. To evaluate cellular immunoreactivity, lectin-induced lymphoblast transformation, and antibody-dependent cell-mediated cytotoxicity (ADCC) and spontaneous natural killer (NK) lymphocytotoxicity tests were performed, and the percentages of peripheral T-, B-, CD4+, and CD8+ cells were determined.

Results
In the silymarin and Aica-P groups, hepatic functions showed marked improvement following one month of treatment compared to the placebo group. In the silymarin group, there were significant reductions in bilirubin ($p < 0.05$), AST ($p < 0.01$), ALT ($p < 0.02$), and GGT ($p < 0.05$). Only AST ($p < 0.01$) and GGT ($p < 0.0$) were reduced in the Aica-P group. The lectin-

induced lymphoblast transformation was increased in both groups ($p < 0.01$), and a decrease was observed in the percentage of suppressor cells (silymarin: $p < 0.05$; Aica-P: $p < 0.01$). Antibody-dependent cell mediated cytotoxicity was significantly decreased by silymarin, and both treatment groups had significantly reduced NK cell activity. None of these changes occurred in the placebo group.

Side effects
No side effects were seen.

Authors' comments
The hepatoprotective effects of silymarin and Aica-P are accompanied by changes in parameters of cellular immunoreactivity of treated patients.

Reviewers' comments
Only the AST and GGT differed significantly from placebo in the two treatment groups. The sample size may have been appropriate, but no power calculation was presented. The deliberate alteration of alcohol consumption introduces a confounding covariable that has the potential to affect agent pharmacokinetics, laboratory values, experienced side effects, etc. The trial length was adequate. The dose choice was standard in comparison to other trials. (0, 5)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus Cerafarm, Spain (Madaus AG, Germany)
Indication	**Alcoholic cirrhosis**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Pares A, Planas R, Torres M, Caballeria J, Viver JM, Acero D, Panes J, Rigau J, Santos J, Rodes J (1998). Effects of silymarin in alcoholic patients with cirrhosis of the liver: Results of a controlled, double-blind, randomized and multicenter trial. *Journal of Hepatology* 28 (4): 615-621.

Trial design
Parallel. Patients were asked to abstain from alcohol.

Study duration	2 years
Dose	150 mg silymarin 3 times daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	6 hospitals
No. of subjects enrolled	200
No. of subjects completed	125
Sex	Male and female
Age	Mean: 50.5 ± 10.8 years

Inclusion criteria
Alcoholics with cirrhosis of the lever. Chronic alcoholism defined as a daily ethanol intake greater than 80 g in men and 60 g in women for a period longer than five years. Criteria for liver cirrhosis supported by histology after percutaneous liver biopsy, performed within the three months before inclusion in the trial, or by laparoscopic examination in those patients with very low prothrombin index or platelet count in whom percutaneous liver biopsy could not be performed.

Exclusion criteria
Patients with other known etiologies for liver cirrhosis, such as hepatitis B virus, primary biliary cirrhosis, autoimmunity or crytogenic cirrhosis; those treated with colchicine, malotilate, penicillamine, or corticosteroids; with a life expectancy of less than six months; drug addicted; or pregnant.

End points
The primary outcome was time to death, and the secondary outcome was progression of liver failure. At entry and every three months, a complete history, including alcohol consumption, was recorded. Serum levels of bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phophatase, albumin, gamma globulins, and the prothrombin index were measured.

Results
Twenty-nine patients (15 receiving silymarin and 14 receiving placebo) died during the trial. Survival was similar in patients receiving silymarin or placebo. The effect of silymarin on survival was not influenced by sex, the persistence of alcohol intake, the severity of liver dysfunction, the baseline Child's classification, or by the presence of alcoholic hepatitis. Silymarin did not have any significant effect on the course of the disease.

Side effects
Seven patients in the silymarin group and four in the placebo group reported side effects, but none were serious. These included: arthralgias, pruritis, headache, and urticaria.

Authors' comments
The results of this study indicate that silymarin has no effect on survival and the clinical course in alcoholics with liver cirrhosis.

Reviewers' comments
The majority of patients had a disease severity of Child's Class B. The effect of silymarin may vary distinctly between Classes A, B, and C. Including patients from all three classes may confound the data profile. The sample size may have been appropriate, however, no power calculation was presented. The deliberate alteration of alcohol consumption introduces a confounding covariable that has the potential to affect agent pharmacokinetics, laboratory values, experienced side effects, etc. The listed side effects could be caused, at least in part, by abstention from alcohol. The trial length was adequate. (5, 6)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Alcoholic or nonalcoholic cirrhosis**
Level of evidence	**I**
Therapeutic benefit	**Trend**

Bibliographic reference
Ferenci P, Dragosics B, Dittrich H, Frank H, Benda L, Lochs H, Mervn S, Base W, Schneider B (1989). Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *Journal of Hepatology* 9 (1): 105-113.

Trial design
Parallel. All patients were advised to abstain from alcohol.

Study duration	2-6 years (mean: 41 months)
Dose	140 mg silymarin 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	4 centers
No. of subjects enrolled	170
No. of subjects completed	105
Sex	Male and female
Age	Mean: 57.5 ± 12 years

Inclusion criteria

Patients with diagnosis of cirrhosis (alcoholic or nonalcoholic) made within two years of the study. All potential candidates were followed for three months before entry into study.

Exclusion criteria

Patients with end-stage liver failure, known malignancies, on immunosuppressive treatment, and primary biliary cirrhosis. The use of D-penicillamine and steroids were not allowed.

End points

At subjects' entry into the study, the severity of the underlying liver disease was classified using the Child-Turcotte criteria, and the etiology was determined using clinical, biochemical, immunological, and histological criteria. At every three months each patient's bilirubin, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), prothrombin time, albumin, pseudocholinesterase, and serum electrophoresis were determined.

Results

The four-year survival rate was 58 ± 9 percent in silymarin-treated patients and 39 ± 9 percent in the placebo group ($p = 0.036$). The two-year survival rate was 82 ± 4 percent for the treatment group and 68 ± 5 percent for the placebo group, an insignificant difference. For those with alcoholic cirrhosis, the number of deaths in the control group was twice that of the treatment group. In addition, treatment was associated with a better outcome ($p = 0.01$). Conversely, in nonalcoholic cirrhotics, the survival rates were not significantly influenced by treatment. In patients originally rated Child's Class A, survival was improved significantly by treatment with silymarin ($p = 0.03$). In those originally rated Classes B or C, survival rates did not differ in comparison to controls. Liver-function lab tests did not reveal a difference in the treatment and control groups.

Side effects
Four patients (two in each group) had side effects of epigastric discomfort and nausea.

Authors' comments
The results of this study suggest that mortality of patients with cirrhosis was reduced by treatment with silymarin. The effect was more pronounced in those with alcoholic cirrhosis.

Reviewers' comments
This is a good-quality study indicating the effectiveness of silymarin in reducing deaths for those with alcoholic cirrhosis and those initially diagnosed as Child's Class A. (5, 6)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Alcoholic or nonalcoholic cirrhosis**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Benda L, Dittrich H, Ferenzi P, Frank H, Wewalka F (1980). The efficacy of silymarin and the survival of patients with hepatic cirrhosis. *Wiener Klinische Wochenschrift* 92 (19): 678-983.

Trial design
Parallel. Patients received either silymarin plus a multivitamin mixture, or a multivitamin mixture alone (two capsules three times daily, as placebo).

Study duration	4 years
Dose	2 (70 mg silymarin + multivitamins) capsules 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No

Site description	Not described
No. of subjects enrolled	172
No. of subjects completed	138
Sex	Not given
Age	Not given

Inclusion criteria
Patients with hepatic cirrhosis verified by biopsy, regardless of etiology.

Exclusion criteria
Patients who are moribund, on immunosuppressive therapy during the past year, prednisolone therapy during the past six months, D-penicillamine therapy during the past three months, or with primary biliary cirrhosis or Wilson's disease.

End points
Patients were followed-up every three months, observing the clinical course of cirrhosis and the value of various laboratory findings pertinent to chronic liver disease. The primary end point was survival rate.

Results
The mortality curve showed that the proportion of survivors in the treated group was consistently above the placebo group. Patients were subdivided into cases of alcoholic and nonalcoholic cirrhosis. The survival curves for silymarin and control groups are similar for patients with nonalcoholic forms of cirrhosis. For patients with alcoholic cirrhosis, the survival curve for the silymarin group is clearly above that of the control group ($p = 0.05$). For the control group, there was no difference in the survival curve for subjects with alcoholic or nonalcoholic cirrhosis. However, for subjects taking silymarin, the survival curve for those with alcoholic cirrhosis was clearly above that for those with nonalcoholic cirrhosis ($p < 0.05$). The results of the laboratory investigation were not published here.

Side effects
None observed in treatment group.

Authors' comments
A silymarin therapy for hepatic cirrhosis showed significant prolongation of survival in patients with alcoholic cirrhosis after four years of treatment.

Reviewers' comments
The study shows a trend toward increased survival for patients with alcoholic cirrhosis. Limitations of the study include a lack of baseline status of the patients, ensuring the treatment and control groups were matched as far as severity of illness, and no measurement of compliance to treatment or absti-

nence to alcohol. The dosage of silymarin was supported by reference to biochemical studies. (4, 5)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	IBI Lorenzini, Italy (Madaus AG, Germany)
Indication	**Alcoholic cirrhosis in diabetics**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Velussi M, Cernigoi AM, De Monte A, Dapas F, Caffau C, Zilli M (1997). Long-term (12 month) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need, and malondialdehyde levels in cirrhotic diabetic patients. *Journal of Hepatology* 26 (4): 871-879.

Trial design
Parallel. Treatment group received silymarin plus standard therapy. Control group received standard therapy alone.

Study duration	1 year
Dose	200 mg silymarin 3 times daily 2 hours after meals
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Diabetes clinic
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Male and female
Age	Mean: 62.5 ± 4 years

Inclusion criteria
Ages 45 to 70 years; non-insulin-dependent diabetics with alcoholic liver cirrhosis; body mass index < 29 kg/m^2; diabetes diagnosed for a period of at

least five years and treated with insulin only; stable insulin therapy for a period of at least two years; raised endogenous insulin secretion; fasting insulin levels and basal and stimulated C-peptide levels above normal range (above 15 mU/ml for insulin, above 1 ng/ml for basal C-peptide levels, and 3 ng/ml stimulated C-peptide levels); negative for markers of hepatitis A, B, and C; not addicted to alcohol for a period of at least two years prior to the start of the study; no bleeding from variceal esophagus; liver biopsy, performed no more than four years prior to enrollment, demonstrating liver cirrhosis.

Exclusion criteria
Not mentioned.

End points
Every 30 days, fasting and mean daily blood glucose levels, glucosuria (glucose in urine), and mean daily insulin requirements were recorded. Every 60 days, glycosylated hemoglobin (HbA1c) levels were recorded. Every 90 days, fasting insulin, basal and stimulated C-peptide, malondialdehyde, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), bilirubin, triglycerides, and total and high-density-lipoprotein (HDL) cholesterol were recorded. Every 180 days, creatinine, microalbuminuria, and hemochrome were recorded.

Results
A significant decrease ($p < 0.01$) was observed in fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria, and HbA1c levels after four months of treatment in the silymarin group. In addition, a significant decrease ($p < 0.01$) was observed in fasting insulin levels and mean exogenous insulin requirements in the treated group, whereas the untreated group showed a significant increase ($p < 0.05$) in fasting insulin levels and a stabilized insulin need. These findings are consistent with the significant decrease ($p < 0.01$) in basal and glucagon-stimulated C-peptide levels in the treated group and the significant increase in both parameters in the control group. A significant decrease ($p < 0.01$) in malondialdehyde levels was observed in the treated group.

Side effects
None reported.

Authors' comments
These results show that treatment with silymarin may reduce the lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and the need for exogenous insulin administration.

Reviewers' comments
The control group did not receive a placebo, and therefore the trial was not blinded. The sample size may have been appropriate, however, no power calculation was presented. The trial length was adequate. (1, 4)

Clinical Study: Legalon®

Extract name	None given
Manufacturer	Madaus AG, Germany
Indication	**Toxin-induced liver disease**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Szilard S, Szentgyorgyi D, Demeter I (1988). Protective effect of Legalon in workers exposed to organic solvents. *Acta Medica Hungarica* 45 (2): 249-256.

Trial design
Parallel. Control group received no treatment. Both groups continued to work in conditions that exposed them to toluene and/or xylene.

Study duration	1 month
Dose	1 (140 mg silymarin) capsule 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Single center
No. of subjects enrolled	49
No. of subjects completed	49
Sex	Male
Age	30-45 years

Inclusion criteria
Workers who had symptoms of liver disease attributable to toluene and/or

xylene exposure, including hepatomegaly, increased AST and ALT (aspartate and alanine aminotransferase) levels, relative lymphocytosis, and decreased platelet counts.

Exclusion criteria
Alcoholics.

End points
Before and after the observation period, the workers were submitted to medical physicals and laboratory tests, including blood cell count, serum AST and ALT, gamma-glutamyl transferase (GGT), cholesterol, and urine urobilinogen.

Results
Workers treated with silymarin reported that appetite improved significantly, headaches were reduced, three of ten cases of moderate hepatomegaly regressed, and tympanites ceased in 13 cases. One case of hemorrhagic predisposition and two cases of gingivitis disappeared or improved by the end of treatment. Laboratory results showed a significant decrease in serum AST and ALT, and a trend toward decrease in GGT. The same parameters increased slightly in the control group. Relative lymphocytosis decreased, and platelet counts increased in the silymarin group. These parameters remained unchanged or showed slight worsening in the control group.

Side effects
None reported.

Authors' comments
Under the influence of Legalon, elevated levels of plasma enzymes associated with liver function and low platelet counts significantly improved. Leukocytosis and relative lymphocytosis showed a trend toward improvement.

Reviewers' comments
Serum levels of liver enzymes and platelet counts improved in patients exposed to toluene and/or xylene for more than five years. However, the trial had a poor experimental design—it was not blinded or randomized. The sample size may have been appropriate, however, no power calculation was presented. (1, 4)

Clinical Study: Legalon IBI

Extract name	None given
Manufacturer	Madaus AG, Germany

Indication	**Toxin-induced liver damage**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Boari C, Baldi E, Rizzoli O, Raffi GB, Caudarella R, Gennari P (1981). Silymarin in the protection against exogenous noxae. *Drugs Under Experimental and Clinical Research* 7 (2): 115-120.

Trial design
Parallel. Fourteen subjects were chronically exposed to phosphor esters and ten subjects were healthy volunteers. The study medication was given to all subjects.

Study duration	1 month
Dose	1 (140 mg silymarin) capsule 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Not described
No. of subjects enrolled	24
No. of subjects completed	24
Sex	Not given
Age	Not given

Inclusion criteria
Subjects chronically exposed to organophosphate pesticide (malathion) (14 in number) and healthy volunteers not exposed to pesticides (ten in number).

Exclusion criteria
None mentioned.

End points
Laboratory measures were tested before the study period and after 30 days. Measures included alkaline phosphatase, gamma-glutamyl transferase (GGT), leucine aminopeptidase (LAP), pseudocholinesterase, total lipemia, and triglyceridemia.

Results
In the group exposed to pesticides, silymarin treatment caused a significant increase in GGT, cholinesterase, and LAP ($p < 0.01$). No change was observed in alkaline phosphatase levels. In nonexposed subjects, there was an increase in GGT and LAP only ($p < 0.05$). Thus, the increase in cholinesterase activity was seen in the exposed group only. The response of lipidemic indices were identical in the two groups, with a marked decrease in serum levels of total lipids and triglycerides after treatment.

Side effects
Mild laxative effect reported in both study groups (by 4 out of 24 subjects).

Authors' comments
Silymarin has a therapeutic efficacy in cases of chronic exposure to phosphor esters, since a clear-cut increase in cholinesterase activity of the serum was found in the subjects studied.

Reviewers' comments
This study had a poor experimental design—it had no placebo, no blinding, and it was not randomized. It is essential to have an exposed, placebo-treated or standard-therapy group to provide a clear and unbiased comparison of treatment efficacy. (1, 3)

Product Profile: Silipide

Manufacturer	**Inverni della Beffa, Italy (Indena S.p.A., Italy)**
U.S. distributor	None
Botanical ingredient	**Milk thistle seed extract**
Extract name	**IdB 1016 (Siliphos®)**
Quantity	120 mg
Processing	Lipophilic complex of silybin combined with phosphatidylcholine from soy in a molar ratio of 1:2
Standardization	29.7-36.3% silybin
Formulation	Capsule

Other ingredients: Phosphatidylcholine from soy bean.

Source(s) of information: Buzzelli et al., 1993; information provided by Indena USA, Inc.

Product Profile: Maximum Milk Thistle™

Manufacturer	**Natural Wellness (Indena S.p.A., Italy)**
U.S. distributor	**Natural Wellness**
Botanical ingredient	**Milk thistle seed extract**
Extract name	**Siliphos®**
Quantity	240 mg
Processing	1 part silybin to 2 parts phosphatidylcholine
Standardization	29.7-36.3% silybin
Formulation	Capsule

Recommended dose: 3 capsules per day, either all at once or at separate times, with or without food (or as recommended by your health care professional).

DSHEA structure/function: Clinically shown to support and promote normal liver function.

Other ingredients: Rice powder, magnesium stearate, silicon dioxide, gelatin capsule.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Product Profile: UltraThistle™

Manufacturer	**Natural Wellness (Indena S.p.A., Italy)**
U.S. distributor	**Natural Wellness**
Botanical ingredient	**Milk thistle seed extract**
Extract name	**Siliphos®**
Quantity	360 mg
Processing	1 part silybin to 2 parts phosphatidylcholine
Standardization	29.7-36.3% silybin
Formulation	Capsule

Recommended dose: One capsule three times per day as a dietary supplement (or as recommended by your health care professional).

DSHEA structure/function: Clinically shown to support and promote normal liver function.

Other ingredients: Rice powder, magnesium stearate, silicon dioxide.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Clinical Study: Silipide

Extract name	IdB 1016
Manufacturer	Inverni della Beffa, Italy (Indena S.p.A., Italy)
Indication	**Chronic hepatits**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Marcelli R, Bizzoni P, Conte D, Lisena MO, Lampertico M, Marena C, De Marco MF, Del Ninno E (1992). Randomized controlled study of the efficacy and tolerability of a short course of IdB 1016 in the treatment of chronic persistent hepatitis. *European Bulletin of Drug Research* 1 (3): 131-135.

Trial design
Parallel.

Study duration	3 months
Dose	1 (120 mg silybin) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	2 gastroenterology units
No. of subjects enrolled	65
No. of subjects completed	65
Sex	Male and female
Age	24-66 years (mean: 47.7)

Inclusion criteria
Outpatients with biopsy-proven chronic persistent hepatitis, not previously under established treatment, with serum alanine aminotransferase and/or

serum aspartate aminotransferase values at least 1.5 times greater than the upper limit of the normal range on two occasions during the year before treatment.

Exclusion criteria
Patients with decompensated liver diseases, or under therapy with interferon, antivirals, immunosuppressants, or immunomodulators within six months before enrollment.

End points
Patients were examined before and after three months of treatment. Serum aminotransferase activity, white blood cell count, direct and total bilirubin, total protein, and albumin, as well as prothrombin activity, were determined.

Results
A statistically significant decrease of mean serum activity of both aspartate ($p < 0.05$) and alanine ($p = 0.01$) aminotransferases was observed in the treatment group compared to the placebo group. Serum bilirubin, albumin, total protein, and prothrombin time were normal at baseline in the majority of patients and did not change in any clinically relevant way.

Side effects
No serious side effects were noted. Three patients in the treated group complained of nausea, heartburn, and transient headache. Five in the control group reported nausea, heartburn, dyspepsia, and skin rash.

Authors' comments
The results of the present study show that IdB 1016, over a period of three months, can induce positive changes in serum aspartate and alanine aminotransferases in patients with chronic persistent hepatitis.

Reviewers' comments
Based on the ALT, AST, and PT percent, the study group appears to have had more severe illness than the control group. There was no intent-to-treat analysis and no measure of compliance to protocol regimen. The sample size may have been appropriate given the significant finds, however, no power calculation was presented. The treatment length was adequate. (3, 6)

Clinical Study: Silipide

Extract name	IdB 1016
Manufacturer	Inverni della Beffa, Italy (Indena S.p.A., Italy)

Indication	**Viral hepatitis (B or C)**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference

Buzzelli G, Moscarella S, Giusti A, Duchini A, Marena C, Lampertico M (1993). A pilot study on the liver protective effect of silybinphosphatidylcholine complex (IdB1016) in chronic active hepatitis. *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 31 (9): 456-460.

Trial design

Parallel.

Study duration	1 week
Dose	2 (120 mg silybin) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Hospital
No. of subjects enrolled	20
No. of subjects completed	20
Sex	Male and female
Age	31-70 years (mean: 53)

Inclusion criteria

Patients with chronic active hepatitis (histologically proven), increased aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) serum activities (two to six times the upper limit of range) for more than 12 months.

Exclusion criteria

Patients who have the following: portal hypertension; hepatic encephalopathy; ascites; hepatocellular carcinoma; cholestasis; drug addiction; positive antinuclear, antimitochondrial, and antismooth muscle antibodies; ethanol intake > 30 g per day; malabsorption syndromes; cardiovascular, renal or endocrine disorders; pregnancy; and any pharmacological treatment three months before the beginning of the trial.

End points
Blood samples were collected before and after seven days of treatment, and several liver function tests were performed, as well as measurements of malonaldehyde as an index of liver peroxidation, and copper and zinc, two trace elements involved in protecting cells against free radical-mediated lipid peroxidation.

Results
A statistically significant reduction of mean serum concentrations of AST ($p < 0.01$), ALT ($p < 0.01$), gamma-glutamyl transpeptidase (GGT) ($p < 0.02$), and total bilirubin ($p < 0.05$) was observed in the treated group. The changes in AST, ALT, and GGT were also significant in comparison to the placebo group, in which these levels did not change significantly compared to baseline. There were no significant changes in malonaldehyde, copper, or zinc serum concentrations.

Side effects
None mentioned.

Authors' comments
These results show that Silipide may improve the biochemical signs of hepatocellular necrosis and/or increased cellular permeability in patients affected by chronic active hepatitis. However, it should be considered that this is a pilot study carried out on a small number of patients treated for only one week.

Reviewers' comments
This was an inpatient study, and fasting and controlled diet introduces a potential confounding covariable. The sample size may have been appropriate given the significant findings, however, no power calculation was presented. The dosage of 480 mg/day is twice that used in the study by Marcelli et al. (1992). The treatment length was adequate for a pilot study. (3, 6)

Product Profile: Silimarina®

Manufacturer	**Biofarm S.A., Romania**
U.S. distributor	None
Botanical ingredient	**Milk thistle seed extract**
Extract name	None given
Quantity	700 mg, equivalent to 35 mg silybin
Standardization	No information
Formulation	Tablet

Comments: According to the trial report, Silimarina is a reproduction of Legalon® (Madaus AG).

Source(s) of information: Tanasescu et al., 1988.

Clinical Study: Silimarina®

Extract name	None given
Manufacturer	Biofarm S.A., Romania
Indication	**Liver disease**
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Tanasescu C, Petrea S, Baldescu R, Macarie E, Chiriloiu C, Purice S (1988). Use of the Romanian product Silimarina in the treatment of chronic liver diseases. *Revue Roumaine de Medecine-Medecine Interne* 26 (4): 311-322.

Trial design

Subjects were split into three groups according to their therapeutic indications (Group A: chronic persistent hepatitis; Group B: chronic active hepatitis; and Group C: hepatic cirrhosis). Patients in each group were randomized to receive either Silimarina or placebo.

Study duration	40 days
Dose	2 tablets (700 mg, containing 35 mg silybin) 3 times daily 1 hour after meals
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	180
No. of subjects completed	177
Sex	Male and female
Age	Mean: 45.2 ± 11.5 years

Inclusion criteria
Patients between the ages of 20 and 60 years with chronic persistent hepatitis, chronic active hepatitis, or hepatic cirrhosis. Diagnosis was based on biopsy (with the exception of some with hepatic cirrhosis—Group C) correlated with clinical and laboratory data. The disease is in its medium state (monotherapy will not be detrimental to subjects), and the length of basic disease is from one to ten years.

Exclusion criteria
None mentioned.

End points
At the beginning and end of the study, clinical examination included 25 symptoms, objective signs characteristic for the disease, and the lab analyses of alanine aminotransferase, gamma-glutanmyl transpeptidase (GTP), zinc sulfate, bilirubin, alkaline phosphatase, serum proteins, IgG, and prothrombin concentration.

Results
The clinical aspect of liver disease was improved in all three groups compared with placebo. The improvement was proportionally similar in those with chronic persistent hepatitis (65 percent compared with 50 percent for controls), chronic active hepatitis (70 percent compared with 60 percent for controls), and in those with hepatic cirrhosis (55 percent compared with 45 percent for controls). Laboratory tests of groups as a whole failed to give conclusive evidence of treatment. However, activity was demonstrated within subgroups.

Side effects
No adverse events were observed.

Authors' comments
The results demonstrate the partial favorable effect of treatment with Silimarina on some clinical and laboratory parameters, as compared with placebo in patients with various forms of chronic liver disease.

Reviewers' comments
The "clinical parameters" were not well described or presented, and the secondary analysis of data was somewhat spurious. The sample size may have been appropriate, however, no power calculation was presented. Only part of Group C was biopsied—this was not explained. The dose of 210 mg/day was much lower than most other studies. Given the lack of side effects, a larger dose could have been used and perhaps yielded a clearer picture of efficacy. A longer duration may have allowed for clear resolution of the data profile. (2, 5)

Product Profile: Milk Thistle (Generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Milk thistle seed extract**
Extract name	None given
Quantity	No information
Processing	No information
Standardization	No information
Formulation	No information

Clinical Study: Milk Thistle (Generic)

Extract name	None given
Manufacturer	None
Indication	**Drug-induced liver damage**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Palasciano G, Portincasa P, Palmieri V, Ciani D, Vendemiale G, Altomare E (1994). The effect of silymarin on plasma levels of malon dialdehyde in patients receiving long-term treatment with psychotropic drugs. *Current Therapeutic Research* 55 (5): 537-545.

Trial design
Parallel. Four treatment groups included Group IA: psychotropic drugs and silymarin (800 mg/d); Group IB: psychotropic drugs and placebo; Group IIA: suspension of psychotropic drugs and silymarin (800 mg/d); Group IIB: suspension of psychotropic drugs and placebo.

Study duration	3 months
Dose	400 mg silymarin twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes

Drug comparison	No
Site description	Hospital psychiatric department
No. of subjects enrolled	60
No. of subjects completed	60
Sex	Female
Age	40-60 years (mean: 51.9)

Inclusion criteria
Patients ages 40 to 60 years receiving chronic psychotropic drug therapy such as phenothiazines and/or butyrophenones for at least five years, and with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) activity more than twice the normal value.

Exclusion criteria
Patients treated with other drugs that could influence the progress of hepatopathy (e.g., interferons or cortisone); other types of hepatopathies (e.g., viral, autoimmune hepatopathy, alcoholic, hemochromatosis, porphyria cutanea tarda, Wilson's disease, or primary or secondary hepatic neoplasia); altered renal function (blood urea nitrogen > 60 mg/dl and/or serum creatinine > 2.5 mg/dl); cardiac and circulatory insufficiency; diabetes; other extrahepatic diseases; pregnancy; or alcohol (> 30 g/d) or opiate abuse.

End points
Serum levels of malondialdehyde (MDA) (an end product of oxidation of polyunsaturated fatty acids) and indices of hepatocellular function were assessed at baseline and 15, 30, 60, and 90 days after beginning treatment, as well as one month after completion of treatment.

Results
The suspension of therapy with psychotropic drugs led to a reduction in serum MDA levels in both placebo- and silymarin-treated patients, with little difference between the two groups (IIA and IIB). There was an increase in serum MDA levels with placebo (group IB). Group IIB's serum MDA levels decreased until rebound occurred when psychotropic drug therapy was reinstated. The decrease over time in ALT and AST was greater in Group II compared with Group I. For those who continued to take the psychoactive drugs (Groups IA and IB), there was a significant improvement with silymarin at the end of three months.

Side effects
No adverse reactions were reported.

Authors' comments
Silymarin, used at submaximal dose, reduced the lipoperoxdative hepatic

damage that occurs during treatment with butyrophenones and phenothiazines. This protective effect is greater in suspended psychotropic drugs.

Reviewers' comments

The study groups were not well-matched at baseline with respect to laboratory test results or age. Based upon the data, the most powerful effect was found with the withdrawal of neuroleptics. Some protection from lipoperoxidation may have been induced by certain phenothiazines and butyrophenones conferred by co-treatment with silymarin, as indicated by the data that showed a significant decrease in MDA levels. The sample size may have been appropriate, however, no power calculation was presented. The dosage of 800 mg/day was significantly beyond the standard range (per Blumenthal et al., 1998). This choice was not discussed in the paper nor substantiated by reference(s). The treatment length was adequate. (1, 5)

Pygeum

Other common names: **African plum**
Latin name: ***Prunus africana* (Hook. f.) Kalkman** [Rosaceae]
Latin synonyms: ***Pygeum africanum* Hook. f.**
Plant part: **Bark**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Pygeum bark has been traditionally used in central and southern Africa to assist bladder and urinary function. In this traditional use, the bark is ground into powder and mixed with milk. Modern formulation of this botanical is a lipophilic extract of the bark. At least three types of active compounds may be responsible for the therapeutic action of the extract: pentacyclic terpenes, phytosterols, and ferulic acid esters (Schulz, Hänsel, and Tyler, 2001).

Tadenan® is manufactured in France by Laboratoires Fournier. The capsules contain 50 mg of a lipophilic extract of pygeum bark. Tadenan is not sold in the United States.

Pigenil contains a pygeum bark extract (PrunuSelect™) manufactured by Indena S.p.A., Italy. This extract has a plant to extract ratio of 180:1, and is standardized to contain 11.7 to 14.3 percent sterols as beta-sitosterol. Pigenil, in 50 mg capsules, was originally manufactured by Inverni della Beffa in Italy. This product is not available in the United States.

Prostatonin® contains extracts of both pygeum bark and nettle (*Urtica dioica* L. spp. *dioica*) roots. This product is manufactured by Pharmaton S.A. in Switzerland, and is sold in the United States by Pharmaton Natural Health Products. It is available in softgel capsules containing 25 mg pygeum extract, PY102 (200:1), and 300 mg nettle extract, UR102 (5:1).

PYGEUM SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
			Single Ingredient Products			
Tadenan® (EU)	Laboratoires Fournier, France/ None	Lipidic sterol extract	100 to 200 mg/day	Benign prostatic hyperplasia	8*	Yes (II-2) Trend (III-3) No (II-1) Undetermined (III-2)
Pigenil (EU)	Inverni della Beffa, Italy (Indena S.p.A., Italy)/None	Soft extract (PrunuSelect™)	100 mg/day	Benign prostatic hyperplasia	2	Yes (II-1) Undetermined (III-1)
			Combination Product			
Prostatonin®	Pharmaton S.A., Switzerland/ Pharmaton Natural Health Products	Pygeum bark extract (PY102), Nettle root extract (UR102)	2 capsules twice daily	Benign prostatic hyperplasia	2	Undetermined (II-2)

*The trial information for one of these studies (Dutkiewicz, 1996) is included after the grass pollen summary, since it is reviewed primarily in that section.

SUMMARY OF REVIEWED CLINICAL STUDIES

Pygeum preparations have been assessed in clinical studies for the treatment of symptomatic benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy and prostatic adenoma. BPH is a nonmalignant enlargement of the prostate common in men over 40 years of age. The symptoms of BPH include increased urinary urgency and frequency, urinary hesitancy, intermittency, sensation of incomplete voiding, and decreased force of the stream of urine. BPH is linked with a normal change in hormone levels that occurs with aging. Testosterone levels decrease while estrogen levels remain constant. This change is implicated in BPH, since estrogens induce hyperplasia (cell growth) in laboratory experiments. Further, BPH is associated with an increase in the activity of 5-alpha-reductase, the enzyme that converts testosterone to dihydrotesterone (DHT). The levels of DHT are not increased, but the number of androgen receptors seems to be. DHT has a greater affinity for androgen receptors than testosterone, and is thought to modulate prostatic growth. However, the pathology of BPH is not completely understood, and although BPH is associated with prostate enlargement, the size of the gland is not necessarily indicative of the degree of obstruction of the urethra and the extent of symptoms (Barrett, 1999).

Predominant pharmaceutical treatments for BPH include alpha-receptor blockers and 5-alpha-reductase inhibitors. Alpha-receptor blockers (e.g., prozosin, terazosin) are thought to relax smooth muscle in the bladder neck and within the prostate, and thus reduce symptoms. Five-alpha reductase inhibitors (e.g., finasteride) prevent the transformation of testosterone into DHT. The rationale for this treatment is that prostate enlargement may be linked to activation of androgen receptors by DHT and a reduction in testosterone levels (Barrett, 1999).

The clinical mode of action of pygeum has not been established, but biochemical studies indicate that it has anti-inflammatory activity and may inhibit 5-alpha-reductase. Nettle root extract, which is combined with pygeum extract in the product Prostatonin®, may have similar activity. Preparations of grass pollen and saw palmetto have also been assessed clinically for treatment of BPH, and more information about these botanicals is given in their sections in this book. The mechanism of action of these botanicals is also not established,

but grass pollen has demonstrated anti-inflammatory activity, and may reduce the growth of epithelial cells and fibroblasts. Suggested pharmacological actions for saw palmetto include antiandrogenic, anti-inflammatory, antiproliferative, and smooth muscle relaxation (Marandola, et al., 1997; Awang, 1997; Barrett, 1999).

Tadenan

Benign Prostatic Hyperplasia

Tadenan was examined for the treatment of BPH in eight controlled clinical studies, including a total of 812 men. The studies suggest a moderate benefit with a reduction in symptoms after a month of treatment. Three of the studies were good-sized, including more than 100 men each, and four were smaller studies of 20 to 40 men each. Five of the studies were placebo controlled, two studies compared Tadenan to other agents, and one study was a dose comparison. One study that compared Tadenan to grass pollen extract (Cernilton®) is primarily included in that file.

The largest placebo-controlled study included 255 men and was rated by our reviewers, Drs. Elliot Fagelman and Franklin Lowe, as well conducted. Treatment with Tadenan, 100 mg per day for two months, led to a statistically significant increase in urinary volume and maximum urinary flow with a decrease in residual urine volume, compared with placebo. Urinary frequency during the day and night was also reduced (Barlet et al., 1990). A smaller, good-quality study with 39 men also reported a significant increase in urinary flow following treatment with 200 mg daily for two months compared to baseline and to placebo. A decrease in urinary frequency and a decrease in painful urination was observed in the treatment group compared to baseline. In addition, the diameter of the prostate was reduced by 11 percent, compared with a 5 percent reduction in the placebo group (Ranno et al., 1986). Two low-quality studies, according to the Jadad criteria, included 20 and 40 participants, respectively, treated with 200 mg pygeum per day or placebo for two months. Both studies reported a significant reduction in symptoms compared to baseline, not shared by the placebo group (Rizzo et al., 1985; Frasseto et al., 1986). A large (120 men) but short (six weeks) study of good quality reported reductions in symptoms for both the treatment group given 200 mg per day and the placebo group. Despite the

very large placebo effect, there was an indication of benefit due to Tadenan (DuFour et al., 1984).

A large study including 209 men compared two dosage regimens, 50 mg twice daily to 100 mg once daily. Both dose regimens reduced symptom scores and increased quality of life scores. Although both forms were equally effective, the lack of a placebo group meant that efficacy could not be determined (Chatelain, Autet, and Brackman, 1999).

A comparison study with 40 participants compared 200 mg Tadenan to standard therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) alone or with antibiotics. After one month of treatment, Tadenan was more effective than NSAIDs in improving symptoms of polyuria (excess urine), urinary frequency at night, urinary retention, and painful urination. The NSAID therapy was only comparable in improving strangury, the constricted passage of urine (Gagliardi et al., 1983).

A trial reviewed in the grass pollen section compared Tadenan with grass pollen extract (Cernilton). The Tadenan group received two tablets twice daily, and the Cernilton group received one to two tablets of Cernilton three times daily. In this trial, which included a total of 89 men, positive therapeutic response was reported for both treatments, with improved peak flow rate, decreased residual urine volume, decreased prostate volume, and improved obstructive and irritative symptom scores. Scores indicated more improvement for the Cernilton group than the Tadenan group (Dutkiewicz, 1996).

Pigenil

Benign Prostatic Hyperplasia

Two trials examined the efficacy of Pigenil on men with symptomatic BPH. Both studies reported a decrease in symptoms following two months of treatment with 50 mg twice daily. The first, a well-conducted, placebo-controlled study with 40 men, reported a decrease in urinary frequency, urgency, and painful urination, as well as an increase in urinary flow, with no change in prostate size compared with placebo (Bassi et al., 1987).

The second study compared Pigenil with mepartricin, an agent that lowers levels of circulating estrogen levels without causing changes in the levels of other hormones, including testosterone. The authors

of a recent review concluded that mepartricin was as effective as alpha-adrenoceptor agonists and 5-alpha-reductase inhibitors in reducing symptoms of BPH (Boehm, Nirnberger, and Ferrari, 1998). The comparison study conducted with Pigenil and mepartricin included 40 men and demonstrated a reduction in urinary frequency, painful urination, and residual urine compared to baseline for both treatments. Pigenil was slightly more effective in reducing painful urination. In addition, after two months treatment, Pigenil reduced the size of the prostate by 11 percent, whereas mepartricin had no effect on prostate size (Scarpa et al., 1989).

A third trial described in this section compared Pigenil with Prostatonin and an extract of *Epilobium parviflorum* (Montanari et al., 1991).

Prostatonin

Benign Prostatic Hyperplasia

Two trials explored the efficacy of Prostatonin, a product containing extracts of both pygeum and nettle. The first study was a dose comparison study, and the second was a treatment comparison study. Unfortunately, neither study included a placebo group, an omission that caused the trials' efficacy to be rated undetermined by our reviewers. The first, a fairly large study of 124 men, compared the usual dose of two capsules twice daily to half that dose and found both to be equally effective in increasing urinary flow and decreasing residual urine and nighttime frequency following two months of treatment (Krzeski et al., 1993). The second, smaller study, including 59 men, compared the combination product Prostatonin (two capsules twice daily) with Pigenil (pygeum alone, 50 mg twice daily) and an extract of *Epilobium parviflorum* (250 mg extract twice daily). Strength of urinary flow was increased with all three treatments, with the combination product being more effective than pygeum alone, and both more effective than *Epilobium*. Both Prostatonin and Pigenil were more effective than *Epilobium* in reducing nighttime urination frequency. No change in prostate size was observed in any of the groups (Montanari et al., 1991).

SYSTEMATIC REVIEWS

A systematic review evaluated 18 randomized, controlled trials including 1,562 men with symptomatic BPH. The mean treatment duration was two months, with a range from one to four months. The doses of pygeum extract ranged from 75 to 200 mg per day. Of the 13 placebo-controlled studies, 12 reported a beneficial effect on at least one measure of effectiveness (overall symptoms, nighttime urination frequency, peak urine flow, or residual volume). Only one small trial with 20 men lasting 12 weeks found no benefit compared to placebo. Six studies involving a total of 474 participants could be pooled in a statistical evaluation of effectiveness. Five of these six studies used Tadenan as the test preparation. The statistical evaluation of the overall effect indicated a significant improvement in symptoms compared with placebo (standard deviation [SD] –0.8; 95 percent confidence interval [CI]: –1.4 to –0.3). The authors concluded that the evidence suggests that pygeum improves urologic symptoms and flow measures modestly, but significantly (Ishani et al., 2000).

ADVERSE REACTIONS OR SIDE EFFECTS

Pygeum extracts were well tolerated with only an occasional report of gastrointestinal discomfort in the trials discussed previously. A systematic review of 18 trials including 1,562 men reported that adverse reactions were mild and similar to those with the placebo. The most frequently reported side effects were gastrointestinal complaints (Ishani et al., 2000).

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DETAILS ON PYGEUM PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Pygeum Products

Product Profile: Tadenan®

Manufacturer	**Laboratoires Fournier, France**
U.S. distributor	None
Botanical ingredient	**Pygeum bark extract**
Extract name	None given
Quantity	50 mg
Processing	Lipidic sterol extract
Standardization	No information
Formulation	Capsule

Recommended dose: One capsule taken in the morning and evening, preferably before meals.

DSHEA structure/function: French drug indication: treatment of mild micturition disorders caused by benign prostatic hyperplasia.

Cautions: Treatment duration is generally 6 weeks; it can be prolonged up to 8 weeks and can be repeated if necessary. The effect of Tadenan on functional disorders does not dispense from routine medical checkups since Tadenan cannot replace necessary surgery. Diag-

nosis and surveillance of benign prostatic hyperplasia must include periodic digital rectal examination for the early detection of a possible prostate cancer.

Other ingredients: Peanut oil, gelatin, glycerol, titanium dioxide (E 171), hydrosoluble copper complexes of chlorophyll (E 141).

Source(s) of information: Barlet et al., 1990; Banque de Données Automatisée sur les Médicaments (BIAM) (2000) Tadenan 50 mg capsules molles, <http://www3.biam2.org/www/Ispe.html>.

Clinical Study: Tadenan®

Extract name	None given
Manufacturer	Laboratories Fournier, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Barlet A, Albrecht J, Aubert A, Fischer M, Grof F, Grothuesmann HG, Masson JC, Mazeman E, Mermon R, Reichelt H, Schonmetzler F, Suhler A (1990). Efficacy of *Pygeum africanum* extract in the treatment of micturitional disorders due to benign prostatic hyperplasia: Evaluation of objective and subjective parameters. *Wiener Klinische Wochenschrift* 102 (22): 667-672.

Trial design
Parallel.

Study duration	2 months
Dose	50 mg capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	8 centers
No. of subjects enrolled	263
No. of subjects completed	255

Sex	Male
Age	50-85 years

Inclusion criteria
Outpatients older than 50 years old with urinary disorders attributable to Stage I benign prostatic hyperplasia that had been present for at least six months, but not over four years. Nocturia had to be marked enough to allow quantitative recording (number of nightly urinations).

Exclusion criteria
Prostatic carcinoma or suspected carcinoma; residual urine over 100 ml, recurrent pollakiuria; urea in blood over 0.8 g/l; acute infections of the urinary tract, or patients' clinical or bacteriologic clearance within the prior four weeks; kidney failure or other recurrent diseases that might affect urinary flow; treatment in the last six months, or concomitant medication, with drugs that might improve the symptoms of bladder-emptying, such as anti-inflammatories, diuretics, and hormones.

End points
Primary end points were objective measurements of residual urine, micturition volume, maximum urine flow rate, and the number of daily and nightly urinations over 24 hours. Secondary subjective symptoms evaluated by patients were delayed urination, weak urine flow, stasis after urination, intermittent flow, and sense of residual urine.

Results
Treatment with pygeum extract led to a significant decrease in the volume of residual urine ($p = 0.001$), and an increase in micturition volume and maximum urine flow rate (both $p = 0.001$). The average number of nightly urination decreased significantly, both quantitatively and subjectively. Daytime urination decreased with treatment. Overall assessment at the end of therapy showed that micturition improved in 66 percent of the patients treated with pygeum extract compared with an improvement of 31 percent in the placebo group. The difference was significant at the statistical level of $p < 0.001$.

Side effects
During therapy with pygeum extract, gastrointestinal side effects occurred in five patients. Treatment was discontinued in three of those cases.

Authors' comments
The use of *Pygeum africanum* appears justified, especially because of its favorable risk-benefit ratio.

Reviewers' comments
Overall, this is a good study demonstrating a benefit in taking *Pygeum africanum* for BPH. (Translation reviewed) (3, 6)

Clinical Study: Tadenan® 50

Extract name	None given
Manufacturer	Roussel Maestretti S.p.A., Italy (Laboratoires Fournier, France)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Ranno S, Minaldi G, Viscusi G, Di Marco G, Consoli C (1986). Efficacy and tolerability of treatment of prostatic adenoma with Tandenan 50. *Il Progresso Medico* 42: 165-169.

Trial design
Parallel.

Study duration	2 months
Dose	2 (50 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single practice
No. of subjects enrolled	39
No. of subjects completed	39
Sex	Male
Age	Mean: 70 years

Inclusion criteria
Patients suffering from adenoma of the prostate in the first and second stages, not requiring surgery, and with disorders of micturition of moderate severity.

Exclusion criteria
Hormone-based drugs, antiprostatics, anti-inflammatory drugs, diuretics, or antibiotics were not allowed during treatment.

End points
Symptoms such as dysuria, diurnal and nocturnal pollakiuria, and urinary flow

were evaluated at the beginning and end of the study. Echographs of the prostate were performed before the trial, after 30 days, and after 60 days.

Results
Treatment with pygeum led to a statistically significant reduction in symptoms (dysuria, diurnal pollakiuria, and nocturnal pollakiuria) ($p < 0.01$, compared to baseline). In contrast, the placebo did not cause any significant change. Pygeum also caused improvement in mean and maximal urinary flow as well as duration of micturition ($p < 0.01$, compared to baseline and placebo). It also caused a slight reduction (11 percent) in the diameter of the prostate in comparison with placebo (5 percent).

Side effects
None observed.

Authors' comments
In comparison with placebo, the extract of pygeum caused appreciable and significant improvement in symptoms.

Reviewers' comments
The study is limited because of the small number of patients and short treatment length. However, symptoms and peak urinary flow were improved with treatment. (Translation reviewed) (3, 4)

Clinical Study: Tadenan® 50

Extract name	None given
Manufacturer	Laboratoires Fournier, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Rizzo M, Tosto A, Paoletti MC, Raugei A, Favini P, Nicolucci A, Paolini R (1985). Medical therapy of prostate adenoma: Comparative clinical evaluation between high dose *Pygeum africanum* extract and placebo. *Farmaci & Terapia* 2 (2): 105-110.

Trial design
Parallel.

Study duration	2 months
Dose	2 (50 mg) capsules twice daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single practice
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Male
Age	42-72 years (mean: 62)

Inclusion criteria
Patients with a diagnosis of an adenoma of prostate for no more than five years, and with urination problems.

Exclusion criteria
None mentioned.

End points
Clinical symptomatology were evaluated subjectively (dysuria, daytime frequency, nocturia, decreased urinary flow) and objectively (rectal exam, uroflow meter, echography). Examination were completed at inclusion into the study, after 30 days, and after 60 days.

Results
A significant improvement for dysuria was observed in the treatment group after 60 days ($p < 0.01$). There was an improvement in nocturia after 30 and 60 days ($p < 0.05$ and $p < 0.01$, respectively). No statistically significant improvement in daytime frequency was observed. According to the uroflow measurements, there was a statistically significant increase in average and maximal flow after 60 days ($p < 0.01$). No change in prostate size was observed. No significant changes in these parameters were seen in the placebo group.

Side effects
None. Treatment was very well tolerated.

Authors' comments
Pygeum africanum is a valid and current therapy for prostate adenoma.

Reviewers' comments
The data show some benefit for *Pygeum africanum,* but a poor study design limits their usefulness. The authors state that patients had symptoms due to prostatic enlargement, but the average maximum uroflow prior to treatment was 715 ml/sec. With such a high maximum flow, and without performing pressure flow studies, the diagnosis of BPH is in doubt. Sixty days is a short duration of therapy. (Translation reviewed) (1, 3)

Clinical Study: Tadenan® 50

Extract name	None given
Manufacturer	Roussel Maestretti S.p.A., Italy (Laboratoires Fournier, France)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Frasseto G, Bertoglio S, Mancuso S, Ervo R, Mereta F (1986). Study of the efficacy and tolerance of *Pygeum africanum* in patients with prostatic hypertrophy. *Il Progresso Medico* 42: 49-53.

Trial design
Parallel.

Study duration	2 months
Dose	2 (50 mg) capsules twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Single-Blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single practice
No. of subjects enrolled	20
No. of subjects completed	20
Sex	Male
Age	51-89 years

Inclusion criteria
Men with an enlarged prostate and subjective symptoms of nocturia, pollackiuria, and decreased flow of urine.

Exclusion criteria
Patients affected by neoplasia of the urinary tract, lithiasis of the urinary tract, urinary infection, sphincter malfunction, urinary tract malfunction, and prostatic hypertrophy needing surgery.

End points
A transrectal echographic test was performed at the beginning and end of treatment. The subjective symptom of dysuria was evaluated before the trial, after 30 days, and at the end of treatment (60 days).

Results
A statistically significant reduction in symptoms of nocturia, pollackiuria, and decreased urinary flow was observed after 60 days of treatment ($p < 0.001$, $p < 0.05$, $p < 0.05$ respectively). There was no significant change in these parameters in the placebo group. Changes in the size of the prostate in the treatment group were insignificant.

Side effects
None observed.

Authors' comments
It is inferred from this study that pygeum acts on the periurethral inflammatory component of prostate hypertrophy and has no noticeable effect on the fibrosclerotic component.

Reviewers' comments
This was a limited study, since it was not randomized and the blinding was not described. A statistical benefit was noted with *Pygeum africanum,* but the differences are small and may not be clinically significant. The study also had a small sample. (Translation reviewed) (1, 4)

Clinical Study: Tadenan®

Extract name	None given
Manufacturer	Laboratoire Dabat., France (Laboratoires Fournier, France)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
DuFour B, Choquenet C, Revol M, Faure G, Jorest R (1984). Controlled study of the effects of *Pygeum africanum* extracts on the symptoms of benign prostatic hypertrophy. *Annales d'Urologie* 18 (3): 193-195.

Trial design
Parallel.

Study duration	6 weeks
Dose	4 (50 mg) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	120
No. of subjects completed	120
Sex	Male
Age	Not given

Inclusion criteria
Prostatic hypertrophy subjects with related urination difficulties that do not require surgery.

Exclusion criteria
None mentioned.

End points
Symptoms of benign prostatic hyperplasia, including nocturnal frequency, urine flow, daily frequency, difficulty in initiating urination, sensation of incomplete emptying of the bladder, terminal drip, sense of residual urine, and interrupted flow.

Results
Statistically greater improvement was observed in the pygeum group in nocturnal frequency, difficulty in starting micturition, and incomplete emptying of the bladder. A large placebo effect was present, with 34 to 55 percent improvement of symptoms.

Side effects
None mentioned.

Authors' comments
The placebo effect is so pronounced that a statistical analysis of each symptom is necessary. The study showed a statistically significant improvement in three functional symptoms with the use of pygeum.

Reviewers' comments
This study did not show a difference in symptoms after treatment of pygeum africanum compared with placebo. The study was short, however, and in a longer study the placebo effect would remain constant, and it is possible a therapeutic benefit would be seen. (Translation reviewed) (3, 5)

Clinical Study: Tadenan®

Extract name	None given
Manufacturer	Laboratoires Fournier, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Chatelain C, Autet W, and Brackman F (1999). Comparison of once and twice daily dosage forms of *Pygeum africanum* extract in patients with benign prostatic hyperplasia: A randomized, double-blind study, with long-term open label extension. *Urology* 54 (3): 473-478.

Trial design
Parallel, with three phases. One-month run-in phase without treatment preceding a two-month dose comparison trial, followed by a ten-month open phase period (100 mg once daily).

Study duration	2 months
Dose	50 mg twice daily or 100 mg once daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No

Drug comparison	No
Site description	Single center
No. of subjects enrolled	235
No. of subjects completed	209
Sex	Male
Age	58-74 years

Inclusion criteria
Age 50 years or older; clinical symptoms of benign prostatic hyperplasia (urinary symptoms, International Prostate Symptom Score [IPSS] 10 or greater, and quality of life [QOL] 3 or greater) confirmed by digital rectal examination and transrectal ultrasound (prostate volume 30 cm^3 or greater); maximum urinary flow rate (Qmax) 15 ml/s or less (voided volume 140 ml or greater); residual volume 150 ml or less; serum prostate-specific antigen (PSA) less than 10 ng/ml; and serum creatinine less than 160 µmol/l.

Exclusion criteria
Indication for or previous prostate or bladder surgery; prostate and/or bladder cancer; urinary symptoms due to other causes; and treatment during the three months preceding inclusion with finasteride, *Pygeum africanum,* or *Serenoa repens,* or with any alpha-blocker during one month before inclusion.

End points
Patients were evaluated at inclusion, after the run-in phase, after one and two months of treatment, and after 5, 8, and 12 months as part of the open phase extension. The IPSS, quality of life, vital signs, and side effects were assessed at all visits. Digital rectal examinations, Qmax, voided volume, postvoid residual volume, and sexual function were assessed at entry and after 2 and 12 months. Prostate volume and serum PSA levels were assessed at entry and after 12 months.

Results
Both treatments had similar efficacy. IPSS (baseline 17 in both groups) improved by 38 percent in Group A (50 mg twice daily) and 35 percent in Group B (100 mg once daily). QOL improved by 28 percent in both. Qmax increased by 1.63 ml/s (16 percent) in Group A and 2.02 ml/s (19 percent) in Group B. After 12 months, the IPSS fell from 16 to 9. Half of the patients had an IPSS less than 8. Mean Qmax increased by 1.65 ml/s (15 percent).

Side effects
The safety profile was similar between groups and study phases. Treatment-emergent side effects were mostly gastrointestinal. Most effects were not treatment related.

Authors' comments
Pygeum africanum extract at 50 mg twice daily and 100 mg once daily proved equally effective and safe at two months. Further improvements in efficacy with a satisfactory safety profile were documented after 12 months.

Reviewers' comments
This study compared two different dosing regimens of *Pygeum africanum* and found their efficacy and safety similar. The therapeutic benefit of this extract cannot be determined from this study. Neither the randomization nor the blinding were adequately described. The treatment length was adequate. (1, 6)

Clinical Study: Tadenan®

Extract name	None given
Manufacturer	Laboratoires Fournier, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Gagliardi V, Apicella F, Pino P, Falchi M (1983). Medical treatment of prostatic hypertrophy: A controlled clinical investigation. *Archivio Italiano di Urologia e Nefrologia* 55: 51-69.

Trial design
Parallel. Comparison trial of pygeum versus standard treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). (NSAIDs were given alone or with antibiotics.)

Study duration	30-35 days
Dose	2 (50 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	NSAIDs

Site description	Single practice
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Male
Age	50-84 years

Inclusion criteria
Patients with prostatic hypertrophy and symptoms associated with micturition and a variable amount of residual urine in the bladder.

Exclusion criteria
None mentioned.

End points
Symptoms of polyuria (excess urine), strangury (constricted passing of urine), dysuria, nocturia, retention of urine, and prostatic volume were assessed at the start and end of treatment.

Results
Tadenan was more effective than anti-inflammatory agents in improving symptoms. Tadenan administration improved symptoms of polyuria, strangury, dysuria, and nocturia ($p < 0.01$). The only symptom improved by anti-inflammatory agents was strangury ($p < 0.05$). Tadenan also decreased residual urine ($p < 0.01$). No statistical improvement was observed in the control group.

Side effects
None observed.

Authors' comments
Since it has been shown to be effective and safe, Tadenan is regarded as a drug of choice for medical treatment of prostatic adenoma prior to surgery.

Reviewers' comments
The inclusion/exclusion criteria were not explained in detail, and the lack of double-blinding limits the utility of the study. In addition, 30 to 35 days is a short treatment length. No adverse effects were noted with either treatment, which is surprising given the known side effects of non-steroidal anti-inflammatory drugs. (Translation reviewed) (1, 4)

Product Profile: Pigenil

Manufacturer	**Inverni della Beffa, Italy (Indena S.p.A., Italy)**
U.S. distributor	None
Botanical ingredient	**Pygeum bark soft extract**
Extract name	**PrunuSelect™**
Quantity	50 mg
Processing	Plant to extract ratio 180:1
Standardization	11:7-14.3% sterols as beta-sitosterol

Source(s) of information: Scarpa et al., 1989; information provided by Indena USA, Inc.

Clinical Study: Pigenil

Extract name	PrunuSelect™
Manufacturer	Inverni della Beffa, Italy (Indena S.p.A., Italy)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Bassi P, Artibani W, De Luca V, Zattoni F, Lembo A (1987). Estratto standardizzato di *Pygeum africanum* nel trattamento dell'ipertrofia prostatica benigna [Standardized *Pygeum africanum* extract in the treatment of benign prostatic hypetrophy]. *Minerva Urologica e Nefrologica* 39 (1): 45-50.

Trial design
Parallel.

Study duration	2 months
Dose	50 mg twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes

Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Male
Age	Mean: 66.8 years

Inclusion criteria
Patients with prostatic hypertrophy and symptoms of obstruction and irritation with minimal residual urine who had not received any treatment for the ailment.

Exclusion criteria
Severe illnesses, especially of renal and/or hepatic origin, hypertrophy of the median lobe, urinary infection, bladder stones, or dilution of the superrenal excretory pathways due to kidney insufficiency.

End points
Patients were assessed before and after treatment for urological symptoms (daytime and nighttime frequency, urgency, posturination drip, dysuria, as well as force and caliber of flow) and objective measurements (physical exam, uroflow measurements).

Results
The preliminary results demonstrate a significant improvement of the frequency ($p < 0.001$), urgency ($p < 0.02$), dysuria ($p < 0.02$), and urinary flow ($p < 0.05$) in patients treated with pygeum compared to placebo. No significant change was observed in the quality of urination, posturination drip, nor the size or consistency of the prostate gland.

Side effects
One patient in 20 had gastric symptoms that resolved on their own.

Authors' comments
This study shows the therapeutic efficacy of the *Pygeum africanum* extract in the treatment of prostatic hypertrophy of mild to moderate degree.

Reviewers' comments
This is a good study demonstrating a benefit of Pigenil. The study was limited, however, by a small sample size, lack of details on randomization, and a short treatment length. (Translation reviewed) (3, 5)

Clinical Study: Pigenil 50

Extract name	PrunuSelect™
Manufacturer	Inverni della Beffa, Italy (Indena S.p.A., Italy)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Scarpa RM, Migliari R, Campus G, De Lisa A, Sorgia M, Usai M, Usai E (1989). Medical treatment of benign prostatic hypertrophy with extract of *Pygeum africanum. Stampa Medica* (Suppl. 465): 25-39.

Trial design
Parallel. Drug comparison with mepartricin (one tablet containing 50,000 U three times daily).

Study duration	2 months
Dose	1 (50 mg) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Mepartricin
Site description	Single center
No. of subjects enrolled	40
No. of subjects completed	40
Sex	Male
Age	42-80 years

Inclusion criteria
Both inpatients and outpatients with specific and mild to medium symptoms of benign prostatic hypertrophy, which impedes the normal voiding of the bladder, but does not require surgical intervention in the short term.

Exclusion criteria
Patients with concomitant diseases of the genitourinary tract (including urinary tract infections), except for morphofunctional sequels directly due to bladder output obstruction.

End points
Before and after treatment, patients were assessed using ultrasound for bladder volume, residual urine, and prostate size. Clinical symptoms (the number of daytime voidings, nighttime voidings, dysuria, sensation of incomplete bladder emptying, perineal or retropubic tenderness or pressure) were assessed at baseline and after 30 and 60 days.

Results
Both treatments reduced urinary frequency, painful urination, and residual urine compared to baseline. After 60 days, the effect on dysuria (painful urination) was significantly greater with Pigenil ($p < 0.01$). In addition, a statistically significant reduction of prostate size (11 percent) was found only in patients treated with *Pygeum africanum* (comparison between groups $p < 0.05$). No statistically significant changes were observed in a panel of laboratory tests.

Side effects
Tolerance was rated as good or very good in all cases.

Authors' comments
Although the medical treatment of benign prostatic hyperplasia with *Pygeum africanum* extract cannot be considered definitive and does not completely remove the cause of the disorder, the maintenance of an acceptable quality of life for long periods is no small achievement.

Reviewers' comments
This study was limited by design, small numbers of patients, and a lack of placebo control. Neither the blinding nor the randomization was adequately described. No difference was observed after treatment with pygeum or mepartricin. However, the treatment length was short. (1, 5)

Product Profile: Prostatonin®

Manufacturer	**Pharmaton S.A., Switzerland**
U.S. distributor	**Pharmaton Natural Health Products**
Botanical ingredient	**Pygeum bark extract**
Extract name	**PY102**
Quantity	25 mg
Processing	Plant to extract ratio 200:1
Standardization	No information
Formulation	Softgel capsule
Botanical ingredient	**Nettle root extract**

Extract name	**UR102**
Quantity	300 mg
Processing	Plant to extract ratio 5:1
Standardization	No information

Recommended dose: Adult males: Take one softgel capsule twice a day with water (in the morning and evening with meals). Optimal effectiveness has been shown after six weeks with continuous uninterrupted use.

DSHEA structure/function: Promotes normal urinary patterns, helps manage frequent urination at night, supports prostate health.

Cautions: In case of accidental overdose, seek the advice of a professional immediately. Consult a physician if receiving medical treatment and taking medication for a prostate problem, or experiencing symptoms of a prostate problem, such as painful, frequent, or difficult urination.

Other ingredients: Rape oil, gelatin, triglycerides, glycerol, sorbitol, soya lecithin, synthetic iron oxides, titanium dioxide.

Source(s) of information: Product package (© Boehringer Ingelheim Pharmaceuticals, Inc., 1999); Krzeski et al., 1993.

Clinical Study: Prostatonin®

Extract name	PY102, UR102
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Krzeski T, Kazon M, Borkowski A, Witeska A, Kuczera J (1993). Combined extracts of *Urtica dioica* and *Pygeum africanum* in the treatment of benign prostatic hyperplasia: Double-blind comparison of two doses. *Clinical Therapeutics* 15 (6): 1011-1020.

Trial design
Parallel. Dose comparison: Either the standard dose of two capsules containing 300 mg of Urtica dioica extract and 25 mg pygeum extract twice daily, or two capsules containing half that amount twice daily.

Study duration	2 months
Dose	2 (either 162 or 325 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	No
Site description	2 medical centers
No. of subjects enrolled	134
No. of subjects completed	124
Sex	Male
Age	53-84 years

Inclusion criteria
Patients showed at least one symptom of benign prostatic hyperplasia: residual urine, decreased urine flow, or nocturia.

Exclusion criteria
Patients with serious diseases, such as diabetes mellitus or recent myocardial infarction.

End points
Data on three target criteria (urine flow, residual urine, and nocturia) were obtained on three pretreatment control days and after four and eight weeks of treatment.

Results
After 28 days of treatment, a significant increase in urinary flow and residual urine was observed. Nocturia was significantly reduced in both treatment groups. After 56 days of treatment, further significant decreases were found in residual urine (half-dose group) and nocturia (both groups). No between-group differences were observed in these measures of efficacy.

Side effects
One case of gastrointestinal discomfort was attributed to the treatment.

Authors' comments
It was concluded that half doses of the Prostatonin extract are as safe and effective as the recommended full doses.

Reviewers' comments
This study demonstrated equivalent effectiveness of therapy of the two different doses. However, since there was no placebo group, it cannot be determined whether the drug has a therapeutic benefit. Eight weeks is also a relatively short duration of treatment. (3, 6)

Clinical Study: Prostatonin®

Extract name	PY102, UR102
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Montanari E, Mandressi A, Magri V, Dormia G, Pisani E (1991). Benign prostatic hyperplasia: Differential therapy with phytopharmacological agents—A randomized study of 63 patients. *Separatum Der Informierte Arzt/Gazette Medicale* 6a: 593-598.

Trial design
Parallel. Three treatment groups. Group 1 received two capsules (25 mg pygeum extract and 300 mg nettle root extract, trade name: Prostatonin) twice daily. Group 2 received two capsules (125 mg of *Epilobium parviflorum* Schreb. extract) daily. Group 3 received two capsules (25 mg of *Pygeum africanum* extract, trade name: Pigenil) twice daily.

Study duration	2 months
Dose	2 (25 mg pygeum extract + 300 mg nettle root extract) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	*Epilobium parviflorum* extract; Pigenil
Site description	Single center
No. of subjects enrolled	63

No. of subjects completed	59
Sex	Male
Age	57-77 years

Inclusion criteria
Patients with micturition disorders attributed solely to benign prostatic hyperplasia.

Exclusion criteria
Patients with other urological diseases.

End points
Patients were interviewed at baseline and after 60 days. Alcohol and coffee consumption, as well as sexual activity, frequency of nocturia, intervals between individual micturitions, strength of urinary flow, and urinary urgency, were noted. Measurements of blood pressure, heart rate, general physical exam, and size and consistency of the prostate were made.

Results
All three treatment groups showed significant extension of micturition interval with no significant difference between them. No significant difference was observed between pygeum and the pygeum/nettle combination therapy in regard to the success of treatment for nocturia. However, treatment with *Epilobium* was notably less successful. Strength of urinary flow was improved in more than half the patients given the combination treatment, followed by 30 percent improvement with pygeum extract and 20 percent improvement with *Epilobium*. There was no significant change in prostate size with any of the treatments. Urinary volumes and maximum and average flow were increased in all three groups, with the greatest improvement being with the combination therapy.

Side effects
Nonspecific epigastric complaints in one patient in the combination group.

Authors' comments
Two months of treatment with a combination of the extracts of nettle root and pygeum bark proved to be superior both to the extract of *Epilobium* and to that of pyguem alone in respect to elimination of improvement of the different symptoms of benign prostatic hyperplasia.

Reviewers' comments
Although the combination of nettle root and pygeum was superior to pygeum alone or the *Epilobium* extract, a lack of a placebo group limits the usefulness of the study. Two months is a short treatment length. (4, 4)

Red Clover

Latin name: ***Trifolium pratense* L.** [Fabaceae]
Plant part: **Leaf**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Red clover is a member of the pea family, and is an extensive agricultural crop. The leaves and flowers contain a class of compounds called isoflavones that includes formononetin, daidzein, and genistein. Red clover products are characterized and standardized according to the quantity and composition of these isoflavones (Kelly, Husband, and Waring, 1998).

Clinical studies have been conducted with a standardized extract of red clover leaves. This extract is incorporated into tablets called Promensil™, manufactured by Novogen Laboratories Pty Ltd., NSW, Australia, and distributed in the United States by Novogen Inc., Stamford, Connecticut. The tablets are characterized as containing 40 mg isoflavones, including biochanin (24.5 mg), formononetin (8.0 mg), genistein (4 mg), and daidzein (3.5 mg). One of the studies (Samman, 1999) used an unnamed Novogen product with a very similar composition. The tablets contained 43 mg isoflavones, consisting of biochanin A (25.7 mg), formononectin (9.3 mg), genistein (4.3 mg), and daidzein (3.7 mg).

SUMMARY OF REVIEWED CLINICAL STUDIES

Some plants in the pea family, including red clover and soy, contain isoflavones that have weak estrogenic activity. With the waning of estrogen levels in menopause, these phytoestrogens are thought to help compensate and thus reduce the symptoms that may include hot flashes, sweating, cardiovascular complaints, fatigue, vertigo, mus-

RED CLOVER SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Promensil™	Novogen Laboratories, Pty Ltd., Australia/Novogen Inc.	Tablets contain 40 mg isoflavones	1-4 tablets daily	Menopausal symptoms	2	No (II-2)
			1-2 tablets daily	Cardiovascular risk factors	2	Undetermined (II-1, III-1)

cle and joint pain, urinary incontinence, vaginal dryness, and atrophy of the vaginal epithelium. Other symptoms of a psychological nature may include irritability, forgetfulness, anxiety, depression, sleep disturbances, and reduced libido. Menopausal symptoms occur when a woman's ovaries no longer contain eggs. The resulting decline in ovarian function causes a reduced production of estrogen and progesterone, and a corresponding increase in follicle stimulating hormone (FSH) and luteinizing hormone (LH) (Murray and Pizzorno, 1999).

An Asian diet is estimated to deliver 25 to 45 mg total isoflavones per day, whereas the Western diet is estimated to contain less than 5 mg. Epidemiological data imply that the lower incidence of menopausal symptoms in Japanese women compared with Western women may be related to an enhanced dietary intake of soy isoflavones. A soy-based diet is also thought to explain the relatively low incidence of cardiovascular disease in Southeast Asia, since the diet is correlated with low levels of plasma cholesterol (Glazier and Bowman, 2001; Barnes, 1998).

Promensil™

The effects of Promensil on menopausal symptoms and risk factors for cardiovascular disease in women have been tested in four clinical trials. Two clinical studies on menopausal symptoms failed to show any significant improvement over placebo. No changes in vaginal cytology or serum hormone levels were noted. Two studies that addressed the use of red clover extracts to reduce the risk of cardiovascular incidents (heart attack and stroke) through improvement of plasma lipid profiles in pre- and postmenopausal women were inconclusive. Further studies are necessary to evaluate any potential beneficial effects on lipid profiles.

Menopausal Symptoms

The first menopausal study was a well-designed, three-month trial including 35 women (40 to 65 years of age) with at least three hot flashes a day, who were distributed into three groups: placebo; 40 mg red clover extract (one tablet Promensil); and 160 mg red clover extract (four tablets Promensil). No significant difference was observed in the incidence of flashes between the three groups after three

months. There was also no difference in vaginal pH or serum levels of FSH or sex hormone binding globulin (SHBG), a hormone-binding protein (Knight, Howes, and Eden, 1999). Our reviewer, Dr. Tieraona Low Dog, noted that the control group had increased urinary isoflavone levels, indicating an inadvertent intake of dietary isoflavones that would be a major flaw for the study.

The second study was a relatively good, randomized, double-blind crossover study that enrolled 51 women with more than three hot flashes a day. Subjects were given either one tablet Promensil daily or placebo for three months, with the two treatment phases separated by a month's washout period. No significant difference was observed between groups in reduction of hot flashes, levels of SHBG, vaginal swab, or ultrasound examinations (Baber et al., 1999). Again the study lacked control of dietary sources of isoflavones.

Cardiovascular Risk Factors

Plasma lipid profiles and elasticity of the main arteries were measured in a study that addressed a heightened cardiovascular risk associated with menopause. A small, double-blind, placebo-controlled pilot study included 13 women who had been clearly postmenopausal for at least one year and free of cardiovascular disease. In this study, a three-week run-in period included a controlled diet. The treatment group received placebo for five weeks, one tablet Promensil for five weeks, and then two tablets Promensil for another five weeks, whereas the control group received placebo only for the 15 weeks. The study concluded that arterial compliance (elasticity of the main arteries as measured using blood flow and blood pressure) was increased by treatment compared to placebo, but that there was no significant difference between dosage of one or two Promensil tablets. Plasma lipid levels were not significantly affected (Nestel et al., 1999). Assessment of the results was complicated by the placement of the participants on a low-fat diet, encouragement to engage in exercise, and the small sample size.

In another small, crossover, single-blind trial, 14 healthy premenopausal women were given either placebo or two tablets red clover (similar to Premensil) per day for two menstrual cycles before switching to the other treatment. The study failed to show any change in low-density lipoprotein (LDL) oxidation, total cholesterol, or tri-

glycerides. However, an increase of high-density lipoprotein (HDL)-3 was noted (Samman et al., 1999).

ADVERSE REACTIONS OR SIDE EFFECTS

No significant side effects or adverse reactions were noted in the four reviewed trials.

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Source of Published Therapeutic Monographs

British Herbal Compendium, Volume 1

Indications

The *British Herbal Compendium (BHC)* states that red clover flowers (dried flowerheads) are used externally to treat skin conditions, such as psoriasis, eczema, and rashes, as well as taken internally for coughs and bronchitis (Bradley, 1992).

Doses

Infusion: dried flowerheads, 2 to 4 g three times daily (Bradley, 1992)

Liquid extract: (1:1, 25 percent ethanol), 2 to 4 ml three times daily (Bradley, 1992)

Externally: ointment prepared from infusion or liquid extract containing 10 to 15 percent of flowerheads or equivalent (Bradley, 1992)

Contraindications

The *BHC* lists no known contraindications (Bradley, 1992).

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Murray MT, Pizzorno JE (1999). Menopause. In *Textbook of Natural Medicine,* Second Edition, Volume 2. Eds. HE Pizzorno, MT Murray. Edinburgh: Churchill Livingstone.

Nestel PJ, Pomeroy S, Kay S, Komesaroff P, Behrsing J, Cameron JD, West L (1999). Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *The Journal of Clinical Endocrinology and Metabolism* 84 (3): 895-898.

Samman S, Lyons Wall PM, Chan GSM, Smith SJ, Petocz P (1999). The effect of supplementation with isoflavones on plasma lipids and oxidisability of low density lipoprotein in premenopausal women. *Atherosclerosis* 147 (2): 277-283.

DETAILS ON RED CLOVER PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Promensil™

Manufacturer	**Novogen Laboratories Pty Ltd., Australia**
U.S. distributor	**Novogen Inc.**
Botanical ingredient	**Red clover leaf extract**
Extract name	None given
Quantity	40 mg (isoflavone phytoestrogens)
Processing	Plant to extract ratio 5:1, ethanol extraction
Standardization	40 mg isoflavones, including genistein (4 mg), biochanin A (24.5 mg), daidzein (3.5 mg), formononetin (8 mg)
Formulation	Tablet

Recommended dose: Take one tablet daily with a meal. It may take four to five weeks of daily use to achieve the desired and full effect. Continue to use to maintain benefits.

DSHEA structure/function: Natural plant estrogens for women experiencing normal midlife changes.

Cautions: Not recommended for pregnant women or for children under the age of 15 years.

Other ingredients: Dicalcium phosphate, microcrystalline cellulose, hydroxypropyl methylcellulose, magnesium stearate, mixed tocopherols, silica, soy polysaccharide, titanium dioxide, polyethylene glycol, organic coloring containing: red 40, yellow 6, yellow 5, blue 1.

Source(s) of information: Product package; information provided by distributor; Nestel et al., 1999.

Clinical Study: Promensil™

Extract name	None given
Manufacturer	Novogen Laboratories Pty Ltd., Australia
Indication	**Menopausal symptoms**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Knight DC, Howes JB, Eden JA (1999). The effect of Promensil, an isoflavone extract, on menopausal symptoms. *Climateric* 2 (2): 79-84.

Trial design
Parallel. Pretrial observation period of one week. Three treatment groups: one tablet (40 mg) Promensil; four tablets (160 mg) Promensil; and placebo. All subjects consumed a total of four tablets daily.

Study duration	3 months
Dose	1 or 4 (40 mg isoflavone) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	University hospital
No. of subjects enrolled	37
No. of subjects completed	35
Sex	Female
Age	40-65 years

Inclusion criteria
Postmenopausal women ages 40 to 65 years who were symptomatic, having at least three hot flashes per day. Menopause was defined by bilateral oophorectomy or amenorrhea for at least six months with typical symptoms

of menopause, and a serum follicle stimulating hormone (FSH) level greater than 40 IU/l.

Exclusion criteria
Hormone replacement therapy (HRT) use within the previous six weeks; allergy to foodstuffs known to contain isoflavones; current history of active bowel, liver, or gallbladder disease; diabetes requiring drug therapy; and malignancy (excluding skin cancers). Women with contraindications to HRT use, vegetarians and/or regular soy product users, and those receiving medications that result in liver enzyme induction.

End points
Pretrial flushing was assessed using a daily diary of hot flashes for the week prior to trial entry. The severity of menopausal symptoms was assessed during this period using the Greene Menopause Scale. A 24-hour urine collection for isoflavone measurement was also performed during this week. After screening and assignment to treatment groups, physical and vaginal examinations were performed. Blood was examined for hematological profile, liver function, and serum levels of FSH and sex hormone binding globulin (SHBG). Subjects were seen every four weeks for clinical assessment. In the final week, physical and vaginal examinations, and urine and blood tests were repeated.

Results
No significant difference was observed in the incidence of hot flashes between the three groups at trial conclusion. There was no difference in the incidence between the groups in Greene Menopause Symptom Scores, vaginal pH, levels of FSH, SHBG, total cholesterol, liver function, or blood parameters. A statistically significant increase in high-density lipoprotein (HDL) cholesterol of 18.1 percent ($p = 0.038$) occurred in the 40 mg group.

Side effects
None mentioned.

Authors' comments
A large placebo response and inadvertent use of dietary isoflavones in the placebo group may have obscured a significant change in hot flash frequency. Previous uncontrolled studies claiming a beneficial effect of foods with a high isoflavone content on menopausal symptoms may have been confounded by a large placebo response.

Reviewer's comments
This was a well-designed and well-conducted study. The red clover preparation had no effect. However, there were some important flaws. The sample size was small (no power calculation), and the control group had increased urinary isoflavone levels, indicating a likely dietary breach in the trial. (5, 5)

Clinical Study: Promensil™

Extract name	None given
Manufacturer	Novogen Laboratories Pty Ltd., Australia
Indication	**Menopausal symptoms**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference

Baber RJ, Templeman C, Morton T, Kelly GE, West L (1999). Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. *Climateric* 2 (2): 85-92.

Trial design

Crossover. Subjects were assessed for one week before the start of trial to ensure entry qualifications. Treatment periods were separated by a one-month washout period.

Study duration	3 months
Dose	1 (40 mg isoflavone) tablet daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-Blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Hospital clinic
No. of subjects enrolled	51
No. of subjects completed	43
Sex	Female
Age	Mean: 54 years

Inclusion criteria

Women with more than three hot flashes per day.

Exclusion criteria

Intercurrent medical problems; hormone replacement therapy or antibiotics in previous three months; FSH < 30 mIU/ml; menstruation in previous six months; hysterectomy; or vegetarian (>10 g legumes per day).

End points
Tests were completed at the start and completion of the first treatment period and at the end of the second treatment period. They included a routine medical examination, blood collection, 24-hour urine sample for isoflavone analysis, endometrial thickness determined by transvaginal ultrasound, and vaginal smear to assess vaginal maturation index. In addition, a nurse examined subjects on a monthly basis, and subjects kept a daily symptom diary.

Results
No significant difference was observed between active and placebo groups in the reduction in hot flashes between start and finish time-points. Analysis performed on interim data time-points revealed a substantially greater reduction in hot flashes in the active group than placebo at four and eight weeks after commencement of treatment, but this was not statistically significant. No significant differences were observed between groups for Greene Menopause Symptom Scores, sex hormone binding globulin levels, hematological or biochemical parameters, and vaginal swab or ultrasound findings. The combined values for all subjects, regardless of treatment group, revealed a strong negative correlation between the level of urinary isoflavone excretion and the incidence of hot flashes.

Side effects
No adverse events.

Authors' comments
These data do not indicate a therapeutic benefit from dietary supplementation with isoflavones in women experiencing menopausal symptoms, but do indicate that the apparent placebo effect in many studies of menopausal symptoms may be attributable to dietary sources of isoflavones. The study also demonstrates that three months of isoflavone supplementation did not cause adverse events or endometrial changes.

Reviewer's comments
Although this was a relatively well-run study, the randomization was not adequately described, and no power calculation was provided for sample size. The Promensil treatment failed to show benefit. (3, 5)

Clinical Study: Promensil™

Extract name	None given
Manufacturer	Novogen Laboratories Pty Ltd., Australia

Indication	**Cardiovascular risk factors** in postmenopausal women
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Nestel PJ, Pomeroy S, Kay S, Komesaroff P, Behrsing J, Cameron JD, West L (1999). Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *The Journal of Clinical Endocrinology and Metabolism* 84 (3): 895-898.

Trial design

Parallel. A three-week run-in phase with placebo and controlled diet preceded randomization into two groups. The active group received placebo for five weeks, one Promensil tablet daily for another five weeks, then two Promensil tablets for the remaining five weeks. The other group, one-fifth the size, received placebo throughout.

Study duration	15 weeks
Dose	1 or 2 (40 mg isoflavone) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	26
No. of subjects completed	13
Sex	Female
Age	41-71 years

Inclusion criteria

Women who had been clearly postmenopausal for at least one year, FSH level greater than 40, plasma cholesterol level between 5 to 7 mmol/l, and free of cardiovascular disease.

Exclusion criteria

Over 70 years of age; hormone replacement therapy in preceding six weeks; supplements such as evening primrose oil or vitamin E in preceding four to six weeks; medication that might affect plasma lipids or cardiovascular func-

tion; smoking, and drinking more than 14 standard alcoholic drinks weekly; and body mass index greater than 32.

End points
Measurements were made at the end of each treatment phase (i.e., after run-in, placebo, and two active periods). Plasma lipid profiles were determined on two consecutive days. Isoflavone excretion in urine was measured to monitor absorption. Systemic arterial compliance, measurement of elasticity of the main conduit arteries, was determined near the end of each period.

Results
Arterial compliance rose by 23 percent with the 80 mg dose relative to the placebo period, and only slightly less with the 40 mg dose. The mean arterial compliance values for the active substance group were: run-in, 18.5; placebo, 19.7; 40 mg isoflavones, 23.7; and 80 mg isoflavones, 24.4 (mmHg/ml/min). The corresponding mean arterial compliance values for the four placebo individuals were: 17, 16, 16, and 16, respectively. For the active treatment group, differences were significant between placebo phase and 40 and 80 mg isoflavone doses (by paired t-tests: placebo versus 40 mg, $p = 0.039$; placebo versus 80 mg, $p = 0.018$). No significant difference was observed between the two treatment phases or between the placebo and run-in periods for the active treatment group. Plasma lipids were not significantly affected. The high dropout rate, higher during placebo phases than intervention phases, was due in part to intolerable menopausal symptoms.

Side effects
None mentioned.

Authors' comments
An important cardiovascular risk factor, arterial compliance, which diminishes with menopause, was significantly improved with red clover isoflavones. Since diminished compliance leads to systolic hypertension and may increase left ventricular work, the findings indicate a potential new therapeutic approach for improved cardiovascular function after menopause.

Reviewer's comments
This is an interesting study. However, participants were placed on a low-fat diet and "encouraged" to exercise, in addition to taking isoflavones. The placebo group had only three participants; the study was too small to draw any significant conclusions. (3, 4)

Clinical Study: Red Clover

Extract name	None given
Manufacturer	Novogen Laboratories Pty Ltd., Australia
Indication	**Cardiovascular risk factors** in premenopausal women
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Samman S, Lyons Wall PM, Chan GSM, Smith SJ, Petocz P (1999). The effect of supplementation with isoflavones on plasma lipids and oxidisability of low density lipoprotein in premenopausal women. *Atherosclerosis* 147 (2): 277-283.

Trial design
Crossover. Subjects took either placebo or red clover for two menstrual cycles, then switched to the other treatment for the following two cycles. Each subject served as her own control. Subjects were requested to maintain their normal eating patterns and alcohol consumption throughout the trial. The tablets used in this study are not Promensil, although the isoflavonoid profile is similar to two Promensil tablets.

Study duration	2 menstrual cycles
Dose	2 (43 mg isoflavone) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-Blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	21
No. of subjects completed	14
Sex	Female
Age	Mean: 27.5 ± 8.2 years

Inclusion criteria
Premenopausal, healthy women, regular menstrual cycle (23 to 35 days), ages 18 to 45.

Exclusion criteria
History of chronic illness; taking medications or oral contraceptives; suffering from liver, bowel, or gall bladder disorders; unstable body weight and exercise patterns; and regular intake of soy products (more than one serving per week).

End points
Normal ovulatory cycles were confirmed by measurement of luteinizing hormone in urine. Blood and urine samples were taken at baseline and during Cycles 2 and 4 to determine lipoprotein profiles and isoflavone concentrations.

Results
Supplementation resulted in a fivefold increase in urinary isoflavone excretion. No significant changes in oxidizability of low-density lipoprotein (LDL), or plasma concentrations of total cholesterol or triglyceride, were observed, with the exception of high-density lipoprotein (HDL) 3, which showed a significant period effect ($p = 0.024$) and a trend toward a carryover effect ($p = 0.086$).

Side effects
None mentioned.

Authors' comments
Supplementation of normocholesterolemic premenopausal women with isoflavones does not affect plasma cholesterol or LDL cholesterol concentrations, but may increase the concentration of HDL3 cholesterol. This observation, together with favorable effects on other cardiovascular risk factors reported previously, namely arterial compliance, supports the notion that isoflavones are cardioprotective.

Reviewer's comments
The therapeutic benefit was not determined. The report did not include a discussion of randomization, and the study was single-blinded. A further flaw was the small sample size. (1, 5)

Red Yeast Rice

Other common names: ***Hong qu***
Latin name: ***Monascus*** purpureus **Went.** [Monascaceae]

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Red yeast rice is a traditional Chinese fermented product made from a red yeast, *Monascus purpureus* Went., that is grown on rice. Documentation of the use of red yeast rice extends back to the Tang dynasty in 800 A.D. Red yeast rice products contain a group of compounds called the monacolins, which are a family of polyketides. The monacolins have been identified as inhibitors of an enzyme involved in the endogenous biosynthesis of cholesterol, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. One of the monacolins, monacolin K, is identical to lovastatin. Lovastatin is a common cholesterol-lowering statin drug that is manufactured by Merck and Co., Inc., West Point, Pennsylvania (Heber et al., 1999; Schulz, Hänsel, and Tyler, 2001).

Cholestin™ capsules are manufactured by Pharmanex, a subsidiary of Nu Skin Enterprises, Provo, Utah. The capsules contained 600 mg red yeast rice product, including 0.4 percent monacolins by weight (RY-2), approximately half of which (0.2 percent) were monacolin K. Recent court action by Merck, due to the similarity of monacolin K in Cholestin to lovastatin (mevinolin) in Mevacor®, blocked the sale of Cholestin as originally formulated in the United States. The original Cholestin, containing red yeast rice, is still available in other countries. The new U.S. formulation includes, as a substitute, a beeswax extract called policosanol. According to Pharmanex, policosanol is a safe and effective ingredient that successfully maintains existing normal cholesterol levels, although the new formulation has not been tested clinically. Each capsule of Cholestin

RED YEAST SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Cholestin™/No longer available in the United States in its original form	Pharmanex LLC/Pharmanex Natural Healthcare	Capsules containing 600 mg extract: 2.4 mg monacolins (RY-2)	1.2-2.4 g daily	Hyperlipid-emia (ele-vated blood lipid levels)	2	Yes (I-1, II-1)
Xue-zhi-kang	Wei-Xin Company, China/None	1.2 g contains 13.5 mg total monacolins (RY-1)	1.2 g daily	Hyperlipid-emia (ele-vated blood lipid levels	1	Trend (III-1)
Zhitai	WBL Peking Univ Biotech Co. Ltd., China/None	5 g contains 10-13 mg total monacolins	5 g daily	Hyperlipid-emia (ele-vated blood lipid levels)	1	Yes (II-1)

sold in the United States now contains 15 mg policosanol (beeswax extract 5:1).

Monascus purpureus Went. yeast is called Xue-zhi-kang in Chinese. The Xue-zhi-kang product (RY-1) produced by Wei-Xin Company (China) delivered a daily dose of 1.2 g red yeast rice containing 13.5 mg total monacolins.

The red yeast rice product called Zhitai, produced by WBL Peking University Biotech Co. Ltd. (China) delivered 10-13 mg total monacolins in a 5 g daily dose. According to a spokesperson from Pharmanex, the former two products were prototypes studied in the development of the original Cholestin.

SUMMARY OF REVIEWED CLINICAL STUDIES

Red yeast rice products have been tested in clinical studies for their effect in reducing elevated serum cholesterol levels. High cholesterol levels, total serum cholesterol more than 200 mg/dl and low-density lipoprotein (LDL) cholesterol more than 130 mg/dl, are indicated as risk factors for cardiovascular disease. Sources for serum cholesterol are dietary intake of animal fats and production by the liver. Cholesterol is transported in the blood by lipoproteins. The major categories of lipoproteins are very low-density lipoproteins (VLDL), low-density lipoproteins, and high-density lipoproteins (HDL). VLDL and LDL transport fats, primarily triglycerides and cholesterol, from the liver to cells throughout the body, whereas HDL returns fats to the liver. Elevations of either VLDL cholesterol or LDL cholesterol are associated with an increase in risk for developing atherosclerosis, which is a primary cause of heart attacks and strokes. The ratio of total cholesterol to HDL cholesterol and the ratio of LDL cholesterol to HDL cholesterol indicate whether cholesterol is being deposited into tissues or broken down and excreted (Pizzorno and Murray, 1999).

Elevated cholesterol levels can be reduced through changes in diet and/or administration of nutritional supplements or drugs. Three classes of drugs have been used to reduce cholesterol levels: bile acid sequestrants, nicotinic acid (niacin), and statins. The largest reduction in serum cholesterol, 25 to 45 percent, is observed with the statin drugs. Statins inhibit the activity of an enzyme involved in the biosynthesis of cholesterol, namely 3-hydroxy-3-methylglutaryl coen-

zyme A (HMG-CoA) reductase. The most familiar statin drugs are lovastatin (Mevacor) and simvastatin (Zocor®) (Hardman et al., 1996).

The monacolins present in red yeast rice are also identified as inhibitors of HMG-CoA reductase. Four studies explored the effect of red yeast rice products on lipid levels. Two trials demonstrated significant cholesterol lowering following eight to twelve weeks of treatment with Cholestin. A trial with another red yeast rice product attempted to demonstrate comparable activity to a statin drug, but the trial was performed in a population too small to be significant. Finally, a large trial, in which a third red yeast rice product was compared with placebo, also demonstrated lipid-lowering effects.

Cholestin

Hyperlipidemia (Elevated Blood Lipid Levels)

A double-blind, placebo-controlled, randomized trial included 83 subjects with slightly elevated cholesterol (total serum cholesterol 204 to 338 mg/dl, LDL cholesterol 128 to 277 mg/dl, triacylglycerol 55 to 246 mg/dl, and HDL cholesterol 30 to 95 mg/dl). Participants received either 2.4 g red yeast rice (Cholestin) or placebo for 12 weeks and were put on the American Heart Association's Step I diet. After eight and twelve weeks, total serum cholesterol and LDL cholesterol measurements in the treatment group decreased significantly from baseline and in comparison to placebo. The reduction in total cholesterol in the treatment group after 12 weeks compared with baseline was roughly 40 mg/dl. Triacylglycerol levels also decreased at week 8 in comparison to placebo, and at weeks 8 and 12 in comparison to baseline. HDL cholesterol levels did not alter significantly in either group (Heber et al., 1999).

A multicenter, single-blind trial included 446 subjects with primary hyperlipidemia (serum total cholesterol greater than 230 mg/dl, LDL cholesterol more than 130 mg/dl, or triglycerides of 200 to 400 mg/dl). Subjects received either 1.2 g red yeast rice (Cholestin) or another traditional Chinese medicine (Jiaogulan) with putative hypolipidemic properties. After eight weeks, serum total cholesterol in the red yeast rice group decreased by 23 percent compared with baseline, LDL cholesterol decreased by 30.9 percent, serum triglycerides decreased by 34.1 percent, and HDL cholesterol increased by 19.9 per-

cent. Ninety-three percent of subjects in the Cholestin group benefited from treatment compared with 50 percent of the Jiaogulan group (Wang et al., 1997).

Xue-zhi-kang

Hyperlipidemia (Elevated Blood Lipid Levels)

In a drug comparison study conducted in China, 28 hyperlipidemic subjects, with total cholesterol levels of more than 230 mg/dl and triglycerides greater than 200 mg/dl, were given either 1.2 g red yeast rice (Xue-zhi-kang) or 10 mg simvastatin (a statin drug) daily for eight weeks. Both treatments decreased total cholesterol and LDL cholesterol after four and eight weeks with no significant differences between the two. Both treatments reduced triglyceride levels, but the reduction with simvastatin was not significant. HDL cholesterol levels were not altered (Lu, 1998). This study was limited by the small sample size and the lack of detail in the report.

Zhitai

Hyperlipidemia (Elevated Blood Lipid Levels)

In a double-blind, placebo-controlled trial, 152 hyperlipidemic subjects were given either 5 g red yeast rice (Zhitai tablets) per day or placebo. Subjects initially had serum total cholesterol levels greater than 250 mg/dl and/or triglyceride levels greater than 200 mg/dl. After two months of treatment, total cholesterol, triglyceride, and LDL cholesterol levels were significantly decreased, and HDL cholesterol levels were significantly increased compared to baseline. Measurements in the placebo group did not change, and a significant difference from the treatment group was observed in all of the lipid levels mentioned previously (Zhiwei et al., 1996).

ADVERSE REACTIONS OR SIDE EFFECTS

Side effects reported in the trials discussed in this section consisted of occasional gastrointestinal discomfort. Contrary to studies with

other statin drugs, no elevations in liver function tests were observed in any of the studies. David Heber, our reviewer, considered the amounts of monacolin K contained in the red yeast rice products to be too low and the sample sizes too small to expect any adverse effects. The monacolin K content in red yeast rice is approximately 0.2 percent. Therefore, a dose of 2.5 g red yeast rice would be expected to contain 5 mg monacolin K or 10 mg total monacolins. Adverse effects on the liver are noted only with the statin drug lovastatin (Mevacor) at doses of greater than 20 mg per day, and the incidence rate is only 1.5 percent at 80 mg per day (Hardman et al., 1996).

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DETAILS ON RED YEAST PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Red Yeast Products

Product Profile: Cholestin™

Manufacturer	**Pharmanex LLC**
U.S. distributor	**Pharmanex Natural Healthcare**
Botanical ingredient	**Red yeast rice extract**
Extract name	**RY-2**
Quantity	600 mg
Processing	Fermented product of rice on which red yeast *(Monascus purpureus)* has been grown
Standardization	0.4% monacolins by weight (0.2% monacolin K)
Formulation	Capsule

Recommended dose: Take two capsules twice daily (morning and evening) with a drink and food to minimize the possibility of digestive discomfort. Must be taken regularly to help maintain healthy cholesterol levels.

DSHEA structure/function: Promotes healthy cholesterol levels.

Cautions: Do not take more than four capsules in a 24-hour period. Immediately discontinue use if you experience any unexplained muscle pain or tenderness, especially if accompanied by flulike symptoms. Do not use if you are pregnant, can become pregnant, or are breast feeding. Consult a physician if you are taking any prescription medication. Cholestin contains several natural HMG-CoA reductase inhibitors, one of which has been associated with rare (in less than 1 to 2 percent of users) but serious side effects. Do not take if: you are at risk of liver disease, have active liver disease, or have any history of liver disease; you consume more than two drinks of alcohol per day; you have a serious infection; you have undergone an organ transplant; you have a serious disease or physical disorder or have undergone major surgery.

Other ingredients: Gelatin.

Comments: This product is no longer available in this form in the United States. Instead of a red yeast rice extract, the product now has policosanol (beeswax extract 5:1) 15 mg per capsule.

Source(s) of information: Product package; Heber et al., 1999; information provided by manufacturer.

Clinical Study: Cholestin

Extract name	RY-2
Manufacturer	Pharmanex LLC
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Heber D, Yip I, Ashley JM, Elashoff DA, Elashoff RM, Go VLW (1999). Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. *American Journal of Clinical Nutrition* 69 (2): 231-236.

Trial design
Parallel. A one-week placebo run-in phase preceded the trial. Subjects were instructed in the American Heart Association's Step I diet (< 30 percent of energy from fat, < 10 percent of energy from saturated fat, and < 300 mg cholesterol per day).

Study duration	3 months
Dose	4 (600 mg red yeast rice) capsules daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	University research center
No. of subjects enrolled	88
No. of subjects completed	83
Sex	Male and female
Age	Not given

Inclusion criteria
Subjects with LDL cholesterol > 4.14 mmol/l and triacylglycerol concentrations < 2.94 mmol/l, who had not being treated previously for hypercholesterolemia, and had normal liver and renal function. Subjects came in twice for screening physical examinations and fasting blood samples.

Exclusion criteria
Subjects taking any lipid-regulating drugs, hormone replacement therapy, immunosuppressive agents, drugs known to affect lipid concentrations, or drugs known to be associated with rhabdomyolysis, including erythromycin and cyclosporine, insulin, or oral hypoglycemic agents; or having an endocrine disease known to lead to lipid abnormalities.

End points
Main outcome measures were total cholesterol, total triacylglycerol, and HDL and LDL cholesterol measured twice at baseline and at weeks 8, 9, 11, and 12. The two baseline measurements were averaged, as were the measurements at weeks 8 and 9 and at weeks 11 and 12. At baseline, eight, and twelve weeks, food-frequency questionnaires were given to patients to assess dietary intake.

Results
Eligible subjects had baseline levels of serum cholesterol of 5.28 to 8.74 mmol/l (204 to 338 mg/dl), LDL cholesterol of 3.31 to 7.16 mmol/l (128 to 277 mg/dl), triacylglycerol of 0.62 to 2.78 mmol/l (55 to 246 mg/dl), and HDL cholesterol of 0.78 to 2.46 mmol/l (30 to 95 mg/dl). Total cholesterol and LDL cholesterol concentrations in the treatment group differed significantly from baseline and the placebo group at weeks 8 and 12 (all $p < 0.05$). Triacylglycerol levels differed significantly from the control group at week 8, and from baseline at weeks 8 and 12 (all $p < 0.05$). HDL cholesterol levels

did not change significantly either from baseline or in comparison to placebo.

Side effects
No serious side effects.

Authors' comments
Red yeast rice reduces total cholesterol, LDL cholesterol, and total triacylglycerol concentrations significantly compared with placebo, and provides a novel food-based approach to lowering cholesterol in the general population.

Reviewer's comments
This study is the first U.S. trial of Chinese red yeast rice, and shows definite effects relative to placebo. (5, 6)

Clinical Study: Cholestin3™

Extract name	RY-2
Manufacturer	Pharmanex LLC
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Wang J, Lu Z, Chi J, Wang W, Su M, Kou W, Yu P, Yu L, Chen L, Zhu J, Chang J (1997). Multicenter clinical trial of the serum lipid-lowering effects of a *Monascus purpureus* (red yeast) rice preparation from traditional Chinese medicine. *Current Therapeutic Research* 58 (12): 964-978.

Trial design
Parallel. Patients were divided into four groups: three received red yeast rice and one received a traditional Chinese medicine (Jiaogulan, 1.2 g per day) with putative hypolipidemic properties.

Study duration	2 months
Dose	0.6 g red yeast rice twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Single-Blind

Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Jiaogulan *(Gynostemma pentaphylla)*
Site description	Multicenter
No. of subjects enrolled	502
No. of subjects completed	446
Sex	Male and female
Age	Mean: 56.2 ± 0.7 years

Inclusion criteria
Clinical diagnosis of primary hyperlipidemia: serum total cholesterol (TC) > 230 mg/dl (5.95 mmol/l), low-density lipoprotein (LDL) cholesterol > 130 mg/dl (3.41 mmol/dl), or triglycerides (TG) of 200 to 400 mg/dl (2.26 to 4.52 mmol/l). In addition, high-density lipoprotein (HDL) cholesterol < 40 mg/dl for men, or < 45 mg/dl for women. Medication for hyperlipidemia was discontinued for more than four weeks.

Exclusion criteria
Patients were excluded from this trial if they had any of the following during the last 6 months: myocardial infarction, stroke, severe trauma or major surgery, nephrotic syndrome, hypothyroidism, acute or chronic hepatobiliary disorders, diabetes mellitus, gout, allergies, or psychosis.

End points
At baseline, and at the end of weeks 4 and 8, patient serum lipids (TC, TG, and HDL cholesterol) were measured after fasting for 12 hours. LDL cholesterol and the ratio of non-HDL to HDL cholesterol were also calculated.

Results
After eight weeks of treatment, TC decreased by 22.7 percent ($p < 0.001$-comparison with baseline) in the red yeast rice patients, and a 7.0 percent reduction was found in the control group ($p < 0.001$-comparison between groups). LDL cholesterol was reduced by 30.9 percent in the red yeast rice group, whereas LDL in the control group was reduced by 8.9 percent. Between-group comparisons were significant ($p < 0.001$). TG followed the same trends as TC and LDL cholesterol, with differences between the groups being highly significant ($p < 0.001$). HDL cholesterol in the red yeast rice group increased by 19.9 percent, and it increased by 8.4 percent in the control group. Differences between the groups were highly significant ($p < 0.001$). The non-HDL cholesterol to HDL cholesterol ratio decreased by 34.5 percent in the red yeast rice group, compared to a decrease of 8.3 percent in the control group ($p < 0.001$-comparison between groups). Treatment with

red yeast rice was effective in 93.2 percent of patients, whereas treatment with control was effective in 50.8 percent of patients.

Side effects
Minor side effects: heartburn, flatulence, dizziness.

Authors' comments
This traditional Chinese rice preparation used as a dietary supplement is extremely effective and well tolerated in reducing elevated serum cholesterol and triglycerides.

Reviewer's comments
Good single-masked study that had clearly defined end points, a large sample, and was well reported. (3, 6)

Product Profile: Xue-zhi-kang

Manufacturer	**Wei-Xin Company, China**
U.S. distributor	None
Botanical ingredient	**Red yeast rice extract**
Extract name	**RY-1**
Quantity	1.2 g contains 13.5 total monacolins
Processing	No information
Standardization	HMG Co-A reductase activity (1.5-1.8%)

Comments: According to personal communication with Pharmanex, this is RY-1, an extract of RY-2 (which is Cholestin). It contains 4 times the quantity of HMG-CoA reductase inhibiting activity (1.5 to 1.8 percent).

Source(s) of information: Lu, 1998; Heber et al., 1999; Pharmanex personal communication, September 2002.

Clinical Study: Xue-zhi-kang

Extract name	RY-1
Manufacturer	Wei-Xin Company, China
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Lu GP (1998). The comparison of the blood lipids lowering effects of Xue-Zhi-Kang and simvastatin on hypercholesterolemic patients. *Chinese Journal of Internal Medicine* 37 (6): 371-373.

Trial design
Parallel. Patients took red yeast rice or simvastatin (10 mg per day) for eight weeks, maintaining food and drink habits throughout the trial. Patients with accompanying hypertension were permitted to continue treatment for these conditions.

Study duration	2 months
Dose	1.2 g red yeast rice daily; 10 mg/day simvastatin
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Simvastatin (Shu-jiang-zhi)
Site description	Outpatient department
No. of subjects enrolled	28
No. of subjects completed	28
Sex	Male and female
Age	Mean: 57 ± 10 years

Inclusion criteria
Hyperlipidemic (IIa or IIb) subjects with total cholesterol (TC) levels > 230 mg/dl or triglycerides (TG) > 200 mg/dl who were not being treated with other drugs or had stopped treatments more than four weeks before the trial.

Exclusion criteria
Patients with diseases of the liver, kidney, or thyroid gland were excluded.

End points
At baseline, and after four and eight weeks, blood samples were taken from patients after they had fasted for 12 hours. TC, TG, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol levels were determined.

Results
Both treatment with red yeast rice and simvastatin decreased TC and LDL cholesterol after four and eight weeks with no significant difference between the groups. Both drugs had a lowering effect on TG, although the decrease with simvastatin was not statistically significant. No obvious effect on HDL cholesterol was indicated. In general, the effect on blood lipids at the end of eight weeks was not different from that at four weeks.

Side effects
Patients experienced no adverse side effects.

Author's comments
Taking 1.2 g daily of red yeast rice significantly lowers serum TC and LDL cholesterol in hypercholesterolemic patients. The lowering degree is nearly the same as that of simvastatin.

Reviewer's comments
This study was limited by several flaws: the inclusion/exclusion criteria were not adequate, the statistical methods were not adequately described or applied, the study was not blinded, and the randomization process was not adequately described. The failure to find significance was due to the small sample size. In addition, bioequivalence of the two drugs was not demonstrated. (0, 3)

Product Profile: Zhitai

Manufacturer	**WBL Peking University Biotech Co. Ltd., China**
U.S. distributor	None
Botanical ingredient	**Red yeast rice extract**
Extract name	None given
Quantity	500 mg
Processing	No information
Standardization	1.0-1.3 mg total monacolins
Formulation	Capsule

Comments: According to personal communication with Pharmanex, this is an earlier version of RY-2 (Cholestin) with much lower potency.

Source(s) of information: Zhiwei et al., 1996; Heber et al., 1999; Pharmanex personal communication, September 2002.

Clinical Study: Zhitai

Extract name	None given
Manufacturer	WBL Peking University Biotech Co. Ltd., China
Indication	**Hyperlipidemia** (elevated blood lipid levels)
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference

Zhiwei S, Pulin Y, Meizhen S, Chi J, Zhou Y, Zhu X, Yang C, He C (1996). A prospective study on Zhitai capsule in the treatment of primary hyperlipidemia. *National Medical Journal of China* 76 (2): 156-157.

Trial design

Parallel. Subjects were divided into three groups: two received active treatment and one received placebo.

Study duration	2 months
Dose	5 tablets Zhitai twice daily (5 g/day)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	152
No. of subjects completed	152
Sex	Male and female
Age	Mean: 55 years

Inclusion criteria

Primary hyperlipidemia: two consecutive blood lipid examinations of one-month interval with serum total cholesterol (TC) > 6.47 mmol/l (250 mg/dl) and/or triglycerides (TG) > 2.26 mmol/l (200 mg/dl). Patients had to have discontinued medications that could affect metabolism of blood lipids at least one month prior to the study. Subjects had a low-fat, low-cholesterol diet for one month before trial.

Exclusion criteria
Patients were excluded if their hyperlipidemia was secondary to other diseases or disease conditions, including diabetes, hypothyroidism, gout, hepatobiliary diseases, pancreatic diseases, or renal diseases. Patients who had in the last six months: acute myocardial infarction, heart surgery, stroke, or other severe diseases.

End points
At baseline, and at one and two months, blood was taken from patients and analyzed for serum TC, TG, high-density lipoprotein (HDL) cholesterol, blood glucose, and serum uric acid. Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. Patients also had their body weight, blood pressure, heart rhythm, and heart rate recorded each month.

Results
After treatment for two months with Zhitai, TC, TG, and LDL cholesterol were dramatically decreased, and HDL cholesterol had markedly increased compared to baseline values ($p < 0.01$). Although no significant changes were seen in the control group, very significant differences were found between the two groups for all of these measurements ($p < 0.01$).

Side effects
No patients complained of side effects.

Authors' comments
This dietary supplement is a new type of blood lipid regulator, functioning by reducing blood cholesterol.

Reviewer's comments
This is a well-designed and well-conducted study that demonstrates lipid lowering effects in an adequate study size of Chinese patients. (2, 6)

Saw Palmetto

Other common names: **Sabal palm**
Latin name: ***Serenoa repens* (W. Bartram) Small** [Arecaceae]
Latin synonyms: ***Sabal serrulata* (Michx.) Nutt. ex Schult. & Schult. f.; *Serenoa serrulata* (Michx.) G. Nichols.**
Plant part: **Fruit**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Saw palmetto is native to North America and grows wild in Texas, Louisiana, South Carolina, and Florida. Traditionally, Native Americans in this region used the berries for food and as a tonic (USP, 2000). In addition, the berries have been used for more than 100 years to treat benign prostatic hyperplasia. Modern saw palmetto preparations contain lipids extracted from the powdered berries. The primary ingredients include saturated and unsaturated fatty acids (mostly free fatty acids), as well as free and conjugated plant sterols (Schulz, Hänsel, and Tyler, 2001).

Permixon®, manufactured in France by Pierre Fabre Médicament, contains the lipidosterolic extract PA109. PA 109 is a hexane extract whose main components are free (90 percent) and esterified (7 percent) fatty acids, of which about half are unsaturated C_{18} fatty acids. Permixon is also sold as Capistan®, Libeprosta®, and Sereprostat®. Permixon, which is the most clinically studied saw palmetto preparation, is not sold in the United States.

Prostaserene® is a single ingredient product manufactured by Therabel Pharma in Belgium. Prostaserene contains the saw palmetto fruit extract SabalSelect™, which is manufactured by Indena S.p.A in Italy. The extract is made using supercritical carbon dioxide as the solvent, and is characterized as containing 85 to 95 percent fatty acids. Prostaserene is available in 160 mg capsules, but is not sold in the United States. SabalSelect is contained in a product called Serenoa

SAW PALMETTO SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
			Single-Ingredient Products			
Permixon® (EU)	Pierre Fabre Médicament, France/None	Hexane extract (PA 109)	320 mg/day	Benign prostatic hyperplasia	13	Yes (I-1) Trend (I-1, II-3, III-3) No (II-1) Undetermined (III-3) MOA (III-1)
Prostaserene® (EU)*	Therabel Pharma, Belgium (Indena S.p.A., Italy/None	Supercritical carbon dioxide extract (SabalSelect™)	320 mg/day	Benign prostatic hyperplasia	2	Yes (I-1) Undetermined (III-1)
Strogen® uno (EU)	Schaper & Brümmer GmbH & Co. KG, Germany/None	Lipophilic extract (IDS 89)	1,920 mg/day	Benign prostatic hyperplasia	1	MOA (III-1)
ProstActive®	Dr. Willmar Schwabe GmbH & Co., Germany/ Nature's Way Products, Inc.	Ethanolic extract (WS 1473)	300 mg/day	Benign prostatic hyperplasia	1	No (I-1)

Combination Products						
ProstActive® Plus (US), Prostagutt® forte (EU)	Dr. Willmar Schwabe GmbH & Co., Germany/ Nature's Way Products, Inc.	Saw palmetto (160 mg extract WS 1473), nettle root (120 mg extract WS 1031)	2 capsules per day	Benign prostatic hyperplasia	2	Yes (II-1) Undetermined (I-1)
Nutrilite® Saw Palmetto with Nettle Root	Access Business Group: Home of Nutrilite/Access Business Group: Home of Nutrilite	Saw palmetto (106 mg), nettle root (80 mg), Pumpkin seed oil (160 mg), lemon bioflavonoid extract (33 mg)	1 capsule 3 times daily	Benign prostatic hyperplasia	1	Trend (I-1)

*A single ingredient product that contains the Indena S.p.A Sabal Select™ extract is listed here. The extract has been tested clinically but the final formulation listed below has not.

Product Name	**Manufacturer**
Serenoa Gelcaps	Thorne Research

Gelcaps, manufactured by Thorne Research, that is sold in the United States.

Strogen® uno is manufactured by Schaper & Brümmer GmbH & Co. KG in Germany. The product contains a lipophilic extract (IDS 89), and is available in 320 mg capsules. Strogen uno is not sold in the United States.

ProstActive® is manufactured in Germany by Dr. Willmar Schwabe GmbH & Co. and contains an ethanolic saw palmetto fruit extract WS 1473 (plant to extract ratio [100:8.5]). ProstActive is available in softgel capsules that contain 320 mg WS 1473, and is sold in the United States by Nature's Way Products, Inc.

ProstActive® Plus contains the nettle (*Urtica dioica* L. spp. *dioica*) root extract WS 1031, in addition to the saw palmetto fruit extract WS 1473. This product is also manufactured by Dr. Willmar Schwabe GmbH & Co. in Germany and sold in the United States by Nature's Way Products, Inc. One softgel capsule of ProstActive Plus contains 160 mg of the ethanolic extract WS 1473 and 120 mg of the ethanolic extract WS 1031. ProstActive Plus is sold in Europe as Prostagutt® forte.

Nutrilite® Saw Palmetto with Nettle Root is manufactured and sold in the United States by the Access Business Group: Home of Nutrilite. Each softgel capsule contains 106 mg saw palmetto fruit extract (characterized as containing > 85 percent fatty acids), 80 mg nettle (*Urtica dioica* L. spp. *dioica*) root extract (characterized as containing > 0.8 percent beta-sitosterol), 160 mg pumpkin (*Cucurbita pepo* L.) seed extract, and 33.3 mg lemon [*Citrus* × *limon* (L.) Osbeck] bioflavonoid concentrate (characterized as containing more than 25 percent total bioflavonoids).

SUMMARY OF REVIEWED CLINICAL STUDIES

Saw palmetto preparations have been assessed in clinical studies for the treatment of symptomatic benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy and prostatic adenoma. BPH is a nonmalignant enlargement of the prostate that is common in men over 40 years of age. Symptoms include increased urinary urgency and frequency (diuresis: increased formation and release of urine; and nocturia: frequent and/or excessive urination at night), urinary hesitancy, intermittency, sensation of incomplete voiding, and

decreased force of the urine stream. BPH is linked with a normal change in hormone levels that occurs with aging. Testosterone levels decrease while estrogen levels remain constant. This change is implicated in BPH since estrogens induce hyperplasia (cell growth) in laboratory experiments. Further, BPH is associated with an increase in the activity of 5-alpha-reductase, the enzyme that converts testosterone to dihydrotesterone (DHT). The levels of DHT are not increased, but the number of androgen receptors seem to be. DHT has a greater affinity for androgen receptors than testosterone and is thought to stimulate prostatic growth. However, the pathology of BPH is not completely understood. Although BPH is associated with prostate enlargement, the size of the gland is not necessarily indicative of the degree of obstruction of the urethra and the extent of symptoms (Schulz, Hänsel, and Tyler, 2001; Barrett, 1999).

Several different rating systems have been developed to characterize the symptoms of BPH: the International Prostate Symptom Score (IPSS), the American Urological Association (AUA) symptom score, the Vahlensieck classification, and the Alken classification.

The IPSS is derived from a questionnaire regarding urinary urgency, frequency, hesitancy, intermittency, sensation of incomplete voiding, and force of urine stream (Schulz, Hänsel, and Tyler, 2001). The AUA symptom score is also a composite score obtained from seven questions covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency (Barry et al., 1992).

The Vahlensieck classification has four stages based upon symptoms: Stage I is characterized by no voiding difficulties, no residual urine, and a urine flow of more than 15 ml per second; Stage II is characterized by transient voiding difficulties and urine flow between 10 and 15 ml per second; Stage III is characterized by constant voiding dysfunction, urine flow less than 10 ml per second, residual urine greater than 50 ml, and a trabeculated (ridged) bladder; and Stage IV is characterized by residual urine volume of more than 100 ml and bladder dilatation (Schulz, Hänsel, and Tyler, 2001).

The Alken classification has three stages. Stages I to III are similar to Vahlensieck Stages II through IV. Stage I is the irritative stage, characterized by an increase in the frequency of urination, pollakiuria (abnormally frequent urination), nocturia, delayed onset of urination, and weak urinary stream. Stage II is the residual urine stage, charac-

terized by the beginning of the decomposition of the bladder function accompanied by formation of residual urine and the urge to urinate. Stage III is the regressive-obstructive stage, characterized by decomposition of the bladder, vesicular overflowing, continuous drip incontinence, and damage to the urinary system and kidneys due to regressive obstruction (Löbelenz, 1992).

Predominant pharmaceutical treatments of BPH include alpha-receptor blockers and 5-alpha-reductase inhibitors. Alpha-adrenergic receptor blockers (e.g., prozosin, terazosin) are thought to relax smooth muscles in the bladder neck and within the prostate and thus reduce symptoms. Five-alpha-reductase inhibitors (e.g., finasteride) prevent the transformation of testosterone to DHT, thus increasing levels of testosterone and reducing levels of DHT (Barrett, 1999).

Suggested pharmacological actions for saw palmetto include anti-androgenic, anti-inflammatory, antiproliferative, and smooth muscle relaxation. Saw palmetto preparations have been shown to inhibit 5-alpha reductase, as well as the binding of DHT to androgen receptors. However, questions remain as to whether these actions, demonstrated in vitro, are clinically relevant (Barrett, 1999).

Permixon

Benign Prostatic Hyperplasia

Thirteen trials were reviewed that studied the use of Permixon as treatment for symptomatic BPH. Included are eight studies controlled with placebo, three controlled with another treatment, one dose-regimen comparison, and one mode of action study. The prevalent dose was 160 mg extract (PA109) twice daily. The benefit of saw palmetto berry (Permixon) in the treatment of BPH appears mostly in terms of symptom relief, which occurred one month to six weeks after beginning treatment.

A large, good-quality, placebo-controlled study of 146 men with BPH showed a statistically significant reduction in symptoms, especially nocturia (30 percent decrease), painful urination (47 percent improvement), and the volume of posturination residue compared to placebo after two to three months (Cukier et al., 1985). Our reviewers, Drs. Elliot Fagelman and Franklin Lowe, commented that this study demonstrated a therapeutic benefit, but that it was short in duration.

Two small studies of good design lasting two months showed statistical benefit compared to placebo. A small trial including 27 men with BPH Stages I or II (rating system not given) reported a reduction in symptoms in 43 percent of the Permixon group and 15 percent of the placebo group after two months (Tasca et al., 1985). Another small study with 22 men with BPH reported a statistical increase in maximal and average urine flow, as well as improvements in daytime and nighttime frequency compared to placebo after two months (Boccafoschi and Annoscia, 1983). Our reviewers rated these two studies as showing merely a trend toward efficacy due to their small sample sizes and short lengths of treatment.

Four trials lasting one month each also showed a trend toward benefit for BPH symptoms. The largest of the four trials, a good-quality study, included 186 men with Stages I or II BPH (rating system not given), as well as a placebo run-in period of a month to eliminate the placebo responders. With Permixon, there was a significant decrease in diuresis (increased formation and release of urine) as well as nocturia (frequent and/or excessive urination at night) compared to placebo. A significant increase in peak urine flow was also observed. However, the global efficacy assessment by both patients and physicians was not significantly different from placebo (Descotes et al., 1995). A trial with 94 men with BPH reported significant improvements in nocturia, flow rate, and postvoiding residue in comparison with placebo. In addition, both the physician and patient self-rating indicated superiority of Permixon in comparison to placebo (Champault, Patel, and Bonnard, 1984). A trial with 59 men with BPH compared Permixon to an extract of *Pygeum africanum* (no details given) and placebo. As a result, a significant difference in improvement in symptoms with Permixon was observed compared to pygeum and placebo. The symptoms with the greatest improvement with Permixon compared to baseline were pain upon voiding (73 percent decrease), urgency (70 percent decrease), tenesmus (spasms of the bladder along with the urge to empty, 82 percent decrease), and nocturia (42 percent decrease) (Mandressi et al., 1983). A small trial with 30 men with BPH reported a reduction in a number of symptoms compared to placebo (Emili, Lo Cigno, and Petrone, 1983). The quality of the smaller three studies was rated as poor due to either the poor trial design or a lack of detail in the trial report.

A good-quality, placebo-controlled study, including 70 men, found a complete lack of benefit beyond the placebo effect. Both groups had a statistical improvement in urinary flow after three months (Reece Smith et al., 1986).

Three drug comparison studies are mentioned later: one compared the activity of Permixon to the 5-alpha reductase inhibitor finasteride, and two compared Permixon to the alpha blockers alfuzosin and prozosin. The largest trial, which included 1,098 men and lasted six months, compared Permixon (320 mg per day) to finasteride (Proscar®, 5 mg per day). Both treatments decreased the IPSS symptom scores, quality-of-life scores, and increased peak urine flow compared to baseline, with no significant difference between the two. Finasteride markedly reduced prostate volume, but Permixon had little effect on volume. Finasteride also reduced levels of PSA (prostate-specific antigen), a serum marker for prostate cancer. Since the potential for confusion exists between the diagnoses of BPH and prostate cancer, the reduction of PSA levels by finasteride is a confounding variable. PSA levels were not altered by Permixon (Carraro et al., 1996). Our reviewers remarked that there was a significant therapeutic benefit compared to baseline for both groups, but that the lack of a placebo group was a limitation. Two small, short studies compared Permixon with two alpha-blockers: alfuzosin and prozosin. Both trials reported the alpha-blockers to be superior to Permixon in reduction of symptoms. A three-week study with 63 men with BPH found alfuzosin (7.5 mg per day) was more effective than Permixon (320 mg per day) in reducing symptoms according to Boyarsky's scale and an obstructive score (Grasso et al., 1995). A three-month study with 41 men with BPH grade I or II (rating system not given), reported that prozosin (4 mg per day) compared to Permixon (320 mg per day) was slightly more effective in reducing frequency of urination and increasing urinary flow. However, this comparison was based upon absolute numbers, and no statistical analysis was completed (Semino et al., 1992). The quality of the last two trials was not good according to the Jadad criteria, and there was no placebo group to act as a benchmark for activity. In addition, the identity of the saw palmetto product was not revealed in the trial report, but gathered from the review by Boyle and colleagues (2000).

A dose-regimen study explored the difference in delivering 320 mg once daily or 160 mg twice daily in a trial including 92 men. After

three months, both treatment groups had significantly reduced IPSS scores, with no difference between them (Stepanov et al., 1999). However, the trial did not include a placebo group and therefore the efficacy was rated as undetermined.

A placebo-controlled mode-of-action study with 25 men examined hormone levels in prostate tissue removed after three months of treatment. The results suggested that Permixon may reduce DHT and epidermal growth factor levels and increase testosterone levels (Di Silverio et al., 1998).

Prostaserene

Benign Prostatic Hyperplasia

In a well-conducted trial, 205 men with mild to moderate BPH were given Prostaserene (160 mg twice daily) or placebo for three months. As a result, Prostaserene caused a significant improvement over placebo according to the total symptom score (frequency, nocturia, dysuria, urgency, and hesitancy), as well as the patient and physician quality-of-life scores (Braeckman, Denis et al., 1997). In the same year, another study was published comparing the dose of 160 mg twice daily to 320 mg once daily in a trial lasting for one year. In this study, with 67 men, both treatment regimens improved the IPSS by 60 percent. However, efficacy in general could not be evaluated because the study did not include a placebo (Braeckman, Bruhwyler et al., 1997).

Strogen uno

Benign Prostatic Hyperplasia

A study on Strogen uno evaluated the biochemical changes in prostate tissue removed from men after three months of treatment with either saw palmetto extract (640 mg three times daily) or placebo. The amounts and substrate affinities of enzymes involved in the formation of DHT (5-alpha-reductase) and removal of DHT (3-alpha and 17-beta hydroxysteroid oxidoreductases) were analyzed. Although significant changes were measured in enzyme levels, the alterations were moderate, and the authors of the report concluded that the clinical significance was unknown (Weisser et al., 1997).

ProstActive and ProstActive Plus

Benign Prostatic Hyperplasia

ProstActive failed to show any significant improvement over placebo in a well-conducted small trial with 60 men with BPH Stages I and II, according to Alken, who were given a dose of 100 mg three times daily (Löbelenz, 1992). Two studies were conducted on a combination product containing saw palmetto extract and nettle extract (Prostagutt forte). One study, with 33 men, compared 160 mg saw palmetto extract plus 120 mg nettle extract twice daily for six months to placebo, and reported a beneficial reduction in BPH symptoms compared with placebo, according to the AUA score (Metzker, Kieser, and Holscher, 1996). A large study with 498 men with BPH Stages I and II, according to Alken, compared the combination product to finasteride over one year. The herbal combination appeared to be equivalent to finasteride in causing the reduction in IPSS and improvement to quality of life, but the herbal preparation was better tolerated (Sokeland and Albrecht, 1997). However, due to the lack of a placebo group, the clinical benefit was deemed undetermined.

Nutrilite Saw Palmetto with Nettle Root

Benign Prostatic Hyperplasia

Nutrilite Saw Palmetto with Nettle Root was compared with placebo in a well-designed, six-month trial including 41 men using a dose of one capsule three times daily. No statistical improvement in symptoms was observed in the treatment group compared to the placebo group. However, morphological changes were noted in biopsy samples. A reduction in size of the prostate according to the percentage of atrophied tissue and percentage of epithelium was seen in the treatment group. No change was observed in the placebo group (Marks et al., 2000).

META-ANALYSES AND SYSTEMATIC REVIEWS

Boyle et al. (2000) conducted a meta-analysis on 11 randomized, controlled trials and two open, uncontrolled trials, including a total of

2,859 men with BPH treated with Permixon. The authors concluded that the agent improved urinary peak flow rate significantly and reduced the number of nighttime urinations compared with placebo. The clinical trial size ranged from 22 to 592 subjects and in duration from 21 days to six months. The 11 randomized, controlled trials are reviewed in detail in this section.

A systematic review of 18 randomized, controlled trials involving 2,939 men, using preparations of saw palmetto alone or in combination with other phytotherapeutic agents, concluded that saw palmetto improves urologic symptoms and flow measures in BPH. This improvement was similar to the drug finasteride, and was associated with fewer adverse effects (Wilt et al., 1998).

ADVERSE REACTIONS OR SIDE EFFECTS

In general, saw palmetto was well tolerated with few side effects reported in the trials reviewed. The largest controlled trial with Permixon, which included 1,098 men, reported hypertension as the most frequent adverse event occurring in 3.1 percent, followed by decreased libido in 2.2 percent, and abdominal pain in 1.8 percent (Carraro et al., 1996). A three-year, uncontrolled study with 435 men given IDS 89 (Strogen uno), 320 mg per day, reported good or very good tolerability, as reviewed by both physicians and patients, in 98 percent of subjects. Forty-six adverse events were documented in 34 patients—30 percent were gastrointestinal disturbances (Bach and Ebling, 1996). A review of controlled trials involving 2,939 men concluded that the adverse effects were mild and infrequent, in contrast to finasteride, which was more commonly associated with erectile dysfunction (Wilt et al., 1998).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

German Commission E
The United States Pharmacopoeial Convention, Inc.

Indications

The German Commission E monograph approves use of the ripe, dried fruit of saw palmetto and its preparations for urination problems in benign prostatic hyperplasia Stages I and II, according to Alken. The Commission further notes that the medication relieves only the symptoms associated with an enlarged prostate but does not reduce the enlargement (Blumenthal et al., 1998).

Traditionally, saw palmetto has been used to strengthen the male reproductive system, and, more specifically, to treat symptoms of an enlarged prostate. Women have used saw palmetto to treat enlarged ovaries and increase the size of undeveloped mammary glands. For both men and women, it has been used to increase sexual vigor, as a general tonic, as a diuretic, and for genitourinary problems (USP, 2000).

Doses

Fruit: 1 to 2 g berries or equivalent preparations (Blumenthal et al., 1998; USP, 2000)

Tea: one cup three times a day. Bring one cup water with one-third daily dose of saw palmetto fruit to a boil and then simmer for five minutes (USP, 2000)

Tincture: (fresh fruit 1:2, dried fruit 1:5, 80 percent alcohol) 1 to 2 ml, 3 to 4 times daily (USP, 2000)

Extract:

- Liquid: (1:1) 0.6 to 1.5 ml per day (USP, 2000)
- Liposterolic: 320 mg daily lipophilic ingredients extracted with lipophilic solvents (10:1, hexane or ethanol 90 percent v/v) (Blumenthal et al., 1998; USP, 2000)

Contraindications

The Commission E lists no known contraindications (Blumenthal et al., 1998).

Adverse Reactions

The Commission E lists stomach problems in rare cases, and the USP lists mild gastrointestinal complaints, such as diarrhea and nausea (Blumenthal et al., 1998; USP, 2000).

Precautions

The USP states that the use of saw palmetto in pregnant or breast-feeding women and in children cannot be recommended, since it has not been studied (USP, 2000).

Drug Interactions

The Commission E lists no known drug interactions (Blumenthal et al., 1998). The USP suggests that although no interactions have been reported, saw palmetto may have endocrine or alpha-adrenergic blocking effects, although these possible interactions have not been studied (USP, 2000).

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treatment with the *Sabal serrulata* extract IDS 89 (Strogen) or placebo. *European Urology* 31 (1): 97-101.

Wilt TJ, Ishani A, Stark G, MacDonaald R, Lau J, Mulrow C (1998). Saw palmetto extracts for treatment of benign prostatic hyperplasia: A systematic review. *Journal of the American Medical Association* 280 (18): 1604-1609.

DETAILS ON SAW PALMETTO PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Saw Palmetto Products

Product Profile: Permixon®

Manufacturer	**Pierre Fabre Médicament, France**
U.S. distributor	None
Botanical ingredient	**Saw palmetto fruit extract**
Extract name	**PA 109**
Quantity	80 mg
Processing	*N*-hexane lipidosterolic extract
Standardization	No information
Formulation	Tablet

Recommended dose: Two tablets twice daily.

Comments: Also sold as Capistan®, Libeprosta®, and Sereprostat®.

Source(s) of information: Descotes et al., 1995; Di Silverio et al., 1998; Champault, Patel, and Bonnard, 1984.

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Cukier, Ducassou, Le Guillou, Leriche, Lobel, Toubol, Doromieux, Grinewald, Pastorini, Raymond, Reziciner, Martinaggi (1985). Permixon versus placebo. *Comptes Rendus de Therapeutique et de Pharmacologie Clinique* 4 (25): 15-21.

Trial design
Parallel.

Study duration	2 to 3 months
Dose	2 (80 mg) tablets twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Open
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	168
No. of subjects completed	146
Sex	Male
Age	60-79 years

Inclusion criteria
Men over 60 years old with prostatic hypertrophy in the “prostatism” stage for whom surgery was not indicated, and with symptoms for at least six months.

Exclusion criteria
Prostatic hypertrophy with mechanical or infectious complications.

End points
Dysuria (painful urination), pollakiuria, and nocturia (nightly urination) were assessed at trial start, day 30, and at the end of the trial. These symptoms were also recorded weekly by the patients. Overall assessment of efficacy and acceptability of the treatment by physician and patient at day 30 and at end of trial.

Results
With Permixon, there was a 30 percent decrease in urination at night, which was significant compared to placebo ($p < 0.001$). The greatest changes were seen with those experiencing more than three visits per night. There was a 47 percent improvement in painful urination compared to placebo ($p < 0.001$). Posturination residue was decreased in the Permixon group, whereas it increased in the placebo group. The difference between the two groups was significant ($p < 0.05$). Assessment of efficacy by the physician was better for Permixon (66.7 percent) than for placebo (26.9 percent).

Side effects
Tolerability was 94.4 percent for Permixon and 91.3 percent for placebo.

Authors' comments
Permixon appears to be a valuable therapeutic solution provided it is used under clearly identified circumstances, in particular in the absence of complications and hence any indication for more aggressive therapeutic measures.

Reviewers' comments
This is a well-run and well-designed trial. The one major drawback of this study is the short duration (two to three months). Also, although the results are statistically significant, the difference may not be clinically significant. (Translation reviewed) (5, 6)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Zambeletti S.p.A, Italy (Pierre Fabre Médicament, France)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Tasca A, Barulli M, Cavazzana A, Zattoni F, Artibani W, Pagano F (1985). Treatment with *Serenoa repens* extract of the obstructive signs and symptoms caused by prostatic adenoma. *Minerva Urologica e Nefrologica* 37 (1): 87-91.

Trial design
Parallel. Pretrial washout period of two months.

Study duration	2 months
Dose	160 mg twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	30
No. of subjects completed	27
Sex	Male
Age	49-81 years

Inclusion criteria
Patients suffering from prostatic adenoma Stages I or II (rating system not given).

Exclusion criteria
Patients having significant hepatic, renal, or cardiac disorders.

End points
Before and after treatment, patients underwent a general physical exam for evaluation of prostate volume, postmicturition bladder residue, uroflowmetrics, urine culture, and a series of clinical chemistry parameters. Subjective aspects were obtained from a questionnaire completed by patients every ten days.

Results
Beneficial results were obtained in 42.9 percent of cases treated with Permixon and in 15.4 percent treated with placebo. A statistical improvement was observed in uroflowmetric recording for Permixon treatment com-

pared to baseline ($p < 0.05$). The placebo group showed no significant change.

Side effects
Tremor, dizziness, and cold sweat in one patient taking Permixon.

Authors' comments
The results obtained with *Serenoa repens* compared with placebo, in homogeneous patient groups, indicate an efficacious action in reducing urinary signs and symptoms and in improving related instrumental parameters.

Reviewers' comments
Overall, this is a good study suggesting a benefit for Permixon versus placebo. However, the number of patients was small, and the treatment duration was short. (Translation reviewed) (3, 4)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Zambeletti S.p.A, Italy (Pierre Fabre Médicament, France)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Boccafoschi C, Annoscia S (1983). Comparison between extract of *Serenoa repens* and a placebo in controlled clinical tests on patients with prostate adenomatoses. *Urology* 50: 1257-1268.

Trial design
Parallel.

Study duration	2 months
Dose	2 (160 mg) capsules (morning and night)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes

Drug comparison	No
Site description	Outpatient clinic
No. of subjects enrolled	22
No. of subjects completed	22
Sex	Male
Age	54-80 years

Inclusion criteria
Patients with benign prostatic hypertrophy that could be treated with medication.

Exclusion criteria
Hypertension, cerebral disorders, or chronic bronchopneumopathy.

End points
Tests were performed at baseline and after 30 and 60 days. The clinical symptoms were dysuria, pelvic heaviness, nocturia, and daytime pollakiuria. In some cases, posturination residue and prostate adenoma dimension were established. Urine cultures were performed at baseline and after 30 and 60 days.

Results
The volume of urine, maximum flow, and average flow were increased in the Permixon group compared to placebo ($p < 0.0005$, $p < 0.02$, and $p < 0.05$, respectively). Dysuria and nocturia were also improved ($p < 0.01$ and $p < 0.05$, respectively). Not significant were changes in urination time, urinary residue, and pelvic heaviness. No change was observed in prostate size.

Side effects
None reported.

Authors' comments
The results confirm the usefulness of Permixon in the treatment of specific clinical forms of prostate hyperplasia.

Reviewers' comments
This is a very limited study based on the sample size (only 22 patients). Hypertension alone should not be an exclusion criterion for benign prostatic hyperplasia. Although some statistical benefit is shown, this should be viewed with caution. The treatment length was relatively short. (Translation reviewed) (5, 3)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Descotes JL, Rambeaud JJ, Deschaseaux P, Faure G (1995). Placebo-controlled evaluation of the efficacy and tolerability of Permixon in benign prostatic hyperplasia after exclusion of placebo responders. *Clinical Drug Investigation* 9 (5): 291-297.

Trial design
Parallel. Trial preceded by a single-blind placebo run-in period of 30 days. Nonresponders were entered into randomized double-blind, placebo-controlled trial for 30 days.

Study duration	1 month
Dose	160 mg twice daily (morning and evening)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	215
No. of subjects completed	186
Sex	Male
Age	57-75 years

Inclusion criteria
Patients with clinically demonstrated mild to moderate (Stages I or II) benign prostatic hyperplasia, symptoms of dysuria, daytime and nocturnal urinary frequency (> 2 at night excluding bedtime and on awaking) of at least eight weeks duration, and a maximum urinary flow rate > 5 ml/sec. Nonresponders to a 30-day placebo run-in (< 30 percent improvement from baseline in peak urinary flow rate).

Exclusion criteria
Patients with excessively mild symptoms of BPH (nocturnal urinary frequency < 1) of recent onset (< 8 weeks), excessively severe symptoms of BPH (peak urinary flow rate < 5 ml/sec, incontinence, bladder distension, acute urinary retention, or other complications), associated urogenital infection, hematuria, diabetes, neuropathy or pelvic cancer, history of surgery for BPH, or any surgery that could induce dysuria.

End points
Urinary symptoms were assessed at entry into the study, after the placebo run-in, and upon completion. Efficacy was assessed on the basis of changes in symptom scores, peak urinary flow rates, and overall opinions of the response to treatment by both physicians and patients.

Results
Improvement in dysuria severity was seen in a significantly greater proportion of Permixon recipients than placebo recipients (31.3 percent versus 16.1 percent, $p = 0.019$). Daytime urinary frequency fell significantly in Permixon-treated patients compared with placebo recipients ($p = 0.012$). Nocturnal urinary frequency fell to a significantly greater extent with Permixon than with placebo (32.5 percent versus 17.7 percent, $p = 0.028$). Permixon produced a significantly greater increase in mean peak urinary flow rate than did placebo (28.9 percent versus 8.5 percent, $p = 0.038$). The global efficacy of Permixon was not judged significantly different from placebo by the patients or physicians.

Side effects
One patient reported fatigue, depression, and stomach upset.

Authors' comments
Permixon appears to be significantly more effective than placebo and well-tolerated in the short-term treatment of mild to moderate symptomatic BPH.

Reviewers' comments
The study is flawed by leaving out placebo responders, thus eliminating the placebo effect and biasing the study in favor of Permixon. In addition, the randomization process was not adequately described. (3, 6)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**

Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Champault G, Patel JC, Bonnard AM (1984). A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia. *British Journal of Clinical Pharmacology* 18 (3): 461-462.

Trial design
Parallel.

Study duration	1 month
Dose	2 (80 mg) tablets twice daily (320 mg extract/day)
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Outpatient clinic
No. of subjects enrolled	110
No. of subjects completed	94
Sex	Male
Age	Not given

Inclusion criteria
Benign prostatic hyperplasia symptoms of dysuria, nocturia, and frequent and poor urinary flow.

Exclusion criteria
Patients with an acute or unstable episode, adenomas requiring early surgery, carcinomas of the prostate, or prostatic syndromes associated with other genitourinary conditions.

End points
Before and after 30 days of treatment, assessments were made of nocturia, intensity of dysuria, flow rate, and postmicturition residue. In addition, global rating by physicians and self-rating by patients was included.

Results
Permixon improved both objective and subjective signs. Nocturia was de-

creased in both groups, but significantly more so for the Permixon group, $p < 0.001$. Flow rate was increased by 50.5 percent compared to 5.0 percent for placebo, $p < 0.001$. Postmicturition residue was decreased by 41.9 percent in the Permixon group, and increased by 9.3 percent in the placebo group, $p < 0.001$. Dysuria was greatly improved compared to placebo, $p < 0.001$. Both patient self-rating and physician rating indicated the superiority of Permixon over placebo, both $p < 0.001$.

Side effects
Minor (e.g., headache).

Authors' comments
As predicted by pharmacological and biochemical studies, Permixon appears to be a useful therapeutic tool in the treatment of benign prostatic hyperplasia.

Reviewer's comments
Although a statistical benefit of Permixon was demonstrated in the trial, a lack of randomization limits the usefulness of this study. The duration of treatment, 30 days, is also relatively short, and the blinding was not described adequately. (1, 5)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Mandressi S, Tarallo U, Maggioni A, Tombolini P, Rocco F, Quadraccia (1983). Medical treatment of benign prostatic hyperplasia: Efficacy of the extract of *Serenoa repens* (Permixon) compared to that of the extract of *Pygeum africanum* and a placebo. *Urologia* 50: 752-758.

Trial design
Parallel. Three-arm trial. Permixon, extract of *Pygeum africanum* (no details given), and placebo.

Study duration	1 month
Dose	320 mg daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Pygeum extract
Site description	Not described
No. of subjects enrolled	60
No. of subjects completed	59
Sex	Male
Age	50-80 years

Inclusion criteria
Patients complaining of dysuric disorders related to benign prostatic hyperplasia (BPH), confirmed on rectal exam.

Exclusion criteria
Patients treated previously for BPH, or complications secondary to the presence of prostactic hypertrophy.

End points
Subjective and objective parameters were assessed before and after 30 days of treatment. Subjective parameters included pollakiuria, nocturia, dysuria, perineal pain, and nocturnal erections. Objective parameters included rectal examination, urology before and after voiding, and retrograde cystourethrography.

Results
There was a pronounced difference in the efficacy of Permixon compared to placebo ($p < 0.01$) and the *Pygeum africanum* extract ($p < 0.05$). There was no clear difference in the results of patients treated with *Pygeum africanum* and those in the placebo group. The greatest improvements with Permixon compared to baseline were in the following symptoms: pain on voiding (73 percent decrease), urgency (70 percent decrease), tenesmus (spasms and urge to empty the bladder, 82 percent decrease), and nocturia (42 percent decrease).

Side effects
None reported.

Authors' comments
It is thus possible to confirm without any doubt the clinical reliability of the extract of *Serenoa repens* (Permixon) regarding efficacy and tolerance. However, it is not possible to reach any definitive conclusions regarding the comparison of Permixon with *Pygeum africanum* extract.

Reviewers' comments
This trial shows a trend toward symptomatic benefit with Permixon. However, small numbers of patients in each group and lack of a significant description of *Pygeum africanum* limit the utility of this study. The treatment length was short, and the randomization process was not adequately described. (Translation reviewed) (2, 5)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Emili E, Lo Cigno M, Petrone U (1983). Clinical results on a new drug in the treatment of benign prostatic hyperplasia (Permixon). *Urologia* 50 (5): 1042-1049.

Trial design
Parallel.

Study duration	1 month
Dose	2 tablets twice daily (morning and evening)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Urology clinic

No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male
Age	44-78 years

Inclusion criteria
Patients with general good health suffering from uncomplicated benign prostatic hyperplasia for whom there is no indication for surgery or immediate endoscopy (due to clinical symptoms and the absence of involvement of the upper urinary tract), and negative urinary cultures.

Exclusion criteria
Patients having a history of surgery of endoscopy on the bladder or urethra.

End points
The number of diurnal or nocturnal urinations, dysuria, the size of the prostate on rectal palpation, and postvoiding residue were evaluated at the start and end of the study.

Results
Permixon decreased the number of diurnal urinations by 32 percent compared with 7.5 percent for placebo. Nocturnal urinations were reduced by 49.8 percent compared with 12.7 percent for placebo. Dysuria (painful urination) was reduced by 88.5 percent compared to 40 percent for placebo. Prostate size was reduced by 26.6 percent compared to no change in the placebo group. Urinary outflow was increased by 32.6 percent, and average urinary output was increased by 28.6 percent (placebo: +2.16 percent and –3 percent, respectively). Postvoiding residue was reduced by 50.9 percent compared with 15.1 percent for placebo.

Side effects
None reported.

Authors' comments
The extract of *Serenoa repens* proved to be an efficacious drug by improving clinical and instrumental parameters in the treated group without causing any side effects.

Reviewers' comments
This is a small study that shows a trend in benefit of saw palmetto fruit. However, the differences may not be clinically significant. Thirty days is also a short duration of therapy. Neither the randomization nor the blinding were described adequately. (Translation reviewed) (1, 4)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**No**

Bibliographic reference
Reece Smith H, Memon A, Smart CJ, Dewbury K (1986). The value of Permixon in benign prostatic hypertrophy. *British Journal of Urology* 58 (1): 36-40.

Trial design
Parallel.

Study duration	3 months
Dose	160 mg twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	One hospital urology department
No. of subjects enrolled	80
No. of subjects completed	70
Sex	Male
Age	55-80 years

Inclusion criteria
Patients with symptom of benign prostatic hyperplasia (BPH).

Exclusion criteria
Malignant prostatic disease.

End points
Measurement of urinary flow rate, midstream specimen of urine, and assessment of residual volume by bladder echography were recorded at baseline and after 2, 4, 8, and 12 weeks. Six months after completion of the trial,

patients were asked via questionnaire whether improvement attained during trial was maintained.

Results
A statistically significant improvement ($p < 0.01$) in urinary flow rate was observed in both treatment and placebo groups, but no significant difference was seen between the two groups. There was no significant difference in bladder residual volume in either group.

Side effects
Two patients stopped taking Permixon because of nausea and vomiting, and withdrew from the trial. One other patient stopped taking Permixon for two to three days due to nausea. One patient developed dizziness and stopped taking Permixon for one day.

Authors' comments
Although the regime of Permixon used in this trial was safe, well tolerated, and associated with considerable symptomatic improvement, no evidence exists that this improvement was due to anything more than the psychosocial value of being involved in the trial and meeting a number sufferers from a similar condition.

Reviewers' comments
Overall, this is a good study demonstrating no difference in efficacy between Permixon and placebo over a 12-week period. The trial duration, however, is short, and a known placebo effect is present in treating BPH. (3, 4)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**I**
Therapeutic benefit	**Trend**

Bibliographic reference
Carraro JC, Raynaud JP, Koch G, Chrisholm GD, Di Silverio F, Teillac P, Calais Da Silva F, Cauquil J, Chopin DK, Hamdy FC (1996). Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: A randomized international study of 1,098 patients. *The Prostate* 29 (4): 231-240.

Trial design
Parallel. Permixon or finasteride (Proscar; 5 mg once daily in the morning). Patients took a total of four pills per day (two morning, two evening). The nontreatment pills were placebo.

Study duration	6 months
Dose	160 mg twice daily (morning and night)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Finasteride
Site description	87 urology centers
No. of subjects enrolled	1,209
No. of subjects completed	1,098
Sex	Male
Age	49-88 years

Inclusion criteria
Over 50 years old, with benign prostatic hyperplasia diagnosed by digital rectal examination and not requiring surgery, International Prostate Symptom Score (IPSS) > 6, maximum urinary flow between 4 to 15 ml/sec, urine volume > 150 ml, postvoiding residue < 200 ml, prostate > 25 ml, serum prostate-specific antigen (PSA) < 10 ng/ml for prostates < 60 ml and < 15 ng/ml for prostates > 60 ml, good physical and mental condition.

Exclusion criteria
Cancer of the prostate, known history of bladder disease, lower urinary tract pathology or infection, any disease potentially affecting urination, abnormal liver function, administered diuretics or drugs with antiandrogenic or alpha-receptor properties in the preceding three months, or prior treatment with either finasteride or Permixon.

End points
Each patient was evaluated prior to entry and at 6, 13, and 26 weeks. At each visit, peak and mean urinary flow rates were measured, the IPSS was determined, and the patient completed a quality of life and sexual function questionnaire. At weeks 13 and 26, patients underwent transrectal and abdominal ultrasound examinations, as well as blood sampling.

Results
Both Permixon and finasteride decreased the IPSS (–37 percent and –39 percent, respectively), improved quality of life (by 38 percent and 41 percent, respectively), and increased peak urinary flow rate (+25 percent and +30 percent, respectively), with no statistical difference in the percent responders. All improvements were compared to baseline ($p < 0.001$). Finasteride markedly decreased prostate volume (–18 percent) and serum PSA levels (–41 percent). Permixon improved symptoms with little effect on volume (–6 percent), and no change in PSA levels.

Side effects
Side effects were similar in both groups, with hypertension being the most common. Decreased libido and impotence were more common in those taking finasteride.

Authors' comments
Both treatments relieve the symptoms of BPH in about two-thirds of patients. Unlike finasteride, Permixon has little effect on so-called androgen-dependent parameters.

Reviewer's comments
This trial had a good study design. A significant therapeutic benefit was present compared with baseline in both groups. However, the lack of a placebo group prevents a determination whether the improvement is simply the result of a placebo effect. The treatment length is relatively short. If the improvement in those taking Permixon was due to a placebo effect, over a longer period those with finasteride would continue to improve while those on Permixon would not. (5, 6)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Grasso M, Montesano A, Buonaguidi A, Castelli M, Lania C, Rigatti P, Rocco F, Cesana B, Borghi C (1995). Comparative effects of alfuzosin versus *Serenoa repens* in the treatment of symptomatic benign prostatic hyperplasia. *Archivos Espanoles de Urologia* 48 (1): 97-103.

Trial design
Parallel. Saw palmetto versus alfuzosin 2.5 mg three times daily. Pretrial run-in of seven days. The trial report does not specify the extract or product name. The designation of Permixon came from a review by Boyle and colleages (2000).

Study duration	3 weeks
Dose	160 mg twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Alfuzosin
Site description	2 urology departments
No. of subjects enrolled	63
No. of subjects completed	63
Sex	Male
Age	Mean: 62 ± 7.5 years

Inclusion criteria
Outpatients ages 50 to 80, diagnosis of symptomatic benign prostatic hyperplasia by digital rectal examination and transrectal ultrasonography, Boyarsky's scale scores for nocturia > 2 and daytime frequency > 1, peak flow rate < 15 ml/sec, and a voided volume > 150 ml.

Exclusion criteria
Concomitant urological disorders; neurologic disturbances; severe cardiac, renal, or hepatic failure; myocardial infarction within the previous six months; taking drugs likely to interfere with the study medication or antihypertensive drugs.

End points
Clinical symptoms (Boyarsky's scale score, visual analog scale, clinical global impression), urinary flow rates (uroflowmetry), and residual urinary volume (transabdominal ultrasound) were recorded. Patients were assessed before pretrial period, at baseline, and after 14 and 21 days.

Results
Statistically significant and clinically relevant differences were found between the two treatments in favor of alfuzosin for Boyarsky's total score (de-

crease in 38.8 percent for alfuzosin and 26.9 percent for saw palmetto) and obstructive score (decrease of 37.8 percent of alfuzosin and 23.2 percent for saw palmetto, $p = 0.01$ for both). The increase in quality of urination was better with alfuzosin. More responders (increase on day 21 in peak flow rate of at least 25 percent relative to the baseline values) were in the alfuzosin group (71.8 percent) compared to the saw palmetto group (48.4 percent), $p = 0.057$.

Side effects
One complaint of mild pruritus that resolved itself.

Authors' comments
The findings confirm the efficacy and safety of alfuzosin in symptomatic BPH, and indicate the superiority of alfuzosin over saw palmetto in the treatment of urinary signs and symptoms of BPH.

Reviewers' comments
The study is flawed by its limited duration. It is difficult to determine whether saw palmetto offered any real clinical benefit because the study did not include a placebo group. However, there is a definite benefit of alfuzosin over saw palmetto berry in this short-term study. Neither the randomization nor the blinding were adequately described. (1, 4)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Semino MA, Ortega JLL, Cobo EG, Banez ET, Rodrigues FR (1992). Symptomatic treatment of benign prostatic hypertrophy: Comparative study of prazosin and *Serenoa repens. Archivos Espanoles de Urologia* 45 (3): 211-213.

Trial design
Parallel. Patients received saw palmetto or prazosin (0.5 mg every 12 hours for four days, then 1 mg every 12 hours for another four days, and finally 2 mg every 12 hours for the remainder of the 12 weeks). The trial report does

not specify the product. The designation of Permixon comes from Boyle and colleagues (2000).

Study duration	3 months
Dose	2 tablets every 12 hours
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Prazosin
Site description	Not described
No. of subjects enrolled	45
No. of subjects completed	41
Sex	Male
Age	55-81 years

Inclusion criteria
Clinical prostatism, with Grades I or II volume on rectal exam, and no suspicion of prostatic cancer or evidence of an obstructive uropathy.

Exclusion criteria
Patients who had undergone prostatic surgery previously or those suffering from a malignant prostatic disorder, hypertension, habitual hypotension, recent myocardial infarction, liver disease, obstructive uropathy, and Grades III or IV volume prostates.

End points
A rectal exam, urography, and a urodynamic exploration (to determine maximum and mean flow, total volume, and urination time, supplemented by an approximate estimate of residual urine by hypogastric echography) were performed. Patients returned for a follow-up visit after six weeks to evaluate the tolerance of treatment and at the end of twelve weeks to have urodynamic exploration and echographic measurement of residual urine.

Results
Improvement of symptoms was seen in both groups. An overall result shows that 12 percent of patients reported a frequency of less than five times for diurnal urination, compared to 0 percent before treatment. Nocturia decreased, with the number of patients having to get up no more than once increasing from 12 to 24 percent. The number of patients who originally

urinated more than 13 times over the course of the day fell from 14 percent to 2.5 percent. Comparing the two groups, a greater number of patients receiving prazosin improved than those receiving saw palmetto, although the difference was small in terms of both diurnal and nocturnal frequency of urination. An improvement in urodynamic changes in mean flow was observed with both treatments, although a larger number of those receiving prazosin benefited than those receiving saw palmetto. Residual urine was decreased in three patients taking prazosin and one treated with saw palmetto.

Side effects
Prazosin group: hypotension and gastric intolerance; saw palmetto group: none.

Author's comments
It can be concluded form the study that prazosin is slightly more effective in controlling the symptoms of irritation produced by benign prostatic hyperplasia. This remark is made on the basis of absolute figures, in the absence of any statistical analysis.

Reviewers' comments
Although the outcome measures were clearly defined, overall this is a limited study because it was nonrandomized, unblinded, and had no placebo. Although a trend was observed toward a benefit with prazosin over saw palmetto, 12 weeks is a short duration of treatment. (1, 3)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Stepanov VN, Siniakova LA, Sarrazin B, Raynaud JP (1999). Efficacy and tolerability of *Serenoa repens* (Permixon) in benign prostatic hyperplasia: A double-blind comparative study of two dosage regimens. *Advances in Therapy* 16 (5): 231-241.

Trial design
Parallel. Dose comparison.

Study duration	3 months
Dose	2 (160 mg) capsules once daily or 1 (160 mg) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Single center
No. of subjects enrolled	100
No. of subjects completed	92
Sex	Male
Age	Mean: 66.2 ± 5.8 years

Inclusion criteria
Age over 50, symptomatic benign prostatic hyperplasia for more than six months, International Prostate Symptom Score (IPSS) > 13, IPSS quality of life item score > 3, an enlarged prostate of > 25 cm^3, maximum flow rate between 5 and 12 ml/s (with voided volume > 150 ml), postvoiding residual urine < 150 ml, and prostate-specific antigen (PSA) < 15 ng/ml (with prostate size > 60 cm^3) or < 10 ng/ml (prostate size < 60 cm^3).

Exclusion criteria
History of urological disorders; undergone bladder, neck, or prostate surgery, transurethral incision of the prostate, balloon dilatation of the prostate, or thermotherapy; had suspected prostate cancer, progressive prostatitis, or urinary tract infection; or had used drugs within the last two weeks likely to alter the voiding pattern.

End points
Primary efficacy criteria was the change in the IPSS between baseline and end point. Other criteria included IPSS quality-of-life item score, maximum and mean urinary flow rate, and residual urine volume. Assessments were made before treatment and after one and three months.

Results
Both Permixon regimens significantly reduced the IPSS mean total score compared with baseline. This improvement was statistically significant after one month of treatment ($p < 0.0001$), and was maintained after three months. A highly significant decrease in residual urine was observed in both

groups ($p < 0.001$). However, no significant differences between the two regimens were seen in any of the measured parameters.

Side effects
None related to treatment.

Authors' comments
Once-daily (2 × 160 mg capsules) and twice-daily (1 × 160 mg capsule) regimens produced marked, comparable, and sustained improvements in the symptoms of BPH, and the drug was well tolerated. The 320 mg once-daily dose might result in better compliance.

Reviewers' comments
Improvement compared with baseline was seen for both doses of Permixon, but the study did not include a placebo group to verify a beneficial effect. Three months is also a relatively short duration of treatment. Neither the randomization nor the blinding were adequately described. (Translation reviewed) (1, 6)

Clinical Study: Permixon®

Extract name	PA 109
Manufacturer	Pierre Fabre Médicament, France
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Di Silverio F, Monti S, Sciarra A, Varasano PA, Martini C, Lanzara S, D'Eramo G, Di Nicola S, Toscano V (1998). Effects of long-term treatment with *Serenoa repens* (Permixon) on the concentrations and regional distribution of androgens and epidermal growth factor in benign prostatic hyperplasia. *The Prostate* 37 (2): 77-83.

Trial design
Parallel. Patients were split into two groups: one group treated with Permixon and one untreated group.

Study duration	3 months
Dose	320 mg/day
Route of administration	Oral
Randomized	Yes

Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Not described
No. of subjects enrolled	25
No. of subjects completed	25
Sex	Male
Age	Mean: 68 ± 6 years

Inclusion criteria
Symptomatic men with established benign prostatic hyperplasia in general good condition, with symptoms of urinary obstruction for one to three years, enlarged prostate (mean volume: 44 ml), mean International Prostate Symptom Score (IPSS) of 15.4, maximum urinary flow rate of less than 15 ml/s, and a voided volume of 150 ml or more.

Exclusion criteria
Patients with residual urinary volume greater than 350 ml if they had a history of previous outlet surgery, histologically diagnosed prostate carcinoma, neurogenic disorders, bacterial prostatis, and other conditions besides BPH known to interfere with normal voiding.

End points
After three months, prostatic specimens were removed, and the tissue was pulverized. In the periurethral, subcapsular, and intermediate regions, testosterone (T), dihydrotestosterone (DHT), and epidermal growth factor (EGF) content was determined.

Results
In the untreated group, T, DHT, and EGF were present in the highest concentrations in the periurethral region compared to the peripheral subcapsular region. In comparison, in the Permixon group, a statistically significant reduction was observed of DHT ($p < 0.001$) and EGF ($p < 0.01$), mainly in the periurethral region. T levels were increased ($p < 0.001$).

Side effects
None mentioned.

Authors' comments
The decrease of DHT and the rise of T in the prostatic tissue of patients treated with Permixon confirms the capacity of this drug to inhibit in vivo 5-alpha-reductase in human pathological prostate. A marked decrease of

EGF associated with DHT reduction was observed. These biochemical effects, similar to those obtained with finasteride, are particularly evident in the periurethral region, whose enlargement is responsible for urinary obstruction. A possible speculation is that the preferential reduction of DHT and EGF content in the periurethral region is involved in the clinical improvement of the obstructive symptoms in BPH during Permixon therapy.

Reviewer's comments
A significant decrease in DHT with increased testosterone was observed in those treated with Permixon, which suggests that inhibition of 5-alpha-reductase is a mechanism of action of Permixon. The sample size was considered small, the randomization process was not adequately described, and the blinding was not described. (1, 5)

Product Profile: Prostaserene®

Manufacturer	**Therabel Pharma, Belgium (Indena S.p.A., Italy)**
U.S. distributor	None
Botanical ingredient	**Saw palmetto fruit extract**
Extract name	**SabalSelect™**
Quantity	160 mg
Processing	Hypercritical carbon dioxide extraction, plant to extract ratio 10:1
Standardization	85-95% fatty acids
Formulation	Capsule

Source(s) of information: Braeckman, Bruhwyler et al., 1997; Indena USA, Inc.

Product Profile: Serenoa Gelcaps

Manufacturer	**Thorne Research (Indena S.p.A., Italy)**
U.S. distributor	**Thorne Research**
Botanical ingredient	**Saw palmetto fruit extract**
Extract name	**SabalSelect™**
Quantity	160 mg
Processing	Plant to extract ratio 10:1
Standardization	Contains 85% liposterols
Formulation	Gelcap

Cautions: If pregnant, consult a health care practitioner before using this, or any other product.

Other ingredients: Gelatin, glycerin, olive oil, and water.

Comments: This product is available only through pharmacies and health care practitioners.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Clinical Study: Prostaserene®

Extract name	SabalSelect™
Manufacturer	Therabel Pharma, Belgium (Indena S.p.A., Italy)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Braeckman J, Denis L, de Leval J, Keuppens F, Cornet A, De Bruyne R, De Smedt E, Pacco J, Timmermans L, Van Vliet P, et al. (1997). A double-blind, placebo-controlled study of the plant extract *Serenoa repens* in the treatment of benign hyperplasia of the prostate. *European Journal of Clinical Research* 9: 247-259.

Trial design
Parallel.

Study duration	3 months
Dose	160 mg twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	238

No. of subjects completed	205
Sex	Male
Age	Mean: 65 ± 6.8 years

Inclusion criteria
Mild to moderate symptoms of prostatic hyperplasia, maximal flow rate between 5 and 15 ml/sec, no suspicion of cancer upon rectal examination, and no abnormalities in the urinary sediment.

Exclusion criteria
Age over 80; postvoiding residual volume greater than 60 ml; any malformation, tumor, or infection of the genitourinary system; previous endoscopy of the lower urinary tract; or debilitated condition due to any chronic disease.

End points
Patients were evaluated at baseline and after 30, 60, and 90 days of treatment. Assessments were made via questionnaire regarding prostate symptoms, a general physical examination, a rectal palpation, a transrectal echographic prostatic volume determination, urinary flow rate parameters, residual volume measurement, and a cytobacteriological urinary examination.

Results
Saw palmetto offered a significant improvement over placebo in the total symptomatological score (pollakiuria, nocturia, dysuria, urgency, and hesitancy) after 60 days ($p < 0.05$) and 90 days ($p < 0.01$). A nonsignificant tendency was observed for flow rate and prostate volume. Global (quality-of-life) evaluations by patients and physicians rated the saw palmetto group as significantly more improved compared to the placebo group.

Side effects
Side effects probably caused by the medication were seen in 2.5 percent of saw palmetto group (gastrointestinal, sexual, fatigue) and 3.7 percent of placebo group.

Authors' comments
The extract of *Serenoa repens* appears to be an efficacious and well-tolerated therapy in early symptomatic benign prostatic hyperplasia.

Reviewers' comments
This is an excellent study demonstrating a symptomatic improvement in lower urinary tract symptoms with saw palmetto berry, which is the primary goal in treating most men with symptomatic BPH. Ninety days is a relatively short study time, but does not invalidate the study. The drug was well tolerated. (5, 6)

Clinical Study: Prostaserene®

Extract name	SabalSelect™
Manufacturer	Therabel Pharma, Belgium (Indena S.p.A., Italy)
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Braeckman J, Bruhwyler J, Vandekerckhove K, Geczy J (1997). Efficacy and safety of the extract of *Serenoa repens* in the treatment of benign prostatic hyperplasia: Therapeutic equivalence between twice and once daily dosage forms. *Phytotherapy Research* 11 (8): 558-563.

Trial design

Parallel. Dose comparison.

Study duration	1 year
Dose	160 mg capsule twice daily or 320 mg capsule once daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	84
No. of subjects completed	67
Sex	Male
Age	Mean: 65.1 ± 7.3 years

Inclusion criteria

Men at least 75 years old with symptoms of benign prostatic hyperplasia (urgency, nocturia, pollakiuria, dysuria, decrease in flow, and terminal dribbling), maximal urinary flow > 5 ml/s and < 15 ml/s for a mictional volume of 150 ml, IPSS between 12 and 24, residual volume < 100 ml, and serum-specific antigen < 10 ng/ml.

Exclusion criteria
Indication for surgical intervention; any malformation, tumor, or infection of the genitourinary system; previous endoscopy of the lower urinary tract and/or hepatic insufficiency; treatment with other agents for BPH, antibiotics or antiseptics.

End points
Medical evaluations took place at baseline and after 1, 3, 6, 9, and 12 months. The efficacy of treatment was evaluated using the international prostate symptom score (IPSS), quality-of-life score, transrectal echographic prostatic volume determination, urinary flow rates (mean and maximal) for micturition volumes superior or equal to 100 ml, residual volume, and global evaluation of efficacy by the patient and the investigator.

Results
Both dosage forms produced a significant improvement in efficacy variables after one year: IPSS score by 60 percent ($p < 0.0001$), quality-of-life score (85 percent of patients were satisfied), prostatic volume by 12 percent ($p < 0.0001$), maximum flow rate by 22 percent ($p < 0.0001$), mean flow rate by 17 percent ($p < 0.0001$), and residual urinary volume by 16 percent ($p < 0.05$). No significant differences were found between the two groups.

Side effects
The medication was well tolerated with no difference in those with either a once-a-day or twice-a-day dose. Two patients in each group stopped the drug due to side effects.

Authors' comments
The extract of *Serenoa repens* in its two dosage forms is a safe and effective treatment for the micturition problems associated with BPH. Consequently, it appears to offer a potential pharmacologic alternative capable of improving BPH symptoms in patients with mild to moderate disease.

Reviewers' comments
Although the study has some design flaws, it offers a suggestion that a once-a-day dose of Prostaserene is equivalent to a twice-a-day dose. The one-year follow-up is helpful in showing the results over a long time. The study was not double-blind and did not include a placebo arm. (0, 5)

Product Profile: Strogen® uno

Manufacturer	**Schaper & Brümmer GmbH & Co. KG, Germany**

U.S. distributor	None
Botanical ingredient	**Saw palmetto fruit extract**
Extract name	**IDS 89**
Quantity	320 mg
Processing	No information
Standardization	No information
Formulation	Capsule

Source(s) of information: Weisser et al., 1997.

Clinical Study: Strogen® uno

Extract name	IDS 89
Manufacturer	Schaper & Brümmer GmbH & Co. KG, Germany
Indication	**Benign prostatic hyperplasia**
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Weisser H, Behnke B, Helpap B, Bach D, Krieg M (1997). Enzyme activities in tissue of human benign prostatic hyperplasia after three months treatment with the *Sabal serrulata* extract IDS 89 (Strogen) or placebo. *European Urology* 31 (1): 97-101.

Trial design
Parallel.

Study duration	3 months
Dose	2 (320 mg) capsules 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	18

No. of subjects completed	16
Sex	Male
Age	Not given

Inclusion criteria
Ages 45 to 75 years with symptoms of urinary obstruction, reduced maximum urinary flow < 15 ml/s, voided volume > 50 ml, enlarged prostate (> 60 g), and indication for benign prostatic hyperplasia surgery.

Exclusion criteria
Concomitant urological diseases (neurogenic bladder, acute or chronic prostatitis, acute or recurrent urinary tract infection, urethral stenosis, urinary tract stones, prostate cancer, severe hematuria), cardiogenic nocturia, peptic ulcer, severe hepatic impairment, renal insufficiency, abuse of alcohol, or taking any other drugs for BPH during the two months prior to the trial.

End points
After three months of treatment, the prostate was removed, and the amounts and substrate affinities of enzymes involved in both the formulation of dihydrotestosterone (DHT) (5-alpha-reductase) and the removal of DHT (3-alpha- and 3-beta-hydroxysteroid oxidoreductase [$HSOR_{red}$]) were measured, along with amounts of creatine kinase (an indication of cellular energy demand). These measurements were taken in the stroma and epithelium of the removed prostate.

Results
In epithelium, the substrate affinity (K_m) of the 5-alpha reductase decreased slightly. In stroma, the amount (V_{max}) value of the 3-alpha-$HSOR_{red}$ increased statistically, leading to a moderate increase in V_{max}/K_m. In stroma, the Vmax value of the 3-beta-$HSOR_{red}$ increased moderately, but not statistically. In stoma, the V_{max} value of creative kinase increased significantly, leading to a statistically distinct increase of V_{max}/K_m.

Side effects
None mentioned.

Authors' comments
This trial revealed significant biochemical changes at the cellular level of BPH tissue. However, the alterations are merely moderate, and their biochemical causes and consequences regarding the pathophysiology of BPH are rather uncertain.

Reviewers' comments
This study was done to evaluate biochemical change after treatment with saw palmetto extract in those for whom surgery was indicated. The authors excluded those with prostates less than or equal to 60 gm—a potential flaw,

since one can have symptomatic BPH with a small prostate. The sample size was small, and 3 months is also a short duration of treatment. Neither the randomization nor the blinding were adequately described. (1, 4)

Product Profile: ProstActive®

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	**Nature's Way Products, Inc.**
Botanical ingredient	**Saw palmetto fruit extract**
Extract name	**WS 1473**
Quantity	320 mg
Processing	Plant to extract ratio 100:8.5, ethanol (w/w) 90%
Standardization	No information
Formulation	Softgel capsule

Recommended dose: Take one softgel daily with water at mealtimes. Allow two to eight weeks of use before noticeable results.

DSHEA structure/function: Promotes prostate health, maintains normal urine flow, and supports normal 5-alpha-reductase activity within the prostate gland.

Other ingredients: Gelatin, glycerin, caramel, carmine, titanium dioxide.

Source(s) of information: Product package (© 2002 Nature's Way Products, Inc.); information provided by distributor.

Clinical Study: ProstActive®

Extract name	WS 1473
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Benign prostatic hyperplasia**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference

Löbelenz J (1992). *Extractum sabal fructus* in the therapy of benign prostatic hyperplasia (BPH). *Tpk Therapeutikon* 6 (1/2): 34-37.

Trial design
Parallel. Pretrial run-in phase of seven days.

Study duration	6 weeks
Dose	1 (100 mg) capsule 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	60
No. of subjects completed	Not given
Sex	Male
Age	40-82 years

Inclusion criteria
Benign prostatic hypertrophy in Stages I and II (according to Alken) with a maximum micturition volume of 20 ml/s. During the trial, patients were only allowed to take medication that would not interfere with the assessment of efficacy, and the dosage was to remain constant.

Exclusion criteria
None mentioned.

End points
Patients were evaluated at the beginning of the seven-day run-in phase and at the start of therapy, as well as on the fifteenth, twenty-ninth, and forty-third days (termination of study). The target parameter was maximum micturitional volume per second. Secondary parameters were residual volume of urine, sonographic evaluation, the force of urine, postmicturitional drip, incontinence, and prostate-specific antigen.

Results
Maximum micturitional volume per second increased by 67 percent in the saw palmetto group compared to baseline, and by 53 percent in the placebo group. Mean urine flow increased in the saw palmetto group by 0.6 ml/s, whereas it increased by 0.3 ml/s in the placebo group. No statistically significant difference was observed for any outcome measure.

Side effects
None mentioned.

Author's comments
The investigation shows that a conservative treatment of patients suffering from benign prostatic hyperplasia in Stages I and II with phytopharmaceuticals can result in an improvement of symptoms.

Reviewers' comments
This was a well-designed study, although it was of short duration and had a relatively small numbers of patients. No statistically significant benefit was seen in the treatment arm, and the differences described were not clinically significant either. (Translation reviewed) (5, 5)

Product Profile: ProstActive® Plus

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	**Nature's Way Products, Inc.**
Botanical ingredient	**Saw palmetto fruit extract**
Extract name	**WS 1473**
Quantity	160 mg
Processing	Plant to extract ratio 12:1, ethanol (w/w) 90%
Standardization	No information
Botanical ingredient	**Nettle root extract**
Extract name	**WS 1031**
Quantity	120 mg
Processing	Plant to extract ratio 10:1, ethanol (w/w) 60%
Standardization	No information
Formulation	Softgel capsules

Recommended dose: Take one capsule twice daily with water. Best results are obtained with continuous use.

DSHEA structure/function: Promotes prostate health, maintains proper urinary flow.

Comments: Sold as Prostagutt® forte in Europe.

Source(s) of information: Product label (© 1998 Nature's Way Products, Inc.); information provided by distributor.

Clinical Study: Prostagutt® forte

Extract name	Saw palmetto WS 1473; Nettle WS 1031
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Benign prostatic hyperplasia**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Metzker H, Kieser M, Holscher U (1996). Efficacy of a combined *Sabal-Urtica* preparation in the treatment of benign prostatic hyperplasia (BPH). *Urologe* 36: 292-300.

Trial design
Parallel. Placebo run-in phase of two weeks. Trial of 24 weeks followed by a another 24 weeks of a therapy phase (single-blind phase during which all patients received active treatment).

Study duration	6 months
Dose	1 (160 mg saw palmetto extract and 120 mg nettle extract) capsule twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	One urology practice
No. of subjects enrolled	40
No. of subjects completed	33
Sex	Male
Age	52-84 years

Inclusion criteria
Symptomatic benign prostatic hyperplasia Stages I to II according to Alken, maximum urinary volume > 150 ml and < 20ml/s, with a maximum change of 3 ml/s between inclusion and the end of the run-in phase.

Exclusion criteria
Patients younger than 50 years, necessity of surgical intervention, infection

of the urinary tract, concomitant medication that might interfere, cardiac insufficiency, or severe organic complaint requiring additional therapy.

End points
Evaluations were carried out at inclusion, after run-in, and after 8, 16, 24, and 48 weeks. They included a uroflowmetric test, transabdominal sonographic determination of residual urine and prostate size, and subjective symptoms and life quality (AUA symptom score).

Results
After 24 weeks of therapy, an improvement of 3.3 ml/s in maximal urine volume per second was seen following treatment with the saw palmetto-nettle combination. In comparison, an improvement of only 0.55 ml/s ($p < 0.001$) was seen in the placebo group. Only marginal changes in residual urine quantity and prostate size occurred in both groups. The AUA symptom score, corresponding to the International Prostate Symptom Score, showed a continuous and noticeable decrease in score due to treatment (after 8, 16, and 24 weeks, $p < 0.001$) but only an insignificant change in the placebo group. Patients in the placebo group who gained only slight improvement during the trial showed a clear improvement once they were given active treatment. Nevertheless, there was a clear advantage for those patients who had been receiving the active treatment from the beginning of the study.

Side effects
No adverse events.

Authors' comments
The present study confirms the efficacy of a combined saw palmetto-nettle preparation in the context of objective and subjective parameters, showing a very good tolerance at the same time.

Reviewers' comments
This is a well-designed study. However, the limited number of patients is a significant flaw. A significant benefit was observed in the treatment group, but these differences may not be clinically significant. Although six months is a relatively short duration, it does not invalidate the results. (5, 5)

Clinical Study: PRO 160/120 (Prostagutt® forte)

Extract name	Saw palmetto WS 1473; Nettle WS 1031
Manufacturer	Dr. Willmar Schwabe GmbH & Co.
Indication	**Benign prostatic hyperplasia**
Level of evidence	**I**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Sokeland J, Albrecht J (1997). A combination of *Sabal* and *Urtica* extracts versus finasteride in BPH (stage I to II acc. to Alken): A comparison of therapeutic efficacy in a one-year double-blind study. *Urologe (A)* 36 (4): 327-333. (Also published by Sokeland J [2000]. *BJU International* 86 [4]: 439-442.)

Trial design

Parallel, drug comparison, double dummy design. PRO 160/120 versus finasteride (one 5 mg capsule daily). Pretrial run-in with placebo for two weeks.

Study duration	1 year
Dose	1 (160 mg saw palmetto extract and 120 mg nettle extract) capsule twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Finasteride
Site description	Multicenter
No. of subjects enrolled	543
No. of subjects completed	489
Sex	Male
Age	50-88 years

Inclusion criteria

Diagnosis of benign symptomatic prostatic hyperplasia in Stages I to II according to Alken; maximum urinary flow < 20 ml/s; micturition volume > 150 ml; change in maximum urinary flow between inclusion and the end of the run-in phase < 3 ml/s.

Exclusion criteria

Age younger than 50 years; need for surgical intervention in the lower urinary tract during trial; symptomatic infections of urinary tract; cardiac insufficiency; severe organic diseases; simultaneous participation in other trials; carcinoma of the prostate; prostate-specific antigen > 10ng/l; or benign prostatic hyperplasia in Stage III according to Alken.

End points
Clinical exams were conducted at the beginning and end of the run-in phase, at six-week intervals, and finally at week 48. The primary variable was maximum urinary flow after 24 weeks of treatment. Secondary endpoints were average urinary flow, micturition volume, and micturition time. Urinary symptoms were recorded by the International Prostate Symptom Score (IPSS) and quality of life was assessed via questionnaire.

Results
An increase of the urinary flow rate could be observed in both treatment groups (1.9 ml/s with PRO 160/120; 2.4 ml/s with finasteride). During the trial, the average urinary flow increased, whereas the micturition time decreased, in both groups. The micturition volume did not show any relevant differences after treatment with either agent. The IPSS decreased from 11.3 at the baseline to 8.2 after 24 weeks and 6.5 after 48 weeks with PRO 160/120, and from 11.8 to 8.0 and 6.2 with finasteride, respectively. Quality of life improved between the start and end of therapy from 7.5 to 4.3 with PRO 160/120 and from 7.7 to 4.1 with finasteride.

Side effects
Seventy-four adverse events occured in 48 patients in the PRO 160/120 group compared to 96 events in 54 patients treated with finasteride. Reduced ejaculation, erectile dysfunction, and pain in joints were more common with finasteride.

Authors' comments
The analysis showed that the efficacy of both PRO 160/120 and finasteride was equivalent and unrelated to prostate volume. PRO 160/120 was better tolerated than finasteride.

Reviewers' comments
Overall, this is a good study demonstrating equivalent benefit of Prostagutt forte and finasteride. However, without a placebo control one cannot tell wjetjer either agent is beneficial over placebo. The treatment length was adequate. (4, 6)

Product Profile: Nutrilite® Saw Palmetto with Nettle Root

Manufacturer	**Access Business Group: Home of Nutrilite**
U.S. distributor	**Access Business Group: Home of Nutrilite**
Botanical ingredient	**Saw palmetto fruit extract**
Extract name	None given
Quantity	106 mg

Processing	Liposterolic (oil) extract
Standardization	> 85% fatty acids
Botanical ingredient	**Lemon fruit concentrate**
Extract name	N/A
Quantity	33.3 mg
Processing	No information
Standardization	> 25% total bioflavonoids
Botanical ingredient	**Pumpkin seed extract**
Extract name	None given
Quantity	160 mg
Processing	Seed oil extract
Standardization	No information
Botanical ingredient	**Stinging nettle root extract**
Extract name	None given
Quantity	80 mg
Processing	Powdered extract
Standardization	> 0.8% beta-sitosterol
Formulation	Capsule (softgel)

Recommended dose: Take one softgel three times per day, preferably with meals.

DSHEA structure/function: For men, saw palmetto and pumpkin seed oil support normal prostate function. Nettle root supports normal urinary flow.

Cautions: Children under 12 years of age, pregnant or lactating women, or anyone with a medical condition should consult with a physician before using this product.

Other ingredients: Vitamin A (100 percent as beta-carotene) 100 IU, gelatin, glycerin, yellow beeswax, soybean oil, lecithin, corn oil, natural caramel color.

Source(s) of information: Product label (© 1997 Amway Corp.); information provided by distributor.

Clinical Study: Nutrilite® Saw Palmetto with Nettle Root

Extract name	None given
Manufacturer	Access Business Group: Home of Nutrilite
Indication	**Benign prostatic hyperplasia**

Level of evidence	**I**
Therapeutic benefit	**Trend**

Bibliographic reference
Marks LS, Partin AW, Epstein JI, Tyler VE, Simon I, Macairan ML, Chan TL, Dorey FJ, Garris JB, Veltri RW, et al. (2000). Effects of a saw palmetto herbal blend in men with symptomatic benign prostatic hyperplasia. *The Journal of Urology* 163 (5): 1451-1456.

Trial design
Parallel.

Study duration	6 months
Dose	1 capsule (including 106 mg saw palmetto extract) 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	One urology practice
No. of subjects enrolled	44
No. of subjects completed	41
Sex	Male
Age	Mean: 64 ± 8.7 years

Inclusion criteria
Ages 45 to 80 years in general good health with clinical diagnosis of benign prostatic hyperplasia based on moderate to severe symptoms and palpation of an enlarged prostate gland on rectal exam; International Prostate Symptom Score > 9, question 5 >1, 2 of any questions 1-4, 6 or 7 must be > 3; prostate-specific antigen (PSA) < 15 ng/ml; prostate volume > 30 cm^3.

Exclusion criteria
History of allergy to saw palmetto, history of any illness or condition that may interfere with the study, significant abnormalities on prestudy screening, treatment with an investigational drug within one month of screening, drug or alcohol abuse or dependence, urethral stricture, previous radiotherapy to pelvis, chronic prostatitis, previous bladder surgery, prostatectomy, or other invasive procedure for BPH, neurogenic bladder, or history of recurrent acute urinary retention.

End points
Routine clinical measures (symptom score, uroflowmetry, and postvoid residual urine volume), blood chemistry studies (PSA, sex hormones, and multiphasic analysis), prostate volumetrics by magnetic resonance imaging, and prostate biopsy for zonal morphometry and semiquantitative histology studies.

Results
Saw palmetto herbal blend and placebo groups had improved clinical parameters with a statistically insignificant advantage for the saw palmetto group. Neither PSA nor prostate volume changed from baseline. Morphological examination of the biopsy samples revealed that the percent epithelium in the transition zone decreased from 17.8 percent at baseline to 10.7 percent after six months of treatment with saw palmetto ($p < 0.01$). The percent atrophic glands increased from 25.2 percent to 40.9 percent after treatment with saw palmetto ($p < 0.01$). These changes were not observed in the placebo group.

Side effects
No adverse effects.

Author's comments
Saw palmetto herbal blend appears to be a safe, highly desirable option for men with moderately symptomatic BPH. Therapy resulted in a contraction of prostatic epithelial tissues, apparently via a nonhormonal mechanism.

Reviewers' comments
This is a well-designed study showing a trend toward improvement in clinical parameters. The small number of patients limited the ability to detect slight clinical changes as noted by the authors. Six months is a reasonable length of time. However, if the study was of longer duration, an increased improvement with treatment may be noted since those with a placebo effect fail to improve. (5, 5)

St. John's Wort

Latin name: ***Hypericum perforatum* L.** [Clusiaceae]
Plant parts: **Flower, leaf**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

St. John's wort is an herb with bright yellow flowers, whose benefit in treating psychiatric disorders may have been recognized by Paracelsus during the Renaissance. St. John's wort is native to Europe, North America, South America, and Asia. Most contemporary preparations of St. John's wort are aqueous alcoholic extracts with plant/extract ratios of 4 to 7:1. St. John's wort products have been characterized and standardized to the content of hypericin and hyperforin. The dried buds, flowers, and distal leaves contain 0.2 to 0.3 percent and 1 to 4 percent of these constituents, respectively (Schulz, Hänsel, and Tyler, 2001).

Hypericin content is often measured using ultraviolet (UV) spectroscopy using a method described by the German Pharmaceutical Codex (Deutscher Arzneimittel-Codex [DAC]) that determines the total quantity of a class of compounds called dianthrones, which includes hypericin, psuedohypericin, protohypericin, and protopseudohypericin. The UV spectroscopy results are quoted as total hypericin. These constituents are also analyzed using high performance liquid chromatography (HPLC), a system that allows for measurement of individual constituents. Measurements generated from UV and HPLC analysis are not interchangeable and should not be confused. The other ingredient commonly used to characterize St. John's wort products, hyperforin, is quantified using HPLC analysis.

Kira® tablets contain 300 mg of the St. John's wort extract LI 160 and are distributed in the United States by Lichtwer Pharma U.S., Inc. The product is manufactuered by Lichtwer Pharma AG, Germany, and sold in Europe under the name of Jarsin® 300. The LI 160 extract

ST. JOHN'S WORT SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Kira®* (US); Jarsin® (EU)	Lichtwer Pharma AG, Germany (Indena S.p.A., Italy)/Lichtwer Pharma US, Inc.	Extract (LI 160/St. John Select™) containing 0.3% hypericin, > 3% hyperforin	3 × 300 mg daily	Depression	13	Yes (I-2, II-3, III-1) Trend (II-3, III-1) Undetermined (III-1) No (I-2)
				Electro-physiological effects	1	MOA (II-1)
				Neuroendo-crine effects	1	MOA (II-1)
Perika™; Movana™ (US); Neuroplant® (EU)	Dr. Willmar Schwabe GmbH & Co., Germany/ Nature's Way Products, Inc.,; Pharmaton Natural Health Products	Ethanolic extract (WS 5572) containing 5% hyperforin, 0.14% total hypericin	3 × 300 mg	Depression	5	Yes (I-2, II-1) Trend (II-1) Undetermined (III-1)
				Electro-physiologi-cal effects	1	MOA (II-1)
				Neuroendo-crine effects	1	MOA (III-1)
St. John's Wort Ze 117™; Remotiv® (EU)	Zeller AG, Switzer-land/General Nutri-tion Corp.; Rexall Sundown	Ethanolic extract (Ze 117™) con-taining 0.2% hypericin	2 × 250 mg	Depression	3	Yes (I-2, II-1)

Hyperiforce (EU)	Bioforce AG, Switzerland/None	Fresh plant alcoholic extract, 0.33 mg hypericin per tablet	3 × 60 mg	Depression	1	Undetermined (II-1)
STEI 300 (EU)	Steiner Arzneimittel, Germany/None	Ethanolic extract containing 0.2%-0.3% hypericins and 2%-3% hyperforin	1,050 mg	Depression	1	Yes (II-1)
Dysto-lux® (EU)	Dr Loges & Co. GmbH, Germany/None	Ethanolic extract (LoHyp-57), plant/extract ratio 5-7:1	4 × 200 mg	Depression	1	Yes (II-1)

*Products sold in the United States that contain the Indena extract in the Lichtwer Pharma product (St. John Select) are listed following. The extract in these products has been tested clinically but the final formulation has not. The exception is the HBC Protocols, Inc. product, which was studied in two drug interaction studies described in the Drug Interactions section (Piscitelli et al., 2000; Burstein et al., 2000).

Product Name	**Manufacturer**
St. John's Wort Extract	Enzymatic Therapy
Hypericum Perforatum II	HBC Protocols, Inc.
Hyper-Ex®	Thorne Research

(aqueous methanol; 4-7:1) is manufactured by Indena S.p.A. in Italy, and is standardized to contain 0.24 to 0.32 percent total hypericins and a minimum of 3 percent hyperforin. The Indena extract is also known as St. John Select™, and is the basis of several other products available in the United States, namely, St. John's Wort Extract by Enzymatic Therapy, Hyper-Ex® by Thorne Research, and Hypericum Perforatum II by HBC Protocols, Inc.

WS 5572 is an extract of the aerial parts of St. John's wort with a plant to extract ratio of 2.5-5:1 (60 percent ethanol w/w). It is manufactured in Germany by Dr. Willmar Schwabe GmbH & Co. and is characterized as containing a minimum of 3 percent hyperforin. WS 5572 is sold in the United States in the products called Perika™, distributed by Nature's Way Products, Inc., and Movana™, distributed by Pharmaton Natural Health Products. Both of these products are available in 300 mg tablets. WS 5572 is sold in Europe in products such as Neuroplant, Neuroplant 300, and Neuroplant forte. A very similar extract, WS 5570, was used in two of the studies we reviewed (Lecrubier et al., 2002; Schüle et al., 2001). Although WS 5570 contains the same hyperforin and hypericin content as the WS 5572 extract, the specifications are slightly different: 80 percent ethanol v/v with a plant to extract ratio of 3-7:1. The WS 5570 extract is not included in any of products described previously. WS 5573 contains a low level of hyperforin (0.5 percent) and was used to delineate the importance of this constituent. It was compared with WS 5572 in two trials (Laakmann et al., 1998; Schellenberg, Sauer, and Dimpfel, 1998), and is not included in any of products described earlier.

Ze 117™ is manufactured in Switzerland by Zeller AG, and is an aqueous ethanolic (50 percent w/w) extract of the flowering tops of St. John's wort (4-7:1). The extract is standardized to contain 0.2 percent hypericin and less than or equal to 0.2 percent hyperforin. Ze 117 is sold in the United States as St. John's Wort Ze 117™, distributed by General Nutrition Corporation, and as St. John's Wort (Ze 117™), distributed by Rexall Sundown. Both of these products are available in 500 mg caplets.

Hyperiforce tablets contain a fresh plant extract of the shoot tips (60 percent alcohol, ratio 3.9-5.0:1) that is standardized to contain 0.33 mg total hypericin per tablet. This product is sold in Europe as Hyperiforce, manufactured by Bioforce AG in Switzerland, but is not available in the United States as a single ingredient product. Bioforce

USA distributes a product called St. John's Wort Complex that contains the St. John's wort extract in addition to extracts of hops flowers and the aerial parts of lemon balm. This formula has not been tested clinically.

STEI 300 is an extract of St. John's wort, and is manufactured by Steiner Arzneimittel in Germany. This extract (60 percent ethanol w/w) is characterized as containing 0.2 to 0.3 percent hypericin and pseudohypericin and 2 to 3 percent hyperforin. STEI 300 is not sold in the United States.

Dysto-lux® is manufactured in Germany by Dr. Loges & Co. GmbH. It contains LoHyp-57, an ethanolic extract (60 percent ethanol w/w) with a plant to extract ratio of 5-7:1. Dyxto-lux is not available in the United States.

SUMMARY OF REVIEWED CLINICAL STUDIES

The most common indication treated with St. John's wort is mild to moderate major depression. The essential feature of a major depressive episode, as defined in the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition), is a period of at least two weeks during which depressed mood or the loss of interest in nearly all activities is observed (American Psychiatric Association, 1994). Additional symptoms of depression include changes in appetite or weight, sleep, and psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty concentrating, or recurrent thoughts of death or suicidal ideation. Major depressive episodes can be mild, moderate, or severe. Depressive disorders are also defined in the World Health Organization's (WHO) *International Classification of Diseases,* Tenth Revision (ICD-10) (WHO, 1992). Some of the reviewed trials had inclusion criteria according to earlier versions of these manuals: DSM-III and ICD-9.

The Hamilton Depression Rating Scale (HAM-D) is an observer rating scale used to evaluate the degree of depression, and is often used to evaluate the success of treatment. The physician interviews the patient and assigns a score based on the severity of 17 or 21 items. The definition of therapeutic success is usually a 50 percent reduction in the total HAM-D score or a total score less than ten.

The usual treatment for depression includes psychotherapy and antidepressant medication, which includes selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, and, more rarely, monoamine oxidase inhibitors.

The majority of the reviewed studies indicate that St. John's wort extracts may be a viable treatment option for patients with mild to moderate depression. However, some recent trials have not shown any efficacy compared to placebo, casting doubt upon the benefit for depression. However, we must keep in mind that at least one-third of published clinical trials of approved antidepressants are negative for efficacy (Thase, 1999). Nevertheless additional studies are required to explore treatment for longer than eight weeks.

Two mode-of-action studies explored the effect of LI 160 and WS 5570 on pituitary hormone secretion as a means of exploring the effects on neurotransmitters. The theory is that antidepressants that act via noradrenaline reuptake inhibition pathways stimulate growth hormone secretion, whereas those that act via serotonin reuptake inhibitors stimulate prolactin. Cortisol secretion is increased by both noradrenaline and serotonin reuptake inhibitors. In addition, plasma levels of growth hormone can be elevated by dopamine reuptake inhibitors. A small, one-day study with eight healthy males exploring the mode of action of LI 160 found that administration of one dose of 2,700 mg LI 160 extract caused an increase in plasma concentrations of growth hormone, a decrease in prolactin levels, and no effect on cortisol levels compared to placebo. The authors of this study interpreted the results to be due to an increase in the dopamine function (Franklin et al., 1999). In contrast, another study found that administration of 300 or 600 mg WS 5570 had no effect on prolactin levels, only a minimal, inconsistent effect on growth factor levels, and a significant effect on cortisol levels. The authors of this study suggested an effect on noradrenaline and serotonin reuptake inhibitors due mainly to the constituent hyperforin. Further, they suggested that the discrepancies between the two studies might be a function of dose (Schüle et al., 2001).

LI 160

Depression

We reviewed 13 studies that explored the effect of LI 160 on depression. The usual dose was 900 mg extract per day for a period of one to two months. Four placebo-controlled studies reported a therapeutic benefit in comparison to placebo, one was undetermined, and two showed no benefit in comparison to placebo. We also reviewed six randomized, controlled, double-blind studies comparing LI 160 with other antidepressants. Four of the trials used tricyclic antidepressants (maprotiline, imipramine, amitriptyline), and two used sertraline, an SSRI. All six studies showed a comparable benefit with both treatments, although in one study both treatments were negative in comparison to placebo. Two studies explored the mode of action of the extract, one measuring brain electroencephalograph (EEG) traces and the other measuring plasma levels of pituitary hormones.

Four trials showed LI 160 to have significant antidepressant activity in comparison to placebo after one month of treatment with 300 mg LI 160 extract three times daily. In a good-quality study with 101 subjects with mild to moderate depression as defined in the DSM-III-R, HAM-D scores fell from 21 to 8.9 in the St. John's wort group (Hänsgen and Vesper, 1996). In another good-quality study with 67 adults with major depression according to the DSM-III-R, the HAM-D score of the treatment group fell from 21.8 to 9.2. In the placebo group, the HAM-D scores fell from 20.4 to 14.7 (Hänsgen, Vesper, and Ploch, 1994). Two smaller studies included participants rated according to the ICD-9 scale. The first study, including a total of 89 subjects, reported that the initial HAM-D score of 15.8 in the treatment group fell to 7.2 (Sommer and Harrer, 1994). The second study, with 39 subjects, reported an HAM-D responder rate of 70 percent for the St. John's wort group and 47 percent for the placebo group (Hübner, Lande, and Podzuweit, 1994).

A six-week study of 60 subjects with mild to moderate depression as defined by the ICD-9 also reported a higher HAM-D responder rate than placebo (66.6 percent compared to 26.7 percent) (Schmidt and Sommer, 1993). However, a lack of detail in the analysis of the results prohibited our reviewers, Drs. Hannah Kim and Debbie

Goebert, from forming any conclusion regarding therapeutic efficacy for depression.

In contrast, a recent, large, well-conducted, placebo-controlled study of 167 patients with initial HAM-D scores of at least 20 who were treated for two months, reported that LI 160 was not more effective than placebo in the treatment of major depression as defined by the DSM-IV (Shelton et al., 2001). It has been suggested that the reason this study was negative was that it used more severely depressed patients than the other studies (mean baseline HAM-D score of 23). However, it is not uncommon for trials with approved antidepressants to be negative, and this phenomenon might be due to the difficulty in measuring depression. Another study of 48 subjects with depression as defined by the ICD-9 scale and an initial HAM-D mean score of 23.7 in the treatment group also reported no significant difference from placebo after four weeks of the standard dose of LI 160 (Lehrl et al., 1993).

Four drug comparison trials compared the effectiveness of LI 160 with tricyclic antidepressants. The first trial compared 900 mg LI 160 extract with 75 mg maprotiline daily for one month in 86 subjects diagnosed as depressed according to the ICD-10, and with an initial HAM-D score greater than 15 (mean of 21). With both treatments, the HAM-D scores fell by approximately 50 percent after one month (Harrer, Hübner, and Podzuweit, 1994). Another trial examined the effectiveness of 900 mg LI 160 and 75 mg amitriptyline on 120 subjects with a current major depressive episode according to the DSM-IV, and with an initial HAM-D score between 17 and 24. After six weeks of treatment, both groups improved with no significant difference in the response to one treatment compared to the other (Wheatley, 1997). A third study compared 900 mg LI 160 extract to 75 mg imipramine in 130 subjects with depression according to DSM-III-R. Again, after six weeks, a significant reduction in HAM-D scores was seen in both groups: from 20.2 to 8.8 in the LI 160 group and from 19.4 to 10.7 in the imipramine group (Vorbach, Hübner, and Arnoldt, 1994). Our reviewers criticized these trials because they all used low, or what is considered subtherapeutic, doses of the tricyclic antidepressant drugs. A fourth trial used twice the dose of imipramine (150 mg rather than 75 mg per day) along with a higher dose of LI 160 (1,800 mg per day) on 186 adults with depression according to the ICD-10. After six weeks, mean HAM-D scores decreased similarly

in both groups according to intent-to-treat analysis (Vorbach, Arnoldt, and Hübner, 1997). The authors of the studies suggested the possibility that St. John's wort could be a more attractive option for treatment of mild to moderate depression due to fewer side effects with LI 160 compared to the tricyclic antidepressant drugs.

Two drug comparison trials compared the effectiveness of LI 160 with the SSRI sertraline (Zoloft). A small trial, which included 20 subjects diagnosed with depression according to DSM-IV, and having an initial HAM-D score of at least 17, compared sertraline, 75 mg per day, with LI 160, 900 mg per day. After seven weeks, both groups improved with no significant difference between treatments (Brenner et al., 2000). A large trial with 245 adults diagnosed with major depression according to DSM-IV criteria, and a minimum HAM-D score of 20, compared sertraline to LI 160, and also included a placebo group. During the two-month trial, the dose of either treatment could be increased if benefit was not apparent. The dose of sertraline ranged from 50 to 100 mg per day, and the dose for LI 160 ranged from 900 to 1,500 mg per day. Assessments of HAM-D scores at the end of the trial revealed that neither LI 160 nor sertraline provided a statistically significant benefit compared to placebo (Hypericum Depression Trial Study Group, 2002). By the authors' own admission, up to 35 percent of trials with approved antidepressants do not show a benefit when compared with placebo.

Electrophysiological Effects

A trial including 24 healthy subjects compared the effect of administration of LI 160 (900 mg per day) to the tricyclic antidepressant maprotiline (30 mg per day) on EEG traces. After one month of treatment, changes in the visually evoked potentials in the beta region were similar for both agents. The authors of the study stated that this finding was in agreement with clinical studies reporting similar antidepressant activity (Johnson et al., 1994).

Neuroendocrine Effects

A small, one-day study of eight healthy males exploring the mode of action of LI 160 found an increase in plasma concentrations of growth hormone, a decrease in prolactin levels, and no effect on

cortisol levels compared to placebo. The authors interpreted these results as an increase in the neurotransmitter dopamine function. The amount given (2,700 mg extract) was three times the usual therapeutic dose (Franklin et al., 1999).

WS 5572

Depression

We reviewed five studies that explored the activity of WS 5572 or WS 5570 for depression. The usual dose was 900 mg extract per day for a period of one to two months. Three placebo-controlled studies reported a therapeutic benefit, and one was undetermined. We also reviewed one study comparing WS 5572 to the tricyclic antidepressant trimipramine. Two studies explored the mode of action of the extract: one measuring brain EEG traces and the other measuring plasma levels of pituitary hormones.

In a landmark trial, Laakmann and colleagues (1998) compared a St. John's wort extract containing 5 percent hyperforin (WS 5572) with one that contained 0.5 percent hyperforin (WS 5573). Previous characterization of products had emphasized another ingredient, hypericin. This trial indicated that hyperforin might be more important in treating depression than hypericin. The trial included 138 mild to moderately depressed subjects as defined by DSM-IV criteria, with a minimum HAM-D score of 17. The three-arm design included the two different extracts containing different amounts of hyperforin and identical amounts of hypericin: Both extracts were given in doses of 900 mg and were compared to placebo. After six weeks, a statistically significant HAM-D score reduction was observed in the group given the extract containing 5 percent hyperforin compared with the placebo group, whereas the activity reported with the extract containing 0.5 percent hyperforin was not different from placebo.

A placebo-controlled phase III trial included 332 subjects with mild to moderate depression (DSM-IV) and a HAM-D total score between 18 and 25 who were given either 900 mg WS 5570 per day or placebo for six weeks. Treatment with WS 5570 caused a significantly greater decrease in the HAM-D score compared to placebo, from a baseline of 21.9 (all subjects) to 12.0, or 13.8, respectively. In addition, there were significantly more treatment responders, as defined by a 50 percent reduction in the total HAM-D score, in the WS

5570 group (52.7 percent compared to 42.3 percent) (Lecrubier et al., 2002). Another trial with WS 5572 included 65 mild to moderately depressed subjects as defined by DSM-IV criteria, with a minimum HAM-D score of 16. After six weeks, there was a significantly greater reduction in HAM-D scores in the treatment group compared to placebo (Kalb, Trautmann-Sponsel, and Kieser, 2001). An earlier placebo-controlled study of 50 subjects with mild to moderate depression according to ICD classification (edition not given) also reported significant reductions in the HAM-D scoring with WS 5572 compared to placebo. The study was rated as having undetermined efficacy due to poor methodology (Reh, Laux, and Schenk, 1992).

A study of 48 mild to moderately depressed subjects according to DSM-III-R compared Neuroplant forte (WS 5572 extract) to a low dose (25 mg/day) of trimipramine, a tricyclic antidepressant. Similar reductions in HAM-D scores were observed, with initial scores of 13.0 (trimipramine) and 11.2 (Neuroplant forte) dropping to 7.9 and 7.7, respectively, after six weeks. A placebo arm was not included in this trial. Neuroplant forte decreased alpha activity as measured by EEG both with resting and while performing a recognition task. Trimipramine produced an increase in alpha activity under these conditions along with a decrease in delta and gamma activity. The authors concluded that these results indicated a sedative effect with trimipramine that was not seen with Neuroplant forte (Woelk et al., 1996).

Electrophysiological Effects

A mode-of-action study compared the extracts containing 5 percent hyperforin (WS 5572) and 0.5 percent hyperforin (WS 5573) with placebo on quantitative topographic electroencephalography (qEEG) in 53 healthy volunteers. QEEG-measured frequency spectra have been used as a tool to study the action of drugs. The spectrum is divided into frequency bands, namely delta, theta, alpha, and beta. After eight days of 900 mg extract per day, both extracts produced power increases in the delta, theta, and alpha-1 bands that could be distinguished from placebo. This effect was greater with the extract containing 5 percent hyperforin. Although changes in the qEEG were consistent with effects by noradrenergic (theta bands) and serotonergic (alpha-1 bands) neurotransmitters, the authors admitted that

the relationship between acute EEG effects of antidepressant drugs and clinical therapeutic efficacy is far from understood (Schellenberg, Sauer, and Dimpfel, 1998).

Neuroendocrine Effects

A mode-of-action study explored the effect of WS 5570 on pituitary hormone secretion as a means of exploring the effects on neurotransmitters. The effects of WS 5570 on cortisol, growth hormone, and prolactin were examined in 12 healthy subjects. Blood samples were taken one hour prior to and up to five hours after oral administration of 300 mg WS 5570, 600 mg WS 5570, or placebo. As a result, a significant increase in cortisol levels with the 600 mg dose compared to placebo occurred 30 to 90 minutes after oral consumption. The lower dose did not affect cortisol levels. No consistent effect on growth hormone levels was observed, and neither dose affected prolactin levels. The authors suggested that WS 5570, at high doses, acts as a noradrenaline and serotonin reuptake inhibitor, thereby increasing the levels of these neurotransmitters, and, in turn, increasing cortical release (Schüle et al., 2001).

Ze 117

Depression

Three large, well-conducted studies found Ze 117 to be better than placebo and equivalent to therapeutic doses of the tricyclic antidepressant imipramine and the SSRI fluoxetine in treating mild to moderate depression. A placebo-controlled study included 136 subjects with mild to moderate depression according to the ICD-10 and HAM-D scores between 16 and 24. The group given 500 mg Ze 117 per day for six weeks showed significant improvement compared to the placebo group, according to both intention-to-treat and protocol-compliant analysis of HAM-D scores (Schrader, Meier, and Brattstrom, 1998). Another study compared the efficacy of 500 mg Ze 117 per day to 150 mg per day of the tricyclic antidepressant imipramine. This study included 277 participants with mild to moderate depression according to ICD-10 criteria, and an initial HAM-D score of at least 18. Both Ze 117 and imipramine were therapeutically equivalent according to the HAM-D ratings (Woelk, 2000). A third study com-

pared the efficacy of 500 mg Ze 117 per day to 20 mg per day of the SSRI fluoxetine (Prozac). This six-week study included 238 patients with mild to moderate depression according to ICD-10 criteria, and an initial HAM-D score between 16 and 24. According to HAM-D scores, the two treatments were equivalent (Schrader, 2000).

Hyperiforce

Depression

Hyperiforce was tested in a dose-comparison study using tablets containing one-sixth, one-third, and the usual amount of the same crude extract (subjects were given the equivalent of 0.16, 0.33, and 1.0 mg hypericin per day, respectively) over a period of six weeks. The trial included 260 subjects with mild to moderate depression according to ICD-10 criteria. An initial average HAM-D score of approximately 16 was reduced significantly in all three groups. The highest dose showed a trend toward better efficacy, but this difference was not significant (Lenoir, Degenring, and Saller, 1997). Because this trial did not include a placebo group, it is difficult to evaluate the effectiveness of any of these doses.

STEI 300

Depression

St. John's wort extract STEI 300 (1050 mg daily) was compared with the tricyclic antidepressant imipramine (100 mg daily) in an eight-week study including 251 moderately depressed patients as defined by the ICD-10, and with an initial HAM-D minimum score of 18. STEI 300 was more effective than placebo and comparable to imipramine in reducing HAM-D scores (Philipp, Kohnen, and Hiller, 1999).

Dysto-lux (LoHyp-57)

Depression

Another St. John's wort extract, LoHyp-57 (800 mg daily), was compared to the SSRI fluoxetine (Prozac, 20 mg per day) for six weeks in a trial that included 137 subjects ages 60 to 80 years with mild to moderate depression according to the ICD-10. Similar re-

sponse rates were demonstrated for these patients, who had initial average HAM-D scores of 14 to 17 (Harrer et al., 1999).

SYSTEMATIC REVIEWS AND META-ANALYSES

A recent meta-analysis of 22 randomized, controlled trials, with a total of 2,517 patients, found that St. John's wort was more effective than placebo and not different in activity from other antidepressants. Numerous St. John's wort products were included (e.g., Jarsin, Neuroplant, Ze 117, and STEI 300). Only two trials tested treatment in severe depression (Vorbach, Arnoldt, and Hübner, 1997; Shelton et al., 2001); the majority tested treatment in mild to moderate depression. An initial analysis was conducted on 14 placebo-controlled studies that met the general criteria of including Hamilton Depression Rating Scale (HAM-D) scores. A secondary analysis was conducted on six placebo-controlled studies that met the stricter criteria of including intention-to-treat analysis (ITTA) and adherence to predefined inclusion and exclusion criteria in addition to HAM-D scores. Both of these analyses came to the conclusion that St. John's wort was significantly better than placebo, with the effect size being smaller in the second analysis. The relative risk (RR) was 1.98 (95 percent confidence interval [CI] 1.49 to 2.62) in the general analysis and 1.77 (1.16 to 2.70) in the stricter analysis. St. John's wort compared to other antidepressants were also analyzed twice—once with nine studies meeting general criteria, and again with four studies meeting the more stringent criteria mentioned earlier. Both comparisons found that the activity of St. John's wort was not significantly different from active antidepressants: RR 1.0 (0.90 to 1.11) and RR 1.04 (0.94 to 1.15), respectively. Most trials compared St. John's wort with tricyclic antidepressants, and only two used an SSRI. There was no publication bias in the trials according to a funnel plot analysis (Whiskey, Werneke, and Taylor, 2001).

Earlier meta-analyses came to similar conclusions. Linde and colleagues (1996) reviewed 23 randomized, controlled trials including 1,757 patients with mild to moderate depression. Analysis of 15 placebo-controlled trials yielded that St. John's wort preparations were significantly better than placebo, with an RR of 2.67 (95 percent CI 1.78 to 4.01). Analysis of eight trials comparing the activity of St. John's wort to tricyclic antidepressants found their activity to be simi-

lar: RR 1.10 (0.93 to 1.31). Kim, Streltzer, and Goebert (1999) conducted an analysis on blinded, controlled studies with well-defined depressive disorders (ICD-10, DSM-III-R or DSM-IV) and outcome measures, including HAM-D scores. Six controlled, double-blind, clinical studies with a total of 651 patients with mild to moderate depression met the entry requirements, including two placebo-controlled studies and four drug comparison studies. In reviewing the placebo-controlled trials, Kim, Streltzer, and Goebert reported that St. John's wort was 1.5 times more likely than placebo to cause an antidepressant response. In reviewing the four comparison trials with tricyclic antidepressants (maprotiline, amitriptyline, imipramine), they found the two treatments to be equivalent.

POSTMARKETING SURVEILLANCE STUDIES

A multicenter postmarketing surveillance study was carried out with 101 children ages 1 through 12 years with depression and psychovegetative disorders. The dose ranged from 300 to 1,800 mg LI 160 extract per day with the median dose being 300 mg. With no standardized measure available to assess depression in children, physicians and parents filled out a questionnaire covering 12 typical symptoms. The number of physicians rating treatment effectiveness as good or excellent was 72 percent after two weeks and 97 percent after four weeks. Although 90 percent of children completed four weeks of treatment, only 75 percent extended their treatment for an additional two weeks. All of those remaining in the study were rated as good or excellent after six weeks (Hübner and Kirste, 2001).

A multicenter postmarketing surveillance study was conducted on 2,166 patients diagnosed with mild to moderate depression who took either one or two (600 mg) WS 5572 tablets (Neuroplant) per day. Patients with more severe depression were given the higher dose, and both groups were followed for six weeks. At that time, the physicians and patients evaluated the efficacy of both doses and found them to be mostly good or very good with no significant difference between the two (Rychlik et al., 2001). An earlier study had administered the customary dosage of 300 mg three times daily to 5,546 patients (Lemmer, von den Driesch, and Klieser, 1999). Because the same standard methods were used for both studies, Rychlik and colleagues (2001)

compared them and concluded that there was no relevant therapeutic disadvantage with the administration of 600 mg once daily compared to 300 mg three time daily.

ADVERSE REACTIONS OR SIDE EFFECTS

The most common side effects of *Hypericum* in the trials reviewed earlier were generally mild and consisted of gastrointestinal disturbances, dry mouth, sleep disturbances, headaches, pruritis, and possible photosensitivity. A meta-analysis of 22 randomized, controlled trials reported that side effects were mild, and those occurring in more than 1 percent of the study population included nausea and vomiting, dry mouth, headaches, fatigue, abdominal pain, dizziness, and restlessness (Whiskey, Werneke, and Taylor, 2001). In a large, prospective, open-label study in which data were systematically gathered from 3,250 patients, only 2.4 percent of patients reported an adverse effect. The most common effects were gastrointestinal complaints, allergic rash, tiredness, anxiety, and confusion (Woelk, Burkard, and Grunwald, 1994).

A multicenter, postmarketing surveillance study carried out with 101 children ages one through twelve years treated with 300 to 1,800 mg LI 160 extract per day for four to six weeks reported good tolerability with no adverse events (Hübner and Kirste, 2001). Another multicenter, postmarketing surveillance study conducted on 2,166 patients given one or two (600 mg) WS 5572 tablets (Neuroplant) per day reported the incidence of adverse drug reactions to be less than 1 percent. The reactions included skin irritation and itching of the area around the eyelids, allergic exanthema, nervousness and unrest, stomach problems, diarrhea, and sleep disorders (Rychlik et al., 2001).

A crossover trial with 12 older women found no effect on rapid eye movement (REM) sleep after a month of administration of 900 mg extract (LI 160). This was in contrast to effects of tricyclic antidepressants, which do interfere with REM sleep (Schulz and Jobert, 1994). A drug comparison study with 160 depressed patients reported no pathological effect on cardiac function as measured via electrocardiogram (ECG) following administration of a high dose of Jarsin 300 (1,800 mg per day) for six weeks compared with 150 mg of the tricyclic antidepressant imipramine. The rationale for this study is that

patients suffering from depression with a preexisting conductive dysfunction are at increased risk for ventricular arrhythmia when taking tricyclic antidepressants. As expected, in susceptible individuals, imipramine caused a prolongation of conduction intervals. In contrast, St. John's wort extract caused a small increase in conduction in those individuals. The authors of the study concluded that in the treatment of patients with a preexisting conductive dysfunction, or elderly patients, a high dose of LI 160 is safer with regard to cardiac function than tricyclic antidepressants (Czekalla et al., 1997).

Although few study participants in clinical trials reported photosensitivity as an adverse effect, photosensitivity has been reported following intravenous administration of hypericin, one of the constituents of St. John's wort. Studies were therefore designed to measure this effect following an oral dose of extract LI 160. In a single-dose trial, 48 volunteers received either six or twelve tablets of LI 160 containing 5.4 or 10.8 mg total hypericins. In a steady-state trial reported in the same publication, 24 volunteers received an initial dose of six tablets (5.4 mg hypericins) and subsequently three tablets per day (2.7 mg hypericins) for seven days. There was no effect from either the single dose or multiple doses on thresholds for producing skin erythema (redness/inflammation) following exposure to ultraviolet light, visible light, or solar-simulated radiation (Schempp et al., 2001). In an earlier study, 50 healthy volunteers were given twice the usual dose of extract, 600 mg three times daily (5.4 mg total hypericins per day), and the minimum dose of UV light required to produce erythema on the skin was measured. At the end of 15 days of administration of the extract, the time required to cause a burn decreased by 21 percent ($p < 0.01$) (Brockmöller et al., 1997). It appears from these studies that photosensitivity is not a major concern following oral administration of the usual dose of 900 mg per day of St. John's wort extract.

DRUG INTERACTIONS

Evidence suggests that St. John's wort preparations can interact with drugs, namely anticoagulants (e.g., phenprocoumon, warfarin), cyclosporin, digoxin, and protease inhibitors used for HIV therapy (e.g., indinavir). Data also suggests that St. John's wort may interact with anti-

depressants, such as the tricyclic antidepressants (e.g., amitriptyline) and the serotonin reuptake inhibitors (e.g., sertraline, nefazodone, paroxetine). A few cases have been reported of breakthrough bleeding with women on low-dose estrogen oral contraceptives while also taking St. John's wort. The basis for these interactions appears to be stimulation of drug-metabolizing enzymes in the P450 family and possible induction of the P-glycoprotein transport mechanism (Schulz, 2001). St. John's wort preparations do not appear to interact with alcohol or carbamazepine, an anticonvulsant drug used to treat epilepsy (Schmidt et al., 1993; Burstein et al., 2000).

In vitro tests have suggested that the St. John's wort constituent responsible for, at least some of, these drug interactions is hyperforin. A study compared the interactions of LI 160 (high hyperforin content, daily dose 25 to 30 mg in 900 mg extract) with digoxin to the interaction between Ze 117 (very low hyperforin content; daily dose approximately 1 mg in 500 mg extract) and digoxin. The study found that whereas administration of LI 160 decreased digoxin plasma levels, Ze 117 did not (Brattström, 2002). More details of this study are given later.

Anticoagulants

Indication for the interaction between St. John's wort and the anticoagulant phenprocoumon comes from a randomized, placebo-controlled, double-blind, crossover study in which ten healthy subjects were given three (300 mg) tablets per day of LI 160 for 11 days. On the last day, subjects were given a single dose of 12 mg phenprocoumon. After a two-week washout period, the same subjects were given a placebo for 11 days and again a single dose of phenprocoumon. Compared to values with placebo, the plasma concentrations of phenprocoumon (area under the curve, 0 to 72 hours) were significantly lower (17.4 percent) with St. John's wort (Maurer et al., 1999). In addition, there have been seven case reports suggesting that St. John's wort reduces the anticoagulant activity of warfarin, causing a decreased International Normalized Ratio (INR) (Yue, Bergquist, and Gerden, 2000).

Immunosuppressants

Indication for the interaction between St. John's wort and cyclosporine comes from reports of acute rejection in two heart transplant patients who were taking cyclosporine to suppress their immune systems. Previously stable cyclosporine plasma levels were decreased by the addition of St. John's wort. This situation was reversed upon cessation of the herb (Ruschitzka et al., 2000). A similar situation was reported in kidney transplant patients (Breidenbach et al., 2000).

Cardiac Glycosides

The interaction between digoxin and St. John's wort LI 160 extract was investigated in a single-blind, placebo-controlled, parallel study with 25 healthy volunteers. Volunteers received digoxin (0.25 mg/day) for five days, then digoxin with either placebo or 900 mg LI 160 per day for another ten days. As a result, no statistically significant change in plasma digoxin levels was observed after the first dose of LI 160. However, after ten days of treatment, a 25 percent decrease in plasma digoxin levels (24 hours area under the curve) was observed compared to the placebo group. The effect on plasma digoxin levels increased over time with the days of coadministration of LI 160 (Johne et al., 1999).

Another study compared the interaction of LI 160 and digoxin with the interaction between another St. John's wort preparation, Ze 117, and digoxin. Twenty-two volunteers were given digoxin for seven days, and their dose was adjusted to achieve a constant plasma level (1 ng per ml). For the next 14 days the volunteers additionally received placebo, Ze 177 (500 mg per day), or LI 160 (900 mg per day). The doses of St. John's wort preparations were different, but they were consistent with those used in their respective clinical efficacy studies. Digoxin plasma measurements were taken over the 14-day period. The results confirmed the interaction between LI 160 and digoxin: digoxin levels were reduced by 27 percent (24 hours area under the curve) after 14 days coadministration. However, the extract Ze 117 had no such effect. The author of the study concluded that the differences in the activity of the two extract was due to differences in hyperforin concentrations. Ze 117 contains a very low quantity of hyperforin (approximately 1 mg in 500 mg extract) compared to LI

160 (25 to 30 mg in 900 mg extract). The differences in total extract quantities may have also played a role (Brattström, 2002).

HIV Protease Inhibitors

An open-label study with eight volunteers found that St. John's wort decreased the plasma levels (area under the curve, 0 to 5 hours) of the protease inhibitor indinavir by 57 percent. Pharmacokinetic profiles of indinavir were measured before and after 14 days of administration of St. John's wort (300 mg three times daily; HBC Protocols, Inc.) (Piscitelli et al., 2000).

Antidepressants

An interaction between the tricyclic antidepressant amitriptyline and St. John's wort was demonstrated in an open study with 12 depressed patients treated with 150 mg amitriptyline-hydrochloride for 12 days, with or without 12 days of pretreatment with 900 mg LI 160. The plasma level (area under the curve [AUC], 1 to 12 hours) of amitriptyline was reduced by 22 percent, and the AUC of its metabolite, nortriptyline, was reduced by 42 percent (Roots, 1999). There may also be an interaction with other classes of antidepressants. Six cases of serotonergic syndrome have been reported following concomitant ingestion of St. John's wort and serotonin reuptake inhibitors sertraline, nefazodone, and paroxetine (Gordon, 1998; Lantz, Buchalter, and Giambanco, 1999).

Birth Control Tablets

Possible interaction of St. John's wort with oral contraceptives was indicated by reports of breakthrough bleeding in five women taking low-dose estrogen preparations (30 microg ethinyloestradiol) (Ernst, 1999). A study with the extract Ze 117 did not find any effect on plasma levels of the hormones ethinylestradiol or desogestrel. In this study, 16 women took the pill (0.02 mg ethinylestradiol and 0.15 mg desogestrel) daily for at least three months. They were then given 500 mg Ze 117 from day 7 through day 22 of their cycle. No decrease was found in plasma levels of the hormones when day 21 was compared to day seven. No spotting or irregular bleeding was reported, and the

levels of the enzyme responsible for metabolizing desogestrel to 3-keto desogestrel, CYP 2C19, was not altered (Brattström, 2002).

Alcohol

A crossover trial, with 32 normal volunteers given 900 mg LI 160 extract or placebo for seven days explored a possible interaction between St. John's wort and alcohol. When the volunteers were given sufficient alcohol to establish blood levels between 0.45 and 0.8 percent, they were subjected to a battery of tests covering cognitive capacities required for operation of machines and for driving. The St. John's wort extract did not have any effect on the action of the alcohol (Schmidt et al., 1993).

Anticonvulsants

St. John's wort does not appear to affect plasma levels of the anticonvulsant drug carbamazepine, which is used to treat epilepsy. In a study of eight healthy men, carbamazepine was administered for 14 days, reaching a steady state with 400 mg once daily. St. John's wort, 300 mg extract (HBC Protocols, Inc.) taken three times daily for 14 days concurrently, did not alter the plasma levels of carbamazepine (Burstein et al., 2000). This finding is somewhat unexpected, since carbamazepine is thought to be primarily metabolized via CYP3A4, a P450 isoenzyme whose activity is thought to be stimulated by St. John's wort (Roby et al., 2000).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

American Herbal Pharmacopoeia
European Scientific Cooperative on Phytotherapy
German Commission E
United States Pharmacopeia—Drug Information

Indications

The German Commission E approves the use of dried, aboveground parts of St. John's wort, taken internally, to treat psychovegetative disturbances, depressive moods, anxiety and/or nervous unrest (Blumenthal et al., 1998). The European Scientific Cooperative on Phytotherapy (ESCOP) states that St. John's wort can be used to treat mild to moderate depressive states (ICD-10 categories F32.0 and F32.1) and somatoformic disturbances, including symptoms such as restlessness, anxiety, and irritability (ESCOP, 1996). The *American Herbal Pharmacopoeia (AHP)* states that, in addition to treating mild to moderate depressions, St. John's wort is used for the treatment of several neurological conditions, including anxiety, insomnia due to restlessness, irritability, neuralgia, trigeminal neuralgia, neuroses, migraine headaches, fibrositis, and sciatica (Upton et al., 1997). According to the *United States Pharmacopeia—Drug Information (USP-DI)* botanical monograph series, St. John's wort extract has been used to treat mild to moderate depression (*USP-DI,* 1998).

Both the Commission E and the *AHP* suggest that oily hypericum preparations be used internally for dyspeptic complaints and externally for treatment and posttherapy of acute and contused injuries, myalgia, and first-degree burns (Blumenthal et al., 1998; Upton et al., 1997).

Other uses listed by the *AHP* include to treat pain and inflammation of nerve origin (painful tooth socket following tooth extraction; shingles; herpes communis; chronic neuralgia stemming from fractures, spinal injuries, musculoskeletal trauma, and surgical trauma; nerve injury resulting in lancinating, burning, or tingling pains; and twitching or spasm following a traumatic injury), gastric conditions (ulcer and functional gastritis, nervous dyspepsia, inflammatory bowel syndrome, and internal hemorrhoids), enuresis due to nervous anxiety or nerve irritation in the bladder, and as an antiviral agent (Upton et al., 1997).

Doses

Preparations containing: 0.2 to 1 mg of total hypericin daily (Blumenthal et al., 1998; ESCOP, 1996); 0.5 to 3 mg total hypericin daily (Upton et al., 1997)

Dried aboveground parts: 2 to 4 g daily (Blumenthal et al., 1998; ESCOP, 1996; Upton et al., 1997).
Infusion: 1 to 2 cups twice daily corresponding to 2 to 4 g herb (Upton et al., 1997; ESCOP, 1996)
Tincture: (1:5) 2 to 4 ml three times daily (Upton et al., 1997); equivalent to 0.2 to 1 mg total hypericin daily (ESCOP, 1996)
Extract: fluid extracts, aqueous alcoholic extracts, equivalent to 0.2 to 1 mg total hypericin daily (ESCOP, 1996)
Oil: (gastric complaints) 1 tsp on an empty stomach morning and evening (Upton et al., 1997)

Treatment Period

ESCOP states there is usually no treatment length restriction. However, an antidepressant effect is not expected before 10 to 14 days of treatment, and if no response is apparent after four to six weeks, treatment should be discontinued (ESCOP, 1996).

Contraindications

The Commission E and ESCOP list no known contraindications for St. John's wort (Blumenthal et al., 1998; ESCOP, 1996). The *USP-DI* suggests that using St. John's wort to treat suicidal and psychotic patients may be inappropriate (*USP-DI,* 1998).

Adverse Reactions

The Commission E states that photosensitization is possible, especially in fair-skinned individuals (Blumenthal et al., 1998). ESCOP adds that photosensitization may occur at higher dosages (ESCOP, 1996). The *USP-DI* states that the following adverse reactions have been reported: phototoxicity, gastrointestinal symptoms, allergic reaction, dizziness, constipation, dry mouth, restlessness, sleep disturbances, and fatigue (*USP-DI,* 1998).

Precautions

The AHP recommends that care should be taken when using external preparations in conjunction with therapies utilizing ultrasound or

ultraviolet light. St. John's wort should also be used with caution in pregnancy (Upton et al., 1997). The *USP-DI* states that the use of St. John's wort is not recommended for children and pregnant or breast-feeding women, and that individuals at risk of phototoxic reactions should use caution when exposed to the sun (*USP-DI,* 1998).

Drug Interactions

The Commission E and ESCOP list no known drug interactions (Blumenthal et al., 1998; ESCOP, 1996). The *USP-DI* warns that although no interactions have been reported, St. John's wort may interact with selective serotonin reuptake inhibitors and monoamine oxidase (MAO) inhibitors (*USP-DI,* 1998).

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DETAILS ON ST. JOHN'S WORT PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to St. John's Wort Products

Product Profile: Kira®

Manufacturer	**Lichtwer Pharma AG, Germany (Indena S.p.A., Italy)**
U.S. distributor	**Lichtwer Pharma U.S., Inc.**
Botanical ingredient	**St. John's wort flower and leaf extract**
Extract name	**LI 160 (St. John Select™)**
Quantity	300 mg
Processing	Plant to extract ratio 4-7:1; aqueous methanolic extract
Standardization	0.24-0.32% total hypericin
Formulation	Tablet

Recommended dose: Take one tablet three times daily with water at mealtimes. Results observed after two to four weeks of usage. Kira's safety profile also supports longer-term use.

DSHEA structure/function: Maintain a healthy emotional balance. Supports emotional well-being. Supports a healthy balance among the brain's chemical messengers to promote a feeling of well-being.

Cautions: If you are pregnant, nursing a baby, or giving to children under age of 12, consult a healthcare professional before using this product. Recent data suggest that if you are taking any drug product, and in particular a blood-thinner or anti-organ rejection medicine, you should consult with your health care professional to avoid any interactions with St. John's Wort. St. John's Wort, and certain other food/herbal products, may affect Cytochrome P-450 enzyme activity within the body, a normal metabolic pathway that is also affected by certain drug products. When taking this product, use caution in exposure to excessive sunlight.

Other ingredients: Lactose, powdered cellulose, hydroxypropyl methylcellulose, silicon dioxide, titanium dioxide (mineral based whitening pigment), magnesium stearate, talc (natural tableting aid), triethyl citrate, vanillin.

Comments: Sold as Jarsin® 300 in Europe.

Source(s) of information: Product package; Kira product information (www.lichtwer.com/kira/kira_prod_info.html); Jarsin® 300 product information, Lichtwer Pharma GmbH, 1996; information provided by Indena USA.

Product Profile: St. John's Wort Extract

Manufacturer	**Enzymatic Therapy (Indena S.p.A., Italy)**
U.S. distributor	**Enzymatic Therapy**
Botanical ingredient	**St. John's wort aerial parts extract**
Extract name	**St. John Select™**
Quantity	300 mg
Processing	Plant to extract ratio 3-4:1, aqueous methanolic extract
Standardization	A minimum of 0.3% hypericin and 3% hyperforin
Formulation	Capsule

Recommended dose: One capsule three times daily.

DSHEA structure/function: Dietary supplement to promote mental well-being.

Cautions: Due to the St. John's wort extract, in extremely rare cases light-skinned people may experience a sensitivity to excessive sun exposure. If taking a prescription drug, consult a physician prior to use.

Other ingredients: Gelatin, magnesium stearate, silicon dioxide, titanium dioxide.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Product Profile: Hypericum Perforatum II

Manufacturer	**HBC Protocols, Inc. (Indena S.p.A., Italy)**
U.S. distributor	**HBC Protocols, Inc.**
Botanical ingredient	**St. John's wort flowering tops extract**
Extract name	**St. John Select™**
Quantity	300 mg
Processing	Plant/extract ratio 3-4:1, aqueous methanolic extract
Standardization	0.3% hypericin and 4% hyperforin
Botanical ingredient	**Grape seed extract**
Extract name	**LeucoSelect®**
Quantity	1 mg
Processing	Plant/extract ratio 100:1
Standardization	95% polyphenols (80-85% oligomeric proanthocyanidins)
Formulation	Tablet

Recommended dose: Take one tablet three times daily.

DSHEA structure/function: Promotes a balanced emotional outlook.

Cautions: Not to be used by people taking MAO inhibitors. May cause hypersensitivity to sunlight. Not to be taken by pregnant women. Talk to your doctor if you are on prescription medication.

Other ingredients: Calcium phosphate dibasic, microcrystalline cellulose, vegetable oil, croscarmelose sodium, magnesium stearate, silicon dioxide.

Source(s) of information: Product label; information provided by Indena USA, Inc.

Product Profile: Hyper-Ex®

Manufacturer	**Thorne Research (Indena S.p.A., Italy)**
U.S. distributor	**Thorne Research**
Botanical ingredient	**St. John's wort flower extract**
Extract name	**St. John Select™**
Quantity	300 mg
Processing	Plant to extract ratio 3-4:1, aqueous methanolic extract
Standardization	0.3% hypericin
Formulation	Capsule

Cautions: If pregnant, consult your health care practitioner before using this, or any other product.

Other ingredients: Cellulose capsule.

Comments: This product is available only through pharmacies and health care practitioners.

Source(s) of information: Product label; information from Indena USA, Inc.

Clinical Study: Jarsin® 300

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference

Hänsgen KD, Vesper J (1996). Antidepressant efficacy of a high-dose extract of St. John's wort. *Münchener Medizinische Wochenschrift* 138 (3): 35-39.

Trial design
Parallel. Patients received either *Hypericum* extract or placebo for four weeks, then both groups received LI 160 for the last two weeks of the trial. All patients were informed that they would receive the active treatment for at least two weeks.

Study duration	1 month
Dose	3 (300 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	17 practices (neurology and psychiatry)
No. of subjects enrolled	108
No. of subjects completed	101
Sex	Male and female
Age	18-70 years (mean: 52)

Inclusion criteria
Outpatients of specialist neurology and psychiatry clinics with mild to moderate major depression as defined in the DSM-III-R; a total score of 16 or more on the Hamilton Depression Scale (HAM-D); and patients who had suffered from their current depression for between two weeks and six months. Psychoactive medication was discontinued at least a week prior to the start of the study.

Exclusion criteria
Patients who had psychotic features or severe systemic diseases, patients who were dependent on alcohol, medication, or drugs of abuse, and patients who were at risk of suicide.

End points
Efficacy was assessed by the HAM-D, the von Zerssen Depression Scale (D-S), the Kasielke and Hänsgen Symptom Rating Scale (BEB), and the Clinical Global Impressions scale (CGI). Response to the HAM-D scale was defined as a total score of less than 10 or a reduction in score by at least 50 percent. Patients were assessed at baseline and at two, four, and six weeks.

Results
In the first four weeks, the response rate on the HAM-D was 70 percent in

the LI 160 group and 24 percent for the placebo group. Scores fell from 21.0 to 8.9 for the LI 160 group and from 20.4 to 14.4 for the placebo group. Differences were highly significant ($p < 0.001$) after both two and four weeks. Scores on the D-S fell from 21.2 to 9.3 for the *Hypericum* group—levels within the range for normal healthy subjects. In the placebo group, mean scores decreased from 19.6 to 14.6. Again, differences were highly significant ($p < 0.001$) after both two and four weeks. Differences between the two groups on the BEB were also significant ($p < 0.01$) after two and four weeks, with marked improvements in the *Hypericum* group in general well-being, cardiovascular symptoms, and anxiety/phobia symptoms. When both groups were given the active treatment, the scores in the original *Hypericum* group fell to 6.3 on the D-S scale, whereas the score reduction in the original placebo group was very similar to that obtained in the active treatment group during the first two weeks of treatment.

Side effects
One patient in the *Hypericum* group reported mild sleep disturbances.

Authors' comments
Over the first four weeks of the study, the changes detected by the self-rating methods were judged to be consistent with the changes detected with the observer-rating method. The degree of improvement was unequivocally greater than that which could be expected from spontaneous remission or statistical regression. St. John's wort extract LI 160 markedly reduces depressive symptoms in mild to moderate depression. In view of its efficacy and lack, or virtual lack, of side effects, it can be recommended as the antidepressant of choice, especially for outpatients.

Reviewers' comments
This is a good, well-designed, and well-conducted study. A minor flaw was the short washout period for pretreatment medications. Also, the authors did not state who administered HAM-D scales and whether a coexisting treatment was allowed. (5, 6)

Clinical Study: Jarsin® 300

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Hänsgen K, Vesper J, Ploch M (1994). Multicenter double-blind study examining the antidepressant effectiveness of the *Hypericum* extract LI 160. *Journal of Geriatric Psychiatry and Neurology* 7 (Suppl. 1): S15-S18. (Also published in Hänsgen K, Vesper J, Ploch M [1993]. Multizentrische doppelblindstudie zur antidepressiven wirchsamkeit des *Hypericum*-extraktes LI 160. *Nervenheilkunde* 12: 285-289.)

Trial design
Parallel. During the first four weeks of the trial, patients received either LI 160 or placebo. During the last two weeks of the study, all patients received LI 160. All patients were informed that every participant in the study would receive the active treatment for at least two weeks during the course of the study, but were not told which weeks.

Study duration	1 month
Dose	3 (300 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	11 practices (neurology, psychiatry, and general)
No. of subjects enrolled	72
No. of subjects completed	67
Sex	Male and female
Age	18-70 years (mean: 53)

Inclusion criteria
Ages 18 to 70 years with major depression according to the DSM-III-R, Hamilton Depression Scale (HAM-D) > 15, duration of depressive episode for a minimum of two weeks and a maximum of six months.

Exclusion criteria
Psychotic episodes, suicide risk, severe mental illness, drug use, or pregnancy.

End points
Efficacy and safety were monitored by the HAM-D, depression scale of Von Zerssen (D-S), complaint inventory (BEB), and by the Clinical Global Im-

pressions Scale (CGI). Patients were monitored at baseline and during treatment at weeks 2, 4, and 6.

Results
HAM-D fell from 21.8 to 9.2 after four weeks for the LI 160 group, and from 20.4 to 14.7 for the placebo group. There was a significant difference from placebo after two and four weeks ($p < 0.001$). Levels further declined at the six-week end point, particularly in the original placebo group, which was now taking *Hypericum* extract. D-S registered the treatment group within the normal range after four weeks, with a significant difference from placebo ($p < 0.001$). The level of symptoms according to the BEB fell significantly more in the LI 160 group than in the placebo group ($p = 0.01$). The CGI scale showed the severity of illness much reduced after four weeks of treatment with *Hypericum* compared with placebo. The CGI also showed a noticeable improvement in the placebo group in the last two weeks after switching to LI 160.

Side effects
One subject in treatment group reported a sleep disturbance.

Authors' comments
Because of its potent and specific efficacy with few or no side effects, *Hypericum* extract LI 160 can be recommended as an antidepressant for treatment of depressed outpatients.

Reviewers' comments
This was a multisite and multidiscipline (neurology, psychiatry, and general practices) study, but the trial report did not describe who and how many subjects were recruited from each site and whether the observer was trained to administer the scales used. (5, 6)

Clinical Study: Jarsin® 300

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Sommer H, Harrer G (1994). Placebo-controlled double-blind study examin-

ing the effectiveness of an *Hypericum* preparation in 105 mildly depressed patients. *Journal of Geriatric Psychiatry and Neurology* 7 (Suppl. 1): S9-S11.

Trial design
Parallel.

Study duration	1 month
Dose	3 (300 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	3 medical practices
No. of subjects enrolled	105
No. of subjects completed	89
Sex	Male and female
Age	24-68 years (mean: 45)

Inclusion criteria
Depressive symptoms according to ICD-9: 300.4 (neurotic depression) and 309.0 (brief depressive reaction).

Exclusion criteria
Severe renal or hepatic dysfunction; heart failure; Parkinson's disease; endocrine or CNS tumors; alcohol, drug, or medication dependency; pregnancy, breast feeding, and inadequate contraceptive measures. Any prior treatment with psychoactive drugs must have been discontinued for at least four weeks.

End points
Patients were evaluated at baseline and at two and four weeks. Depressive symptoms were estimated using the Hamilton Depression Scale (HAM-D). Responders were those whose total score fell to a value below 10 or by at least 50 percent of the baseline value.

Results
The values of the mean basic HAM-D scores fell from 15.8 to 9.6 and 7.2 after two and four weeks, respectively, in the hypericum group. In the placebo group, scores fell from 15.8 to 12.3 and 11.3 after two and four weeks, respectively. The differences between the groups were statistically significant

at two weeks, increasing after four weeks ($p < 0.05$ and $p < 0.01$, respectively). Clinical improvement was noted in depressive mood, difficulty initiating sleep, and psychological anxiety. At the end of four weeks, according to the HAM-D, 67 percent of the *Hypericum* group could be classified as responders, compared to 28 percent receiving placebo.

Side effects
Two patients in the *Hypericum* group experienced skin reddening, itching, and tiredness.

Authors' comments
Hypericum preparations have therapeutic effects that are very similar to those of traditional antidepressants, but they are not burdened with side effects. *Hypericum* is, therefore, a low-risk antidepressant for treatment of mild and moderate depression.

Reviewers' comments
This trial is greatly limited by its poor statistics. The report did not clarify how many men and women were in the sample, and no standard deviations or indication of variability (range) were given. It is unclear why the authors used nonparametric tests. They also did not use intent-to-treat analysis. (3, 3)

Clinical Study: Jarsin 300®

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Hübner W, Lande S, Podzuweit H (1994). *Hypericum* treatment of mild depressions with somatic symptoms. *Journal of Geriatric Psychiatry and Neurology* 7 (Suppl. 1): S12-S14. (Also published in Hübner W, Lande S, Podzuweit H [1993]. Behandlung larvierter depressionen mit Johanniskraut. *Nervenkeilkunde* 12: 278-280.)

Trial design
Parallel. Pretrial washout period of two weeks.

Study duration	1 month
Dose	3 (300 mg) tablets daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	1 internal medicine practice
No. of subjects enrolled	40
No. of subjects completed	39
Sex	Male and female
Age	20-64 years (mean: 51)

Inclusion criteria
Neurotic depression (300.4) and temporary depressive neurosis (309.0) according to the ICD-9.

Exclusion criteria
No other neurotic or psychiatric illness, and no other psychiatric substances two weeks prior to trial.

End points
Outcome was measured by the Hamilton Depression Scale (HAM-D), the von Zerssen Health Complaint Survey (B-L), the Clinical Global Impressions (CGI), and questions on typical somatic symptoms. Patients were examined at baseline and at the end of weeks 2 and 4. Baseline values on the HAM-D tests were compared to final scores. The responder rate (decrease of 50 percent or below 10 points on final HAM-D) was calculated and compared for the two treatment groups.

Results
Treatment and placebo groups began with a HAM-D score of 12.55 ± 1.28 and 12.37 ± 1.34, respectively. The *Hypericum* group showed a responder rate of 70 percent, compared to 47 percent for the placebo group. (Actual HAM-D scores were displayed in a graph and not given numerically.) A significant difference of 5 percent was observed between the two groups at the end of four weeks ($p < 0.05$). The CGI scale showed change in condition as "very much better" in nine of the *Hypericum* patients and "unchanged" or "slightly worse" in another seven. In the placebo group, four cases were "very much better," whereas 14 were "unchanged" or "slightly/very much worse."

Side effects
None reported by patients.

Authors' comments
The results of the present study show that these patients benefited from taking the investigational product in contrast to placebo. Because of good tolerability, and thus high compliance, LI 160 may be helpful for patients with masked depressions.

Reviewers' comments
The authors did not state exclusion/inclusion criteria clearly, and the sample size was very small. The clinical generalizability of the results is therefore unclear. The authors also used the ICD-9, an outdated reference, to rate patients' depression. They did not state clearly who administered the instruments and whether they were trained. Also, the washout period for previous medication was short. (5, 3)

Clinical Study: Jarsin®

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Schmidt U, Sommer H (1993). Extract of St. John's Wort in the outpatient therapy of depressions with unimpaired attention and reaction faculties. *Fortschritte der Medizin* 111 (19): 339-342.

Trial design
Parallel.

Study duration	6 weeks
Dose	300 mg 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes

Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	65
No. of subjects completed	60
Sex	Male and female
Age	24-68 years

Inclusion criteria
Mild to moderately severe depression; outpatients; a short-duration depressive condition classified by the ICD-9: neurotic depression; total score on the Hamilton Depression Scale (HAM-D) between 16 and 20 points; no medical treatment within two weeks of study; possession of a valid driver's license for at least four years; and several years experience in driving a motor vehicle

Exclusion criteria
Depression resulting from organic causes; HAM-D over 20, indicating severe depression; chronic depressive clinical pictures; attempted suicide; accompanying medical treatment with verified cognitative influences; and abuse of narcotics, alcohol, or medical drugs.

End points
The HAM-D test was administered to patients prior to the study and at the end of the study; response to treatment was defined as a total score of less than 10 on the HAM-D after treatment, or at least a 50 percent decrease in HAM-D score. Patients were given the Vienna Determination Unit test, which measures reactions necessary for driving in traffic. Patients also took the d_2 Brickenkamp attention load test to measure concentration ability.

Results
In the St. John's Wort group, the HAM-D response rate was 66.6 percent, whereas it was 26.7 percent in the placebo group. None of the psychomotor tests or the d2 attention load test indicated impaired cognitive performance due to treatment.

Side effects
Two patients experienced redness, itching, and fatigue; overall tolerability was good to very good.

Authors' comments
The recommended daily dose of Jarsin did not influence attention, concentration, or reaction. This herbal antidepressant can thus be recommended for continued long-term treatment, especially in cases where the use of chemical substances produces distressing side effects.

Reviewers' comments
This was a descriptive study only. Insufficient data/statistical results were given for depression results. The data emphasized the driving reaction time results, which have nothing to do with depression effectiveness ratings. The authors also do not give enough data information to replicate for antidepressant effects. Due to the lack of results regarding depression, no clear conclusions could be made regarding this treatment. (Translation reviewed) (2, 3)

Clinical Study: LI 160

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Shelton RC, Keller MB, Gelenberg A, Dunner DL, Hirschfeld R, Thase ME, Russell J, Lydiard RB, Crits-Cristoph P, Gallop R, et al. (2001). Effectiveness of St. John's wort in major depression: A randomized trial. *Journal of the American Medical Association* 285 (15): 1978-1986.

Trial design
Parallel. Single-blind pretrial washout period of one week with placebo. If insufficient improvement was seen by week 4, the dose of 300 mg three times daily was increased to 300 mg four times daily for the remainder of the trial.

Study duration	2 months
Dose	1 (300 mg) tablet 3-4 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	11 academic medical centers
No. of subjects enrolled	200
No. of subjects completed	167
Sex	Male and female
Age	Mean: 42 years

Inclusion criteria
Physically healthy outpatients, 18 years or older, diagnosed as having major depressive disorder (single episode or recurrent), without psychotic features according to DSM-IV, of at least four weeks' duration, and a score of at least 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D). Patients in psychotherapy were allowed to continue treatment if they had been in therapy for at least three months prior to baseline, and if the frequency of sessions remained the same during the study.

Exclusion criteria
DSM-IV diagnosis of a current cognitive disorder, post-traumatic stress disorder, eating disorder, or a substance use disorder in the last six months; panic disorder in the last year; current or past history of bipolar disorder, any psychotic disorder, or borderline, antisocial, or schizotypal personality disorder; HAM-D suicide score greater than 2 or significant risk of suicide; prior trial of St. John's wort (at least 450 mg/day) for the treatment of depression or those who had taken St. John's wort in the last month; failure to respond to a trial of fluoxetine hydrochloride (20 mg/day) for at least four weeks (or equivalent) in the current episode, or failure to respond to more than one adequate trial of antidepressants in a previous episode; improvement greater than 25 percent or score of less than 20 on the 17-item HAM-D after the washout period. No other psychotropic medications were allowed, with the exception of zolpidem tartrate, up to 10 mg/day for sleep for the first three weeks of the trial.

End points
Efficacy and safety assessments were performed at screening, baseline, and at the end of weeks 1, 2, 4, 6, and 8. The primary outcome measure was the rate of change of the HAM-D over the treatment period. Secondary outcome measures included the physician-rated Clinical Global Impression-Improvement (CGI-I) and -Severity (CGI-S) scales, vital signs, and a review of adverse events. The Beck Depression Inventory (BDI) (self-rated) and the Global Assessment of Function scale were performed at screening, baseline, and at week 8. The Hamilton Anxiety (HAM-A) scale was performed at weeks 2 and 8. Laboratory assessments and an EEG were completed at screening and at the end of the trial. Response was defined as a HAM-D score of 12 or less (at least 50 percent improvement from baseline) and a CGI-I score of 1 or 2. Remission was defined as an HAM-D score of 7 or less with a CGI score of 1 or 2.

Results
In terms of the change in HAM-D scores during the trial, the intent-to-treat sample revealed a significant time effect ($p < 0.001$), but no significant treatment effect or time-by-treatment interaction. In addition, no significant differ-

ence in the response rates was seen in the ITT sample by week 8. There was, however, a significantly higher remission rate for St. John's wort compared to placebo ($p = 0.02$). A nonsignificant difference in both response rate and remission rate between St. John's wort and placebo ($p = 0.07$ for both) was seen in those who completed the trial. Analysis of HAM-A scores revealed a significant time effect ($p < 0.001$) and a significant treatment effect ($p = 0.02$), but did not find a significant treatment-by-time interaction. Similar results to the primary efficacy analysis of the HAM-D scores were obtained for the CGI scales (significant time effects, but no significant treatment effect or treatment-by-time interactions). In the ITT sample, nonsignificant treatment effects were seen for the BDI and the Global Assessment of Function scale. To address the possibility that St. John's wort could be effective for less severely depressed patients, patients with HAM-D scores of 22 (median) or less (20 to 22) were evaluated separately. However, no significant different in the rate of change in HAM-D scores were seen between St. John's wort and placebo, nor were there any significant differences in responder rates or remission rates.

Side effects
Abdominal discomfort, insomnia, and headaches occurred in 10 percent or more of patients in one or both treatment groups, with a greater proportion of St. John's wort patients reporting headaches. One patient in each group withdrew due to adverse events.

Authors' comments
These results do not support significant antidepressant or antianxiety effects for St. John's wort when contrasted with placebo in a clinical sample of depressed patients. The results of this study suggest that persons with significant major depression should not be treated with St. John's wort. Although the primary data analyses were negative, St. John's wort did produce a significantly greater proportion of remission in the ITT analysis compared with placebo.

Reviewers' comments
This is a very good study that addressed many previous studies' flaws. It was multisite and used trained evaluators (for DSM-IV). The trial length was adequate, and the dose of St. John's wort was increased if no improvement was observed by week 4. Good statistics! (5, 6)

Clinical Study: Jarsin® 300

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany

Indication	**Depression**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Lehrl S, Willemsen A, Papp R, Woelk H (1993). Results of measurements of the cognitive capacity in patients treated with hypericum extract. *Nervenheilkunde* 12: 281-284.

Trial design
Parallel. Pretrial run-in with placebo for two weeks.

Study duration	1 month
Dose	3 (300 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	4 general practices
No. of subjects enrolled	50
No. of subjects completed	48
Sex	Male and female
Age	Mean: 49 years

Inclusion criteria
Subjects between 20 and 64 years of age with a diagnosis of "neurotic depression" (ICD-9: 300.4) and "short-term depressive reaction" (ICD-9: 309.0) with an initial score of 16 to 26 on the Hamilton Depression Scale (HAM-D), and an initial score of more than 16 points in the Multiple-Choice Vocabulary test A (MWT-A).

Exclusion criteria
Serious organic diseases or a history of drug and alcohol abuse and suicidal tendencies. Those who had an increase in HAM-D scores by about 20 percent or more during the two-week pretreatment period.

End points
End points were: HAM-D, the Hamilton Anxiety Scale (HAM-A), the subjective complaints scale (SB-S), the short general information processing test (KAI), and the Clinical Global Impression scale (CGI).

Results
During the treatment period, the mean HAM-D of the active treatment group fell from 23.7 to 17.4. In the placebo group, the HAM-D fell from 21.6 to 16.8. No significant difference was observed between the two groups. Evaluation using the HAM-A revealed a drop from 28.5 to 21.9 in the St John's wort group, and from 30.1 to 20.9 in the placebo group. On the subjective complaints scale, under the active substance, the score fell from 39.7 to 34.5, and in the placebo group, from 41.2 to 37.7. Under the active treatment, IQ increased from 92.6 to 95.9 (by 3.2 points), and in the placebo group, IQ increased from 95.8 to 96.7 (by 0.9 points)—the difference is not significant ($p < 0.10$)

Side effects
None mentioned.

Authors' comments
The results suggest that under treatment with *Hypericum* extract, cognitive capacity not only does not decline further, but even starts to increase again. An increase in cognitive capacity, indicated here by the KAI results, would have considerable positive effects on many aspects of career and everyday activities. However, from this viewpoint, the study reported here is a pilot study.

Reviewers' comments
There was a trend toward an increase in cognitive capacity in depressed patients. The outcome measures are clearly defined, and the sample size is appropriate. However, the botanical preparation was not described adequately. (Translation reviewed) (3, 4) (*Note:* the product information was obtained from a literature review citing this study and from correspondence with the manufacturer.)

Clinical Study: LI 160

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Harrer G, Hübner W, Podzuweit H (1994). Effectiveness and tolerance of the hypericum extract LI 160 compared to maprotiline: A multicenter double-

blind study. *Journal of Geriatric Psychiatry and Neurology* 7 (Suppl. 1): S24-S28. (Also published in Harrer G, Hübner W, Podzuweit H [1993]. Wirsamkeit und verträglichkeit des *Hypericum*-präparates LI 160 im vergleich mit Maprotilin. *Nervenheilkunde* 12: 297-301.)

Trial design
Parallel. Patients received either LI 160 extract or maprotiline (75 mg daily).

Study duration	1 month
Dose	3 (300 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Maprotiline
Site description	6 practices (neurology and psychiatry)
No. of subjects enrolled	102
No. of subjects completed	86
Sex	Male and female
Age	24-65 years

Inclusion criteria
Depressed according to ICD-10, F32.1 (single, moderately depressive episode for at least two weeks), and Hamilton Depression Scale (HAM-D) > 15.

Exclusion criteria
Treatment with other drug therapies within four weeks.

End points
At baseline, and at weeks 2 and 4, antidepressant efficacy was assessed using the HAM-D, the von Zerssen's Depression Scale (D-S), and the Clinical Global Impressions scale (CGI). Response to the HAM-D scale was defined as a score of less than 10 or a decrease in score of at least 50 percent. Twenty-two symptoms were also assessed according to four grades of severity. At the end of the trial, physicians and patients judged the efficacy and tolerance of the medications.

Results
Under both treatments, HAM-D scores fell by approximately 50 percent after four weeks. Although maprotiline appeared more effective after two weeks,

no significant difference was observed at the end of four weeks. The mean score with LI 160 decreased 49.3 percent, from 20.5 to 12.2, and with maprotiline the score decreased 50.7 percent, from 21.5 to 10.5. Similar results were measured using the D-S.

Side effects
Side effects reported for 25 percent of subjects treated with LI 160 , with gastrointestinal symptoms, dizziness, and confusion accounting for more than half. Side effects reported for 35 percent of subjects receiving maprotiline included tiredness, gastrointestinal symptoms, dizziness, confusion, and dryness of mouth.

Authors' comments
The action of maprotiline begins more rapidly than that of *Hypericum,* and the D-S scale actually showed a significant difference between the two groups after two weeks of treatment. This difference had disappeared after four weeks, however.

Reviewers' comments
This was a relatively well-designed study. A subtherapeutic dose of maprotiline was used, which the authors acknowledge and explain. The treatment period was also short. (5, 6)

Clinical Study: LI 160

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Wheatley D (1997). LI 160, an extract of St. John's wort, versus amitriptyline in mildly to moderate depressed outpatients—A controlled 6-week clinical trial. *Pharmacopsychiatry* 30 (Suppl. 2): S77-S80.

Trial design
Parallel. Pretrial single-blind placebo run-in phase of three to seven days. Patients then received either LI 160 or amitriptyline (75 mg daily).

Study duration	6 weeks
Dose	3 (300 mg) tablets daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Amitriptyline
Site description	Multicenter
No. of subjects enrolled	165
No. of subjects completed	120
Sex	Male and female
Age	20-65 years (mean: 40)

Inclusion criteria
Mildly to moderately depressed outpatients ages 20 to 65 years, with a current major depressive episode according to DSM-IV criteria and an initial Hamilton Depression Scale (HAM-D) score between 17 and 24. Antidepressants had to be omitted at least 14 days before the placebo run-in period; for fluoxetine, 42 days were required.

Exclusion criteria
Major exclusion criteria included pregnancy or lactation; known history or presence of serious renal, hepatic, or cardiovascular diseases; blood dyscrasia or anemia; organic brain diseases; and the established exclusion criteria for the use of tricyclic antidepressants. Patients who improved during the placebo run-in phase to a HAM-D total score of less than 16, or with a reduction of more than 25 percent. The use of psychoactive medication was contraindicated, with the exception of temazepam, zopiclone, or zolpidem as hypnotics.

End points
Six visits were performed: pretreatment screening (day –7 to –3), baseline visit (day 0), safety visit (day 7), two maintenance visits (days 14 and 28), and final evaluation (day 42). Depression was rated on visits 1, 2, 4, and 6. The primary outcome was response to treatment, defined as an HAM-D total score of less than 10 at the end of the treatment period, or a reduction in HAM-D score of at least 50 percent compared to baseline. Secondary efficacy parameters were the Montgomery-Asberg Rating Scale for Depression (MADRS) and the Clinical Global Impressions (CGI). The main tolerability parameter was the number of adverse events. At visits 1 and 6, blood samples were taken for routine hematology and biochemistry screens. Adverse events were recorded at baseline and at visits 3 through 6.

Results
No statistically significant difference between the two groups was shown in response rate to treatment. 59.7 percent in the LI 160 group and 77.8 percent in the amitriptyline group were classified as responders ($p = 0.064$). A significantly better result was seen in the amitriptyline group in total HAM-D and MADRS scores ($p < 0.05$ for both rating scales). No significant difference between the two groups could be shown in CGI severity-of-illness scores ($p = 0.73$). The same applies to the CGI global improvement scores ($p = 0.49$). In terms of the HAM-D sleep factor, the amitriptyline group was significantly more improved at week 2 compared to the LI 160 group ($p = 0.004$). The trend still existed at the end of the study ($p = 0.053$).

Side effects
Thirty-seven percent of the patients in the LI 160 group and 64 percent of patients in the amitriptyline group reported adverse events ($p < 0.05$). The most common side effects in the LI 160 group were headache, nausea/vomiting, dry mouth, and constipation.

Author's comments
LI 160 possesses a comparable efficacy to amitriptyline with a clear tolerability advantage. The reported trial may have one major limitation: the dose of 75 mg of amitriptyline per day is about half of the maximally recommended dose of this drug in outpatient settings. However, 75 mg/day is the dose that most depressed patients receive, and is regarded as sufficiently effective in this context. Since side effects are the most important limiting factor for patient compliance, *Hypericum* extract offers the possibility to treat patients more adequately with antidepressant pharmacotherapy. Patient information concerning possible adverse events specifically associated with tricyclics may have biased the incidence of these in the LI 160 group.

Reviewers' comments
This was a good study overall. However, a subtherapeutic dose of amitriptyline (one-half the usual dose) was used. Also, no statements/descriptions of the outpatient sites were provided. The doctors were trained on HAM-D. (5, 6)

Clinical Study: Jarsin® 300

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Vorbach EU, Hübner WD, Arnoldt KH (1994). Effectiveness and tolerance of the hypericum extract LI 160 in comparison with imipramine: Randomized double-blind study with 135 outpatients. *Journal of Geriatric Psychiatry and Neurology* 7 (Suppl. 1): S19-S-23. (Also published in Vorbach EU, Hübner WD, Arnoldt KH [1993]. Wirksamkeit und verträglichkeit des *Hypericum*-extraktes LI 160 im vergleich mit imipramin: Randomisierte doppleblind-studie mit 135 ambulanten patienten. *Nervenkeilkunde* 12: 290-296.)

Trial design
Parallel. Pretrial washout phase of at least two weeks. Subjects received either LI 160 or imipramine (75 mg daily).

Study duration	6 weeks
Dose	3 (300 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Imipramine
Site description	20 centers
No. of subjects enrolled	135
No. of subjects completed	130
Sex	Male and female
Age	Mean: 53.4 ± 12.6 years

Inclusion criteria
Ages 18 to 75 with typical depression according to DSM-III-R, with a single episode (296.2) or recurrent episodes (296.3), neurotic depression (300.4), and adjustment disorder with depressed mood (309.0).

Exclusion criteria
Severe depression requiring inpatient treatment; schizophrenia or marked agitation requiring additional medication; a known history of attempted suicide or acute suicidal state; chronic alcohol or drug dependency; acute confusional state; use of drugs with cerebral effects; use of monoamine oxidase (MAO) inhibitors within the previous two weeks; and use of drugs taken for research purposes within the previous three months.

End points
At baseline and at the end of the study, patients were examined clinically, including neurologic and psychiatric assessment, and various blood tests. Main assessment criteria were the Hamilton Depressive Scale (HAM-D), the Depression Scale according to von Zerssen (D-S), and the Clinical Global Impressions (CGI).

Results
A significant reduction in HAM-D scores was observed in both groups ($p < 0.001$), from 20.2 to 8.8 in the *Hypericum* group, and from 19.4 to 10.7 in the imipramine group. Group comparisons showed no significant differences. Similar therapeutic effects were also shown by the D-S, and by three criteria in the CGI scale (therapeutic effect, alteration in status at the end of treatment, and change in severity of the illness). Improvement was seen in 81.8 percent of patients on LI 160 versus 62.5 percent of patients on imipramine. No patients on *Hypericum* and two patients on imipramine experienced worsening of their condition. The rest of the patients were unchanged. In the group of patients with HAM-D scores of 21 or more at baseline, LI 160 efficacy was significantly better than imipramine with regard to HAM-D score and CGI ($p < 0.05$). No clinically relevant changes were seen in either group with regard to safety parameters or blood parameters measured at the start of the trial.

Side effects
Eleven symptoms were reported in *Hypericum* group. The most common were dry mouth (four) and dizziness (two).

Authors' comments
The difference between the two groups was statistically significant in favor of LI 160 in patients with a HAM-D score greater than 21. However, no statistically significant differences in efficacy were observed between the two treatment groups. It is significant that side effects occurred less frequently and were less severe in the LI 160 group than in the imipramine group.

Reviewers' comments
This is a good study, but a subtherapeutic dose of imipramine was used. It is not clear, therefore, whether this was more of a placebo comparison study for St. John's wort. (5, 6)

Clinical Study: Jarsin®

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany

Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Vorbach EU, Arnoldt KH, Hübner WD (1997). Efficacy and tolerability of St. John's wort extract LI 160 versus imipramine in patients with severe depressive episodes according to ICD-10. *Pharmacopsychiatry* 30 (Suppl. 2): 81-85.

Trial design
Parallel. Pretrial, single-blind, placebo washout phase of three to five days. Dose was increased step-wise within one week until the final dose of 1,800 mg LI 160 or 150 mg imipramine per day was reached.

Study duration	6 weeks
Dose	3 × 600 mg LI 160 daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Imipramine
Site description	20 centers
No. of subjects enrolled	209
No. of subjects completed	186
Sex	Male and female
Age	Mean: 49.5 ± 11.9 years

Inclusion criteria
Subjects ages 18-70 years diagnosed in accordance with ICD-10 F 33.2 (severe episode of a major depressive disorder, recurrent, without psychotic symptoms); at least two prior episodes of two-weeks or longer duration were required. Lithium was allowed if prescribed at least three months before the trial and continued unchanged. Any treatment with MAO inhibitors had to be discontinued at least 14 days before the start of the trial.

Exclusion criteria
Patients with suicidal tendency, hallucinations, and depressive delusional content were not included. Likewise, patients with possible preexisting schizophrenic disorders or pronounced agitation, chronic alcohol or drug dependency, as well as acute confusional state were excluded. Patients with

an improvement of more than 20 percent on the HAM-D scale during the three- to five-day washout phase before the study were also excluded. No psychotropic medication (excluding chloralhydrate in cases of sleep disturbance) was allowed.

End points

Patients were assessed at days –3, 0, 7, 14, 28, and 42 using the Hamilton Depression Scale (HAM-D), the Clinical Global Impressions (CGI) scale and the Depression Scale according to von Zerssen (D-S). Adverse events were also recorded. Tolerability and safety measures were performed at days 0 and 42. Response to the HAM-D was defined as a reduction of at least 50 percent of the HAM-D total score. Patients and investigators rated improvement following treatment as very good, good, moderate, or unsatisfactory.

Results

Mean HAM-D values decreased similarly in the two study groups: from 25.3 to 14.4 in the LI 160 group, and from 26.1 to 13.4 in the imipramine group. No statistically significant difference was seen between the two groups in the D-S scale ($p = 0.36$). The CGI showed a trend in favor of imipramine ($p = 0.079$). Response rate, defined by a 50 percent decrease in HAM-D score, was 35.3 percent in the LI 160 group, and 41.2 percent in the imipramine group. Post hoc analysis of a subgroup with a reduction of at least 33 percent in the total HAM-D score resulted in 62.7 percent responders with imipramine and 57.9 percent with LI 160, confirming the equivalent efficacy of the two treatments.

Side effects

Statistically fewer (25 percent interval) adverse events were reported with LI 160 (23 percent compared to 41 percent of those on imipramine). The most frequent side effects with hypericum included restlessness, dizziness, tiredness/sedation, and gastric symptoms.

Authors' comments

LI 160 can be used to treat severely depressed patients, provided that the dose is adjusted from 900 to 1800 mg per day. LI 160 provides treatment with a considerably reduced side effect profile compared to tricyclics.

Reviewers' comments

Impressive study that replicated previous work on mild major depression and treated patients with higher (but still subtherapeutic) doses of imipramine. The authors used intent-to-treat analysis. (5, 6)

Clinical Study: LI 160

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Brenner R, Azbel V, Madhusoodanan S, Pawlowska M (2000). Comparison of an extract of *Hypericum* (LI 160) and sertraline in the treatment of depression: A double-blind, randomized pilot study. *Clinical Therapeutics* 22 (4): 411-419.

Trial design
Parallel. Patients in the hypericum group received 600 mg/day during week 1, followed by 900 mg/day for the remainder of the trial. Patients in the sertraline group received 50 mg/day during week 1, followed by 75 mg/day for the remainder of the trial. Doses of either drug could be reduced to the week 1 amount if patients experienced adverse effects.

Study duration	7 weeks
Dose	900 mg hypericum daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Sertraline (an SSRI)
Site description	Community hospital
No. of subjects enrolled	30
No. of subjects completed	20
Sex	Male and female
Age	Mean: 45.5 ± 12.6 years

Inclusion criteria
Outpatients ages 18 to 65 years with a score of at least 17 on the Hamilton Rating Scale for Depression (HAM-D) and a DSM-IV diagnosis of major depressive disorder (single or recurrent episodes), dysthymic disorder, adjustment disorder with depressed mood, or depressive disorder not otherwise

specified. All patients had discontinued selective seratonin reuptake inhibitor (SSRI) or tricyclic antidepressant (TCA) therapy for seven days before randomization.

Exclusion criteria
Pregnant women or women not using medically accepted birth control; patients with severe depression and a history of attempted suicide or acute suicidal state; schizophrenia or marked agitation requiring additional medication; chronic alcohol or drug dependency; failure to respond to adequate trials of an antidepressant drug; patients who had received an investigational drug within four weeks of the study, or who had been treated with hypericum or sertraline previously; patients with mental retardation or emotional or intellectual difficulties hindering consent or compliance; patients whose HAM-D scores improved by more than 20 percent between screening and baseline.

End points
Primary outcome: changes in the HAM-D and Clinical Global Impressions (CGI) global severity scores. Treatment response was defined as a reduction of at least 50 percent in total HAM-D score from baseline to end of trial. At the baseline visit, each patient completed the Depression Scale (D-S) before seeing the investigator. Weekly for the next seven weeks, the investigator obtained HAM-D and CGI scores, and recorded adverse events and concomitant medications. Patients again completed the D-S at weeks 3 and 7.

Results
In both treatment groups, symptoms of depression were significantly improved ($p < 0.05$), with no significant differences between patients receiving hypericum and those receiving sertraline. A clinical response (at least 50 percent reduction in HAM-D scores) was seen in a similar proportion of patients in the hypericum group (47 percent) and sertraline group (40 percent). The between-group difference was not statistically significant. At week 2, mean HAM-D scores were reduced 29 percent and 30 percent in the hypericum and sertraline groups, respectively. At week 4, the respective reductions were 54 percent and 46 percent, and at the end point they were 40 percent and 42 percent.

Side effects
In hypericum group, one patient complained of headache and numbness of hands, and another complained of headache and dizziness.

Authors' comments
The results demonstrate that hypericum is at least as efficacious as the SSRI sertraline. The failure to reach statistical significance between treatments appears to be attributable primarily to the lack of a clinically signifi-

cant difference rather than the small sample size. Both drugs were well tolerated.

Reviewers' comments
Good study, but the sample size was small. The authors also used an inappropriate statistical method (analysis of covariance [ANCOVA]), which was not optimal because of the small sample size. The lack of difference between the two groups may be due to the small sample size. (3, 4)

Clinical Study: LI 160

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Depression**
Level of evidence	**I**
Therapeutic benefit	**No**

Bibliographic reference
Hypericum Depression Trial Study Group (2002). Effect of *Hypericum perforatum* (St. John's Wort) in major depressive disorder: A randomized controlled trial. *Journal of the American Medical Association* 287 (14): 1807-1814.

Trial design
Parallel. One week, single-blind, placebo run-in phase before baseline. Patients then received either hypericum (900 mg/d), sertraline (50 mg/day), or placebo. Daily doses of the three treatments could be increased to 1,200 mg (hypericum), 75 mg (sertraline), or placebo equivalent after three or four weeks, and to 1,500 mg (hypericum), 100 mg (sertraline), or placebo equivalent at week 6 if the Clinical Global Impression Scale for severity (CGI-S) was 4 or more at week 3, or 3 or more at weeks 4 or 6.

Study duration	2 months
Dose	900 mg *Hypericum* daily (in three doses)
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes

Drug name	Sertraline
Site description	Multicenter
No. of subjects enrolled	340
No. of subjects completed	245
Sex	Male and female
Age	Mean: 42 years

Inclusion criteria
At least 18 years of age; current diagnosis of major depression (meeting DSM-IV criteria for major depressive disorder); minimum total score of 20 on the 17-item Hamilton Depression (HAM-D) scale and a maximum score of 60 on the Global Assessment of Functioning (GAF) at screening and baseline following a one-week, single-blind, placebo run-in; no more than a 25 percent decrease in HAM-D total score between screening and baseline; capacity to give informed consent and follow study procedures; and identification of personal contact to be notified if warranted by clinical concerns.

Exclusion criteria
Score above 2 on the HAM-D suicide item; attempted suicide in the past year or current suicide or homicide risk; being pregnant, planning pregnancy, breastfeeding, or not using medically acceptable birth control; clinically significant liver disease or liver enzyme levels elevated to at least twice the normal upper limit; serious unstable medical illness; history of seizure disorder; severe combined immunodeficiency (SCID) diagnoses indicating alcohol or other substance-abuse disorder, bipolar disorder, panic disorder, or obsessive-compulsive disorder; history of psychotic features of affective disorder; evidence of untreated or unstable thyroid disorder; no response to at least two adequate trials of antidepressants in any depressive episode; daily use of hypericum or sertraline for at least four weeks within the past six months; current use of other psychotropic drugs, other medicines, dietary supplements, natural remedies, or botanical preparations with psychoactive properties; use of investigational drugs within 30 days of baseline or of other psychotropic drugs within 21 days of baseline (within six weeks for fluoxetine); allergy or hypersensitivity to study medications; positive urine drug screen; introduction of psychotherapy within two months of enrollment or any ongoing psychotherapy specifically designed to treat depression; and mental retardation or cognitive impairment.

End points
The primary end points were the change in HAM-D total scores from baseline to week 8, and the incidence of full response (defined as a CGI-I score of 1 or 2 and a HAM-D score of 8 or less). Secondary end points included GAF, CGI, Beck Depression Inventory (BDI), and the Sheehan Disability Scale (SDS). Patients were assessed either weekly or biweekly for the eight

weeks of the study. All tests were assessed at each visit, except the SDS, which was assessed only at baseline and week 8.

Results
Neither hypericum nor sertraline preformed significantly different from placebo on either of the two primary outcome measures. The mean differences in HAM-D scores were –8.68 for hypericum, –10.53 for sertraline, and –9.20 for placebo. Full response occurred in 23.9 percent of hypericum patients, 24.8 percent of sertraline patients, and 31.9 percent of placebo patients. Hypericum did not differ from placebo on any of the secondary outcome measures. At week 8, sertraline was significantly better than placebo on the CGI-I score ($p = 0.02$). In a later analysis it was also found to be superior to hypericum ($p = 0.01$).

Side effects
No serious adverse effects occurred. Rates of nausea, diarrhea, and sweating (sertraline); anorgasmia (sertraline and hypericum); and frequent urination and swelling (hypericum) were all higher than those of placebo.

Author's comments
According to the available data, hypericum should not be substituted for standard clinical care of proven efficacy, including antidepressant dedications and specific psychotherapies, for the treatment of major depression of moderate severity.

Reviewers' comments
The overall response to sertraline on primary measures was not better than placebo, an outcome that is not uncommon in trials of approved antidepressants. According to the author, this occurs in up to 35 percent of trials on antidepressants. (5, 6)

Clinical Study: LI 160

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Electrophysiological effects** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**MOA**

Bibliographic reference
Johnson D, Ksciuk H, Woelk H, Sauerwein-Giese E, Frauendorf A (1994).

Effects of *Hypericum* extract LI 160 compared with maprotiline on resting EEG and evoked potentials in 24 volunteers. *Journal of Geriatric Psychiatry and Neurology* 7 (Suppl. 1): S44-S46. (Also published in Johnson D, Ksciuk H, Woelk H, Sauerwein-Giese E, Frauendorf A [1993]. Wirkungen von Johanniskraut-extrakt LI 160 im vergleich Maprolitin auf Ruhe-EEG und evozierte potentiale bei 24 probunden. *Nervenheilkunde* 12: 328-330.)

Trial design
Parallel. Pretrial washout phase of one week. Subjects were either given LI 160 or maprotiline (3 × 10 mg daily).

Study duration	1 month
Dose	3 (300 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Maprotiline
Site description	Not described
No. of subjects enrolled	24
No. of subjects completed	Not given
Sex	Male and female
Age	18-45 years (mean: 28)

Inclusion criteria
Healthy volunteers.

Exclusion criteria
All concomitant medications, apart from contraceptives, were not allowed.

End points
Subjects were assessed at baseline and after two, four, and five weeks. Resting EEG was recorded for five minutes over the frequency range of 0.1 to 200 Hz using the Cz-Fz and Oz-T6 leads. Subjects also rated their well-being using the von Zerssen scale (Bf-S).

Results
Changes at various frequencies in the resting EEGs were associated with both treatments. Changes in the theta region were in opposite directions; all of the other changes were in the same direction. For auditory evoked poten-

tials in the theta region, no relevant changes in amplitude P320 occurred with either drug, but the *Hypericum* group showed a clear reduction in latent times for amplitudes N80, P150, and N240. Clear reductions in latent times for visually evoked potentials were seen in all amplitudes for both groups.

Side effects
None mentioned.

Authors' comments
After four weeks of treatment with *Hypericum,* enhanced activation was seen in the theta and beta-2 regions, which can be interpreted as a relaxing but not sedative effect. In general the evoked potentials showed shortened latency, suggesting more rapid general information processing by the brain. It is clear from the results of measurements of visually evoked potentials in the beta region that similarities exist between the neurophysiologic effect profiles of *Hypericum* extract and maprotiline.

Reviewers' comments
Mode-of-action study exploring changes in EEG following treatment. (2, 4)

Clinical Study: Jarsin® 300

Extract name	LI 160
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Neuroendocrine effects** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**MOA**

Bibliographic reference
Franklin M, Chi J, McGavin C, Hockney R, Reed A, Campling G, Whale RWR, Cowen PJ (1999). Neuroendocrine evidence for dopaminergic actions of *Hypericum* extract (LI 160) in healthy volunteers. *Biological Psychiatry* 46 (4): 581-584.

Trial design
Crossover design. Treatment periods were separated by at least one week.

Study duration	1 day
Dose	9 (300 mg) tablets LI 160
Route of administration	Oral
Randomized	No

Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Single center
No. of subjects enrolled	12
No. of subjects completed	8
Sex	Male
Age	22-49 years (mean: 32.5)

Inclusion criteria
Healthy male volunteers not taking any psychotropic medication.

Exclusion criteria
Patients with elevated baseline growth hormone values were eliminated from the analysis.

End points
Subjects fasted after a light breakfast and came to the research unit at 12:30 p.m., when an indwelling venous cannula was inserted and maintained with heparinized saline. Two baseline blood samples were taken during the next half hour, following which either hypericin or placebo was administered. Blood samples were removed at 30-minute intervals for the following 240 minutes for assay. Plasma concentrations of growth hormone (GH), prolactin (PRL), cortisol, as well as hypericin and hyperforin were measured.

Results
Following hypericum administration, plasma GH levels increased, peaking at about 120 min. Plasma PRL was significantly lowered following hypericum treatment relative to placebo, with the lowest point occurring at 180 minutes. Plasma cortisol profiles were similar in both treatments. Plasma hypericin concentrations increased initially from 150 minutes after administration of LI 160, and were still rising at the end of the test period. Plasma mean hyperforin concentrations rose from 60 minutes after LI 160 treatment and peaked at 210 minutes. Neither peak plasma hypericin nor plasma hyperforin concentrations correlated significantly with any of the peak changes in hormone responses (all p values > 0.05)

Side effects
Flatulence in two subjects.

Authors' comments
The most likely explanation for our neuroendocrine findings is that LI 160 en-

hances some aspects of dopamine neurotransmission. This is because dopamine pathways facilitate growth hormone release and suppress prolactin secretion. Plasma concentrations of hypericin, one of the possible active components of LI 160, were not detectable until 150 minutes into the test, and were still rising at the end of the test. The plasma profile suggests that hypericin was not involved either in the increase of growth hormone or in the decrease of prolactin found in this study. In contrast, plasma concentrations of hyperforin rose from 60 minutes after treatment, and peaked at 210 minutes. Although plasma concentrations of hyperforin did not correlate with hormone responses, the time course of hormonal changes are more consistent with an effect of hyperforin than of hypericin.

Reviewers' comments
This study indicates that LI 160 may increase some aspects of dopamine function. The dose used is two times greater than the usual therapeutic dose. (3, 5)

Product Profile: Perika™

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	**Nature's Way Products, Inc.**
Botanical ingredient	**St. John's wort aerial parts extract**
Extract name	**WS 5572**
Quantity	300 mg
Processing	Plant to extract ratio 2.5-5:1, 60% ethanol (w/w)
Standardization	A minimum of 3% hyperforin
Formulation	Tablet

Recommended dose: Take 1 tablet three times daily with water at mealtimes. Benefits are best realized after two to four weeks of regular usage.

DSHEA structure/function: Scientifically advanced to maintain a healthy emotional outlook.

Cautions: Do not use this product while taking any prescription drug without the advice of your prescribing physician. Avoid excessive exposure to UV radiation (e.g., sunlight; tanning) when using this product. Not recommended for use by pregnant or lactating women.

Other ingredients: Vitamin C (ascorbic acid, 4 mg), cellulose, modified cellulose, starch, silica, magnesium stearate, titanium dioxide.

Comments: WS 5572 is sold in Europe as Neuroplant, Neuroplant 300, and Neuroplant forte.

Source(s) of information: Product label (© Nature's Way Products, Inc., 2000); information provided by distributor.

Product Profile: Movana™

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	**Pharmaton Natural Health Products**
Botanical ingredient	**St. John's wort flower and leaves extract**
Extract name	**WS 5572**
Quantity	300 mg
Processing	Plant to extract ratio 2.5-5:1, 60% ethanol (w/w)
Standardization	A minimum of 3% hyperforin
Formulation	Tablet

Recommended dose: Take one tablet three times per day. Optimal effectiveness has been shown in as little as two weeks with continued use. Doses above 900 mg per day have not shown any greater effectiveness.

DSHEA structure/function: Mood support dietary supplement. Balances emotions and promotes a feeling of well-being. Maintains healthy motivation and self-esteem. Acts safely and naturally to promote normal levels of neurotransmitters responsible for maintaining positive emotions.

Cautions: St. John's Wort may reduce the effect of many prescription drugs, including drugs used to treat conditions such as heart disease, depression, seizures, certain cancers or to prevent conditions such as transplant rejection or pregnancy (oral contraceptives). Ask a healthcare professional before using this product if you are taking a prescription medication, are pregnant, or are nursing a baby. If you have fair skin, avoid prolonged direct sunlight, as photosensitivities may occur. There have been rare reports (< 1 percent) of gastrointestinal disturbances, allergic reactions, unrest or fatigue. In case of accidental ingestion/overdose, seek the advice of a healthcare professional immediately.

Other ingredients: Microcrystalline cellulose, corn starch, croscarmellose sodium, hydroxypropyl methylcellulose, PEG-4000, magnesium stearate, silicon dioxide, ascorbic acid, synthetic iron oxides, titanium dioxide, talc, vanillin.

Comments: WS 5572 is sold in Europe as Neuroplant, Neuroplant 300, and Neuroplant forte.

Source(s) of information: Product package (© Boehringer Ingelheim Pharmaceuticals, Inc., 2000); information about Perika™ from Nature's Way Products, Inc.

Clinical Study: WS 5572

Extract name	WS 5572
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Depression**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Laakmann G, Schüle C, Baghai T, Kieser M (1998). St. John's wort in mild to moderate depression: The relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* 31 (Suppl. 1): 54-59. (Also published in Laakmann G, Dienel A, Kieser M [1998]. Clinical significance of hyperforin for the efficacy of *Hyperium* extracts on depressive disorders of different severities. *Phytomedicine* 5 [6]: 435-442.)

Trial design
Parallel. Pretrial run-in with placebo for three to seven days. WS 5573 (0.5 percent hyperforin) was compared to WS 5572 (5 percent hyperforin) and placebo.

Study duration	6 weeks
Dose	3 × 300 mg WS 5573 or WS 5572 daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes

Drug comparison	Yes
Drug name	WS 5573
Site description	11 centers
No. of subjects enrolled	147
No. of subjects completed	138
Sex	Male and female
Age	Mean: 49 ± 12.1 years

Inclusion criteria
Outpatients with mild or moderate depression according to DSM-IV criteria (either single or recurrent episode). Patients had to be between 18 and 65 years of age, and were required to have an initial score of at least 17 on the Hamilton Rating Scale for Depression (HAM-D).

Exclusion criteria
Risk of suicide or a score of at least 2 on the HAM-D item 3 (suicidality), organic brain syndrome, compulsive, schizophrenic or other delusive disorders, serious organic or metabolic disorders, pregnancy or lactation, and known hypersensitivity to hypericum preparations. The use of other antidepressants, benzodiazepines, and neuroleptics was prohibited.

End points
Patients were assessed at baseline and on days 7, 14, 28, and 42 using the HAM-D and the Depression Self-Rating Scale (D-S) according to von Zerssen. The primary efficacy variable was the change in the HAM-D total score between day 0 and the end of the study. At prestudy, as well as on days 0 and 42, the investigators also rated the patients' severity of illness and changes from the last visit with the Clinical Global Impressions scale (CGI). A global assessment of the patients' overall condition (similar to the CGI, but self-rated by the patients) was obtained on days 0 and 42. Adverse events were documented at all visits.

Results
Patients receiving WS 5572 showed the largest HAM-D reduction between day 0 and treatment end (10.3 points), followed by the WS 5573 group (8.5 points) and placebo group (7.9 points). In pairwise comparison, WS 5572 was significantly superior to placebo ($p = 0.004$). No statistically significant differences were found between WS 5573 (0.5 percent hyperforin) and placebo. 49 percent of the individuals treated with WS 5572 had treatment end scores that were at least 50 percent lower than at baseline, compared to 32.7 percent and 38.8 percent for WS 5573 and placebo, respectively. The results from D-S and CGI support the HAM-D findings.

Side effects
One-third of patients in each treatment group experienced adverse events during the trial.

Authors' comments
This study demonstrated a clear-cut relationship between hyperforin dose and antidepressant efficacy. WS 5572 (5 percent hyperforin extract) is an effective antidepressant in the treatment of mild to moderate depression. The improvements from baseline achieved using WS 5573 were too narrow to conclude systematic superiority of the 0.5 percent hyperforin extract over placebo. To arrive at extracts with comparable antidepressant potency, the hyperforin rather than the hypericin content of St. John's wort preparations should be standardized.

Reviewers' comments
This study indicates that hyperforin may be an important active ingredient in St. John's wort preparations used for depression. A trend analysis indicates that the number of individuals improving is greater for the higher concentration of hyperforin. Side effects were not an issue. (5, 6)

Clinical Study: WS 5570

Extract name	WS 5570
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Lecrubier Y, Clerc G, Didi R, Kieser M (2002). Efficacy of St. John's wort extract WS 5570 in major depression: A double-blind, placebo-controlled trial. *The American Journal of Psychiatry* 159 (8): 1361-1366.

Trial design
Parallel. Single-blind placebo run-in phase of three to seven days.

Study duration	6 weeks
Dose	1 (300 mg) tablet 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	375
No. of subjects completed	332
Sex	Male and female
Age	18-66 years (mean: 40)

Inclusion criteria
Outpatients ages 18 to 65 years giving written informed consent with a current major depressive episode of at least two weeks duration (meeting the DSM-IV code 296.21, 296.22, 296.31, or 296.32 criteria), and a total score of between 18 and 25 on the Hamilton Depression Scale (HAM-D) (including a score of 2 or higher on item 1 ["depressed mood"] at screening and at baseline).

Exclusion criteria
Depression of any other type, any serious psychiatric disease other than depression, serious suicidal risk (score of 3 or higher on item 3 of the HAM-D), or response to placebo in the run-in phase (25 percent or greater reduction of the HAM-D score).

End points
Efficacy was evaluated after one, two, four, and six weeks of treatment. The primary end point was the change from baseline in the total score on the 17-item HAM-D. Secondary end points included the total score on the Montgomery-Åsberg Depression Rating Scale (MADRS), the Clinical Global Impression (CGI), and the 58-item version of the Symptom Check List (SCL-58). Physical examinations and laboratory tests were also carried out before and after the treatment.

Results
Initial mean value for the HAM-D for all subjects was 21.9. Treatment with WS 5570 caused a significantly greater reduction in the HAM-D total score (9.9) compared to placebo (8.1). Also compared to placebo, significantly more patients in the WS 5570 group experienced a treatment response (WS 5570: 52.7 percent, placebo: 42.3 percent, $p < 0.05$) or remission (24.7 percent, 15.9 percent, respectively, $p = 0.03$). The WS 5570 group also saw greater reductions on the MADRS and the depression subscore of the SCL, but these differences were not significant. The score difference on the Bech melancholia subscale of the HAM-D was significantly different (mean decrease WS 5570: 5.5; placebo: 4.4, $p = 0.001$).

Side effects
More patients in the placebo group (37 percent) experienced adverse events, compared to the WS 5570 group (30.6 percent). The adverse events included nausea, headache, dizziness, abdominal pain, and insomnia. However, they did not indicate any treatment-emergent risks associated with WS 5570.

Authors' comments
This study demonstrates the existence of an antidepressant effect of *Hypericum perforatum* in mildly and moderately depressed patients.

Reviewers' comments
This was a phase III trial showing efficacy for mild to moderate depression according to ITT analysis. Interestingly, the decrease from baseline in HAM-D scores for the subset with initial scores equal to or greater than 22 was greater than the placebo group, while the decrease for the subset with initial scores between 10 and 21 was not. (3, 6)

Clinical Study: Neuroplant® 300

Extract name	WS 5572
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Depression**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Kalb R, Trautmann-Sponsel RD, Kieser M (2001). Efficacy and tolerability of hypericum extract WS 5572 versus placebo in mildly to moderately depressed patients. A randomized, double-blind, multicenter clinical trial. *Pharmacopsychiatry* 34 (3): 96-103.

Trial design
Parallel. Study was preceded by a three- to seven-day (three days in patients without premedication, seven days in patients with premedication), single-blind, placebo run-in phase.

Study duration	6 weeks
Dose	3 (300 mg) hypericum tablets daily
Route of administration	Oral
Randomized	Yes

Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	72
No. of subjects completed	65
Sex	Male and female
Age	24-70 years (mean: 48.5)

Inclusion criteria
Outpatients between 18 and 65 years of age; total score for the Hamilton Rating Scale for Depression (HAM-D, 17-item version) of at least 16 at study entry and during subsequent baseline investigation (three to seven days later); diagnosis of mild or moderate major depressive disorder with single or recurrent episodes according to DSM-IV criteria (diagnostic codes 296.21, 296.31, 296.22, or 296.32).

Exclusion criteria
Suicidal tendency (known attempted suicide or a score of 2 or greater on item 3 [suicide] of HAM-D); organic brain syndrome; major psychiatric diseases (other than depression); disorders caused by psychotropic substances; pretreatment with fluoxetine during the last six weeks, with paroxetine or doxepin during the last two weeks before baseline; concomitant medication with other antidepressants, psychotropic drugs, or reserpine; severe metabolic, internal, or neoplastic diseases; substance abuse; pregnancy or lactation period. Concomitant medication doses required for the treatment of nonpsychiatric conditions were required to be maintained unchanged during the course of the study (where possible).

End points
HAM-D scores were assessed on days 7, 14, 28, and 42, and the differences in scores were compared to baseline. Additional end points were self-rating by patients using von Zerssen's Depression Scale (D-S), evaluation based on the Clinical Global Impressions (CGI), and the Global Patient Assessment (GPA).

Results
Patients treated with hypericum showed a larger HAM-D total score reduction between day 0 and treatment end, with superiority over placebo reaching statistical significance by days 28 ($p = 0.011$) and 42 ($p = 0.001$). The two study groups showed rates of 50 percent responders of 62.2 percent and 42.9 percent for hypericum and placebo, respectively. More pronounced dif-

ferences were determined for 60 percent responders (hypericum: 51.4 percent; placebo: 17.1 percent). The total score time course of the D-S showed increasingly large treatment group differences in favor of hypericum, p = 0.002 (day 14), p = 0.001 (day 28) and p = 0.0002 (day 42). In CGI item 2 (global improvement) and in the global patient self-rating, more than twice as many patients were evaluated as very much improved under hypericum extract than in the placebo group.

Side effects
Five adverse reactions were noted, three of which were seen in the hypericum group (bronchitis, sinusitis, influenza). These were not considered to be related to the treatment.

Authors' comments
The data substantiate the superior antidepressant efficacy of *Hypericum* extract WS 5572 versus placebo in the treatment of mild to moderate depression. With an adverse event rate comparable to placebo, the excellent benefit-risk ratio is impressive.

Reviewers' comments
This is a well-conducted trial in which *Hypericum* performed better than placebo. (5, 6)

Clinical Study: Neuroplant®

Extract name	WS 5572
Manufacturer	Spitzner Arzneimittelfabrik/ Pharmaceutical, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Depression**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Reh C, Laux P, Schenk N (1992). *Hypericum* extract in depressions—An effective alternative. *Therapiewoche* 42: 1576-1581.

Trial design
Parallel. Pretrial washout phase of two weeks.

Study duration	2 months
Dose	2 capsules

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	50
No. of subjects completed	50
Sex	Male and female
Age	Mean: 48.3 ± 8.1 years

Inclusion criteria
Mild to medium severe depression according to ICD classifications 300.4 (neurotic depression), 309.0 (short-term depression), and 311.0 (different, non-classifiable depressive symptoms); and Hamilton Depression Scale (HAM-D) scores between 13 and 25 points. Treatment of accompanying pathological conditions was continued unchanged. In cases of preceding treatment with psychotropic drugs, medication was discontinued two weeks prior to trial start.

Exclusion criteria
Patients suffering from severe or chronic depression, disclosing an attempted suicide in their patient history, as well as patients with severe organic damage were not included in the study.

End points
The following tests were used to monitor patients before and after two, four, six, and eight weeks of treatment: HAM-D, Hamilton Anxiety Scale (HAM-A), Depressivity Scale according to von Zerssen (D-S), and the Clinical Global Impressions scale (CGI). Efficacy and tolerance were also recorded by the patients at each monitoring date. Responder criteria for the HAM-D scale was a reduction in score by at least 50 percent or a final score of 10 or less.

Results
After eight weeks of treatment, the total HAM-D score was reduced by 70 percent in the hypericum group and by 45 percent in the placebo group (significant difference $p < 0.05$). In addition, 80 percent of the hypericum group versus 44 percent of the placebo group had achieved a HAM-D score of less than 10 (significant difference $p < 0.02$). The most positively influenced aspects were depressive instability, disturbances falling or remaining asleep, and work or other activities. The HAM-A scale showed similar results, with

the symptom "mental anxiety" showing particular improvement in the hypericum group. The D-S and the CGI scale also yielded results similar to the HAM-D scale.

Side effects
No adverse drug reactions occurred during the trial.

Authors' comments
Therapy with this St. John's wort extract represents an effective and low-risk alternative to synthetic antidepressants for patients who usually complain only of mild to medium severe conditions of emotional instability, particularly in the case of first treatment where ambulant, depressive patients are concerned.

Reviewers' comments
This is a longer trial than other studies, but the inclusion/exclusion criteria were not clear and the statistical methods were not described adequately. Overall, insufficient information exists to replicate the study. (2, 3)

Clinical Study: Neuroplant® forte

Extract name	WS 5572
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Depression/electrophysiological effects**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Woelk H, Johnson D, Frauendorf A, Ksciuk H, Sauerwein-Geisse E (1996). Study to evaluate the effects of Neuroplant forte (extr. *Hypericum perforatum* L., St. John's wort) compared to trimipramine on cerebral activity in depressed patients. Internal report.

Trial design
Parallel. After a one-week run-in phase, patients took hypericum or trimipramine (2 × 12.5 mg daily) for six weeks, followed by one-week post-observation period, after which a final control was performed.

Study duration	6 weeks
Dose	2 (112-138 mg extract, 0.5 mg total hypericin) capsules daily

Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Trimipramine
Site description	Single center
No. of subjects enrolled	48
No. of subjects completed	48
Sex	Male and female
Age	Mean: 48 years

Inclusion criteria
Patients were at least 18 years of age and had a history of depression; mild to moderately depressed patients according to DSM-III-R (296.21, 296.22, 296.31, 296.32).

Exclusion criteria
Patients with endogenic or pharmacogenic depressions; patients who received any prescribed systemic or topical medications within two weeks of the study; alcoholic consumption greater than 100 g alcohol/week or 10 g/day; systemic or topical nonprescription medications within 48 hours of the study; participation in a clinical trial within three months; a history of alcohol or chemical/drug abuse; clinically important psychiatric illness other than depression; serious hepatic, biliary, renal, cardiac, or metabolic disorder; another clinically important illness within two weeks of the study; drug allergies, asthma, or a general history of allergic reactions; pregnant or lactating women; women without adequate contraception; acute deliria; heavily disturbed conduction; MAO inhibitor use; patients with a known history of attempted suicide or a value of 4 on the Hamilton Depression Scale (HAM-D) scale, point 3; and patients with narrow-angle glaucoma.

End points
Assessments were made at baseline and after two, four, six, and seven weeks. Efficacy was measured by changes in latency of visually and acoustically evoked potentials (VEP, AEP), changes in EEG spectra, and psychometric tests (HAM-D, Clinical Global Impressions [CGI] scale, Befindlichkeits-skala [Bf-S], State Trait Anxiety Inventory [STAI], and other tests). Safety was evaluated by measurements of blood, circulatory, and urine parameters.

Results
Results from the EEG and cortical evoked potentials indicated an improvement in cortical function with Neuroplant forte, that is, after two weeks a decrease in power in the alpha range (activation) under resting and controlled vigilance. No significant effect on the beta range was measured. Trimipramine showed an increase in the alpha (relaxation) range and a decrease in the delta and gamma ranges. Trimipramine showed a latency increase in AEP on the component P200 after four weeks of treatment (minimal effect) and a latency decrease for one component of the VEP (N270) after six weeks. Neuroplant forte showed no effect on AEPs or VEPs. Under the HAM-D test and the CGI scale, significant improvement was seen in both treatment groups. Initial HAM-D scores of 13.0 (trimipramine) and 11.2 (Neuroplant forte) dropped to 7.9 and 7.7, respectively, with no significant difference between groups before or after treatment. Both groups made fewer mistakes under monotone stress conditions with the MackWorth Clock.

Side effects
No clinically relevant side effects were measured.

Authors' comments
Neuroplant forte appears to show mild central effects corresponding to antidepressant activity at low dose, i.e., central nervous system (CNS) activation under vigilance and resting conditions. These are seen after two to six weeks. The subjective state was stable during the study period or improved. Neuroplant forte even showed superiority to trimipramine in the EEG and some psychometric parameters such as anxiety reduction, sleep, and general mental state.

Reviewers' comments
Neuroplant forte had similar antidepressant effects to the low dose of trimipramine in this small study. (5, 5)

Clinical Study: WS 5572

Extract name	WS 5572
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Electrophysiological effects** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**MOA**

Bibliographic reference

Schellenberg R, Sauer S, Dimpfel W (1998). Pharmacodynamic effects of two different hypericum extracts in healthy volunteers measured by quantitative EEG. *Pharmacopsychiatry* 31 (Suppl. 1): 44-53.

Trial design

Parallel. WS 5573 (0.5 percent hyperforin) was compared to WS 5572 (5 percent hyperforin) and placebo.

Study duration	8 days
Dose	900 mg daily of either WS 5573 or WS 5572
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	WS 5573
Site description	Not described
No. of subjects enrolled	55
No. of subjects completed	53
Sex	Male and female
Age	18-35 years

Inclusion criteria

Healthy volunteers free of any concomitant medication, except for oral contraceptives, for two weeks prior to entering the study, and negative drug and alcohol tests.

Exclusion criteria

Volunteers with pathological findings of any kind, clinically relevant diseases, or a history of serious physical illness were excluded from the study.

End points

Quantitative topographic electroencephalography (qEEG) was performed on days 1 and 8, prior to application of the trial medication and two, four, six, eight, and ten hours after administration. Immediately prior to each qEEG recording, blood pressure and heart rate were measured and blood samples were taken.

Results
The qEEG results of both WS 5572 and WS 5573 showed power increases in the delta, theta, and alpha-1 frequency bands compared to placebo. A peak effect was seen between four and eight hours after administration. The extract containing 5 percent hyperforin produced higher increases in qEEG baseline power performances than the one containing 0.5 percent hyperforin. Compared to placebo, there was a significant increase in qEEG power performance in the delta and beta-1 frequency exclusively for the extract containing 5 percent hyperforin. The effect on theta and alpha-1 frequencies was stronger on day 8 than on day 1. Following the first dose of the 5.0 percent extract, the maximum concentration was attained after 2.9 hours (Tmax). Tmax after administration of the 0.5 percent extract was 3.9 hours. On day 8, Tmax for both extracts was three hours. Pharmacokinetic data and EEG power values did not correlate.

Side effects
None that could be attributable to the trial medication.

Authors' comments
It may be concluded that extracts of St. John's Wort induce significant line-dependent changes in the electrical power performance of lower frequencies in the qEEG, and that repetitive, once-daily administration leads to stabilization of their effects, in particular with the extract containing 5 percent hyperforin. However, the relationship between acute EEG effects of antidepressants and clinical effectiveness is far from understood.

Reviewers' comments
This was a mode-of-action study that demonstrated the central effects of an extract standardized to 5 percent hyperforin compared to 0.5 percent hyperforin and placebo. (3, 6)

Clinical Study: WS 5570

Extract name	WS 5570
Manufacturer	Dr. Willmar Schwabe GmbH & Co., Germany
Indication	**Neuroendocrine effects** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Schüle C, Baghai T, Ferrera A, Laakmann G (2001). Neuroendocrine effects of *Hypericum* extract WS 5570 in 12 healthy male volunteers. *Pharmacopsychiatry* 34 (Suppl. 1): S127-S133.

Trial design
Crossover. On three different test days, subjects were given either placebo, 300 mg WS 5570, or 600 mg WS 5570. Subjects were instructed not to consume alcohol in the 24 hours before each test and to abstain from medication beginning four weeks before the study start.

Study duration	1 day
Dose	300 or 600 mg
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Not described
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Laboratory
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male
Age	Between 20 and 35 years

Inclusion criteria
Healthy subjects (determined via psychiatric and medical history, physical examination, and laboratory parameters) between 20 and 35 years of age with normal weight.

Exclusion criteria
None mentioned.

End points
After fasting overnight, subjects were fitted with an intravenous catheter kept open with physiological saline solution. Blood was drawn one hour before and at the time of administration of treatment or placebo as well as every 30 minutes thereafter for up to five hours. Primary end points included plasma concentrations of cortisol (COR), growth hormone (GH), and prolactin (PRL). Blood pressure, heart rate, and side effects were also recorded every half hour.

Results
The 300 mg dose of WS 5570 and placebo had no effect on COR levels. However, the 600 mg dose WS 5570 caused a clear-cut stimulation of COR secretion between 30 and 90 minutes after treatment application. A significant difference in comparison to placebo appeared after 30 minutes ($p < 0.05$), and significance increased until 90 minutes ($p < 0.01$). The area under the curve for GH was significantly greater for the 300 mg WS 5570 group compared to placebo ($p < 0.05$). The 600 mg dose produced levels of GH comparable to placebo. WS 5570 did not have any influence on PRL secretion. There was also no influence on blood pressure or heart rate.

Side effects
No side effects occurred during the study.

Authors' comments
The cortisol stimulation caused by 600 mg WS 5570 suggests that the extract is able to influence noradrenalin reuptake and serotonin reuptake, thereby causing the effects on cortisol release.The best explanation for the significant elevation of growth hormone values after 300 mg of WS 5570 compared to placebo is that the elevation was caused by spontaneous episodes of growth hormone hypersecretion in 2 of the 12 volunteers. We could not replicate the findings of Franklin et al. (1999) that Saint John's wort extracts may stimulate GH release and inhibit PRL secretion. The reason for these conflicting results is probably the fact that the dosages given to the male volunteers differed to a considerable extent (300 and 600 mg in our study; 2,700 mg in Franklin et al. [1999]).

Reviewers' comments
This mode-of-action study is similar to Franklin et al. (1999), but with different results. (1, 6)

Product Profile: St. John's Wort Ze 117™

Manufacturer	**Zeller AG, Switzerland**
U.S. distributor	**General Nutrition Corporation**
Botanical ingredient	**St. John's wort flowering tops extract**
Extract name	**Ze 117**
Quantity	500 mg
Processing	Plant to extract ratio 4-7:1, ethanol 50% (w/w)
Standardization	0.2% hypericin, less than or equal to 0.2% hyperforin
Formulation	Tablet

Recommended dose: Take one tablet daily.

Cautions: May cause skin sensitivity. Care should be taken during exposure to sunlight. Avoid excessive UV sources and discontinue use if sensitivity occurs.

Other ingredients: Cellulose, titanium dioxide (natural mineral whitener), ferric oxide (colorant).

Comments: Ze 117 is also sold as Remotiv and Rebalance (Zeller AG, Switzerland); Valverde Hyperval (Novartis, Switzerland); Remotiv (Bayer, Germany/Hungary/South America); Esbericum forte (Schaper and Brümmer, Germany).

Source(s) of information: Woelk, 2000; Schrader, 2000; Brattström, 2002; product label; personal correspondence with manufacturer.

Product Profile: St. John's Wort (Ze 117™)

Manufacturer	**Zeller AG, Switzerland**
U.S. distributor	**Rexall Sundown, Inc.**
Botanical ingredient	**St. John's wort flowering tops extract**
Extract name	**Ze 117**
Quantity	500 mg
Processing	Plant to extract ratio 4-7:1, ethanol 50% (w/w)
Standardization	0.2% hypericin, less than or equal to 0.2% hyperforin
Formulation	Caplet

Recommended dose: One caplet per day.

DSHEA structure/function: Advanced mood enhancement.

Cautions: Do not use this product if you are pregnant or nursing. If you are under a physician's care or taking medication, consult with your health professional before using this product. Do not take with antidepressant medications. May cause skin sensitivity. Care should be taken during exposure to sunlight. Avoid excessive UV sources and discontinue use if sensitivity develops. Discontinue use two weeks prior to surgery.

Other ingredients: Microcrystalline cellulose, croscarmellose sodium, hydroxypropyl methylcellulose, PEG, titanium dioxide (color), madgesium stearate, ferric oxide (color), stearic acid, silica.

Comments: Ze 117 is also sold as: Remotiv® (Zeller AG, Switzerland); Valverde Hyperval (Novartis, Switzerland); Remotiv® (Bayer, Germany/Hungary/South America); Esbericum forte (Schaper and Brümmer, Germany).

Source(s) of information: Woelk, 2000; Schrader, 2000; Brattström, 2002; product label; personal correspondence with manufacturer.

Clinical Study: Ze 117™

Extract name	Ze 117
Manufacturer	Zeller AG, Switzerland
Indication	**Depression**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Schrader E, Meier B, Brattström A (1998). *Hypericum* treatment of mild-moderate depression in a placebo-controlled study: A prospective, double-blind, randomized, placebo-controlled, multicenter study. *Human Psychopharmacology* 13 (3): 163-169.

Trial design
Parallel.

Study duration	6 weeks
Dose	2 (250 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	16 centers
No. of subjects enrolled	162
No. of subjects completed	136
Sex	Male and female
Age	30-60 years

Inclusion criteria
Patients over the age of 18 presenting with mild-moderate depression defined according to ICD-10 (F32.0; F32.1) and who had total scores between 16 and 24 on the Hamilton Depression Scale (HAM-D) were admitted to the study. Medication that might interfere with the trial medication was withdrawn one week prior to the start of the study, extended to four weeks for patients taking fluoxetine. Any preexisting therapy that could not be discontinued was maintained at the same dosage.

Exclusion criteria
Patients who had taken part in other clinical trials in the previous four weeks or during the study itself, psychiatric disorders that might impair accurate history, those unable to give consent, the presence of neoplasia, Parkinson's or Alzheimer's disease, pregnancy or inadequate contraception, risk of suicide (score of at least 2 on the suicidality item of HAM-D), known hypersensitivity to St. John's wort, severe concomitant systemic diseases, chronic alcohol or drug abuse, and concomitant psychotherapy or drug therapy that could influence the assessment of efficacy variables.

End points
Patients were assessed after one, two, three, four, and six weeks with the 21-item HAM-D, the Clinical Global Impressions (CGI) scale, and patient self-assessment on a visual analogue scale (VAS). Criteria for clinically relevant response were a reduction of at least 50 percent in HAM-D score from baseline and/or a score of 10 or less on the final HAM-D.

Results
Both intention-to-treat and protocol-compliant analysis showed that treatment with Ze 117 was associated with significantly superior efficacy than placebo ($p < 0.001$). The responder rate on the HAM-D test was 56 percent with Ze 117 and 15 percent with placebo. A significant difference between the two treatment arms in the CGI and patient self-rated VAS ($p < 0.001$) was also observed.

Side effects
Adverse events occurred in five placebo patients and six hypericum patients. The most common were nonspecific gastrointestinal problems.

Authors' comments
This clinical study, involving a sufficiently large sample size to allow robust statistical evaluation, demonstrated that the hypericum extract (Ze 117) is a safe and effective treatment for mild to moderate depressive episodes. Further clinical trials will be required to evaluate conclusively the efficacy of hypericum in more severe depression.

Reviewers' comments
This was a good intent-to-treat study with protocol-compliant analysis and adequate washout. The treatment was better than placebo, with few side effects for treatment of mild to moderate major depression. (5, 6)

Clinical Study: Remotiv®

Extract name	Ze 117
Manufacturer	Zeller AG, Switzerland
Indication	**Depression**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Woelk H (2000). Comparison of St. John's wort and imipramine for treating depression: Randomised controlled trial. *British Medical Journal* 321 (7260): 536-539.

Trial design
Parallel. To ensure that participants could tolerate imipramine, the dose was increased from 25 mg twice daily (three days) to 50 mg twice daily (four days), and then to the final dose of 75 mg twice daily on the eighth day.

Study duration	6 weeks
Dose	2 × 250 mg hypericum
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Imipramine
Site description	40 outpatient clinics
No. of subjects enrolled	324
No. of subjects completed	277
Sex	Male and female
Age	Mean: 46 ± 12.8 years

Inclusion criteria
Participants ages 18 or older, with mild to moderate depression, without increased suicidal ideation, who fulfilled ICD-10 criteria for a depressive episode or recurrent depressive disorder (ICD-10 codes F32.0 or F33.0 and F32.1 or F33.1), and had a score of at least 18 on the 17-item Hamilton Depression Scale (HAM-D) on two consecutive visits.

Exclusion criteria
Pregnant or breast feeding, not using contraception, known to be allergic to the drugs being studied, serious disease, abnormal thyroid function, other relevant abnormalities, bipolar disorder, previous serious psychiatric disease, or alcohol or drug abuse histories. Participants who had taken any of the following medications within two weeks of the trial start: monoamine oxidase inhibitors, antidepressant drugs, lithium, antipsychotic drugs, neuroleptic drugs, cimetidine, oral corticosteroids, anticonvulsants, theophylline, or thyroid hormones.

End points
HAM-D was completed during the screening visit, when allocated to treatment, at the third visit (week 1), fourth visit (week 3), and fifth visit (week 6). The Clinical Global Impressions (CGI) scale was completed by the clinicians during the third, fourth, and fifth visits. Participants completed a global impressions scale the first time they were seen, during treatment (third visit), and at the end of the trial (fifth visit). Benzodiazapines were allowed at a maximum daily dose of 10 mg diazepam for no longer than three consecutive days on not more than three occasions over the six-week study.

Results
The two treatments were therapeutically equivalent with regard to overall effect on depression. Among the 157 subjects taking hypericum, mean HAM-D scores decreased from 22.4 at baseline to 12.00 at end point. Among the 167 subjects taking imipramine, mean HAM-D scores fell from 22.1 to 12.75. All secondary analyses of efficacy supported the conclusions of the primary analysis, although in one exploratory parameter (the anxiety-somatization subscale of the HAM-D scale) hypericum had a significant advantage. Rates of response to treatment were essentially similar.

Side effects
Participants tolerated hypericum better than imipramine ($p < 0.01$). The most common side effect in the hypericum group (8 percent) was dry mouth.

Author's comments
Hypericum is therapeutically equivalent to imipramine, but is better tolerated by patients. In view of the mounting evidence of hypericum's comparable efficacy to other antidepressants and its safety record, hypericum should be

considered for first-line treatment in mild to moderate depression, especially in the primary care setting.

Reviewers' comments
This study had a large number of participants at many sites, and the coordinators made an effort to train on HAM-D. The dose of imipramine was still on the lower end of therapeutic dose (normal therapeutic range is between 150 to 250 mg). It is also unfortunate that the report gives the HAM-D scores at baseline and week six only (not in times between). (5, 6)

Clinical Study: Ze 117™

Extract name	Ze 117
Manufacturer	Zeller AG, Switzerland
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Schrader E (2000). Equivalence of St. John's wort extract (Ze 117) and fluoxetine: A randomized, controlled study in mild-moderate depression. *International Clinical Psychopharmacology* 15 (2): 61-68.

Trial design
Parallel. Patients received either hypericum or fluoxetine (20 mg daily). Patients treated with monoamine oxidase (MAO) inhibitors underwent a two-week washout period, which was extended to five weeks for SSRIs (selective seratonin reuptake inhibitors).

Study duration	6 weeks
Dose	1 (250 mg) hypericum tablet twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Fluoxetine
Site description	7 internal medicine practices

No. of subjects enrolled	240
No. of subjects completed	238
Sex	Male and female
Age	Mean: 46.5 ± 18 years

Inclusion criteria
Patients with mild to moderate depression (ICD-10; depressive episode/recurrent depressive disorder; F32.0 mild; F32.1 moderate) with entry Hamilton Depressive Scale (HAM-D) 21-item scores in the range of 16 to 24.

Exclusion criteria
Excluded from the study were patients with a history of alcohol/substance abuse or dependence; dementia or other severe intellectual impairment; history of seizures; glaucoma; pituitary deficiency; suicidal ideation (score 2 to 4 on HAM-D item 3); thyroid or parathyroid pathology; Parkinson's disease; pregnant or breast-feeding women; any serious concomitant medical condition; or patients taking quinidine, anticholinergic drugs, cimetidine, cardiac glycosides, neuroleptics, sympathomimetic drugs, MAO inhibitors, tryptophan, and any other antidepressant.

End points
The 21-item HAM-D and Clinical Global Impression (CGI) (item 1) tests, as well as the patient self-evaluation test, were conducted at baseline and at the end of the study. CGI items 2 and 3 were evaluated at end point. Other assessments were patients' self-assessment by a validated visual analogue scale, withdrawal rates, and incidence of adverse events. Responders were those with at least a 50 percent decrease from baseline or final score of 10 or less on the HAM-D. The protocol hypothesis was that hypericum would be considered equivalent to fluoxetine if an improvement in mean HAM-D score for the hypericum group was within 3 points of the improvement observed on the fluoxetine group at end point (alpha = 0.05, one-sided).

Results
Analysis of the main efficacy variable rejected the hypothesis of hypericum being inferior to fluoxetine. In the analysis of secondary variables, a trend was observed in favor of hypericum relative to fluoxetine in improving overall HAM-D ($p = 0.09$), and CGI item I ($p = 0.03$) Similarity of effects of the two treatments was observed in most other parameters. The responder rate for hypericum was significantly greater ($p = 0.005$) than for fluoxetine (60 percent versus 40 percent, respectively).

Side effects
Thirty-four adverse events possibly related to fluoxetine and 13 to hypericum occurred. The most common for hypericum was gastrointestinal disturbance.

Author's comments
Hypericum and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. The main difference between the two treatments is safety. *Hypericum* was superior to fluoxetine in overall incidence of side effects, number of side effects, and the type of side effect reported.

Reviewers' comments
This was a strong study using a therapeutic dose of SSRI with a good wash-out period from other medications. Overall a good study with *Hypericum* equivalent to fluoxetine (Prozac), but with fewer side effects. The randomization process was not described. (3, 6)

Product Profile: Hyperiforce

Manufacturer	**Bioforce AG, Switzerland**
U.S. distributor	None
Botanical ingredient	**St. John's wort aerial parts (shoots and tips) extract**
Extract name	None given
Quantity	40-73 mg
Processing	Extract of the fresh plant, ratio 3.9-5.0:1, 60% alcohol
Standardization	0.33 mg dianthrones (total hypericin)
Formulation	Tablet

Recommended dose: Take one tablet three times daily.

Other ingredients: Microcrystalline cellulose, corn starch, polysaccharide of soy, oil (1.3 mg).

Source(s) of information: Information provided by Bioforce USA.

Clinical Study: Hyperiforce

Extract name	None given
Manufacturer	Bioforce AG, Switzerland
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Lenoir S, Degenring FH, Saller R (1997). Hyperiforce tablets for the treatment of mild to moderate depression. *Schweizerische Zeitschrift für Ganzheits Medizin* 9 (5): 226-232.

Trial design

Parallel. Dose comparison study with tablets containing one-sixth, one-third, or the usual amount of the same crude extract.

Study duration	6 weeks
Dose	3 tablets providing either 1.0, 0.33, or 0.16 mg hypericin per day in either 180, 60, or 30 mg extract
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	No
Site description	38 centers
No. of subjects enrolled	348
No. of subjects completed	260
Sex	Male and female
Age	19-94 years

Inclusion criteria

Patients with mild to moderate depression (HAM-D score ≥ 10) of at least 20 years of age, with an initial diagnosis in accordance with ICD-10 criteria of: depressive episodes, recurrent depressive disorder, persistent affective disorder, anxiety disorder, stress and adjustment disorder, and other conditions with accompanying affective mood disorders.

Exclusion criteria

Allergy to St. John's wort; treatment with antidepressants, tranquilizers, hypnotics, or neuroleptics within the last two weeks prior to the study; or acute risk of suicide.

End points

Assessments were made at baseline and after one and six weeks of treatment with the Hamilton Depression Scale (HAM-D)-17 and -21 scores, by the physician with the Clinical Global Impressions (CGI) scale, and with a self-

assessment by the patient using the HAD (Hospital Anxiety and Depression) scale.

Results

During the course of the six weeks of treatment, the HAM-D-17 score decreased appreciably in all three groups ($p < 0.001$). Related efficacy was about 4 percent better in the highest dose group than in the group receiving the lowest dose (no significant difference). The response rate established on the basis of the HAM-D score was about 39 percent after 14 days, and 62 to 68 percent by the end of the treatment period. In the assessment of the physicians, severity of the disease (CGI scale) decreased on average from moderate to marked before treatment to mild at the end of treatment. Self-assessment scores of the patients for anxiety and depression (HAD) decreased appreciably in all three treatment groups.

Side effects

In the assessment of the physicians, tolerability was good, namely 84 percent (high dose), 95 percent (medium dose), and 90 percent (low dose), with no clear differences between the doses. Eighty-two events were observed in 74 patients affecting the nervous system, gastrointestinal tract, and general well-being. An increase in events of "questionable" causality was seen in the high dose group, but no difference in effects of "possible" or "probable" causality was observed.

Authors' comments

The response rates of between 62 and 68 percent, including that of the lowest daily dose of 0.17 mg hypericin, were better than the 55 percent reported by other hypericum studies employing 0.5 to 2.7 mg hypericin/day. It is possible that this reflects the advantage of using only the fresh shoot tips of St. John's wort. On the basis of these results, it may be recommended that treatment with Hyperiforce tablets could be started at a dose of one tablet three times a day, and then continued over the long term with one to two tablets per day.

Reviewers' comments

The study was flawed by the lack of a placebo group. The placebo comparison, which is important when comparing different doses of the same preparation, was especially important because of the authors' unusual findings that no statistical differences existed between the doses. In addition, no description was provided of how patients were randomized. (3, 6)

Product Profile: STEI 300

Manufacturer	**Steiner Arzneimittel, Germany**
U.S. distributor	None
Botanical ingredient	**St. John's wort extract**
Extract name	**STEI 300**
Quantity	350 mg
Processing	Extracted with 60% ethanol (w/w)
Standardization	0.2%-0.3% hypericin and pseudohypericin and 2%-3% hyperforin
Formulation	Capsule

Source(s) of information: Philipp, Kohnen, and Hiller, 1999.

Clinical Study: STEI 300

Extract name	STEI 300
Manufacturer	Steiner Arzneimittel, Germany
Indication	**Depression**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Philipp M, Kohnen R, Hiller KO (1999). *Hypericum* extract versus imipramine or placebo in patients with moderate depression: Randomised multicenter study of treatment for eight weeks. *British Medical Journal* 319 (7224): 1534-1538.

Trial design
Parallel. Trial was preceded by a one-week washout period. *Hypericum* was given in a constant dose of 1,050 mg/day throughout the study. Imipramine doses were increased from 50 mg on day 1, to 75 mg (days 2 through 4), and to 100 mg thereafter.

Study duration	8 weeks
Dose	1,050 mg daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Imipramine
Site description	18 general practices
No. of subjects enrolled	263
No. of subjects completed	251
Sex	Male and female
Age	Mean: 47 ± 12 years

Inclusion criteria
Patients ages 18 to 65 with a diagnosis of moderate depressive according to ICD-10 codes F32.1 and F33.1; minimum score of 18 on the Hamilton Depression scale (HAM-D), Clinical Global Impressions (CGI) rating of severity of moderately, markedly, or severely ill; minimum depression duration of four weeks and maximum of two years.

Exclusion criteria
Mild and severe depressive disorders; bipolar disorders; comorbidity from alcohol or drug dependence; suicidal risk; long-term prophylaxis with lithium or carbamazepine; nonsufficient washout phase of previous psychotropic drug; any interfering psychotropic drug taken concurrently; any previous long-term (> 3 months) treatment with benzodiazapines; and patients at general and specific risk (imipramine contraindications).

End points
Efficacy and safety were evaluated after one, two, four, six, and eight weeks with the 17-item HAM-D, the Hamilton Anxiety scale (HAM-A), the CGI scale, Zung self-rating depression scale (ZSDS), and quality of life was determined using the 36-item short form health survey (SF-36). The hypericum group was compared to placebo after six weeks and to imipramine after eight weeks. Data for evaluation of safety comprised of adverse events, clinically relevant changes in electrocardiogram, measurements of vital signs, and physical examination.

Results
Hypericum extract was more effective at reducing HAM-D scores than placebo, and as effective as imipramine (mean –15.4, –12.1 and –14.2, respectively). The HAM-A, ZSDS, and SF-36 had similar results to those obtained with the HAM-D. Compared with placebo (50 percent), the number of patients who improved in the CGI was noticeably higher under active treatments: 74 percent in the hypericum group and 71 percent in the imipramine group.

Side effects
Adverse events were reported for 22 percent of the hypericum group, compared with 19 percent for placebo and 46 percent for the imipramine group. The most frequent (8 percent) side effect in the hypericum group was nausea.

Authors' comments
Hypericum extract, 350 mg three times daily, was more effective than placebo, and at least equally effective to 100 mg imipramine daily, in the treatment of moderate depression. Treatment with hypericum extract is safe and improves the quality of life.

Reviewers' comments
This is a good study, but unfortunately a low dose (subtherapeutic) of imipramine was used. Also the report did not specify the number of drop-outs/withdrawals. (4, 6)

Product Profile: Dysto-lux®

Manufacturer	**Dr. Loges & Co. GmbH, Germany**
U.S. distributor	None
Botanical ingredient	**St. John's wort extract**
Extract name	**LoHyp-57**
Quantity	200 mg
Processing	Plant to extract ratio 5-7:1, ethanol 60% (w/w)
Standardization	No information
Formulation	Tablet

Source(s) of information: Harrer et al., 1999.

Clinical Study: Dysto-lux®

Extract name	LoHyp-57
Manufacturer	Dr. Loges & Co. GmbH, Germany
Indication	**Depression in elderly patients**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Harrer G, Schmidt U, Kuhn U, Biller A (1999). Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine. *Arzneimittel-Forschung/Drug Research* 49 (4): 289-296.

Trial design
Parallel. Patients received either hypericum or fluoxetine (20 mg daily).

Study duration	6 weeks
Dose	2 (200 mg) tablets twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes
Drug name	Fluoxetine
Site description	17 centers
No. of subjects enrolled	161
No. of subjects completed	137
Sex	Male and female
Age	Mean: 69 years

Inclusion criteria
Patients ages 60 to 80, suffering from their first psychiatric illness, with symptoms diagnosed as F32.0 and F32.1 according to the ICD-10.

Exclusion criteria
Patients with a dementia disorder according to the Mini Mental Status Test.

End points
Hamilton Global 17-item (HAM-D-17) scores were determined on entry to the study and at the end of one, two, four, and six weeks of treatment. Responders were defined as patients who decreased their HAM-D score by at least 50 percent or to below 10. Secondary target parameters were the Self-rating Depression Scale (SDS), the Everyday Life questionnaire (AL), and the Clinical Global Impressions scale (CGI). At all visits, doctors and patients were asked to provide assessment of efficacy and tolerability, patient satisfaction with the medication, and adverse events.

Results
During the six-week treatment, HAM-D scores fell in both groups, from

16.60 to 7.91 in the hypericum group, and from 17.18 to 8.11 in the fluoxetine group. In patients with mild depression, scores showed a mean fall from 14.21 to 6.21 on LoHyp-57, and from 15.21 to 7.46 on fluoxetine. In patients with moderate depression, mean scores fell from 18.73 to 9.43 on LoHyp-57, and from 19.10 to 8.75 on fluoxetine. Equivalence of the two treatments was confirmed for both the total sample and for the two subgroups. At the end of week 6, the response rate in the LoHyp-57 group was 71.4 percent, whereas it was 72.2 percent in the fluoxetine group. CGI and SDS data support the HAM-D findings.

Side effects
Twelve patients in the hypericum group and 17 patients in the fluoxetine group reported adverse events.

Authors' comments
The St. John's wort extract LoHyp-57 was found to be both statistically and clinically equivalent to fluoxetine in its efficacy in the sample of elderly patients investigated here. For elderly patients who often have multiple pathologies and are consequently subjected to multiple drug treatments, hypericum has the advantage over the tricyclics and SSRIs in that it does not cause drug interactions.

Reviewers' comments
This good trial included severity in relation to side effects and used well-trained examiners at all sites. However, the authors did not give actual HAM-D scores as allowance for comparison, and thus readers can only compare response rate (which does not allow enough information). In addition, it is unclear whether patients with any coexisting psychiatric medical treatment were excluded. (5, 5)

Valerian

Other common names: **Garden heliotrope, garden valerian**
Latin name: ***Valeriana officinalis* L.** [Valerianaceae]
Latin synonyms: ***Valeriana exaltata* J.C. Mikan**
Plant part: **Root**

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Valerian species grow worldwide. The root (or more precisely the underground parts including the rhizome, roots, and stolons) of European valerian, *Valeriana officinalis* L., is used as an official drug in many European countries. There is no scientific agreement regarding valerian's active constituents, but sesquiterpenes, valerenic acid, and acetoxyvalerenic acid have been used as quality control markers, usually described simply as valerenic acid. Pharmaceutical products are produced mainly from aqueous extracts or aqueous alcoholic extracts. The two extract types are not equivalent. The aqueous extracts are based on traditional teas with an herb to extract ratio of 5:1 (2 g herb resulting in 400 mg extract). Aqueous alcoholic extracts are often made with 70 percent ethanol, and have an herb to extract ratio of 4 to 7:1 (Schulz, Hänsel, and Tyler, 2001).

Valerian products are commonly formulated with lemon balm, hops, or passionflower. In fact, the German Commission E has approved the use of combinations in fixed proportions of passionflower herb, valerian root, and lemon balm, as well as valerian with hops (see the Information from Pharmacopoeial Monographs section) (Blumenthal et al., 1998).

Sedonium™, manufactured by Lichtwer Pharma GmbH, Germany, and distributed in the United States by Lichtwer Pharma U.S., Inc., contains an aqueous alcoholic valerian extract named LI 156 (ratio 3 to 7:1, 300 mg extract/tablet).

VALERIAN SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Single Ingredient Products						
Sedonium™	Lichtwer Pharma AG, Germany/ Lichtwer Pharma US, Inc.	Ethanolic extract (LI 156)	2 (300 mg) tablets an hour before bed	Insomnia	4	Yes (I-2) Trend (III-1) Undetermined (III-1)
				Mental stress	1	Undetermined (III-1)
				Cognitive functioning	1	Yes (III-1)
Valdispert® (EU), Baldrian-Dispert® (EU)	Solvay Arzneimittel GmbH, Germany/ None	Aqueous alkaline dry extract	3 (135 mg extract) tablets 3 times daily	Insomnia	1	Undetermined (III-1)
				Nervous disorders	1	Undetermined (III-1)
Generic, aqueous extract	None/None	Freeze-dried aqueous extract	400 to 900 mg per day	Insomnia	1	Trend (III-1)
				Sleep quality	2	Trend (II-2) Undetermined (III-1)

Combination Products						
Valerian Night-time™ (US), Euvegal® forte (EU)	Dr. Willmar Schwabe GmbH & Co., Germany/ Nature's Way Products, Inc.	Aqueous/ ethanolic extracts of valerian root and lemon balm leaf	1 to 4 (valerian: 160 mg/lemon balm: 80 mg) tablets daily	Insomnia	1	Yes (II-1)
				Sleep quality	1	Undetermined (III-1)
Songha Night® (EU)	Pharmaton S.A., Switzerland/None	Extracts of valerian root and lemon balm leaf	3 (valerian 120 mg/lemon balm: 80 mg) tablets daily	Sleep quality	1	Undetermined (II-1)
Alluna™ Sleep (US), IVEL® (EU), ReDormin® (EU)	Zeller AG, Switzerland/ GlaxoSmithKline	Extracts of valerian root and hops (Ze 91019)	1-3 (valerian 500 mg/hops 120 mg) tablets daily	Electrophys-iological effects	1	MOA (III-1)

Valdispert®, or Baldrian-Dispert®, is manufactured by Solvay Arzneimittel GmbH in Germany, and is not available in the United States. It is an aqueous alcoholic extract with a ratio of 5 to 6:1. The tablets contain 135 mg extract.

Several trials were conducted with a generic aqueous extract characterized with a plant-to-extract ratio of 2.8 to 3.1:1.

A valerian and lemon balm (*Melissa officinalis* L.) product known as Valerian Nighttime™ in the United States and Euvegal® forte in Europe is manufactured by Dr. Willmar Schwabe GmbH & Co. in Germany and distributed in the United States by Nature's Way Products, Inc. Each tablet contains 160 mg valerian extract (ratio 4.5:1) and 80 mg lemon balm (ratio 5.5:1).

Another valerian (120 mg, ratio 4.5:1) and lemon balm (80 mg, ratio 5:1) product produced by Pharmaton S.A. in Switzerland is sold in Europe with the name of Songha Night®.

A valerian and hops (*Humulus lupulus* L.) combination called Alluna™ Sleep is manufactured in Switzerland by Zeller AG and distributed in the United States by GlaxoSmithKline. Each tablet contains 250 mg valerian (ratio 4 to 6:1) and 60 mg hops (ratio 5 to 7:1) extracts in a combination called Ze 91019. Ze 91019 is sold as IVEL® and ReDormin® in Europe.

SUMMARY OF REVIEWED CLINICAL STUDIES

Traditional uses for valerian products include states of tension, restlessness, irritability, unrest, and insomnia. Insomnia, is one of several sleep disorders, defined as difficulty falling asleep, difficulty sleeping through the night, frequent night awakenings, early awakening, or unrefreshing sleep. It is most commonly a transient problem of less than two weeks, but it can also be chronic. Primary insomnia is a sleeping problem not associated with any other health problem. Secondary insomnia is related to a health condition, such as depression, heartburn, cancer, asthma, pain, or related to administration of a medication or alcohol.

Sleep stages have been defined according to polysomnographic recordings, including electroencephalograms (EEG). Stage 1 sleep is the transition from drowsy wake to sleep, and Stage 2 is light sleep. Stages 3 and 4 are deep sleep, also known as slow wave or delta sleep. REM (rapid eye movement) sleep occurs in Stage 5, in which dream-

ing occurs. Sleep stages occur in cycles throughout the night (Pagel and Parnes, 2001).

Sedative/hypnotic agents are commonly prescribed to treat insomnia. The benzodiazepines (i.e., flurazepam, oxazepam, trizolam) are very effective at inducing sleep, but they also can suppress REM sleep, may result in dependence, and can cause hangover effects the morning after. Ethanol can assist with sleep, but can cause tolerance, dependency, and diminished sleep efficiency and quality. Antihistamines can help, but may lead to daytime sleepiness. Antidepressants have also been used with some success if the individual also has symptoms of depression (Pagel and Parnes, 2001).

We include 15 controlled clinical trials using valerian to improve sleep or reduce stress that studied both single-ingredient valerian products and valerian in combination with either lemon balm or hops. Of these studies, six were considered to be of sufficient quality to substantiate findings of subjective reports of improvement in sleep quality and/or improvements in objective measures of sleep structure.

Sedonium (LI 156)

We reviewed five studies conducted on LI 156 related to insomnia and/or stress and one study that examined morning alertness, concentration, or reaction time compared to a benzodiazepine sleep aid. Two good-quality insomnia studies indicated a significant improvement in insomnia following a dose of 600 mg for at least two weeks. A comparative study found that valerian was equal to the benzodiazepine oxazepam in treating insomnia. A pilot study compared the effects of kava and valerian on stress-induced insomnia. Another trial evaluated the effects of valerian and kava on blood pressure and heart rate before and during a mental performance task.

Insomnia

The largest sleep study with Sedonium is a double-blind, placebo-controlled trial with 117 subjects with primary (nonorganic) insomnia (according to the World Health Organization's [1992] *International Classification of Diseases,* Tenth Revision [ICD-10]) given either two tablets Sedonium (600 mg extract) or placebo one hour before bed for 28 days. According to sleep questionnaires, significant im-

provements were seen in the degree of insomnia, the restored feeling after sleep, and general well-being compared to placebo. Some improvement was described after 14 days, and after 28 days it was more pronounced (Vorbach, Görtelmeyer, and Brüning, 1996).

A pilot crossover trial with 16 patients, with primary insomnia, used objective measures of sleep, as recorded with polysomnographic recordings, as well as questionnaires to measure sleep efficiency. Subjects were rotated through two 14-day treatment periods of two tablets Sedonium or placebo one hour before bed. After a single dose of valerian, no significant effect was observed on sleep structure or subjective sleep assessment. After 14 days, sleep efficiency increased significantly for both groups. However, Sedonium produced a comparative reduction in slow-wave sleep latency and an increase in the percentage of time in slow-wave sleep (Stages 3 and 4) (Donath et al., 2000).

Another study with 65 primary (nonorganic, nonpsychiatric) insomniacs (as defined by ICD-10) compared the effectiveness of two tablets Sedonium to 10 mg oxazepam. According to sleep questionnaires, valerian caused an improvement in sleep quantity after one month that was equivalent to that from oxazepam (Dorn, 2000). Although the addition of a placebo group would have strengthened the evidence, the quality of the study was still considered to be good.

A pilot crossover trial included 19 subjects with stress-induced insomnia (not defined) who were treated with kava (120 mg LI 150), valerian (120 mg per day LI 156), and both kava and valerian together. Each subject received each of the three treatments for a six-week period, in the order given earlier. Each treatment was separated by a two-week washout period. The subjects assessed their degree of stress and insomnia using a subjective visual analogue scale. As a result, a significant decrease in stress was observed during the first six weeks with kava, but no subsequent change during the washout period or treatments with valerian or the combination of the two. A similar pattern was observed with insomnia, with a significant decrease with initial kava treatment and no further decrease with valerian. Here, however, there was another decrease during treatment with both kava and valerian (Wheatley, 2001). This study was neither double-blinded nor placebo-controlled. In addition, all subjects were treated in the same order, and that may have had an influence on the outcome.

Mental Stress

A parallel study with 54 healthy volunteers compared the effects of valerian to kava or no treatment on psychological stress induced under laboratory conditions. The authors of the study suggested that both preparations might be beneficial in reducing physiological reactions to stressful situations. A standardized color/word mental stress task was performed before and after seven days of treatment with valerian extract (600 mg LI 156 per day), kava extract (120 mg LI 150 per day), or nothing. Comparing the resting state of groups before and after treatment, in the valerian group there was a significant reduction in systolic blood pressure and heart rate, but an insignificant reduction in diastolic blood pressure. In the kava group, a significant reduction in diastolic blood pressure was observed. No changes occurred in the control group. Comparing the response to the stress task before and after treatment revealed significant reductions in systolic blood pressure for both the valerian and kava groups with no significant change for the control group. No change was observed in diastolic blood pressure for any group. A significant reduction in heart rate was observed in the valerian group but no change was seen in the kava or control groups. Both the valerian and kava groups reported a reduction in mental pressure following treatment both before and during the task. The control group did not indicate any change in mental pressure (Cropley et al., 2002).

Cognitive Functioning

The effect of valerian extract (LI 156) on morning alertness, concentration, and reaction time was tested in a two-part study using 91 healthy volunteers. In the first part, one dose of 600 mg LI 156 extract was compared with one dose of 1 mg flunitrazepam (a benzodiazepine) taken before bed. The next morning, reaction time and performance were decreased by flunitrazepam, but not by LI 156. In the second part of the study, valerian was compared to placebo following two weeks of treatment. No negative impact on morning alertness, concentration, or reaction time was observed (Kuhlmann et al., 1999).

Valdispert

The effectiveness of Valdispert forte, 405 mg three times daily, was deemed undetermined in two poor-quality trials with elderly persons with insomnia or nervous disorders.

Insomnia

The first was a placebo-controlled pilot study with 14 elderly patients who complained of primary insomnia. Polysomnography was conducted on three nights at one-week intervals: on an adaptation night, after one dose, and after one week of treatment. There was no effect on sleep after one dose. However, after one week, subjects in the valerian group showed an increase in slow-wave sleep (sleep Stages 3 and 4) and a decrease in sleep Stage 1 compared to baseline. There was no effect on REM sleep. There was also no difference from placebo in self-rated sleep quality (Schulz, Stolz, and Muller, 1994).

Nervous Disorders

The second study with Valdispert used 78 elderly subjects with low scores in a questionnaire measuring subjective "well-being," and with behavioral disorders. Valerian increased scores for "well-being," improved behavior, and improved sleep compared with placebo (Kamm-Kohl, Jansen, and Brockmann, 1984). However, efficacy in this trial was rated as undetermined because method details, including randomization, blinding, and inclusion and exclusion criteria, were not well described.

Generic

Insomnia and Sleep Quality

Three trials with crossover designs rated as moderate to poor in methodology were conducted on a generic aqueous extract. The first study was a single-blind, placebo-controlled crossover trial conducted with 128 volunteers. Approximately half described themselves as poor or irregular sleepers, and the other half described themselves as good sleepers. Each person received three different preparations to be taken on three nonconsecutive nights for a total study length of nine

days. The treatments were a generic aqueous valerian extract, a commercial preparation of valerian and hops (Hova® tablets [Zyma S.A., Switzerland] containing 60 mg valerian extract and 30 mg hops flower extract), and placebo. Both valerian preparations delivered a dose of 400 mg valerian extract per evening. Sleep was assessed using a subjective questionnaire. Sleep quality increased and time to fall asleep decreased with both valerian preparations compared to placebo. The effect was most notable for those who considered themselves poor sleepers. Little change was seen in those with normal sleep patterns. The participants reported being sleepier than normal the next morning after taking Hova (valerian/hops combination) but not the generic valerian preparation (Leathwood et al., 1982).

Another crossover study included seven volunteers who complained that they usually have problems falling sleep. In three blocks of four nights each, 450 and 900 mg aqueous valerian extract were compared to placebo. Using the criteria of five minutes without movement as monitored by a wrist-worn activity meter to determine sleep start, both doses of valerian significantly decreased the time taken to fall asleep. A sleep questionnaire that subjects filled out also indicated a decrease in time to sleep for valerian. Increasing the dose from 450 mg to 900 mg extract did not increase the effect on sleep, but did cause subjects to feel sleepier the next morning compared to placebo (Leathwood and Chauffard, 1985).

One more crossover trial included ten healthy volunteers who slept at home and eight who slept in the laboratory. The home study monitored the effects of 450 and 900 mg aqueous extract and placebo using questionnaires. One dose of 900 mg extract reduced the time taken to fall asleep and time spent awake after falling asleep by 50 percent. The lower dose had less of an effect. The laboratory study compared one dose of 900 mg extract to placebo, and used objective polysomnographic recordings. In this study, no significant differences from placebo were observed, although some trends toward improvement of sleep were noted (Balderer and Borbely, 1985).

Valerian Nighttime (Euvegal forte)

Valerian Nighttime (valerian/lemon balm combination) was studied for its effect on sleep in both a placebo-controlled trial and in comparison with the benzodiazepine, triazolam.

Insomnia

In a good-quality, placebo-controlled, double-blind study, 66 subjects with mild insomnia according to the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised (DSM-III-R), (American Psychiatric Association, 1987) or ICD-10 were given either two tablets Euvegal forte or placebo for two weeks. According to sleep questionnaires, sleep quality increased in both groups, but the extent of improvement was greater with treatment than placebo. No hangover effects or rebound insomnia were reported following treatment (Dressing, Kohler, and Muller, 1996).

Sleep Quality

A poorly described, comparison, crossover trial included 20 healthy volunteers monitored in a sleep laboratory. Effects of a single dose of one tablet Euvegal forte or 0.125 mg triazolam were compared to placebos in a double dummy design. Triazolam caused significant increases in sleep efficiency and a decrease in time to fall asleep. However, the latency for REM sleep was significantly lengthened. No significant effect on sleep was reported for Euvegal (valerian/lemon balm combination) until the volunteers were divided into groups of "good" and "bad" sleepers according to the median of sleep efficiency for the placebo group. In the subgroup of bad sleepers who received Euvegal, there was a significant increase in sleep efficiency compared to placebo and a tendency toward an increase in deep sleep (sleep Stages 3 and 4) (Dressing et al., 1992).

Songha Night

Sleep Quality

Songha Night (valerian/lemon balm combination) was studied in a placebo-controlled trial with 95 healthy volunteers given three tablets before bed for one month. The treatment produced a trend toward improving subjective sleep quality, with 33 percent of the treatment group reporting a higher quality of sleep compared to 9 percent of the placebo group (Cerny and Schmid, 1999).

Alluna Sleep

Electrophysiological Effects

Alluna Sleep (valerian/hops combination) was tested in a small trial, with 12 healthy young adults, in which quantitative topographical electroencephalograms (qEEG) were recorded following administration of a low dose (two tablets) and high dose (six tablets). The authors suggested that the slight power reduction in beta2-frequency band after administration of the higher dose might be in agreement with the benefits for relaxation and sleep disorders (Vonderheid-Guth et al., 2000). In the opinion of our reviewers, Drs. Lynn Shinto and Barry Oken, the high dose led to some EEG changes, although the report included limited methodological detail, and the results were confounded by a large number of variables with no statistical adjustment of *p* values.

ADVERSE REACTIONS OR SIDE EFFECTS

In the trials we reviewed, valerian was reported to have good tolerability and a low number of side effects. Eight of the 15 studies reported some adverse reactions or side effects during valerian use. These side effects included dizziness, headache, sweating, tremors, nausea, nighttime itching, sleep disturbances, and tiredness. However, more side effects were often reported in the placebo group in these studies, and many of the side effects reported from the placebo groups were similar to those reported in the valerian group.

An open, multicenter field study reported that side effects occurred in eight out of 1,448 patients, an incidence rate of 0.55 percent. Patients received three to nine tablets of Baldrian Dispert (Valdispert) for ten days. The side effects that were recorded were headache and gastrointestinal complaints (Siefert, 1988).

A randomized, placebo-controlled, double-blind study with 54 participants concluded that administration of Euvegal forte did not affect concentration or attentiveness required to drive vehicles or operate machinery and that there was no additive effect with alcohol. Healthy volunteers were given four tablets per day of the valerian/lemon balm product or placebo for three weeks. After this time, the

participants additionally received sufficient 70 percent ethanol in juice to obtain blood alcohol levels of 0.5 percent. They were then subjected to a battery of psychometric tests (Albrecht et al., 1995).

INFORMATION FROM PHARMACOPOEIAL MONOGRAPHS

Sources of Published Therapeutic Monographs

American Herbal Pharmacopoeia
British Herbal Compendium
European Scientific Cooperative on Phytotherapy
German Commission E
United States Pharmacopeia—Drug Information
World Health Organization

Indications

The German Commission E approves the use of valerian root (fresh underground plant parts, carefully dried below 40°C) for restlessness and sleeping disorders based on nervous conditions (Blumenthal et al., 1998). The World Health Organization (WHO) states that the subterranean parts of valerian, including the rhizomes, roots, and stolons, carefully dried below 40°C, are used as a mild sedative and sleep-promoting agent for nervous excitation and anxiety-induced sleep disturbances (WHO, 1999). The European Scientific Cooperative on Phytotherapy (ESCOP) and the *British Herbal Compendium (BHC)* also add that valerian can be used for tenseness and restlessness (ESCOP, 1997; Bradley, 1992). Based on pharmacologic literature, the *American Herbal Pharmacopoeia (AHP)* states that valerian fragments or whole, fresh or dried, rhizomes, roots, and stolons are indicated for the symptomatic relief of insomnia, spasms due to nervous tension, and restlessness (Upton et al., 1999*). The United States Pharmacopeia—Drug Information (USP-DI)* botanical monograph series also states that preparations of the rhizome, roots, and/or stolons of valerian are reportedly used for the short-term treatment of insomnia (poor sleep quality and difficulty falling asleep) (*USP-DI,* 1998).

Doses

Infusion: 2 to 3 g of valerian per cup, once to several times per day (Blumenthal et al., 1998; ESCOP, 1997; WHO, 1999); 1 to 3 g by infusion or dried (Bradley, 1992)
Tincture: ½ to 1 teaspoon (1 to 3 ml), once to several times per day (Blumenthal et al., 1998); 1:5, ethanol 70 percent v/v (ESCOP, 1997; WHO, 1999); 3 to 5 ml up to three times daily (Bradley, 1992)
Essential oil: 0.05 to 0.25 ml (2 to 6 drops) up to two times daily (Upton et al., 1999)
Extracts: amount equivalent to 2 to 3 g of drug, once to several times per day (Blumenthal et al., 1998)
External use: 100 g for one full bath (Blumenthal et al., 1998; WHO, 1999)

Treatment Period

ESCOP lists no restriction for the treatment period, since neither dependence nor withdrawal symptoms have been reported (ESCOP, 1997).

Contraindications

The Commission E and the *BHC* list no known contraindications (Blumenthal et al., 1998; Bradley, 1992). However, ESCOP lists valerian as contraindicated for children under three years of age (ESCOP, 1997), and the WHO states that it should not be used during pregnancy or lactation (WHO, 1999). The *USP-DI* agrees with both ESCOP and the WHO (*USP-DI,* 1998).

Adverse Reactions

The Commission E and ESCOP list no known adverse reactions (Blumenthal et al., 1998; ESCOP, 1997). However, the WHO states that headaches, excitability, uneasiness, and insomnia have been associated with chronic use of valerian (WHO, 1999). The *AHP* also cautions that valerian can cause nervousness and heart palpitations in sensitive individuals and occasional headache and gastrointestinal

distress (Upton et al., 1999). According to the *USP-DI,* no side effects have been reported with the recommended dose, but acute overdose or chronic use of valerian has been associated with restlessness, excitability, headaches, nausea, blurred vision, uneasiness, and cardiac disturbances (*USP-DI,* 1998).

Precautions

ESCOP lists no precautions (ESCOP, 1997), but the WHO and *AHP* warn that valerian may cause drowsiness (WHO, 1999; Upton et al., 1999). The WHO also advises that patients should avoid consuming alcoholic beverages or other sedatives in conjunction with valerian (WHO, 1999). According to the *AHP,* abrupt discontinuation after long-term use may result in withdrawal symptoms (valerian may work like benzodiazepines) (Upton et al., 1999). The *USP-DI* warns that patients that have impaired liver function should use valerian with care (*USP-DI,* 1998).

Drug Interactions

The Commission E and ESCOP list no known drug interactions (Blumenthal et al., 1998; ESCOP, 1997). However, the *AHP* states that valerian potentiates the effects of barbiturates (Upton et al., 1999). The *USP-DI* also states that data from animal studies suggest that valerian may boost the effects of alcohol and those of other medications that depress the central nervous system (*USP-DI,* 1998).

Official Combination with Other Herbs

The German Commission E approves of fixed combinations of valerian with other herbs. A combination consisting of passionflower herb, valerian root, and lemon balm is approved for conditions of unrest and difficulty falling asleep due to nervousness. The individual components must each be present at 30 to 50 percent of the daily dosage given in the monographs for the individual herbs. A combination of valerian and hops is approved for nervous sleeping disorders and conditions of unrest. The individual components must each be present at 50 to 75 percent of the daily dosage given in the monographs for the individual herbs (Blumenthal et al., 1998).

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DETAILS ON VALERIAN PRODUCTS AND CLINICAL STUDIES

Product and clinical study information is grouped in the same order as in the Summary Table. A profile on an individual product is followed by details of the clinical studies associated with that product. In some instances, a clinical study, or studies, supports several products that contain the same principal ingredient(s). In these instances, those products are grouped together.

Clinical studies that follow each product, or group of products, are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Index to Valerian Products

Product Profile: Sedonium™

Manufacturer	**Lichtwer Pharma AG, Germany**
U.S. distributor	**Lichtwer Pharma U.S., Inc.**
Botanical ingredient	**Valerian root extract**
Extract name	**LI 156**
Quantity	300 mg
Processing	Plant to extract ratio 3-7:1, 70% (v/v) ethanol
Standardization	Valerenic acid, acetoxyvalerenic acid, and hydroxyvalerenic acid, tested using high-performance liquid chromatography (HPLC)
Formulation	Tablet

Recommended dose: Two tablets one to two hours before retiring. Swallow whole with cool liquid. Sedonium is non-habit forming and can be taken on a regular basis.

DSHEA structure/function: Clinically proven to help promote restful sleep. Awake refreshed and alert. LI 156 formula has been clinically proven to help support normal gamma aminobutyric acid (GABA) production, a neurotransmitter known for its beneficial effect on sleep.

Cautions: If one is taking prescription medicine, pregnant, nursing a baby, or administering to children under the age of 12, a health professional should be consulted before using this product.

Other ingredients: Sucrose, glucose, lactose, talc, powdered cellulose, silicon dioxide, hydroxypropyl methylcellulose, castor oil, polyvinylpyrrolidone, magnesium stearate, polyethylene glycol, gelatin, titanium dioxide, carnauba wax.

Source(s) of information: Product package; Sedonium™: Product information (Lichtwer Pharma, 1996).

Clinical study: Sedonium™

Extract name	LI 156
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Insomnia**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Vorbach EU, Görtelmeyer R, Brüning J (1996). Treatment of insomnia: Effectiveness and tolerance of a valerian extract. *Psychopharmakotherapie* 3 (3): 109-115.

Trial design
Parallel.

Study duration	1 month
Dose	2 (300 mg extract) tablets 1 hour before bed
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes

Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	23 practices (general, internal, psychiatric)
No. of subjects enrolled	121
No. of subjects completed	117
Sex	Male and female
Age	24-68 years (mean: 47)

Inclusion criteria
Nonorganic insomnia according to the ICD-10 (F51.0)

Exclusion criteria
Severe organic and mental concomitant illnesses; administration of a synthetic hypnotic more than three times a week 14 days before the trial; taking an herbal remedy to treat sleep disorder; medication with drugs that affect sleeping patterns or waking state; pregnancy, breast feeding, or women wishing to become pregnant; unwillingness to cooperate; and participation in a clinical trial within the previous three months.

End points
Examinations were conducted on day 0 (recruitment) and on days 14 and 28 of treatment. The following methods were used to assess efficacy and tolerance: Gortelmeyer's sleep questionnaire B, form B3 (SF-B); von Zerssen's well-being scale (Bf-S); Clinical Global Impressions (CGI); overall assessment of effectiveness and tolerance by doctor and patient; blood pressure and pulse rate; and documentation of adverse events and compliance.

Results
Significant differences after 28 days of treatment were seen in the following measures: quality of sleep according to the type B (SF-B) sleep questionnaire ($p = 0.035$); restored feeling after sleep ($p = 0.032$); patients' assessment of well-being (Bf-S) ($p = 0.002$); change of condition based upon the CGI scale ($p < 0.001$); degree of severity of insomnia ($p = 0.002$); and assessment of therapeutic effect ($p = 0.001$). The effect of valerian was rated as good or very good by doctors in 61 percent of cases and by patients in 66 percent of cases. In contrast, placebo was rated good or very good in 26 percent of cases by doctors and patients alike.

Side effects
Tolerability was rated very good by doctors among 91.5 percent of patients taking valerian and 72.4 percent of those taking placebo. Five subjects re-

ported "undesirable" effects: three in valerian group (two reports of headache, one report of dizziness in the morning), and two in the placebo group (tiredness, nausea, and vomiting with gastric ulcer).

Authors' comments
The results of the trial show that treatment with the valerian extract LI 156 has significant effects on nonorganic insomnia (ICD-10: F51.0). The absence of potential for dependency, the lack of any hangover effect, and the possibility of long-term treatment are arguments for using herbal sedatives as an initial treatment for insomnia.

Reviewers' comments
This well-designed and well-reported study used subjective measures of sleep (no objective measures). Effects were observed after 14 days, and were more pronounced at 28 days. (Translation reviewed) (5, 6)

Clinical Study: Sedonium™

Extract name	LI 156
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Insomnia**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Donath F, Quispe S, Diefenbach K, Maurer A, Fietze I, Roots I (2000). Critical evaluation of the effect on valerian extract on sleep structure and sleep quality. *Pharmacopsychiatry* 33 (2): 47-53.

Trial design
Crossover. Two 15-day treatment periods. Patients did not receive any treatment on day one, and received either placebo or valerian from day 2 through day 15. Treatment periods were separated by a 13-day washout period.

Study duration	15 days
Dose	2 (300 mg extract) pills 1 hour before bed
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No

Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	16
No. of subjects completed	16
Sex	Male and female
Age	22-55 years (median: 49)

Inclusion criteria
Primary insomnia (International Classification of Sleep Disorders [ICSD] code 1.A.1.) confirmed by polysomnographic recording throughout one night and subjective sleep disturbances from three months to several years.

Exclusion criteria
Patients suffering from organic or psychiatric diseases that could cause sleep disturbances; sleep apnea syndrome; periodic limb movements or restless-legs syndrome; taking psychotropic drugs, including alcohol, cocaine, benzodiazepines, barbiturates, etc. Patients were not allowed to take any drugs influencing sleep structure and daytime vigilance 14 days before the trial start and until the end of the trial.

End points
Patients underwent eight study nights of polysomnographic recordings, four nights during each treatment phase: day 1 (baseline recording), day 2 (after one day treatment), day 14 (treatment baseline), and day 15 (treatment recording). The target variable of the study was sleep efficiency. Other parameters describing sleep structure were sleep-stage analysis, based on the rules of *Rechtschaffen* and *Kales,* and the arousal index (ASDA criteria). Subjective parameters were assessed by questionnaires.

Results
After a single dose of valerian, no significant effect on sleep structure and subjective sleep assessment was observed. After 14 days of treatment, sleep efficiency increased significantly for both placebo and valerian groups compared to baseline. In both groups, sleep period time and REM sleep percentage increased, whereas NREM 1 percentage decreased. The arousal index did not change with either group. Slow-wave sleep latency was reduced by valerian compared to placebo, $p < 0.05$. The percentage of time in slow-wave sleep was increased by valerian compared to baseline, $p < 0.05$.

Side effects
Three with valerian (migraine, headache, pruritis); 18 with placebo (headache, migraine, gastrointestinal complaints, flu and common cold, left thoracic pain).

Authors' comments
Treatment with an herbal extract of *radix valerianae* at relatively high dose levels demonstrated a number of positive effects on the sleep structure and sleep perception of insomnia patients, and can therefore be recommended for the treatment of patients with mild psychophysiological insomnia.

Reviewers' comments
This was a small pilot trial. Positive effects were reported in the objective measures of sleep structure and slow-wave sleep latency. No difference was seen, however, between the placebo and valerian groups on the primary outcome measure: sleep efficiency. The study had well-defined inclusion and exclusion criteria, but the randomization and blinding were not well described. (1, 5)

Clinical Study: Sedonium™

Extract name	LI 156
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Insomnia**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Dorn M (2000). Baldrian versus oxazepam: Efficacy and tolerability in non-organic and non-psychiatric insomniacs: A randomized, double-blind, clinical, comparative study. *Forschende Komplementarmedizin und Klassische Naturheilkunde* 7 (2): 79-84.

Trial design
Parallel. Patients received either valerian or oxazepam (2 × 5 mg) 30 minutes before bed.

Study duration	1 month
Dose	2 (300 mg) valerian capsules
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	No
Drug comparison	Yes

Drug name	Oxazepam
Site description	8 general practices
No. of subjects enrolled	75
No. of subjects completed	65
Sex	Male and female
Age	18-70 years (mean: 52)

Inclusion criteria
Nonorganic, nonpsychiatric insomniacs as defined in ICD-10 (F51.0); ages 18-70.

Exclusion criteria
Persons with known hypersensitivity to valerian and/or oxazepam; participation in a different study within 30 days of the trial start; lack of contraception in premenopausal women; pregnant or breastfeeding; taking other psychotropically active drugs during the study and within four weeks of its start; known medicine/drug/alcohol dependency; poor overall condition; with severe renal or hepatic dysfunctions or illnesses; leukocyto-, granulocyto-, or thrombocytophenia; noncompensated cardiac insufficiency; neurological/psychiatric illnesses (morbus Parkinson, spinal or cerebral ataxia, myasthenia gravis, cerebral organical psychosyndrome, or psychosis); malign diseases; hypotonia; glaucoma; or sleep apnea.

End points
Primary outcome was sleep quality according to Gortelmeyer's sleep questionnaire B (SF-B). Secondary outcomes were other sleep characteristics of the SF-B, Von Zerssen's well-being scale (Bf-S), the Hamilton Anxiety scale (HAM-A), as well as sleep-rating by the doctor. Testing was performed before treatment and after one, two, and four weeks.

Results
In both groups, sleep quality improved significantly ($p < 0.001$), but no statistically significant differences could be found between groups ($p = 0.70$). At the end of the study 55 percent of patients on valerian and 70 percent on oxazepam assessed the treatment as good or very good ($p = 0.6$)

Side effects
Two subjects terminated the trial from the valerian group (sweating, tremors, nausea, night-time pruritis). Three terminated the trial from the oxazepam group (tiredness, hangover, angina pectoris).

Author's comments
The study showed no differences in the efficacy for valerian and oxazepam. Because of the more favorable adverse effect profile of valerian compared to oxazepam, this hypothesis should be confirmed.

Reviewers' comments
This well-designed and well-described study compared valerian with oxazepam. Statistically significant outcomes were seen in both groups on subjective measures for sleep quality. The inclusion of a placebo group would have strengthened the validity of positive outcome findings. The addition of a "withdrawal" effect comparison would have also increased the quality of the study. (Translation reviewed) (5, 6)

Clinical Study: LI 156

Extract name	LI 156
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Insomnia, stress-induced**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Wheatley D (2001). Stress-induced insomnia treated with kava and valerian: Singly and in combination. *Human Psychopharmacology and Clinical Experiments* 16 (4): 353-356.

Trial design
Crossover. Patients received treatments for three six-week periods with two-week washout periods in between. Patients first received kava (LI 150, 120 mg daily), then received valerian (LI 156, 600 mg daily), then received kava and valerian in combination.

Study duration	6 weeks
Dose	120 mg daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Kava extract (LI 150)
Site description	Not described
No. of subjects enrolled	24
No. of subjects completed	19

Sex	Male and female
Age	23-65 years (mean: 44)

Inclusion criteria
Outpatients with stress-induced insomnia of varying intensity and duration.

Exclusion criteria
Subjects taking other psychotropic drugs, with symptoms of depressed mood that were severe and/or included suicidal ideation, or women of child-bearing potential not using adequate contraception methods.

End points
To determine the severity of stress, three parameters were studied: social, personal, and life events. An additional three parameters were studied to determine sleep disturbance: time to fall asleep, hours slept, and mood on final waking. The different parameters of stress severity and sleep disturbance were measured by subjects with visual analogue scales (VAS). Subjects made assessments at the beginning, middle, and end of each six-week treatment.

Results
After the first six-week treatment period with kava alone, the mean total stress score was significantly reduced ($p < 0.01$). This reduction was virtually unchanged during subsequent treatment periods with valerian alone and the kava plus valerian, as well as the washout periods in between. The difference between the baseline and final stress score was highly significant ($p < 0.001$). The severity of insomnia was similarly reduced by kava ($p < 0.05$ compared to baseline), with no further decrease with the subsequent treatment with valerian. However, treatment with valerian plus kava produced an additional decrease ($p < 0.05$). The overall decrease from baseline was highly significant ($p < 0.001$).

Side effects
Slightly more subjects experienced side effects with valerian (47 percent) and kava plus valerian (47 percent) than with kava alone (33 percent). The most common side effects for the three groups were vivid dreams for both valerian and kava plus valerian (16 and 21 percent, respectively), dizziness and gastric discomfort with kava (12 percent for each), and dry mouth for kava and kava plus valerian (8 and 11 percent, respectively).

Author's comments
Kava was undoubtedly effective in this study, and would seem to have a number of desirable properties for use as a general hypnotic and anxiolytic. The role of valerian is less clear: it does not appear to be as effective in inducing sleep, but has beneficial effects on the sleep EEG, indicating that it may well improve the quality of sleep. Thus it might be useful in chronic in-

somnia and in the elderly, and to give an additive effect in improving sleep in patients who may be particularly refractory to treatment with kava alone.

Reviewers' comments
The goal of this pilot study was to collect preliminary data to support future research in determining whether kava, valerian, or the combination are safe and effective treatments for stress-induced insomnia. This was an open label study that included no objective outcome measures. The mean stress and insomnia scores reflect no change during the washout phases between treatments, which may indicate that these self-reported measures may be significantly influenced by subjects' knowledge of treatment. Including a laboratory measurement for adverse events, especially liver function tests, would have improved the study design for safety issues. Given that the primary goal of this study was exploratory in nature, the results do provide some evidence for future studies to determine whether the combination of kava and valerian is effective for stress-induced insomnia. (1, 4)

Clinical Study: LI 156

Extract name	LI 156
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Mental stress**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Cropley M, Cave Z, Ellis J, Middleton RW (2002). Effect of kava and valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions. *Phytotherapy Research* 16 (1): 23-27.

Trial design
Parallel. Subjects were randomized to receive either valerian extract (LI 156: 600 mg/day), kava extract (LI 150: 120 mg/day), or nothing (nonplacebo controls). Subjects were asked to refrain from eating and drinking caffeinated or alcoholic drinks, or smoking 1.5 hours before test periods.

Study duration	1 week
Dose	2 (300 mg) tablets daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open

Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Kava extract (LI 150)
Site description	University psychology lab
No. of subjects enrolled	54
No. of subjects completed	Not given
Sex	Male and female
Age	18-30 years (mean: 24)

Inclusion criteria
Healthy volunteers.

Exclusion criteria
None mentioned.

End points
A standardized color/word mental stress task was performed before (T1) and after seven days of treatment (T2). At each test session heart rate (HR) and blood pressure (BP) were recorded after resting for five minutes, and patients rated their perceived feeling of pressure at that moment. Then the subjects completed the color/word interference task, lasting six minutes. During this task, BP and HR were recorded at 0.5, 2.5, and 4.5 minutes. After completing the task, participants rated the feeling of pressure experienced during the task. After resting five minutes, final HR and BP measurements were taken.

Results
In the resting state at the second testing period (T2), a significant reduction in systolic BP and HR was observed in the group that received valerian compared to T1. Diastolic BP decreased in this group, but not significantly. The kava group experienced a significant decrease in resting diastolic BP at T2 compared to T1. While undergoing the stress task at T2, systolic BP was significantly lower than at T1 (under the same stress conditions) for both kava and valerian (both $p < 0.001$). No differences in diastolic BP were observed for either group, however. Heart rate was significantly reduced at T2 compared to T1 for the valerian group ($p < 0.001$), but was not changed for the kava group. Both the kava and valerian groups reported less pretask pressure at T2 compared to T1 ($p < 0.001$), and a significant reduction in pressure was experienced during the mental stress task for both groups ($p < 0.001$). The control group experienced no changes in BP, HR, or perceived pressure.

Side effects
None mentioned.

Authors' comments
Consistent with expectations, kava and valerian appeared to moderate the subjective effects of stress. Some caution is warranted in the interpretation of the results, since the study incorporated a nonplacebo design.

Reviewers' comments
The primary goal of this study was to investigate whether kava or valerian would moderate physiological and psychological reactivity to laboratory induced stress. Given the goal of this study, a placebo control group should have been included. The physiological outcome measures of HR and BP are known to be influenced strongly by placebo. Therefore, it cannot be determined whether the outcomes of this study reflect treatment or placebo effect. Self-report of stress, one week after completing a stressful mental task, may also be bias-related to the subject's knowledge of treatment. In general, subject demographics by group assignment at baseline, inclusion and exclusion criteria, study medication, dropouts, and adverse events are not well described. (0, 3)

Clinical Study: LI 156

Extract name	LI 156
Manufacturer	Lichtwer Pharma AG, Germany
Indication	**Cognitive functioning** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Yes**

Bibliographic reference
Kuhlmann J, Berger W, Podzuweit H, Schmidt U (1999). The influence of valerian treatment on "reaction time, alertness, and concentration" in volunteers. *Pharmacopsychiatry* 32 (6): 235-241.

Trial design
Study in two sections: (1) three-armed study with a single dose of valerian, flunitrazepam (1 mg), or placebo, and psychometric testing the morning after, followed by a seven-day washout phase; (2) two weeks of valerian or placebo.

Study duration	1 day, 2 weeks
Dose	2 (300 mg valerian extract) capsules or tablets
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Flunitrazepam
Site description	Single center
No. of subjects enrolled	102
No. of subjects completed	91
Sex	Male and female
Age	30-60 years (mean: 41)

Inclusion criteria
Healthy volunteers with normal daylight vision, social drinking behavior, low caffeine consumption, and no nicotine consumption.

Exclusion criteria
Usual exclusion criteria, along with any sleep disorder (ICD-10: G47), any disease that was known to lead to secondary sleep disorders, and simultaneous use of psychoactive drugs or other pharmaceuticals that could influence sleep patterns.

End points
The primary evaluation was the median of reaction time measured with the Vienna Determination Unit (VDU). Secondary criteria were the alertness test, tracking test (two-handed coordination), sleep quality (via questionnaires Visuelle Analogskalen abends [VIS-A] and Visuelle Analogskalen morgens [VIS-M], and further VDU paremeters.

Results
Single administration of LI 156 did not impair reaction abilities, concentration, or coordination. In contrast, reaction time and performance were decreased by flunitrazepam. After 14 days, improvement in median reaction time of the valerian group did not differ from the placebo group ($p = 0.4481$). Evaluations of secondary criteria were consistent with the results of the primary criteria. After 14 days of treatment, sleep quality showed a trend toward improvement in the valerian group compared to placebo.

Side effects
Eleven cases of dizziness were reported in the valerian group; 12 adverse events were reported in the placebo group; 19 events were reported in the flunitrazepam group (dizziness, tiredness, hypokinesis, lack of concentration).

Authors' comments
Neither single nor repeated evening administrations of 600 mg LI 156 have a relevant negative impact on reaction time, alertness, and concentration the morning after intake.

Reviewers' comments
This is a good study with well-defined inclusion/exclusion criteria and a good description of ingredients of placebo and active treatment capsules. There is a limited description of blinding and no description of the randomization method (minor flaw). The flaws mentioned do not negate observations that single or repeated evening administration of 600 mg LI 156 have a low negative impact on alertness, concentration, and reaction time. (1, 6)

Product Profile: Valdispert®

Manufacturer	**Solvay Arzneimittel GmbH, Germany**
U.S. distributor	None
Botanical ingredient	**Valerian root extract**
Extract name	None given
Quantity	135 mg
Processing	Plant to extract ratio 5-6:1, aqueous alkaline dry extract
Standardization	Valerenic acid
Formulation	Tablet

Comments: Also sold as Baldrian-Dispert®.

Source(s) of information: Schulz, Stolz, and Muller, 1994; Kamm-Kohl, Jansen, and Brockmann, 1984.

Clinical Study: Valdispert®

Extract name	None given
Manufacturer	Solvay Arzneimittel GmbH, Germany

Indication	**Insomnia** in elderly females
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Schulz H, Stolz C, Muller J (1994). The effect of valerian extract on sleep polygraphy in poor sleepers: A pilot study. *Pharmacopsychiatry* 27 (4): 147-151.

Trial design
Parallel. Subjects spent three nights in a sleep lab. The first (N_0) was an adaptation night, followed by a week of subjective monitoring of sleep patterns. The second night (N_1) followed the first treatment dose (of either valerian or placebo), and the third night (N_2) followed a week of treatment.

Study duration	3 nights with 1-week intervals
Dose	3 (135 mg extract) tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Sleep lab
No. of subjects enrolled	14
No. of subjects completed	14
Sex	Female
Age	Mean: 61.6 years

Inclusion criteria
Elderly females who were poor sleepers and fulfilled at least two of the following subjective inclusion criteria: (1) sleep latency > 30 minutes; (2) more than three awakenings per night and inability to go back to sleep within five minutes; (3) total sleep time < 5 hours. Subjects also had to have a normal, age-related health status, normal clinico-chemical values, and an uneventful anamnesis.

Exclusion criteria
Indications of organic or psychiatric causes of the sleep disturbances; abnormal body weight; or hypnotics, sedatives, or other central nervous system (CNS) active drugs two weeks prior to the study.

End points
Polysomnography was conducted on three nights at one-week intervals (N_0, N_1, N_2). The following parameters were recorded: time in bed, total sleep time (TST), sleep period time, sleep efficiency index, sleep latencies, and sleep stages in minutes and percentages of TST. The density of sleep spindles and K-complexes were also visually evaluated. Sleep was also measured subjectively with sleep questionnaires (Visuelle Analogskalen abends [VIS-A] at night and Schlaf-fragebogen A [SF-A] in the morning), and with a sleep diary, starting after N_0 and until the end of the trial.

Results
At baseline, the two groups differed significantly in sleep period time, sleep efficiency, and in sleep latency. During the second night of polysomnographic measurement (N_1), the two treatment groups differed in none of the sleep parameters. After repeated administration of treatment, slow-wave sleep (SWS) increased in the valerian group ($p = 0.027$), but not in the placebo group. There was a significant decrease in Stage 1 sleep ($p = 0.027$). In the placebo group, a slight reduction of movement time indicates a decrease of large body movements ($p = 0.031$). No effect on REM sleep was observed in either group. The two groups were not significantly different with respect to spindle or K-complex density on any of the three nights. No changes were seen in any of the subjective sleep parameters measured by questionnaires and sleep logs.

Side effects
None mentioned in this paper.

Authors' comments
Various shortcomings in the design of this study restrict interpretation of the results. Even allowing for these limitations, the results suggest that valerian has selective effects on non-REM sleep. We conclude from the present results and those in the literature that valerian has a mild tranquilizing quality.

Reviewers' comments
In this pilot study, the authors list several shortcomings: a small sample size with some resultant baseline differences in two groups, and a lack of good baselines, since only a limited number of polysomnography studies were conducted on each subject. Both groups had no true baseline, so changes in treatment or placebo within groups were compared against the sleep adaptation night. The study had well-defined inclusion and exclusion criteria, but did not describe the randomization process (minor flaw) or blinding techniques. Comparing active and placebo groups, no significant differences in polysomnographic measures were observed, although there were some differences when compared to baseline measures in non-REM sleep, favoring valerian. (1, 5)

Clinical Study: Valdispert® (Baldrian-Dispert®)

Extract name	None given
Manufacturer	Solvay Arzneimittel GmbH, Germany
Indication	**Nervous disorders in elderly patients**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Kamm-Kohl AV, Jansen W, Brockmann P (1984). Modern valerian therapy of nervous disorders in elderly patients. *Medwelt* 35: 1450-1454.

Trial design
Parallel.

Study duration	2 weeks
Dose	2 tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Senior care facility and geriatric hospital
No. of subjects enrolled	80
No. of subjects completed	78
Sex	Male and female
Age	59-79 years (mean: 70)

Inclusion criteria
Elderly patients suffering from disturbances of subjective well-being and behavioral disorders of nervous origin.

Exclusion criteria
None mentioned.

End points
Patients were evaluated at baseline and on days 7 and 14 of treatment. Psychometric evaluation was based on von Zerssen's scales of subjective well-being (Bf-S) and on the Nurses' Observation Scale for Inpatient Evaluation (NOSIE), an objective rating scale.

Results
Scales for rating subjective well-being indicated improvement in the valerian group compared to the placebo group ($p < 0.01$). Evaluation on the basis of the NOSIE also revealed that patients in the valerian group exhibited a marked improvement in behavior compared to placebo ($p < 0.01$). The ability to fall asleep and sleep through the night improved in the valerian group compared to placebo ($p < 0.001$). Valerian also helped with fatigue ($p < 0.02$).

Side effects
Four patients (two in each group) complained of mild dizziness.

Authors' comments
The study succeeded in confirming the efficacy of Valdispert therapy.

Reviewers' comments
The study is not well described. It has no description of randomization or blinding, and no well-defined inclusion and exclusion criteria. The sample size is appropriate, however, and the outcome measures are clearly defined. (Translation reviewed) (1, 2)

Product Profile: Valerian (Generic)

Manufacturer	None
U.S. distributor	None
Botanical ingredient	**Valerian rhizome extract**
Extract name	None given
Quantity	200-225 mg
Processing	Plant to extract ratio 2.8-3.2:1, freeze-dried aqueous extract
Standardization	No information
Formulation	Capsule

Source(s) of information: Leathwood et al., 1982; Balderer and Borbely, 1985.

Clinical Study: Valerian (Generic)

Extract name	None given
Manufacturer	None

Indication	**Insomnia**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Leathwood PD, Chauffard F (1985). Aqueous extract of valerian reduces latency to fall asleep in man. *Planta Medica* 51 (2): 144-148.

Trial design
Crossover with random treatment order comparing placebo to two doses of valerian extract. Samples were administered in random order four nights a week for three weeks (12 samples total: four samples from each treatment).

Study duration	3 blocks of 4 nights each
Dose	450 mg or 900 mg valerian extract
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Sleep lab
No. of subjects enrolled	8
No. of subjects completed	7
Sex	Male and female
Age	33-59 years (mean: 45)

Inclusion criteria
Volunteers who complained that they usually have problems falling asleep.

Exclusion criteria
None mentioned.

End points
Subjective sleep ratings were assessed by questionnaire, and movements were recorded throughout the night with wrist-worn activity meters.

Results
Using a criterion of five minutes without movement as the onset of sleep, valerian (450 mg) produced a significant decrease in this measure of time to fall asleep ($p < 0.01$). Increasing the dose to 900 mg led to no further improvement. For the rest of the night, activity levels were similar for all three

treatments. There was no evidence of carryover of valerian effects to the next consecutive night. Valerian had no significant effect on total sleep time, nor did it influence the number of minutes with movement or the total number of movements. The subjective ratings of sleep mirrored the results from the objective ratings. Subjects reported feeling more sleepy the next morning with the larger dose of valerian (900 mg) than with placebo ($p < 0.05$).

Side effects
No side effects were reported by patients.

Authors' comments
These results show that an aqueous extract of valerian root decreases sleep latency in people who have problems falling asleep.

Reviewers' comments
This was a small pilot study ($n = 7$) with inadequate inclusion and exclusion criteria. (3, 3)

Clinical Study: Valerian (Generic)

Extract name	None given
Manufacturer	None
Indication	**Sleep quality**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Leathwood PD, Chauffard F, Heck E, Munoz-Box R (1982). Aqueous extract of valerian root (*Valeriana officinalis* L.) improves sleep quality in man. *Pharmacology, Biochemistry & Behavior* 17 (1): 65-71. (Also published in Leathwood PD, Chauffard F, Munoz-Box [1982]. Effect of *Valeriana officianalis* L. on subjective and objective sleep parameters. Sleep 1982. *Sixth European Congress on Sleep Research,* Zurich, pp. 402-405.)

Trial design
Crossover. Each subject received 3 × 3 different samples: (1) aqueous valerian extract; (2) commercial preparation (Hova®, Zyma S.A. Switzerland containing valerian extract and hops extract; patients were given a dose containing 400 mg valerian extract daily); and (3) placebo. Samples were taken in random order on nine nonconsecutive nights. Volunteers were instructed to take one sachet of pills per night, one hour before going to sleep, and to

avoid taking the pills on evenings following abnormal or excessive food intake, drinking, exercise, etc.

Study duration	9 nights
Dose	2 (200 mg) capsules daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Hova
Site description	Not described
No. of subjects enrolled	166
No. of subjects completed	128
Sex	Male and female
Age	59% of subjects were 40 years old or younger, 41% were older

Inclusion criteria
None mentioned.

Exclusion criteria
None mentioned.

End points
Subjects filled out sleep questionnaires the morning after taking each sample.

Results
With valerian, 37 percent of patients had shorter than normal sleep latency, whereas reduced sleep latency was 31 percent with Hova and 23 percent with placebo. The difference between placebo and valerian was statistically significant ($p = 0.01$). Sleep quality was improved with valerian compared with placebo ($p < 0.05$). The effect was most notable among people who consider themselves poor or irregular sleepers, smokers, and people with difficulty falling asleep. With Hova, no significant change was observed in the response pattern. For the whole population, no significant changes were observed either in night awakenings or dream recall. The frequency of "more sleepy than usual" the next morning was significantly greater with Hova than with placebo ($p < 0.01$) or valerian ($p < 0.05$).

Side effects
One patient withdrew from the study due to nausea, but it is unknown which treatment he received. No other side effects were mentioned in study.

Authors' comments
In this study, an aqueous extract of valerian root improved sleep quality of poor or irregular sleepers without producing a detectable hangover effect the next morning.

Reviewers' comments
This is an adequately powered, randomized study with self-rated outcomes in a large group of volunteers, only a subset of which described themselves as poor sleepers. However, no inclusion or exclusion criteria were described. (3, 5)

Clinical Study: Valerian (Generic)

Extract name	None given
Manufacturer	None
Indication	**Sleep quality** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Balderer G, Borbely AA (1985). Effect of valerian on human sleep. *Psychopharmacology* 87 (4): 406-409.

Trial design
Crossover trial with two parts. One group ($N = 10$) slept at home, whereas the other group ($N = 8$) slept in the laboratory. The home study tested the effects of two doses of valerian (450 mg and 900 mg) compared to placebo. Subjects took medication on a Wednesday or Thursday night of each week for three weeks, and were evaluated based on their sleep that night. The lab study compared 900 mg valerian to placebo. Subjects slept five consecutive nights in the sleep lab. The first night for these patients served as an adaptation night, and the following four nights the patients received placebo (three of the nights) or valerian (one night).

Study duration	Home study: 1 night a week for 3 weeks; lab study: 4 nights
Dose	450 mg or 900 mg valerian extract
Route of administration	Oral

Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Home and sleep lab
No. of subjects enrolled	H = 10; L = 8
No. of subjects completed	H = 10; L = 8
Sex	Male and female
Age	H = 24-44 years; L = 21-26 years

Inclusion criteria
Subjects were in apparently good health and did not report major sleep disturbances.

Exclusion criteria
None mentioned.

End points
Sleep was evaluated on the basis of questionnaires, self-rating scales, and nighttime motor activity. In addition, polygraphic sleep recordings and spectral analysis of the sleep EEG were performed in the laboratory group.

Results
Home Study: Sleep latency and wake time after sleep onset were reduced by more than 50 percent after the higher dose, whereas the lower dose had a somewhat smaller effect. A declining trend was also seen for the number of awakenings. Nighttime motor activity was enhanced in the middle of the night and reduced in the last third. The self-rating of sleep quality and of the momentary state in the morning and at noon showed no significant differences between the three treatments. Laboratory Study: No significant differences from placebo were obtained. However the trend of the changes in the subjective and objective measures of sleep latency and wake time after sleep onset, as well as nighttime motor activities, corresponded to that observed under home conditions. There was no evidence for a change in sleep stages and EEG spectra between the valerian night and the three placebo nights.

Side effects
None mentioned.

Authors' comments
The present study, in conjunction with previous experiments, provides evidence for a mild hypnotic action of the aqueous valerian extract.

Reviewers' comments

In this pilot study, inclusion and exclusion criteria were not well defined. The study reported no significant effect of valerian on objective polysomnographic outcome measures in the lab component, although some trends were noted. The subjective home component observed a significant effect on decrease in sleep latency for the valerian group. (3, 4)

Product Profile: Valerian Nighttime™

Manufacturer	**Dr. Willmar Schwabe GmbH & Co., Germany**
U.S. distributor	**Nature's Way Products, Inc.**
Botanical ingredient	**Valerian root extract**
Extract name	None given
Quantity	160 mg
Processing	Plant to extract ratio 4.5:1, aqueous/ethanolic dried extract
Standardization	A minimum of 0.2% valerenic acid
Botanical ingredient	**Lemon balm leaf extract**
Extract name	None given
Quantity	80 mg
Processing	Plant to extract ratio 5.5:1, aqueous/ethanolic dried extract
Standardization	No information
Formulation	Tablet

Recommended dose: Take one to two tablets one hour before bedtime. Up to three tablets may be taken.

DSHEA structure/function: Clinically proven to promote restful sleep.

Cautions: If sleeplessness persists for more than two weeks, consult your doctor. Insomnia may be a symptom of serious underlying medical illness. Do not take this product if you are taking sedatives or tranquilizers without first consulting your doctor. Avoid alcohol and do not drive or operate machinary while taking this product.

Other ingredients: Calcium (calcium phosphate 25 mg), cellulose, maltodextrin, modified cellulose, modified cellulose gum, stearic acid, titanium dioxide, gylcerin, silica, riboflavin, carmine.

Comments: Sold as Euvegal® forte in Europe.

Source(s) of information: Product label (© 2000 Nature's Way Products, Inc.); Dressing, Kohler, and Muller, 1996; Dressing et al., 1992.

Clinical Study: Euvegal® forte

Extract name	None given
Manufacturer	Spitzner Arzneimittel GmbH, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Insomnia**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Dressing H, Kohler S, Muller WE (1996). Improvement of sleep quality with a high-dose valerian/lemon balm preparation: A placebo-controlled, double-blind study. *Psychopharmakotherapie* 3: 123-130.

Trial design
Parallel. The trial was preceded by a one-week, single-blind, placebo run-in phase. Following the two-week placebo-controlled trial, a one-week, single-blind, placebo observation period was conducted.

Study duration	2 weeks
Dose	2 (160 mg valerian and 80 mg lemon balm extract) tablets twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	10 general practices
No. of subjects enrolled	68
No. of subjects completed	66
Sex	Male and female
Age	22-86 years (mean: 57)

Inclusion criteria
Patients at least 18 years of age with mild insomnia requiring treatment ac-

cording to the DSM-III-R or ICD-10; subjectively reported falling asleep latency of greater than 30 minutes; subjective sleep duration less than six hours per night or subjective difficulties in continued sleep (at least three interruptions per night).

Exclusion criteria
Exclusion criteria included: schizophrenia and depressive psychoses; conditions of acute cerebral confusion; sleep apnea syndrome; medication, drug, or alcohol abuse; chronic intake of psychotropic medications and potent analgesics within one week prior to the study; pregnancy or breast-feeding; poor patient compliance; simultaneous participation in another clinical study or such participation during the 30 days immediately preceding the study; improvement in sleep quality during the placebo run-in phase; severe liver, kidney, heart, or metabolic diseases; myasthenia gravis; or phases of acute delirium.

End points
Patients were evaluated weekly for major outcome measures: sleep quality (Visuelle Analogskalen morgens [VIS-M] item 2); and either day-to-day well-being (Visuelle Analogskalen abends [VIS-A] item 2) or change in condition of clinical global impression (CGI item 2). In addition, sleep questionnaire B was used. Secondary parameters also included: time to fall asleep; total sleep duration; ability to concentrate; performance; aftereffects of sedation; and anxiolytic effects.

Results
Mean sleep quality during treatment increased in both groups, but the extent of improvement with valerian/balm was significantly greater than with placebo ($p = 0.02$). Motivational status throughout the day also improved relative to placebo ($p = 0.001$). The CGI scale also indicated improvement compared to placebo ($p = 0.05$). Advantages for active treatment compared to placebo were also found in the secondary parameters: time participants required to fall asleep ($p = 0.08$), sleep quality ($p = 0.005$), relaxedness after sleep ($p = 0.0004$), psychosomatic symptoms during the sleep phase ($p = 0.03$), mentally balanced in the evening ($p = 0.06$), and mentally exhausted in the evening ($p = 0.04$). No hangover, discontinuation, or rebound phenomena were observed. Some positive effects of therapy remained during the week following treatment.

Side effects
Thirteen adverse events were reported: eight in the treatment group and five in the placebo group. Adverse events included: stomachache, headache, and cramps in the calves.

Authors' comments
High-dose valerian/lemon balm preparations constitute a therapeutic alter-

native or complement in the treatment of insomnia cases that may be mild, but nevertheless require treatment.

Reviewers' comments
This is a reasonably well-designed and well-reported study. The inclusion and exclusion criteria are well-defined, and there is a nice description of side effects and adverse events. The randomization process was not described. (Translation reviewed) (3, 5)

Clinical Study: Euvegal® forte

Extract name	None given
Manufacturer	Spitzner Arzneimittel GmbH, Germany (Dr. Willmar Schwabe GmbH & Co., Germany)
Indication	**Sleep quality** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Dressing H, Riemann D, Low H, Schredl M, Reh C, Laux P, Muller WE (1992). Insomnia: Are valerian/balm combinations of equal value to benzodiazepine? *Therapiewoche* 42 (12): 726-736.

Trial design
Crossover. Volunteers were monitored for a total of nine nights in the sleep laboratory: five nights, followed by a one-week washout period, and then another four nights. The first night was used for adaptation. Using a double dummy approach, one capsule and one tablet containing either placebo or active substance were given every night in the sleep lab. Either the valerian/balm preparation or the benzodiazepine triazolam (0.125 mg) was administered on the third/fourth or on the seventh/eighth night.

Study duration	4 nights
Dose	1 (160 mg valerian and 80 mg lemon balm extract) tablet
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes

Drug comparison	Yes
Drug name	Triazolam
Site description	Sleep laboratory
No. of subjects enrolled	20
No. of subjects completed	20
Sex	Male and female
Age	30-50 years (mean: 37.2)

Inclusion criteria
Healthy volunteers ages 30 to 50.

Exclusion criteria
Physical and/or psychiatric conditions, family history of psychiatric diseases.

End points
Sleep EEG was recorded on all nine nights and evaluated for continuity, sleep architecture, and REM sleep parameters. Before, during, and after the trial, well-being (subjective condition status) and other psychopathological variables were recorded, and heart rate was monitored. During the interval week, participants were given stress tests: Concentration Performance Test (CPT) and Labyrinth test.

Results
After ingestion of triazolam, sleep efficiency increased significantly, falling-asleep latency decreased, the awake stage was reduced, Stage 2 was increased, and REM latency was significantly lengthened. No significant effects were established for the valerian/lemon balm preparation until the participants were divided into groups of "good" or "bad" sleepers. The "good" sleepers showed a significant reduction of REM-phase sleep and duration of the first REM phase. The groups of 'bad' sleepers showed a significant increase in sleep efficiency compared to placebo and a tendency to increase deep sleep Stages 3 and 4. There was a tendency toward reduction of REM density. The valerian/balm preparation did not have any influence on concentration or performance of participants. No rebound effect or daytime sedation effect were observed.

Side effects
None reported.

Authors' comments
In the assessment of the "bad" sleepers, the effects of the valerian/balm preparation were comparable to triazolam. The results here obtained demonstrate that plant-based combination preparations, such as high-dosage

valerian/balm combinations, present a thoroughly effective and safe alternative to benzodiazepines in the treatment of specific sleeping disturbances.

Reviewers' comments
This study was limited by several factors: small sample size, inappropriate inclusion/exclusion criteria, and unclear outcome measures. Neither the blinding nor the randomization were adequately described. Overall, this was not a well-described study. (Translation reviewed) (1, 3)

Product Profile: Songha Night®

Manufacturer	**Pharmaton S.A., Switzerland**
U.S. distributor	None
Botanical ingredient	**Valerian root extract**
Extract name	None given
Quantity	120 mg
Processing	Plant to extract ratio 4.5:1
Standardization	No information
Formulation	Tablet
Botanical ingredient	**Lemon balm leaf extract**
Extract name	None given
Quantity	80 mg
Processing	Plant to extract ratio 5:1
Standardization	No information

Source(s) of information: Cerny and Schmid, 1999.

Clinical Study: Songha Night®

Extract name	None given
Manufacturer	Pharmaton S.A., Switzerland
Indication	**Sleep quality** in healthy volunteers
Level of evidence	**II**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Cerny A, Schmid K (1999). Tolerability and efficacy of valerian/lemon balm in healthy volunteers: A double-blind, placebo-controlled, multicenter study. *Fitoterapia* 70 (3): 221-228.

Trial design
Parallel.

Study duration	1 month
Dose	3 (120 mg valerian and 80 mg lemon balm extract) tablets 30 minutes before bed
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	3 hospitals, 3 general practices
No. of subjects enrolled	98
No. of subjects completed	95
Sex	Male and female
Age	20-70 years (mean: 34)

Inclusion criteria
Healthy volunteers between the ages of 20 and 70 who were fit for work.

Exclusion criteria
Patients with renal insufficiency, hepatic dysfunction, cardiovascular disease, psychic disorder, drug and alcohol abuse, concomitant treatment with other drugs including herbal sedatives, known hypersensitivity to any of the ingredients of the study drug, pregnancy, lactation, women of childbearing potential who did not use an established contraceptive, and participation in another study within the past 30 days.

End points
Primary parameters were assessment of tolerability and incidence of adverse events. Secondary parameters included laboratory tests, physical examination, and assessments of well-being and sleep quality rated on the 100 mm visual analogue scale (VAS).

Results
Tolerance was acceptable to excellent for both valerian/balm and placebo (no significant difference between groups). There was no significant difference between the two groups in reporting of adverse events and none were severe. The valerian/balm group reported a significantly higher quality of sleep, 33 percent compared to 9 percent of the placebo group ($p = 0.04$).

Analysis of the results of the visual analogue scale showed a slight but nonsignificant improvement in sleep quality. Well-being in both groups remained unchanged. No significant differences were found between groups in terms of physical examination or laboratory tests.

Side effects
About 28 percent in both groups reported adverse events. The two most often reported were sleep disturbances and tiredness (both groups). One patient in each group quit the study because of nausea and sleep disturbances.

Authors' comments
In the present study, sleep quality improved significantly in subjects who received valerian/lemon balm, which was surprising since only healthy volunteers not complaining of insomnia participated. The observed effect has to be considered with caution because it was shown only in the assessment of change and not in the assessment of the actual state by VAS.

Reviewers' comments
This is a fairly well-designed phase I, tolerability study. No difference was observed between the valerian and placebo groups on the secondary outcome measure of sleep quality (subjective rating by visual analogue scale). (5, 5)

Product Profile: Alluna™ Sleep

Manufacturer	**Zeller AG, Switzerland**
U.S. distributor	**GlaxoSmithKline**
Botanical ingredient	**Hops extract**
Extract name	**Ze 91019**
Quantity	60 mg
Processing	Plant to extract ratio 5-7:1
Standardization	No information
Botanical ingredient	**Valerian root extract**
Extract name	**Ze 91019**
Quantity	250 mg
Processing	Plant to extract ratio 4-6:1
Standardization	No information
Formulation	Tablet

Recommended dose: Take two tablets one hour before bedtime with a glass of water. Not habit forming.

DSHEA structure/function: Promotes a healthy sleep pattern. Helps promote calm and relaxation so you can fall asleep naturally and rest through the night. Helps your body maintain its own natural sleep pattern so you wake up refreshed.

Cautions: Contact your doctor before use if you are pregnant or lactating. Driving or operating machinery while using this product is not recommended. Chronic insomniacs should consult their doctor before using this product.

Other ingredients: Microcrystalline cellulose, soy polysaccharide, hydrogenated castor oil, hydroxypropyl methylcellulose. Contains less than 2 percent titanium dioxide, propylene glycol, magnesium sterate, silica, polyethylene glycol (400, 6,000, and 20,000), blue 2 lake, artificial flavoring.

Comments: Sold as IVEL® and ReDormin® in Europe.

Source(s) of information: Product package (© 1999 SmithKline Beecham); Vonderheid-Guth et al., 2000.

Clinical Study: IVEL® or ReDormin®

Extract name	Ze 91019
Manufacturer	Zeller AG, Switzerland
Indication	**Electrophysiological effects** in healthy volunteers
Level of evidence	**III**
Therapeutic benefit	**MOA**

Bibliographic reference
Vonderheid-Guth B, Todorova A, Brattstrom A, Dimpfel W (2000). Pharmacodynamic effects of valerian and hops extract combination (Ze 91019) on the quantitative-topographical EEG in healthy volunteers. *European Journal of Medical Research* 5 (4): 139-144.

Trial design
Crossover. Subjects participated in two trials separated by several months. First trial: low dose (500/120 mg valerian/hops) compared to placebo; second trial: high dose (1,500/360 mg valerian/hops) compared to placebo. In each trial, valerian/hops was compared to placebo on two days with a one-week washout period in between.

Study duration	2 days
Dose	2 or 6 (250 mg valerian and 60 mg hops) pills
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	12
No. of subjects completed	12
Sex	Male
Age	18-30 years (mean: 24)

Inclusion criteria
Healthy young adults.

Exclusion criteria
Relevant pathological findings.

End points
Quantitative topographical EEG (qEEG) was recorded at baseline and one, two, and four hours after drug intake. Recording conditions were eyes open, eyes closed, and under mental demand (taking the Concentration Performance Test [CPT]).

Results
After administration of low-dose valerian/hops, qEEG power changes remained more or less equivalent to placebo, except for a tendency toward reduction of alpha- and beta1-activity after four hours. The high dose of valerian/hops led to a power increase in the delta region, decreases in alpha-power, and a weak decrease in beta-power. No significant EEG changes were measurable during CPT. A minimal increase in answer time and time for correct answers was observed four hours after administration of low dose and one hour after administration of high dose.

Side effects
None mentioned.

Author's comments
Within four hours after oral administration, the valerian-hops extract combination Ze 91019 produces slight though clear visible EEG power changes in

healthy subjects. These EEG changes have been related to the time after administration and the dose used, whereby the pharmacodynamic response of the target organ (CNS) to Ze 91019 is clearly demonstrated.

Reviewers' comments

This evaluation of 17-channel EEG data following a single dose of drug or placebo has limited methodologic detail for EEG analysis. The EEG data is confounded by large numbers of variables with no statistical adjustment of *p* values. This results in an uncertain effect on EEG. (0, 3)

2nd Wind™

Ingredients:

Ginseng (*Panax ginseng* C.A. Meyer) root
Cordyceps [*Cordyceps sinensis* (Berk.) Sacc.]
Reishi mushroom [*Ganoderma lucidum* (Curtis: Fr.) P. Karst.]
Enoki mushroom [*Flammulina velutipes*]
Siberian ginseng [*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.] root
Tangerine (*Citrus reticulata* Blanco) peel

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

2nd Wind™ is a proprietary blend of six different ingredients: ginseng (root extract), cordyceps (fermentation), reishi mushroom (fermentation), enoki mushroom (fermentation), Siberian ginseng (root extract), and tangerine (peel extract). It is manufactured and distributed by Botanica BioScience Corporation.

SUMMARY OF REVIEWED CLINICAL STUDIES

2nd Wind is formulated to accelerate recovery after exercise by enhancing the clearance of lactic acid (lactate) from the muscles during

2ND WIND™ SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
2nd Wind™	Botanica BioScience Corporation/Botanica BioScience Corporation	Blend of six ingredients	1-1.35 g daily	Recovery after exercise	2	Undetermined (III-2)

and after exercise. Lactic acid is produced during exercise, and its accumulation in muscles can result in soreness and fatigue. With intense exercise, lactic acid buildup can reduce blood pH and cause a condition known as acidosis. Thus, enhancing the clearance of lactic acid is a key principle in increasing athletic performance, and is a means to speeding recovery from exercise. Lactate measurements in the blood give an indirect, but reliable indication of lactate levels in muscle cells (Burke, 1996).

2nd Wind

Recovery After Exercise

Two unpublished, placebo-controlled clinical studies were reviewed. In the first study, including 20 healthy young males, 1 g of the formula per day caused a statistically significant increase in the clearance of lactic acid in the blood following exercise after two weeks of treatment compared to baseline measurements. Clearance of lactic acid in the placebo group did not improve (Burke, 1996). The second study, with 12 healthy students given 1.35 g 2nd Wind or placebo daily for five weeks, also reported comparatively less lactic acid in the blood following exercise. The plasma pH following exercise appeared to be more stable in the treatment group as well (Seifert, Burke, and Lahr, 1998). A review by Dr. Mary Hardy found that neither study established therapeutic benefit due to an inadequate description of the methods and results in the trial reports.

ADVERSE REACTIONS OR SIDE EFFECTS

No side effects were reported in either trial.

REFERENCES

Burke ER (1996). Clinical study to evaluate effects of 2nd Wind ARX (athletic recovery x-celerator) on blood lactate clearance in healthy human subjects. Conducted at Beijing Medical University Sports Research Institute. Unpublished clinical report.

Seifert JG, Burke ER, Lahr J (1998). The effects of herbal intake on clearance of lactic acid and cycling performance. Unpublished report.

DETAILS ON 2ND WIND PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: 2nd Wind™

Manufacturer	**Botanica BioScience Corporation**
U.S. distributor	**Botanica BioScience Corporation**
Formula botanicals	***Cordyceps sinensis*** (fermentation); ***Ganoderma lucidum*** (fermentation); ***Flammulina velutipes*** (fermentation); **Siberian ginseng** (*Eleutherococcus senticosus;* std. Root extract); ***Panax ginseng*** (std. Root extract); ***Citrus reticulata*** (extract from peel)
Quantity	450 mg
Processing	See Formula botanicals
Standardization	No information
Formulation	Capsule

Recommended dose: Take two capsules once daily as part of a normal workout regimen. Optimal results have been shown after three to four weeks of continued use.

DSHEA structure/function: Clinically proven to double clearance of lactic acid in the blood. Reduces muscle soreness and fatigue.

Cautions: In case of accidental overdose, seek professional advice immediately. If taking prescription medicine, pregnant, or lactating, consult with a doctor before taking.

Other ingredients: Cellulose, magnesium stearate (vegetable grade), silica.

Source(s) of information: Product package (© 1999 Botanica Bioscience Corporation).

Clinical Study: 2nd Wind™

Extract name	N/A
Manufacturer	Botanica BioScience Corporation
Indication	**Recovery after exercise; lactate clearance**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Burke ER (1996). Clinical study to evaluate effects of 2nd Wind ARX (athletic recovery x-celerator) on blood lactate clearance in healthy human subjects. Conducted at Beijing Medical University Sports Research Institute. Unpublished clinical report.

Trial design
Parallel. Subjects were treated with either placebo or 2nd Wind each morning for two weeks. Treatment continued, unblinded, for an additional two weeks in the 2nd Wind group.

Study duration	2 weeks with additional 2-week follow-up
Dose	1 g every morning
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Sports medicine research institute
No. of subjects enrolled	20
No. of subjects completed	Not given
Sex	Male
Age	Mean: 18.5 years

Inclusion criteria
Healthy students with normal health history, physical examination, and blood liver function tests.

Exclusion criteria
None mentioned.

End points
An exercise challenge test was performed before ingesting the study material, after two weeks of treatment with either 2nd Wind or placebo, and again after four weeks of treatment for the 2nd Wind group. Lactic acid was measured from blood samples obtained from the earlobe taken at rest 30 minutes before exercise, immediately upon finishing exercise as the maximum lactic acid level, and 15 minutes after stopping exercise as the end point level (recovery level).

Results
After treatment with 2nd Wind for two weeks, lactate clearance after exercise recovery increased to 27.4 mg/dl, up from 15.4mg/dl prior to the study. In the placebo group, lactate clearance was 10.1 mg/dl after two weeks compared to 14.3 mg/dl prior to the study. After four weeks of 2nd Wind treatment, lactate clearance in the verum group increased to 31.6 mg/dl.

Side effects
No side effects were reported by the study participants.

Author's comments
These results show a statistically significant improvement in lactate clearance after stopping exercise with the usage of 2nd Wind, as well as a trend of increasing lactate clearance improvement the longer the product is taken.

Reviewer's comments
This trial was double-blinded and randomized, however, the randomization process was not described adequately. Although the outcome measures were defined clearly, the sample size was insufficient to allow full statistical analysis, and no mean or standard deviations were given for the results. (2, 2)

Clinical Study: 2nd Wind™

Extract name	N/A
Manufacturer	Botanica BioScience Corporation
Indication	**Recovery after exercise; lactate clearance**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Seifert JG, Burke ER, Lahr J (1998). The effects of herbal intake on clearance of lactic acid and cycling performance. Unpublished report.

Trial design
Parallel.

Study duration	5 weeks
Dose	1,350 mg daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	36
No. of subjects completed	12
Sex	Not given
Age	18-45 years

Inclusion criteria
Active, healthy subjects.

Exclusion criteria
None mentioned.

End points
Prior to the study, subjects were assessed on a ramped cycling performance test in which workload increased every four minutes. At the end of every four-minute interval, a blood sample was taken and analyzed for lactic acid. This test was repeated after five weeks to assess whether fitness levels of subjects had changed over the study period. After the five-week treatment period, subjects cycled at a power output level higher than their lactate threshold for 20 minutes. After this period, subjects were seated, and blood samples were taken every three minutes for 12 minutes during recovery. At 12 minutes, subjects had to cycle as fast as possible to complete 60,000 joules of work. Blood samples were analyzed for lactic acid, blood bicarbonate, and pH.

Results
Compared to placebo, 2nd Wind led to significantly greater change in lactic

acid levels during exercise recovery. Lactic acid values at the end of the 12-minute recovery period were 7 percent below baseline for the 2nd Wind group and 22 percent above baseline for the placebo group. Compared to placebo, the 2nd Wind group had more stability in plasma pH and bicarbonate buffering system. The 2nd Wind group completed the time trial 56.2 seconds faster than the placebo group, although this difference was not statistically significant. No significant differences were observed in the pre- and poststudy fitness levels both within and between groups. Only six subjects in each group were appropriately verified as placebo or treatment product due to administrative difficulties.

Side effects
None mentioned in paper.

Authors' comments
Compared to the placebo group, 2nd Wind led to statistically less lactic acid accumulation following intense cycling, less stress placed upon bicarbonate buffering system, and a strong trend toward improvement in high-intensity cycling performance.

Reviewer's comments
This study was not blinded and the randomization process was not adequately described. The article is poorly referenced and the clinical significance of the results is not clear. The outcome measures were clearly defined. (Publication draft reviewed) (0, 5).

Cystone®

Ingredients:

Shilapushpa (*Didymocarpus pedicellata* R. Br.) leaves
Pasanabheda (*Saxifraga ligulata* Wall.) root
Rough chaff tree (*Achyranthes aspera* L.) seed
Indian madder (*Rubia cordifolia* L.) root
Ash-colored fleabane (*Vernonia cinerea* [L.] Less.) whole
Umbrella's edge (*Cyperus scariosus* R. Br.) tuber
Sedge (*Onosma bracteatum* Wall.) aerial parts
Mineral pitch

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Cystone® tablets contain a combination of seven herbal extracts and mineral pitch, a total of 540 mg per tablet. Current labels suggest a dose of one to two tablets twice daily, for a total quantity of 1.08 to 2.16 g per day. Cystone is manufactured by The Himalaya Drug Company in India, and distributed in the United States by Himalaya USA. Cystone is also available under the name UriCare®. The current Cystone product label lists the ingredients indicated previously. The material used in the clinical study had the same name, but contained an additional ingredient: Hajrul yahood bahsma.

The material used in the clinical trial is described as tablets containing 223 mg of the proprietary blend. The ingredients and their quantities were listed in the trial report as: extracts of *Didymocarpus pedicellata* (65 mg), *Saxifraga ligulata* (49 mg), *Rubia cordifolia* (16 mg), *Cyperus scariosus* (16 mg), *Achyranthes aspera* (16 mg), *Onosma bracteatum* (16 mg), *Vernonia cinerea* (16 mg) and Shilajeet (purified mineral pitch) (13 mg), as well as Hajrul yahood bahsma (16 mg). Hajrul yahood bahsma was prepared with *Ocimum basilicum, Tribulus terrestris, Mimosa pudica, Dolichos biflorus, Pavonia odorata, Equisetum arvense,* and *Tectona grandis* seed. The

CYSTONE® SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Cystone®*	The Himalaya Drug Company, India/ Himalaya USA	Blend of 7 extracts and purified mineral pitch	1.34 g daily	Kidney and bladder stones	1	Undetermined (III-1)

*The product used in the trial was slightly different.

dose used in the study was two tablets three times daily or a total of 1.34 g per day (Misgar, 1982).

SUMMARY OF REVIEWED CLINICAL STUDIES

Cystone is an herbal formula tested in the treatment of kidney and bladder stones. Urinary tract stones form in the bladder and kidney. Human urine is saturated with calcium oxalate, uric acid, and phosphates that normally remain in solution. However dehydration, urinary stasis, pH changes, foreign bodies, and infection can lead to the formation of stones. Stones are hard buildups of mineral composed mostly of calcium salts, uric acid, or struvite (phosphate of magnesium and ammonia). Treatment depends upon differentiation between the various stone types as well as recognition and control of any underlying metabolic diseases or structural abnormalities of the urinary tract (Pizzorno and Murray, 1999).

Cystone

Kidney and Bladder Stones

The effect of Cystone on patients with kidney and bladder stones (nephroureterolithiasis) was studied in a four-arm, open, clinical trial including 100 participants. Two groups were given Cystone (two tablets three times daily) and either encouraged to drink plenty of liquids or given forced diuresis (intravenous liquids). Two control groups were given antispasmodics and also either encouraged to drink plenty of fluids or given forced diuresis. In the Cystone treatment groups, 76 and 80 percent, respectively, of participants were able to pass their stones over a period of one to six months and thereby avoid surgery. In the control groups given antispasmodics, only 20 and 28 percent, respectively, were able to avoid surgery (Misgar, 1982). However, due to poor methodological flaws, including the lack of characterization of the size of the kidney and bladder stones in the various treatment groups, our reviewers, Drs. Elliot Fagelman and Franklin Lowe, found the benefit to be undetermined.

ADVERSE REACTIONS OR SIDE EFFECTS

No adverse effects were reported in a clinical trial in which 50 subjects were given two tablets three times daily for six months (Misgar, 1982).

REFERENCES

Misgar MS (1982). Controlled trial in 100 cases with nephro-ureterolithiasis by cystone—An indigenous drug and other advocated methods. *PROBE* 21 (4): 281-287.

Pizzorno JE, Murray MT, eds. (1999). *Textbook of Natural Medicine,* Second Edition, Volume 2. London: Churchill Livingstone.

DETAILS ON CYSTONE PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Cystone®

Manufacturer	**The Himalaya Drug Company, India**
U.S. distributor	**Himalaya USA**
Formula Botanicals	**Shilapushpa leaves** (*Didymocarpus pedicellata* R. Br.); **pasanabheda root** (*Saxifraga ligulata* Wall.); **rough chaff tree seed** (*Achyranthes aspera* L.); **Indian madder root** (*Rubia cordifolia* L.); **ash-colored fleabane whole** (*Vernonia cinerea* [L.] Less.); **umbrella's edge tuber** (*Cyperus scariosus* R. Br.); **sedge aerial parts** (*Onosma bracteatum* Wall.); **mineral pitch**
Quantity	540 mg
Processing	Blend of 7 extracts and purified mineral pitch
Standardization	No information
Formulation	Tablet

Recommended dose: Take one or two tablets two times per day with meals.

DSHEA structure/function: Natural urinary support. Helps regulate calcium absorption and precipitation for efficient kidney and urinary functions.

Other ingredients: Lime silicate, magnesium stearate, sodium carboxymethyl cellulose, microcrystalline cellulose, crospovidone, aerosil.

Comments: Also sold as UriCare®.

Source(s) of information: Product label; Misgar, 1982.

Clinical Study: Cystone®

Extract name	N/A
Manufacturer	Himalaya Drug Company, India
Indication	**Kidney and bladder stones** (nephroureterolithiasis)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Misgar MS (1982). Controlled trial in 100 cases with nephro-uretero-lithiasis by Cystone—An indigenous drug and other advocated methods. *PROBE* 21 (4): 281-287.

Trial design

Parallel. Four groups of 25 each. Group I was given Cystone for two to six months and encouraged to drink plenty of fluids. Group II was given Cystone for two to six months, along with forced diuresis (intravenous fluids). Group III was given antispasmodics and encouraged to drink plenty of fluids; this group was followed for a year. Group IV was put on antispasmodics and forced diuresis; they were followed for a year.

Study duration	2-6 months to 1 year
Dose	2 tablets 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Antispasmodics
Site description	One surgical department
No. of subjects enrolled	100
No. of subjects completed	100
Sex	Male and female
Age	10-60 years

Inclusion criteria

Patients with nephroureterolithiasis (stones in the kidney and ureter).

Exclusion criteria
None mentioned.

End points
X-rays were taken every four weeks to compare the effectiveness of each method. Patients who passed their stones without surgery within the allotted time frame for that group (six months or one year) were assessed as responders to therapy.

Results
In Group I, 19 of 25 cases showed good response to treatment with Cystone, and thereby averted an operation. Six cases underwent surgery. Of the 19 cases that passed stones, 16 expelled the stones between four to eight weeks, two at the end of 12 weeks, and one after six months. All 19 cases observed remarkable relief in the burning sensation during micturition. In Group II, 20 of 25 cases responded well to the treatment, and five cases had to have surgery. Eighteen cases passed stones at the end of eight weeks, and two cases at the end of 16 and 24 weeks respectively. In Group III, only five cases responded to treatment, and 20 had to have surgery. In Group IV seven cases responded to the treatment and 18 cases underwent surgery.

Side effects
No adverse side effects from Cystone.

Author's comments
Of the four different methods tried in the treatment of nephroureterolithiasis, Cystone tablets gave excellent results as compared to other methods. The present study thus establishes that Cystone has a potent role in early cases of nephroureterolithiasis, and should therefore be used in every such case before resorting to surgical intervention.

Reviewers' comments
This study has several flaws. The subjects were not randomized, and there was no control for kidney stone size. The chance of a stone passing is much greater for a small stone. It is possible that the patients treated with Cystone had smaller stones than the other groups, thus skewing the results in favor of Cystone. (1, 3)

Gastrim®

Ingredients:

Crowfoot (*Aconitum palmatum* D. Don.) root
Black pepper (*Piper nigrum* L.) fruit
False black pepper (*Embelia ribes* Burm. f.) fruit
Ginger (*Zingiber officinale* Rosc.) rhizome
Triphala:
Amalaki (*Emblica officinalis* Gaertn.) fruit
Vibhitaka (*Terminalia bellerica* [Gaertn.] Roxb.) fruit
Haritaki (*Terminalia chebula* Retz.) fruit rind
Mint (*Mentha arvensis* L.) leaves
Lemon (*Citrus limon* [L.] Burm. f.) fruit
Papaya (*Carica papaya* L.) fruit

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Gastrim® (previously called Gasex®) is manufactured by the Himalaya Drug Company in India, and distributed in the United States by Himalaya USA. Gastrim is also available under the name GastriCare®. The current product label lists the ten herbal ingredients indicated earlier. Also listed on the label, in the category of other ingredients, are purified conch shell ash and purified cowrie shell ash. The recommended dose is one to two 515 mg tablets, before meals or as needed.

The material used in one of the clinical trials is described as tablets containing 214 mg total ingredients. The dose in the trial was two tablets three times a day, for a total of 1.28 g per day. The ingredients and their quantities were listed in one trial report as *Aconitum palmatum* (65 mg), *Piper nigrum* (19 mg), extract of *Embelia ribes* (22 mg), extract of Triphala (22 mg), extract of *Zingiber officinale* (22 mg), cowrie bhasma (purified cowrie shell ash) (32 mg), and shankh bhasma (purified conch shell ash) (32 mg)—all prepared in the juices

GASTRIM® SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Gastrim® (previously Gasex®)	The Himalaya Drug Company, India/ Himalaya USA	Blend of 10 herbs plus purified ash	2 tablets 2-3 times daily	Dyspepsia (indigestion)	1	Undetermined (III-1)
				Postopera-tive gastric distress	1	Undetermined (III-1)

and decoctions of *Mentha arvensis, Moringa pterygosperma, Carica papaya, Citrus limon,* etc. (Chandra et al., 1978). The other clinical trial did not provide a list of product ingredients (Mishra and Singh, 1981). The current product differs from that described in the trial in that *Moringa pterygosperma* is not mentioned on the label.

SUMMARY OF REVIEWED CLINICAL STUDIES

The two studies reviewed here test Gastrim (Gasex) for its ability to relieve gastric complaints. As described in the studies, complaints of indigestion or dyspepsia included symptoms of belching, sour eructations, frequent or excessive passage of gas, abdominal fullness, vague abdominal pain, epigastric burning, nausea, and unsatisfactory evacuation. These symptoms were linked to gas in the abdomen.

Gastrim

Dyspepsia (Indigestion)

A trial included 100 patients with symptoms of dyspepsia (indigestion) who were given either Gasex or placebo for two weeks. The dose of Gasex was two tablets three times daily for one week, and then two tablets twice daily for the second week. Thirty-six of the 50 patients in the placebo group did not have any response after two weeks and were switched to Gasex treatment. Of all the subjects given Gasex, 71 of 86 were judged as having a good to excellent therapeutic response (Mishra and Singh, 1981). Our reviewers, Drs. Karriem Ali and Richard Aranda, commented that the crossing over of the placebo nonresponders to the treatment arm, without any distinction in the reporting of the results, obscures the purpose of having a placebo group.

Postoperative Gastric Distress

Another trial with Gasex studied 150 women recovering from gynecological surgery. Treatment began on the postoperative day at the onset of bowel sounds, with either Gasex (two tablets three times daily) or vitamin B complex tablets as placebo, and continued for one

to two weeks. All patients taking Gasex showed considerable improvement in symptoms compared to the controls. In the Gasex group, a good to excellent response was observed in 95 percent of patients with abdominal discomfort, and in 88 percent with flatulence, compared to 14 percent and 4 percent of the control group, respectively (Chandra et al., 1978). The randomization and blinding processes were inadequate, and the use of vitamin B complex as placebo was not explained.

ADVERSE REACTIONS OR SIDE EFFECTS

Neither study observed or mentioned any side effects.

REFERENCES

Chandra R, Agrawal S, Bajaj S, Goel S (1978). A clinical trial of Gasex in gastro-intestinal disorders in post-operative gastro-intestinal symptoms. *PROBE* 17 (4): 330-333.

Mishra DN, Singh T (1981). Clinical trial of Gasex in functional dyspepsias. *PROBE* 20 (3): 208-211.

DETAILS ON GASTRIM PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Gastrim®

Manufacturer	**The Himalaya Drug Company, India**
U.S. distributor	**Himalaya USA**
Formula Botanicals	**Crowfoot root** (*Aconitum palmatum* D. Don.); **black pepper fruit** (*Piper nigrum* L.); **false black pepper fruit** (*Embelia ribes* Burm. f.); **ginger rhizome** *(Zingiber officinale* Rosc.); **Triphala** [including amalaki fruit (*Emblica officinalis* Gaertn.); vibhitaka fruit (*Terminalia bellerica* [Gaertn] Roxb.); haritaki fruit rind (*Terminalia chebula* Retz.); **mint leaves** (*Mentha arvensis* L.); **lemon fruit** (*Citrus limon* [L.] Burm. f.); **papaya fruit** (*Carica papaya* L.)
Quantity	515 mg
Processing	No information
Standardization	No information
Formulation	Tablet

Recommended dose: Take one or two tablets before meals or whenever needed.

DSHEA structure/function: Natural digestive support. Provides support for the whole digestive function, and is an effective antiflatulent that alleviates bloating and relieves upset stomach or occasional heartburn.

Other ingredients: Purified conch shell ash, purified cowrie shell ash, magnesium stearate, sodium carboxymethylcellulose, microcrystalline cellulose, crospovidone, aerosil.

Comments: Previously called Gasex®. Also sold as GastriCare®.

Source(s) of information: Product label.

Clinical Study: Gasex®

Extract name	N/A
Manufacturer	The Himalaya Drug Company, India
Indication	**Dyspepsia** (indigestion)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference

Mishra DN, Singh T (1981). Clinical trial of Gasex in functional dyspepsias. *PROBE* 20 (3): 208-211.

Trial design

Parallel. Patients in the placebo group without significant relief after two weeks were switched to Gasex treatment.

Study duration	2 weeks
Dose	2 tablets 3 times daily for 1 week, then 2 tablets twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	100
No. of subjects completed	100
Sex	Male and female
Age	10-80 years

Inclusion criteria

Patients with symptoms of dyspepsia and indigestion, including belching, sour eructations, frequent or excessive passage of flatus, abdominal fullness, vague abdominal pain, epigastric burning, nausea, and unsatisfactory evacuation.

Exclusion criteria

Patients with any organic disease or demonstrable structural abnormalities.

End points
Effectiveness was judged subjectively on weekly visits by the patients.

Results
Thirty-six out of 50 patients started on placebo did not have any response in two weeks time and were subsequently put on Gasex tablets. Ten patients with hyperacidity received significant and sustained relief with Gasex. Fourteen patients had cysts of *Entamoeba histolytica* and were given antiamebic treatment. Gasex gave long-lasting relief to these patients. Fourteen of 50 cases responded to placebo. None of these patients had their illness for more than two weeks. Overall, 71 of 86 (82.6 percent) patients responded to Gasex.

Side effects
No side effects were noted.

Authors' comments
Gasex was found to be effective against dyspepsia in 82.6 percent of cases. The drug also seems to have an antacid property, as concluded from subjective relief obtained in ten cases of hyperacidity. The drug also proved beneficial in 14 cases of chronic mucus passers following amebiasis. The response was poor in the relative minority of cases with deep-seated emotional problems.

Reviewers' comments
This is an unsatisfactory trial of poor design. The stated objectives of the study were not met. Efficacy in the treatment of functional dyspepsia was not determined because there was no comparison between the treatment group and controls, and there was no presentation of the methodology data relevant to the treatment of hyperacidity. The crossing over of the placebo nonresponders to the treatment arm and simply including their data as part of the treatment group without any distinction obscures the entire trial. The statement made that the failure of treatment in certain patients was secondary to emotional problems is conjecture not supported by the data or references. The appropriateness of sample size was not subjected to power analysis, but it would appear adequate. The dosage choice was not discussed in the paper nor was it substantiated by reference(s), and the trial length was inadequate for a functional dyspepsia study. (0, 2)

Clinical Study: Gasex®

Extract name	N/A
Manufacturer	Himalaya Drug Company, India

Indication	**Postoperative gastric distress**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Chandra R, Agrawal S, Bajaj S, Goel S (1978). A clinical trial of Gasex in gastro-intestinal disorders in post-operative gastro-intestinal symptoms. *PROBE* 17 (4): 330-333.

Trial design
Parallel. Patients were given treatment for 7 to 15 days starting on the post-operative day when bowel sounds began. One hundred patients received either Gasex, and 50 patients were given vitamin B complex tablets (as placebo).

Study duration	7-15 days
Dose	2 tablets 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Medical college hospital
No. of subjects enrolled	150
No. of subjects completed	150
Sex	Female
Age	21-70 years

Inclusion criteria
Patients in the gynecological section of the hospital recovering from surgery.

Exclusion criteria
None mentioned.

End points
Responses in the patients were subjectively interpreted in terms of the relief of symptoms, with responses of excellent, good, fair, or poor.

Results
One hundred subjects were in the treatment group and 50 were in the control group. All patients taking Gasex showed considerable improvement in

their symptoms compared to the controls taking placebo. In the treatment group, a good to excellent response was observed in 95 percent of subjects with abdominal discomfort, compared to only 14 percent in the control group. Good to excellent responses were reported by 88, 40, 88, 56, and 70 percent of those with flatulence, regurgitation, epigastric discomfort, acidity/epigastric pain, and nausea, respectively. The comparative responses in the control group were 4, 20, 10, 25, and 17 percent, respectively.

Side effects
No side effects were observed.

Authors' comments
These observations prove the definite usefulness of Gasex tablets in the postoperative period to relieve symptoms associated with gaseous distension of the abdomen. Gasex is recommended for use until the patient assumes full normal dietary and working routine.

Reviewers' comments
The effect of opiates, given for pain, was noted, but no data were presented regarding other medications taken by the subjects. The dosage choice was not discussed in the paper nor substantiated by reference(s). It appears that the dosage form was "prepared in the juices and decoctions" of various additional plant species. It is unclear whether this reference to preparation is in regard to the procedure implemented in the study site prior to administration of the test agent to study subjects, or whether it is part of the description of the proprietary formulation. The selection of vitamin B complex tablets as placebo also was not discussed in the paper or substantiated by reference(s). As well, their specific composition was not revealed. The treatment length was adequate. (1, 4)

Geriforte®

First nine of a total thirty ingredients (for more information, see the Product Profile):

Chyavanprash concentrate
Cow-itch plant (*Mucuna pruriens* [L.] DC.) seed
Gotukola (*Centella asiatica* [L.] Urb.) leaves
Shatavari (*Asparagus racemosus* Willd.) root
Loosestrife (*Asparagus adscendens* Roxb.) root
Ashwagandha (*Withania somnifera* [L.] Dunal.) root
Arjuna (*Terminalia arjuna* [Roxb. ex. DC.] Wight & Arn.) bark
Elephant creeper (*Argyreia speciosa* [L. f.] Sweet) root
Licorice (*Glycyrrhiza glabra* L.) root

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Geriforte® is manufactured by The Himalaya Drug Company in India, and distributed in the United States by Himalaya USA. Each tablet contains 1.005 g of a proprietary herbal blend of thirty ingredients (see the product report for a full list of ingredients). The current recommended dose is one tablet twice a day (Himalaya USA, 2002). A prior formulation of Geriforte, label dated May 1999, also cited 12 mg vitamin C and 40 mg calcium. No details of the product used in the following trial were included in the trial report. Geriforte is also available under the name of GeriCare®.

GERIFORTE® SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Geriforte®	The Himalaya Drug Company, India/ Himalaya USA	Formula containing 29 herbal ingredients plus mineral pitch	2 tablets (unknown weight) 3 times daily	Menopausal symptoms	1	Undetermined (III-1)

SUMMARY OF REVIEWED CLINICAL STUDIES

Geriforte

Geriforte is described by the manufacturer as a "unique complex rejuvenative tonic with strong adaptogenic action" that "offers a broad range of health benefits and balances the body's organs and systems for increased mental alertness and greater fitness" (Geriforte label).

Menopausal Symptoms

The benefits of Geriforte were assessed in a small controlled study that included 25 women with postmenopausal depression and symptoms of headache, vague body ache, hot flashes, chest pain, palpitations, personality change, insomnia, loss of appetite, weight loss, and others. The study participants were given placebo for six weeks and then Geriforte (two tablets three times a day) for six weeks. They were evaluated every week during the 12-week period. Geriforte was effective in reducing symptoms of headache, hot flashes, insomnia, and improved self-confidence compared to placebo (Damle and Gore, 1983). However, the study was not well described and appeared to have significant methodological limitations. Thus, according to our reviewer, Dr. Tieraona Low Dog, any potential benefit for menopausal symptoms cannot be determined from this trial.

ADVERSE REACTIONS OR SIDE EFFECTS

No significant side effects were reported and no abnormalities were revealed by laboratory tests. Epigastric distress was reported in six patients (24 percent) in the initial phase of the study. The study report explained that this side effect disappeared with a reduction in dose, but did not give any further details such as how much the dose was reduced (Damle and Gore, 1983).

REFERENCES

Damle VB, Gore AG (1983). A controlled trial of Geriforte in post-menopausal depression. *Capsule* 3: 50.

Himalaya USA. GeriCare by Himalaya. <http://www.himalayausa.com>. Accessed November 11, 2002.

DETAILS ON GERIFORTE PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Geriforte®

Manufacturer	**The Himalaya Drug Company, India**
U.S. distributor	**Himalaya USA**
Formula Botanicals	**Chyavanprash concentrate; ashwagandha root** (*Withania somnifera* [L.] Dunal.); **asparagus root** (*Asparagus racemosus* Willd.); **gotukola leaves** (*Centella asiatica* [L.] Urb.); **licorice root** (*Glycyrrhiza glabra* L.); **haritaki fruit rind** (*Terminalia chebula* Retz.); **capers root bark** (*Capparis spinosa* L.), **wild chicory seed** (*Cichorium intybus* L.); **Malabar nut, whole** (*Adhatoda vasica* Nees.); **elephant creeper root** (*Argyreia speicosa* [L. f.] Sweet); **loosestrife root** (*Asparagus adscendens* Roxb.); **tree turmeric root** (*Berberis aristata* DC.); **teri pod seed** (*Caesalpinia digyna* Rottl.); **thistles, whole** (*Eclipta alba* [L.] Hassk.); **cow-itch plant seed** (*Mucuna pruriens* [L.] DC.); **nutmeg seed and mace** (*Myristica fragrans* Houtt.); **Indian long pepper fruit** (*Piper longum* L.); **saffron flower** (*Crocus sativus* L.); **black nightshade, whole** (*Solanum nigrum* L.); **arjuna bark** (*Terminalia arjuna* [Roxb. ex. DC.] Wight & Arn.); **bishop's weed/lovage mericap** (*Carum copticum* Benth. & Hook); **staff tree seed** (*Celastrus paniculatus* Wild.); **turmeric rhizome** (*Curcuma longa* L.); **cardamom fruit** (*Elettaria cardamomum* [L.] Maton.), **cloves, dried flower bud** (*Syzygium aromaticum* Merr. & L. M.

	Perry), **yarrow, aerial parts** (*Achillea millefolium* L.); **Negro coffee seed** (*Cassia occidentalis* L.), **tamarisk, whole** (*Tamarix gallica* L.); **mace aril** (*Myristica fragrans* Houtt.); **mineral pitch.**
Quantity	1.005 g
Processing	No information
Standardization	No information
Formulation	Tablet

Recommended dose: Take one tablet twice per day with meals.

DSHEA structure/function: Natural antistress and rejuvenative. Has strong adaptogenic action that helps cope with life's daily stress. Balances all of the body's organs and systems for increased mental alertness and greater physical fitness.

Other ingredients: Biotite ash, zinc oxide, ferric oxide, iron oxide, magnesium stearate, sodium carboxymethylcellulose, microcrystalline cellulose, crospovidone, aerosil.

Comments: Also sold as GeriCare®.

Source(s) of information: Product label.

Clinical Study: Geriforte®

Extract name	N/A
Manufacturer	The Himalaya Drug Company, India
Indication	**Menopausal symptoms**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Damle VB, Gore AG (1983). A controlled trial of Geriforte in post-menopausal depression. *Capsule* 3: 50.

Trial design
Parallel. Two-stage study. During Stage I, patients received placebo for six weeks, and in Stage II, patients received Geriforte for six weeks. Patients were then followed for an additional four to six weeks.

Study duration	3 months
Dose	2 tablets 3 times daily

Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	25
No. of subjects completed	25
Sex	Female
Age	35-59 years

Inclusion criteria

Patients with postmenopausal depression. Patients also presented with somatic symptoms, such as headache, vague body ache, hot flashes, chest pain, palpitations, personality change, insomnia, loss of appetite, weight loss, and others.

Exclusion criteria

Patients with hepatic, renal, or cardiac diseases.

End points

Patients were assessed every two weeks in Stage I and every week in Stage II. Patients were followed up for four to six weeks after the trial. Responses to therapy were graded as poor (less than 50 percent improvement), fair (50 to 75 percent improvement), good (75 to 90 percent improvement) and excellent (greater than 90 percent improvement).

Results

Response to Geriforte was mostly good or excellent (64 percent of patients), whereas the response to placebo was mostly poor (68 percent of patients). The symptoms that showed improvement were headache, hot flashes, and insomnia, among others. Six cases regained self-confidence. Six cases showed relapse after discontinuation of therapy. When these six were given repeat treatment with Geriforte, all of them responded again.

Side effects

No significant side effects. Epigastric distress was seen in six cases, but disappeared with reduction in dosage (further details were not given).

Authors' comments
As indicated by the present study, Geriforte could be an important drug in the management of postmenopausal depression.

Reviewer's comments
The trial methodology was described inadequately, and the study was small. Although the study population was described, the inclusion criteria were vague. (3, 1)

Iberogast™

Ingredients:
German chamomile (*Matricaria recutita* L.) flower
Clown's mustard (*Iberis amara* L.) plant
Angelica (*Angelica archangelica* L.) root and rhizome
Caraway (*Carum carvi* L.) fruit
Milk thistle (*Silybum marianum* [L.] Gaertn.) fruit
Lemon balm (*Melissa officinalis* L.) leaf
Celandine (*Chelidonium majus* L.) aerial part
Licorice (*Glycyrrhiza glabra* L.) root
Peppermint (*Menthae* × *piperita* L.) leaf

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Iberogast™ is named for the herb *Iberis amara* L. (commonly called bitter candytuft or clown's mustard plant), the principal ingredient in this formula containing a total of nine plant extracts. Iberogast, also known as STW 5, is manufactured in Germany by Steigerwald GmbH, and distributed in the United States by Enzymatic Therapy.

SUMMARY OF REVIEWED CLINICAL STUDIES

Iberogast has been tested in several trials for its ability to benefit dyspepsia. Symptoms of dyspepsia include belching, sour eructation, frequent or excessive passage of gas, abdominal fullness, vague abdominal pain, epigastric burning, nausea, and unsatisfactory evacuation. Three different subtypes of functional dyspepsia have been described, attributing the symptoms to ulcers, dysmotility, or some unspecified cause. Symptoms can be rated according to the gastrointestinal symptom (GIS) score, a sum of ten dyspepsia symptoms.

IBEROGAST™ SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Iberogast™	Steigerwald GmbH, Germany/ Enzymatic Therapy	Ethanolic extracts of nine botanicals	20 drops after meals	Dyspepsia (indigestion)	2	Trend (I-1, III-1)

Treatments for functional dyspepsia include prokinetic drugs that stimulate gastric motility (e.g., metoclopramide, domperidone, and cisapride) (Hardman et al., 1996).

Iberogast

Dyspepsia (Indigestion)

We reviewed two trials that compared Iberogast with either metoclopramide or cisapride in treatment for functional dyspepsia. A single-blind, drug comparison trial included 77 patients with functional dyspepsia given either Iberogast or metoclopramide (both 20 drops three times daily) after meals for up to two weeks. As a result, an almost parallel improvement in dyspepsia symptoms was observed in both groups. A statistically significant change compared to baseline was reached for symptoms (pressure/pain, nausea, belching, heartburn, stomach cramps, vomiting, fullness, and lack of appetite) between days three and seven (Nicolay, 1984). The trial did not score well in the quality rating because it was single-blind (the two liquids were different colors) and the randomization process was not adequately described.

Another trial, with excellent methodology, compared Iberogast (STW 5, 20 drops three times daily) to another similar research formula (with three fewer herbal ingredients than STW 5, called STW 5-II) and cisapride (10 mg three times daily). The one-month study used a double placebo to ensure double-blinding. Included were 137 participants with a clinical diagnosis of functional dyspepsia of the dysmotility type. As a result of treatment, the mean GIS scores decreased in all groups with no statistical difference between them. For those in all groups who were symptom free at the end of the trial, there was no difference in the relapse rate after six months (Rösch, Vinson, and Sassin, 2002). Our reviewers, Drs. Karriem Ali and Richard Aranda, rated this trial as demonstrating a trend toward efficacy. His reason for doing so is the absence of a placebo group.

Iberogast also demonstrated efficacy for functional dyspepsia in two placebo-controlled studies that we did not review, either because we did not obtain a copy or because we did not obtain an English translation (Buchert, 1994; Madisch et al., 2001). In the latter trial, 60 patients with functional dyspepsia were divided into three groups and

given either Iberogast (STW-5), STW 5S (the Iberogast formula minus one botanical ingredient), or placebo for four weeks. Compared to placebo, both extracts showed clinically significant improvement in GIS scores after two and four weeks (Madisch et al., 2001).

ADVERSE REACTIONS OR SIDE EFFECTS

No serious adverse effects were noted in the two trials we reviewed. In one trial, two of 61 patients taking Iberogast reported abdominal cramps, dizziness, and nausea that may have been associated with the medication (Rösch, Vinson, and Sassin, 2002). The formula has been available in Europe for 40 years and has been well tolerated during this time. A postmarketing surveillance study, with 2,267 dyspeptic patients who took Iberogast for one to four weeks, reported only one adverse event that was not related to treatment with Iberogast (Sassin and Buchert, 2000).

REFERENCES

Buchert D (1994). Wirksamkeit und Vertraglichkeit von Iberogast bei patienten mit gesicherter non ulcus dyspepsia. *Zeitschrift für Phytotherapie* 15: 45-46.

Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman-Gillman A (1996). *Goodman and Gillman's the Pharmacological Basis of Therapeutics,* Ninth Edition. New York: McGraw-Hill.

Madisch A, Melderis H, Mayr G, Sassin I, Hotz J (2001). Ein phytotherpeutikum und seine modifizierte rezeptur bei funktioneller dyspepsia. Ergebnisse einer doppelblinden plazebokontrollierten vergleichsstudie. [Commercially available herbal preparation and its modified dispense in patients with functional dyspepsia, results of a double-blind, placebo-controlled, randomized multicenter trial.] *Zeitschrift für Gastroenterologie* 39 (7): 511-517.

Nicolay K (1984). Functional gastroenteropathies in the therapeutic double blind trial of metoclopramide and the phytopharmaceutical agent Iberogast. *Gastro-Entero-Hepatologie* 2 (4): n.p.

Rösch W, Vinson B, Sassin I (2002). A randomized clinical trial comparing the efficacy of a herbal preparation STW 5 with the prokinetic drug

cisapride in patients with dysmotility type of functional dyspepsia. *Zeitschrift für Gastroenterologie* 40 (6): 401-408.

Sassin I, Buchert D (2000). Efficacy and tolerability of the herbal preparation Iberogast in the therapy of functional dyspepsia. *Phytomedicine* 7 (Suppl. II): 91-92.

DETAILS ON IBEROGAST PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Iberogast™

Manufacturer	**Steigerwald Arzneimittel GmbH, Germany**
U.S. distributor	**Enzymatic Therapy**
Formula botanicals	**Clown's mustard plant** (*Iberis amara* L.); **German chamomile flower** (*Matricaria recutita* L.); **angelica root and rhizome** (*Angelica archangelica* L.); **caraway fruit** (*Carum carvi* L.); **milk thistle fruit** (*Silybum marianum* [L.] Gaertn.); **lemon balm leaf** (*Melissa officinalis* L.); **celandine aerial part** (*Chelidonium majus* L.); **licorice root** (*Glycyrrhiza glabra* L.); **peppermint leaf** (*Menthae × piperita* L.)
Quantity	No information
Processing	Ethanolic extracts of the fresh plants
Standardization	No information
Formulation	Liquid

Recommended dose: Adults take 20 drops (1 ml) with a favorite drink (warm water is recommended) three times daily; children 12 and under take ten drops three times daily.

DSHEA structure/function: Dietary supplement for the entire digestive system. Provides synergistic advantages for the entire intestinal tract and digestive system.

Other ingredients: Water, alcohol (31%).

Source(s) of information: Product label; Iberogast product information page <http://www.enzy.com/>.

Clinical Study: Iberogast®

Extract name	STW 5
Manufacturer	Steigerwald Arzneimittel GmbH, Germany
Indication	**Dyspepsia** (indigestion)
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference

Nicolay K (1984). Functional gastroenteropathies in the therapeutic double-blind trial of metoclopramide and the phytopharmaceutical agent Iberogast. *Gastro-Entero-Hepatologie* 2 (4): n.p.

Trial design

Parallel. Trial was single-blind because the two medications differed in color. Patients were given either Iberogast or metoclopramide (20 drops three times daily after meals). Duration of treatment was planned for one to two weeks with discontinuation for cases with a complete lack of symptoms after one week.

Study duration	1-2 weeks
Dose	20 drops 3 times daily (after meals)
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Single-blind
Blinding adequate	No
Placebo	No
Drug comparison	Yes
Drug name	Metoclopramide
Site description	Multicenter
No. of subjects enrolled	94
No. of subjects completed	77
Sex	Male and female
Age	18-60 years

Inclusion criteria

Patients suffering from functional dyspepsia with at least three of the following symptoms: pressure or pain in the abdominal area, stomach cramps, fullness, eructation, nausea, vomiting, pyrosis, or lack of appetite.

Exclusion criteria
Patients suffering from organic diseases of the gastrointestinal tract, as well as patients who were simultaneously treated with H2 histamine receptor blockers, antacids, anticholinergics, psychotropic substances, antibiotics, or antirheumatic agents.

End points
Evaluation by doctors occurred at baseline and on days 3, 7, and 14 of treatment. Doctors evaluated patients with a questionnaire. Patients also took notes in a diary.

Results
A notable, almost parallel improvement of all symptoms was observed in both groups. Between days 3 and 7, statistical significance of almost all the parameters reached $p < 0.01$ compared to baseline. In treating the symptoms of fullness and lack of appetite, Iberogast seems to have a tendency to take effect faster than metoclopramide.

Side effects
Metoclopramide five cases; Iberogast two cases (tiredness after three days, none after seven and 14 days).

Author's comments
In the treatment of nonspecific gastrointestinal symptoms, Iberogast practically does not cause any side effects, and is an alternative of absolutely equal value to the standard substance metoclopramide. Special attention should be paid to the fact that an equal therapeutic effect is achieved without targeting the central nervous system.

Reviewers' comments
The exclusion of organic causes of disease/diagnosis was not well defined. The lack of a placebo arm is a flaw in the study of a nonspecific functional gastrointestinal disorder. The sample size may have been appropriate; but no power calculation was presented. Although the trial length was adequate, the dosage choice was not discussed in the paper nor was it substantiated by reference(s). (Translation reviewed) (1, 4)

Clinical Study: Iberogast®

Extract name	STW 5
Manufacturer	Steigerwald Arzneimittel GmbH, Germany
Indication	**Dyspepsia** (indigestion)
Level of evidence	**I**
Therapeutic benefit	**Trend**

Bibliographic reference
Rösch W, Vinson B, Sassin I (2002) A randomized clinical trial comparing the efficacy of a herbal preparation of STW 5 with the prokinetic drug cisapride in patients with dysmotility type of functional dyspepsia. *Zeitschrift für Gastroenterologie* 40 (6): 401-408.

Trial design
Parallel. Pretrial washout period of one week. Patients received one of three treatments three times daily: 20 drops STW 5 (Iberogast) plus one tablet placebo; 20 drops STW 5-II (a research formula missing three herbal ingredients present in STW 5) plus one tablet placebo; 20 drops placebo plus one (10 mg) tablet cisapride.

Study duration	1 month
Dose	20 drops 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	Yes
Drug name	Cisapride, STW 5-II
Site description	Multicenter
No. of subjects enrolled	186
No. of subjects completed	137
Sex	Male and female
Age	Mean: 45 years

Inclusion criteria
Outpatients ages 21 to 70 years; clinical diagnosis of functional dyspepsia of the dysmotility type, relapsing or with symptoms for more than six months; two or more of the symptoms of the Gastrointestinal Symptom Score (GIS) had to be classified as moderate or more (except the symptoms “acidic eructation/heartburn” and “retrosternal pain”); echosonography of upper abdomen and endoscopy of the upper gastrointestinal tract did not show relevant disorders; written and informed consent of the patient.

Exclusion criteria
Known organic disease that could have explained the dyspeptic symptoms: reflux esophagitis, gastrointestinal tumors or findings suspicious of tumors,

gastric or duodenal ulcer, acute erosive gastritis/duodenitis with more than five erosions, Whipple's disease, diverticulitis, polyposis coli, ulcerative colitis, Crohn's disease, diabetic or infectious enteropathy, food allergies, malabsorption, maldigestion; bulbous scars as signs of chronic ulcer; predominance of symptoms of an irritable bowel disease; relevant defecation frequency anomalies; mesenteric vascular disorders; cholecystitis, cholangitis; pancreas tumors, pancreatitis; thyroid disorders; relevant hepatic disease; diseases of the urogenital system; history of abdominal surgery (with exception of appendectomy, hysterectomy, or cholecystectomy, when at least six months before study start, without complications and without connection to dyspeptic symptoms); history of gastrointestinal ulcers; abuse of laxatives, regular intake of nonsteroidal anti-inflammatory drugs; concomitant medication influencing the gastrointestinal tract.

End points
Patients were examined before the pretrial washout, at baseline (day 0), and on days 14 and 28, as well as six months later. The primary efficacy measure was the difference of the GIS sum score between the start and the end of therapy for cisapride compared to STW 5 and STW 5-II. Secondary endpoints included efficacy and tolerability assessments, recurrences and safety parameters.

Results
The mean values of the GIS decreased considerably between day 0 and day 28 for all study groups. The decreases from baseline values for STW 5, STW 5-II, and cisapride were 84 percent, 81 percent, and 75 percent, respectively. Both investigators and patients evaluated the efficacy of three treatments (STW 5, STW 5-II, and cisapride) favorably: investigators rated the treatments as good or excellent for 77 percent, 78 percent, and 62 percent of the patients, respectively. A majority of patients in the three groups also rated the treatments as good or excellent (70 percent, 76 percent, and 58 percent, respectively). No difference in relapse rate for the three groups was observed at the six-month follow-up.

Side effects
No serious adverse effects were noted. Three adverse events were classified as probably or possibly caused by the study medication: two of them were in the STW 5 group (abdominal cramps; dizziness and nausea); one was in the cisapride group (diarrhea).

Authors' comments
The equal efficacy of STW 5 and cisapride in this study indicates that the well-tolerated herbal preparation STW 5 is a potent therapeutical option for the treatment of functional dyspepsia of dysmotility type.

Reviewers' comments

This is an excellent study except that it lacks a placebo arm. Functional dyspepsia typically shows a significant (~20 to 30 percent) placebo response. The dosage is appropriate to the product literature, and the treatment length is appropriate to the disorder. (5, 6)

Padma®

Ingredients:

Bengal quince [*Aegle marmelos* (L.) Corrêa] fruit
Allspice [*Pimenta officinalis* Lindl., syn. *P. dioica* (L.) Merr.] fruit
Colombine (*Aquilegia vulgaris* L.) aerial part
Marigold/calendula (*Calendula officinalis* L.) flower
Cardamom [*Elettaria cardamomum* (L.) Maton] fruit
Clove [*Syzygium aromaticum* (L.) Merr. & L.M. Perry] flower
Costus (Indian) [*Saussurea lappa* (Decne.) C.B. Clarke, syn. *Sassurea costus* (Falc.) Lipsch.] root
Ginger lily (*Hedychium spicatum* Sm.) rhizome
Lettuce (*Lactuca sativa* L.) leaf
Iceland moss (*Cetraria islandica* L. Ach.)
Licorice (*Glycyrrhiza glabra* L.) root
Neem/margosa (*Azadirachta indica* A. Juss., syn: *Melia azadirachta* L.) fruit
Myrobalan (Tropical almond) (*Terminalia chebula* Retz.) fruit
Ribwort/English plantain (*Plantago lanceolata* L.) aerial part
Knotgrass (*Polygonum aviculare* L.) aerial part
Golden cinquefoil (*Potentilla aurea* L.) aerial part
Red sandalwood (*Pterocarpus santalinus* L. f.) heart wood
Country mallow/heartleaved sida (*Sida cordifolia* L.) aerial part
Valerian (*Valeriana officinalis* L.) root
Gypsum/calcium sulfate
Dextro-camphora/natural camphor

Note: This is the ingredient list for Padma® BASIC. Full scientific names have been added where they were missing on the product label.

PADMA® SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Padma® 28 (EU), Padma® BASIC (US)	Padma Inc., Switzerland/ EcoNugenics Inc.	Proprietary blend of 19-20 herbs plus camphor and calcium sulfare	1-2 (340-403 mg) capsules/tablets 2-3 times daily	Peripheral arterial occlusion	5	Yes (I-2, II-2) Trend (II-1)
				Angina pectoris	1	Trend (III-1)
				Multiple sclerosis	1	Trend (III-1)
				Respiratory tract infection	1	Undetermined (III-1)

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Padma® 28 (recipe No. 28 of the Padma recipe series) is an herbal remedy consisting of 22 ingredients prepared according to Tibetan medicine principals. The recipe was brought to St. Petersberg, Russia in the middle of the nineteenth century by a physician/monk, Sultim Badma. The original formula has been altered with its entry into Western Europe, in that some of the ingredient plants from Tibet and India have been substituted with plants from Europe. The European version has been tested in numerous clinical studies and is registered as a drug in Switzerland. It is indicated for symptoms of poor circulation, including tingling, formication (feeling of insects crawling on the skin), feeling of heaviness, and tension in the arms and legs, as well as numbness of the hands and feet (Saller and Kristof, 1997).

The formula available in the United States is Padma® BASIC, which is Padma 28 minus one ingredient. The missing ingredient is aconite tuber (*Aconitum napellus* L.), which is considered an "unsafe herb" in the United States, subject to import restriction (CADHS, 1996). Thus, Padma BASIC is a blend of 19 herbs plus camphor and calcium sulfate. Padma BASIC is manufactured in Switzerland by Padma AG, and distributed in the United States by EcoNugenics Inc.

Although Padma 28 and Padma BASIC are not equivalent, their ingredients are very similar, and the products are both made by the same manufacturer. Thus, we decided to include Padma BASIC in this listing. Another product for sale in the United States that is also similar to Padma 28 is Adaptrin, manufactured by Pacific BioLogic. However, we determined that the ingredients in that formula are sufficiently different from Padma 28 and so have decided not to include it here.

Obtaining sufficient information to evaluate the similarity of Padma 28, Padma BASIC, and Adaptrin products was not a trivial task. The ingredient lists often quoted either common names or Latin names, requiring some research on our part. Some common names are distinctive, but others are ambiguous and may refer to more than one plant. Although we had obtained the Latin names of all botanical ingredients in Padma 28 from the clinical literature (Sallon et al., 1998), the Latin names of all ingredients were not included on the Padma Basic label. We therefore had to correlate common names

with Latin names to compare the two ingredient lists. In addition, since the formulas are listed as proprietary blends without disclosing the amount of each ingredient, there is no way for us to know whether the ingredients in Padma BASIC and Padma 28 are present in the same amounts.

SUMMARY OF REVIEWED CLINICAL STUDIES

Experimental studies with Padma 28 indicate that it may have antioxidant and anti-inflammatory properties (Saller and Kristof, 1997). We reviewed two trials that included adults with multiple sclerosis or children with recurrent respiratory tract infections. However, the majority of the studies (six) that we reviewed focused on the ability of Padma 28 to treat symptoms of circulatory disorders.

Intermittent claudication is a symptom that occurs when the blood supply is adequate to meet the needs of the exercising muscle. This occurs most commonly due to occlusive arterial disease, also known as peripheral arterial disease, or more commonly known as peripheral arterial occlusion (PAO). PAO is a condition in which narrowing of the arteries, generally caused by atherosclerosis, limits the blood supply to the legs. Early stages of the disease are without symptoms, but later stages are associated with leg pain and muscle cramps upon walking, and ultimately, ischemic ulceration, gangrene, and tissue loss. The stages have been classified in a system according to Fontaine: Stage I represents those who are asymptomatic with isolated arterial stenosis of the lower limb; Stage II is mild to moderately severe leg pain and muscle cramps upon walking; Stage III are those with pain while resting; and Stage IV are those with ulcerations and gangrene (Dicter et al., 2002). The Padma studies included patients with Stage II of the disease. After the subject walks a "pain-free distance," cramplike ischemic pains begin. These pains eventually force the subject to stop walking, determining the "maximal walking distance." Upon rest, the legs recover from deficiencies of blood and oxygen, the pain disappears, and the subject can again walk a certain distance (Schrader, 1985).

Padma 28

Peripheral Arterial Occlusion

Five good-quality, placebo-controlled trials explored the use of Padma 28 in treatment of peripheral arterial disease or peripheral arterial occlusion. A large trial included 93 patients with a diagnosis of PAO of the lower extremities (Fontaine Stage II), given either 760 mg Padma twice daily or placebo for four months. Patients receiving Padma 28 had an increase in maximum walking distance from 95.7 to 205 yards (87.5 to 187.7 m), whereas the placebo group only had an insignificant increase in maximum walking distance. The treatment group also had significant reductions in cholesterol, triglycerides, and total lipid levels, as well as platelet aggregation, compared to baseline (Smulski and Wojcicki, 1995).

Another study of 100 subjects with PAO, Fontaine Stage II, were given either 760 mg Padma 28 twice daily or placebo for four months. With treatment, maximal walking distance was nearly doubled in the treatment group, whereas it did not change in the placebo group. As with the trial mentioned earlier, there were significant reductions in cholesterol, triglycerides, and total lipid levels, as well as platelet aggregation, in the treatment group. These changes were not observed in the placebo group (Samochowiec et al., 1987).

Two smaller trials also reported significant increases in maximal walking distance after four months of treatment, with no change in the placebo groups. In the first trial, including 43 patients with PAO Stage II according to Fontaine, pain-free walking distance also improved compared to the placebo group. However, this difference was not significant. Blood pressure differences between the arm and ankle decreased in the Padma group and increased in the placebo group (Schrader, 1985). In the second trial, with 36 subjects with PAO (Fontaine stage not given), there was a significant increase in pain-free walking distance compared to baseline and placebo. No difference was observed in the blood pressure ratio between the arm and leg (Drabaek et al., 1993).

Another placebo-controlled trial of 59 subjects with PAO (Fontaine stage not given) reported significant improvements in ankle blood pressure and recovery following exercise after six months of treatment compared to baseline levels and the placebo group. This

improvement correlated with an increase in pain-free walking distance reported by the patients. No such improvement was observed in the placebo group (Sallon et al., 1998).

Angina Pectoris

One poor-quality study explored the ability of Padma 28 to reduce the number of angina attacks in those with chronic angina, averaging seven or more attacks per week. The study included 50 subjects who were given placebo before and after two weeks of treatment so that each patient served as their own control. As a result, the number of attacks during the treatment decreased by 69 percent compared to the initial two-week control period. Similarly, the demand for nitroglycerin tablets decreased during the treatment period. With treatment, patients were able to exercise longer before developing anginal pain, and the heart rate at peak exercise was reduced. In addition, the threshold for platelet aggregation was increased, and total lipids were significantly reduced (Wojcicki and Samochowiec, 1986). Our reviewer, Dr. Mary Hardy, reported that the strength of the evidence was hard to judge since the trial methods were poorly described in the available translation, and the data were not presented in detail.

Multiple Sclerosis

An open trial with 100 subjects examined the ability of Padma 28 to improve symptoms of multiple sclerosis. For one year, the Padma group was given two tablets three times daily. The control group was treated symptomatically with drugs (not named) to reduce pain, spasticity, and cramps. The authors reported a positive effect in 44 percent of subjects given Padma, with improvement in their general condition, an increase in muscle strength, and a decrease or disappearance of disorders affecting sphincters. In the control group, none felt better, and 40 percent showed a deterioration of symptoms (Korwin-Piotrowska et al.,1992). However, our reviewer determined that the trial methodology was very poor, and it was therefore difficult to evaluate the strength of this study.

Respiratory Tract Infection

A controlled study tested the ability of 19 children, ages two to four, with recurrent infections of the respiratory tract, to improve their capacity to resist infection. Treatment with one tablet Padma 28 three times daily for one month improved spontaneous bactericidal activity in blood samples taken from the children. No such changes were seen in the adults who served as controls (Jankowski et al., 1991). Our reviewer commented that the ex vivo intermediate outcome (bactericidal activity in blood) was not clearly linked to the disease outcome (recurrent infections of the respiratory tract). Thus, the trial was rated as having undetermined efficacy.

ADVERSE REACTIONS OR SIDE EFFECTS

The trials reviewed earlier did not report any major side effects. Minor side effects, such as gastrointestinal complaints and fatigue, were similar in the treatment and placebo groups.

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Smulski, HS and Wojcicki J (1995). Placebo-controlled, double-blind trial to determine the efficacy of the Tibetan plant preparation Padma 28 for intermittent claudication. *Alternative Therapies* 1 (3): 44-49.

Wojcicki J, Samochowiec L (1986). Controlled double-blind study of Padma-28 in angina pectoris. *Herba Polonica* 32 (2): 107-114.

DETAILS ON PADMA PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Padma® BASIC

Manufacturer	**Padma Inc., Switzerland**
U.S. distributor	**EcoNugenics Inc.**
Formula Botanicals	**Iceland moss** (*Cetraria islandica* L. Ach.); **costus root; margosa fruit** (*Azadirachta indica* A. Juss.); **cardamom fruit; red sandalwood heart wood; tropical almond fruit; allspice fruit; Bengal quince fruit** (*Aegle marmelos* [L.] Corrêa); **calcium sulfate; columbine aerial part** (*Aquilegia vulgaris* L.); **English plantain aerial part; licorice root; knotgrass aerial part** (*Polygonum aviculare* L.); **golden cinquefoil aerial part** (*Potentilla aurea* L.); **clove flower; gingerlily rhizome** (*Hedychium spicatum* Sm.); **heartleaved sida aerial part** (*Sida cordifolia* L.); **valerian root, lettuce leaf** (*Lactuca sativa* L.); **calendula flower; natural camphor**
Quantity	402 mg
Processing	No information
Standardization	No information
Formulation	Tablet

Recommended dose: Take two tablets two or three times each day with a full glass of water, preferably on an empty stomach, at least 30 minutes before or approximately two hours after a meal. Maximum dose, two tablets three times daily. It is recommended that the tablets be chewed before swallowing with plenty of water.

DSHEA structure/function: Promotes healthy circulation. Supports the immune system. Supports with antioxidant activity.

Cautions: Check with your health care practitioner before using if you are pregnant or nursing, taking medication, or if you have a medical condition (including allergies or food sensitivities).

Other ingredients: Sorbitol, silicon dioxide.

Comments: This formula plus *Aconitum napellus* L. is sold in Europe as Padma® 28.

Source(s) of information: Product package (© 1999 PADMA Health Products, Inc.); product leaflet (© 1999 PADMA Health Products, Inc.).

Clinical Study: Padma® 28

Extract name	N/A
Manufacturer	Padma Inc., Switzerland
Indication	**Peripheral arterial occlusion**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Smulski, HS, Wojcicki J (1995). Placebo-controlled, double-blind trial to determine the efficacy of the Tibetan plant preparation Padma 28 for intermittent claudication. *Alternative Therapies* 1 (3): 44-49.

Trial design
Parallel.

Study duration	4 months
Dose	2 (380 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	100
No. of subjects completed	93

Sex	Male and female
Age	35-65 years

Inclusion criteria
Inclusion criteria included: preestablished documented diagnosis of peripheral arterial occlusive (PAO) disease of the lower extremities, Fontaine Stage II, with intermittent claudication; positive anamnesis; positive clinical status with missing or deficient pulse on the back of the foot; maximum walking distance not exceeding 250 m; and minimum six-month duration of disease.

Exclusion criteria
Patients having PAO other than Fontaine Stage II; having a concomitant severe disease or a disease that might impede walking ability such as venous insufficiency, anemia, myocardial infarction within the last 8 months, cardiac insufficiency, severe arthralgia; and deficient steady state of PAO Stage II or manifestations of Stages III or IV. Patients were further excluded from the study if they changed their lifestyle (e.g., starting a walking program); changed medication therapy for concomitant disease; were intolerant to the test medication; had poor compliance; or did not show up to follow-up test sessions.

End points
The main target parameter was maximum walking distance and the secondary parameter was patients' subjective evaluation at the end of the 16-week treatment period. As part of a screening for potential efficacy mechanisms, upper arm blood pressure, blood fats, and platelet aggregation were evaluated. Patients were examined at baseline and 4, 8 ,12, and 16 weeks later.

Results
Patients receiving Padma 28 exhibited on standardized ergometry an increase of maximum walking distance from 87.5 to 187.7 m. The patients receiving placebo showed an insignificant increase of 12.5 m. The increase in walking distance of the group receiving Padma 28 compared with placebo was highly significant after 12 and 16 weeks ($p < 0.01$ and $p < 0.001$, respectively). Subjective evaluation by patients revealed that 82 percent of the Padma 28 group thought that the efficacy was good or very good, compared with only 16 percent of the placebo group. The Padma 28 group had significant reductions in cholesterol, triglyceride, and total lipid levels, as well as platelet aggregation, compared to baseline. No significant change was observed in the placebo group.

Side effects
None observed.

Authors' comments
Padma 28 shows clinically relevant effectiveness in peripheral arterial occlu-

sive disease of the lower extremities, Fontaine II, with intermittent claudication.

Reviewer's comments
The following positive outcomes were seen in the treatment group: an increase in maximum walking distance; and the patients' subjective evaluation favored the treatment. The randomization and double-blinding are well described and adequate, all withdrawals and drop-outs are accounted for, the data are well presented, and the statistical methods were well described and applied. (5, 5)

Clinical Study: Padma® 28

Extract name	N/A
Manufacturer	Padma Inc., Switzerland
Indication	**Peripheral arterial occlusion**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Samochowiec L, Wojcicki J, Kosmider K, Dadej R, Smulski H (1987). Clinical test of the effectiveness of Padma 28 in the treatment of patients with chronic arterial occlusion. *Herba Polonica* 33 (1): 29-41.

Trial design
Parallel. Two-week pretrial run-in period without treatment.

Study duration	4 months
Dose	2 (380 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	100
No. of subjects completed	100

Sex	Male and female
Age	Not given

Inclusion criteria
Patients diagnosed with peripheral arterial occlusion, Stage II according to Fontaine, having maximal walking distance on ergometer of less than 150 m, and having had the disease for a minimum of eight months.

Exclusion criteria
Patients having peripheral arterial occlusion other than Fontaine Stage II; concurrent diseases, such as venous disorders, anemia, myocardial infarction within eight months, uncontrollable hypertension, and significant kidney or liver insufficiency.

End points
Patients were examined at inclusion, at the beginning of the treatment period, and after 4, 8, 12, and 16 weeks. An anamnesis, treadmill ergometry, and measurement of upper-arm blood pressure were done every four weeks and after 16 weeks of treatment. Blood serum laboratory tests and hematological tests were conducted before and after treatment.

Results
Patients receiving Padma 28 registered an increase in maximal walking distance of 98 percent ($p < 0.001$). No significant change was observed in the placebo group, and the difference in maximal walking distance between the two groups was significant ($p < 0.001$). The biochemical tests showed that 16 weeks of treatment with Padma 28 led to significant reductions in levels of cholesterol, triglycerides, total lipids, and beta lipoproteins. In the placebo group, beta lipoprotein levels increased significantly. Padma 28 inhibited the thrombocyte aggregation, reducing the tendency of thrombocytes to form plaque deposit on the walls of the blood vessels. In the placebo group these variables remained unchanged.

Side effects
No negative effects were observed.

Authors' comments
The fundamental treatment of chronic peripheral arterial occlusive disease is connected with the regulation of lipid metabolism. Padma 28 represents an effective new therapeutic method of treating peripheral arterial occlusive (PAO) disease.

Reviewer's comments
The following positive outcomes were also reported in this group: a decrease in both systolic and diastolic blood pressure; an increase in walking distance; a decrease in triglycerides, total lipids, and beta lipoproteins; and an increased threshold to adenosine diphosphate (ADP)-induced aggrega-

tion. The blinding in this study was well described, but the randomization was not. No adverse events were reported in the treatment group. The evaluation of the degree of detail of the data and the adequacy of the statistical methods was difficult because the tables were missing in the translation reviewed. (Translation reviewed) (3, 4)

Clinical Study: Padma® 28

Extract name	N/A
Manufacturer	Padma Inc., Switzerland
Indication	**Peripheral arterial occlusion**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference
Schrader R (1985). Effectiveness of PADMA 28 for intermittent claudication in chronic peripheral arterial occlusion: A controlled, double-blind study. Thesis. (Shortened version published in Schrader R [1985] *Swiss Weekly Medical Review* 115: 752-756.)

Trial design
Parallel. Trial was preceded by a two-week washout phase.

Study duration	4 months
Dose	2 capsules 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Multicenter
No. of subjects enrolled	53
No. of subjects completed	43
Sex	Male and female
Age	Mean: 69 years

Inclusion criteria
Patients older than 50 years of age diagnosed with atherosclerotic periph-

eral arterial occlusion (PAO) in Stage II according to Fontaine, with an initial walking distance of 250 meters, duration of anamnesis of more than 8 months, and an anamnestic steady state.

Exclusion criteria
Patients with concomitant vasoactive therapy; serious diseases, such as cardiac infarct within the last eight months, cardiac insufficiency, or walking disorder other than claudication; or a wide variance in walking distance or stability of the disease. Subjects were also terminated from the study for the following reasons: strong adverse reaction to the test substance; deterioration of PAO with development of more advanced stages (III or IV); concurrent serious diseases; changes in concomitant medication (e.g., therapy for cardiac insufficiency); change in lifestyle (e.g., beginning walking training); or lack of compliance with study protocol.

End points
Physical examinations were performed at inclusion, at the beginning of treatment, and after 4, 8, 12, and 16 weeks. Efficacy was assessed by anamnesis, treadmill ergometry, measurements of blood pressure in upper arm and ankle arteries, and subjective analysis of treatment by the physician and the patient.

Results
Maximum walking distance significantly increased in the Padma 28 group after 16 weeks of treatment ($p < 0.001$). No statistical improvement was observed in the placebo group, and the difference between the two groups was significant ($p = 0.03$). Pain-free walking distance increased in the Padma 28 group by 66 meters ($p = 0.002$) and by 30 meters ($p < 0.01$) in the placebo group. However, the difference between the two groups was not significant ($p = 0.06$). Pressure differences between arm and ankle blood pressure decreased in the Padma 28 group by 16 mm Hg at rest ($p = 0.03$) and 11 mm Hg after effort. Pressure differences increased by 4 mmHg in the placebo group.

Side effects
Eight patients in each group had minor side effects.

Author's comments
Padma 28 caused an increase in pain-free and maximal walking distances of about 100 percent after four months in Stage II PAO. The positive results provide a basis for regarding Padma 28 as an effective treatment for intermittent claudication.

Reviewer's comments
This trial was fairly well designed and well conducted. Positive outcomes were seen in the average maximal walking distance (clinically relevant),

pain-free walking distance, decrease in the inner arm and ankle pressure difference, and a preference by subjective measure for the verum. However, the randomization process was not adequately described. Some tables were missing from the translation that was reviewed, making it difficult to determine whether the data was present in sufficient detail to permit alternative analysis. (3, 5)

Clinical Study: Padma® 28

Extract name	N/A
Manufacturer	Padma Inc., Switzerland
Indication	**Peripheral arterial occlusion**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Drabaek H, Mehlsen J, Himmelstrup H, Winther K (1993). A botanical compound, Padma 28, increases walking in stable intermittent claudication. *The Journal of Vascular Diseases* 44 (11): 863-867. (The biochemical aspects of this trial were published in Winther K, Kharazmi A, Himmelstrup H, Drabaek H, Mehlsen J [1994]. PADMA-28, a botanical compound, decreases the oxidative burst response of monocytes and improves fibrinolysis in patients with stable intermittent claudication. *Fibrinolysis* 8 [2]: 47-49.)

Trial design
Parallel.

Study duration	4 months
Dose	2 (340 mg) tablets twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	36
No. of subjects completed	36
Sex	Male and female
Age	44-81 years

Inclusion criteria
Patients with stable peripheral arterial insufficiency in the lower extremities were included if they had a typical intermittent claudication history, clinical steady state for more than six months, a maximal walking distance between 50 and 300 meters, and a ratio lower than 0.85 between systolic blood pressure at the ankle with symptoms and the upper limb. Patients were not allowed to make lifestyle (e.g., diet or exercise) or medication changes during the study.

Exclusion criteria
Patients with symptoms of chronic lung disease, diabetes mellitus, osteoarthrosis in the lower extremities, or other diseases limiting the walking distance.

End points
Patients were assessed at baseline and at each month during the study. Measurements were made of systolic blood pressure at the ankle and the first toe, systemic blood pressure on both upper limbs, walking distance (both pain-free and maximum), and ankle pressure index (ankle systolic pressure/arm systolic pressure). Blood for evaluation of fibrinolytic activity, platelet aggregation, and monocyte oxidative burst reaction was taken before inclusion and after four months of therapy.

Results
After four months of taking Padma 28, patients attained a significant increase in pain-free walking distance (from 52 to 86 meters, $p < 0.05$) and in maximal walking distance (from 115 to 227 meters, $p < 0.05$). The group receiving placebo treatments did not show any significant changes in either parameter. There was no significant change to the ankle pressure index for either group. During treatment with Padma 28, the oxidative burst response of monocytes after stimulation with zymozan decreased, fibrinolytic activity increased, as shown by a shortening of the euglobulin clot lysis time by more than 40 percent, and the level of plasminogen activator inhibitor Type I fell ($p < 0.05$). Again, no such change was observed in the placebo group.

Side effects
None mentioned.

Authors' comments
Treatment with Padma 28 over a period of four months significantly increased the walking distance in patients with stable intermittent claudication of long duration. Whether the augmentation of fibrinolysis and decrease in oxidative burst by monocytes was a direct effect of Padma 28 or an indirect effect of the improved walking capacity is not clear.

Reviewer's comments
The following positive outcomes were seen: increase in pain-free walking distance; increase in maximum walking distance; and no change in ankle pressure index. The blinding, but not the randomization, is adequately described. The small patient population limits the interpretation of this study. (3, 4)

Clinical Study: Padma® 28

Extract name	N/A
Manufacturer	Padma Inc., Switzerland
Indication	**Peripheral arterial occlusion**
Level of evidence	**I**
Therapeutic benefit	**Yes**

Bibliographic reference
Sallon S, Beer G, Rosenfeld J, Anner H, Volcoff D, Ginsberg G, Paltiel O, Berlatzky Y (1998). The efficacy of Padma 28, a herbal preparation, in the treatment of intermittent claudication: A controlled double-blind pilot study with objective assessment of chronic occlusive arterial disease patients. *Journal of Vascular Investigation* 4 (3): 129-136.

Trial design
Parallel.

Study duration	6 months
Dose	2 (403 mg) capsules twice daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Outpatient clinic
No. of subjects enrolled	72
No. of subjects completed	59
Sex	Male and female
Age	Mean: 73 years

Inclusion criteria
Outpatients with peripheral arterial occlusive disease (intermittent claudication) according to the following criteria: abnormal wave-form recordings, a preexercise ankle/arm pressure ratio of 0.85 or less, a postexercise drop in the ankle/arm pressure ratio of 15 percent or more, and a depressed systolic ankle pressure during three minutes after exercise.

Exclusion criteria
Exclusion criteria were lower extremity rest pain, ulceration or need for revascularization, previous peripheral arterial surgery, use of the anticoagulant warfarin, active peptic ulcer disease, serious liver or renal disease, mental disease, a significant or serious cardiac condition, carcinoma, and other life-threatening conditions.

End points
Effectiveness of treatment was evaluated by measuring resting ankle/brachial pressure indices, treadmill exercises tests with postexercise ankle pressure measures, hemodynamic tests, self-assessment by patients of perceived changes in walking ability, as well as various parameters of well-being recorded in a questionnaire. Questionnaires were completed at outpatient visits after the first, third, and sixth month. Physical examinations were conducted at the beginning and end of the study.

Results
Padma 28 patients displayed a significant mean improvement of 12.5 percent ($p = .031$) in exercise-induced drop of ankle blood pressure and 0.8 min ($p = .076$) in pressure recovery time compared to pretreatment values. An improvement in pressure drops by more than 15 percent, compared to a deterioration or no change, occurred in 48 percent of Padma 28 patients compared to 22 percent of controls. Calculation of the "ischemic window," a quantitative expression of postexercise hyperemia, showed a significant reduction of 54 percent following treatment with Padma 28 compared to 18.8 percent in controls. Self assessment by patients revealed that perceived improvement in pain-free walking ability in the Padma 28 group correlated significantly with improvement in exercise-induced drop of ankle pressure.

Side effects
Side effects included gastrointestinal complaints and tiredness, similar to those in the placebo group.

Authors' comments
The current pilot study is the first to demonstrate that, following the stress of exercise, changes in ankle systolic pressure and its recovery time are positively affected by Padma 28.

Reviewer's comments
The following positive outcomes were seen in the treatment group: less of a drop in exercise induced ankle/arterial pressure; a decrease in amount of recovery time; and self assessment by patients favored Padma 28. This was a well-conducted and well-described study with an appropriate sample size. The randomization and blinding were also described adequately. (5, 6)

Clinical Study: Padma® 28

Extract name	N/A
Manufacturer	Padma Inc., Switzerland
Indication	**Angina pectoris**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Wojcicki J, Samochowiec L (1986). Controlled double-blind study of Padma-28 in angina pectoris. *Herba Polonica* 32 (2): 107-114.

Trial design
Crossover. Subjects had a two-week pretrial period with placebo followed by two weeks with Padma 28, and then two subsequent weeks with placebo.

Study duration	2 weeks
Dose	2 (380 mg) capsules twice daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Hospital inpatient clinic
No. of subjects enrolled	50
No. of subjects completed	50
Sex	Male and female
Age	40-69 years (mean: 51.2)

Inclusion criteria
Patients with chronic angina (at least six months) that is relatively stable in

duration and severity, which family doctors have been unable to control. Angina attacks averaging seven or more per week.

Exclusion criteria
Patients who were hypertensive, with clinical or radiologic evidence of cardiac enlargement or failure or acute myocardial infarction within the past six months.

End points
Patients were examined at the beginning and at the end of the placebo pretrial period, after two weeks of Padma 28 administration, and again after the two subsequent weeks on placebo. Variables included the clinical response to therapy, exercise tolerance testing, platelet aggregation, and blood lipid levels. Patients kept a record of their daily consumption of nitroglycerin tablets as well as the number of daily angina attacks.

Results
The mean number of anginal attacks was reduced from 37.5 in the two weeks before treatment to 11.5 (by 69 percent) after two weeks of Padma administration ($p < 0.001$), and it was increased to 28.7 during the following two weeks of placebo application. At the same time, the mean number of nitroglycerin tablets decreased from 27.7 before treatment to 7.9 in the two weeks of Padma administration ($p < 0.001$). Patients were able to exercise longer before developing anginal pain after taking Padma. At peak exercise, heart rate was lower during Padma administration than during placebo. The threshold of platelet aggregation was increased by Padma ($p < 0.001$). Total lipids and triglycerides were slightly but significantly reduced after two weeks of Padma administration ($p < 0.05$ and $p < 0.01$, respectively).

Side effects
No side effects were observed.

Authors' comments
Padma 28 can be effective in a considerable percentage of patients with angina. This is probably due to the reduction of platelet aggregation, and may be due to the decrease of myocardial oxygen consumption.

Reviewer's comments
This was a very short study in which patients served as their own control. The report is poorly written, however, and it is very difficult to tell whether this is a case series or a strange kind of crossover trial. The study was double-blinded adequately, but it was not randomized. The sample size was also small, and the data were not described in sufficient detail. (Translation reviewed) (3, 4)

Clinical Study: Padma® 28

Extract name	N/A
Manufacturer	Padma Inc., Switzerland
Indication	**Multiple sclerosis**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Korwin-Piotrowska T, Nocon D, Stankowska-Chomicz A, Starkiewicz A, Wojcicki J, Samochowiec L (1992). Experience of Padma 28 in multiple sclerosis. *Phytotherapy Research* 6 (3): 133-136.

Trial design
Parallel. The control group was treated only symptomatically, receiving drugs to reduce pain, spasticity, and cramps, and to inhibit detrusor contractions.

Study duration	1 year
Dose	2 tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Outpatients clinic
No. of subjects enrolled	100
No. of subjects completed	100
Sex	Male and female
Age	26-60 years

Inclusion criteria
Patients suffering from progressive (and proceeding with attacks) multiple sclerosis.

Exclusion criteria
None mentioned.

End points
The neurological state and visual and auditory evoked potentials were studied prior to the study and during the course of treatment. To evaluate the effi-

cacy of the medication, the following were assessed according to a numerical scale: the number of attacks, the dynamic with which the symptoms regressed after a new attack, the delay in the slowly intensifying course of multiple sclerosis, as well as the diminution in intensity of certain neurological symptoms.

Results
A positive effect of Padma 28 was observed in 44 percent of patients with improvement of their general condition, increase in muscle strength, and a decrease or disappearance of disorders affecting sphincters. In 41 percent of patients with initially abnormal tracing of visual evoked potentials, an improvement or normalization was achieved. Of patients who did not receive Padma 28, none felt better. Moreover, 40 percent showed a deterioration.

Side effects
No side effects were observed.

Authors' comments
The results of this study may be subjective to an extent, in that it is known that multiple sclerosis is characterized by irregular periods of disease activity interspersed by intervals of spontaneous remission. However, Padma 28 may be useful in slowing or arresting the symptoms of chronic multiple sclerosis.

Reviewer's comments
This was an open trial with a mixture of objective and subjective end points. The subjective end points are not described adequately, nor are the statistical methods, the data, or the randomization process. The sample size, however, was adequate. (1, 2)

Clinical Study: Padma® 28

Extract name	N/A
Manufacturer	Padma Inc., Switzerland
Indication	**Respiratory tract infection**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Jankowski S, Jankowski A, Zielinska S, Walczuk M, Brzosko WJ (1991). Influence of Padma 28 on the spontaneous bactericidal activity of blood serum

in children suffering from recurrent infections of the respiratory tract. *Phytotherapy Research* 5: 120-123.

Trial design
Parallel. Children (two to four years old) were given Padma 28 for one month, then had a two-week interruption before another two weeks of treatment. During treatment, the children did not receive antibiotics. The control group consisted of ten blood donors (mean age: 23 years) who had not been infected with bacteria such as *Pseudomonas aeruginosa, Salmonella,* or *Escherichia coli.*

Study duration	2 months
Dose	1 tablet 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Not described
No. of subjects enrolled	19
No. of subjects completed	19
Sex	Male and female
Age	2-4 years

Inclusion criteria
Children suffering from recurrent infections of the respiratory tract were accepted into the study if they had developed at least once a month, for the last nine months, illnesses such as purulent angina, bronchitis, or bronchopneumonia.

Exclusion criteria
None mentioned.

End points
Blood was collected from children and donors before the start of treatment and two months later. The bactericidal activity of the serum was determined using three strains of bacteria: *Salmonella typhimurium* strain 568, and *Escherichia coli* strains 044 and 055.

Results
Results indicate that an increase in spontaneous bactericidal activity (SBA)

in sera of children receiving Padma 28 occurred in almost 85 percent of cases. A considerable increase (bactericidal index less than 2) was observed in 12 children, a lesser increase was seen in four children and no improvement was observed in three children. No change occurred in the SBA in sera of the control blood donors.

Side effects
None mentioned in paper.

Authors' comments
Padma 28 in its multiple modes of action enhances the spontaneous bactericidal activity of the serum of children in comparison with a control group of healthy subjects.

Reviewer's comments
This trial was an ex vivo study without clear clinical significance (i.e., the effect of this intermediate outcome is not clearly linked to the disease studied). The trial was neither randomized nor blinded, the sample size was small, and the data were not described in sufficient detail. (0, 4)

Phytodolor™

Ingredients:
Common ash (European ash) (*Fraxinus excelsior* L.) bark
Aspen (quaking aspen) (*Populus tremula* L.) bark and leaf
Goldenrod (European goldenrod) (*Solidago virgaurea* L.) aerial parts

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Phytodolor™ is a formula containing extracts of common ash (*Fraxinus excelsior* L.) bark, aspen (*Populus tremula* L.) bark and leaves, and goldenrod (*Solidago virgaurea* L.) aerial parts. Aspen bark and leaves contain salicylates (Schulz, Hänsel, and Tyler, 2001). Salicylates are perhaps more widely known as constituents of willow bark, and for the synthetic derivative acetylsalicylic acid (known as aspirin). Salicylates are generally known for their ability to reduce inflammation, pain, and fever. Ash preparations contain coumarins that have anti-inflammatory and analgesic properties (Bruneton, 1999). Goldenrod preparations contain flavonoids, saponins, and phenol glycosides. Extracts and individual constituents have demonstrated diuretic, anti-inflammatory, and analgesic activity (Blumenthal, Goldberg, and Brinkmann, 2000).

Phytodolor is a combination of the extracts of common ash bark, aspen bark and leaves, and goldenrod aerial parts in the ratio of 1:3:1. The individual extracts are prepared according to the following plant-to-extract ratios: ash (4.5:1), aspen (4.5:1), and goldenrod (4.8:1). The formula as a whole is standardized to contain salicin (0.75 mg/ml), salicylic alcohol (0.042 mg/ml), isofraxidin (0.015 mg/ml), and rutin (0.06 mg/ml). The recommended dose is 20 drops (1 ml) three to four times daily. Phytodolor is manufactured in Germany by Steigerwald Arzneimittel GmbH and is no longer distributed in the United States.

PHYTODOLOR™ SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Phytodolor™	Steigerwald Arzneimittel GmbH, Germany/ None	Extracts of common ash, aspen, and goldenrod	30 to 40 drops three times daily	Arthritis (rheumatoid and degenerative joint diseases)	3	Trend (II-1, III-1) Undetermined (III-1)

SUMMARY OF REVIEWED CLINICAL STUDIES

We reviewed three double-blind, placebo-controlled trials that examined the use of Phytodolor to treat the pain and inflammation associated with various degenerative rheumatic joint diseases or arthritis. The most common degenerative disease is osteoarthritis, caused by wear and tear on the joint. It is characterized by the breakdown of joint cartilage and adjacent bone in the neck, lower back, knees, hips, and/or fingers. The symptoms include pain, stiffness, and swelling in the joints. Degeneration of the joints also occurs with rheumatoid arthritis, an autoimmune disease in which the body's own immune system attacks the membranes surrounding the joints.

Common first-line treatments for relief of symptoms of degenerative joint diseases are the nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin and other salicylic acid derivatives, acetaminophen, indomethacin, ibuprofen, and diclofenac (Hardman et al., 1996).

Phytodolor

Arthritis (Rheumatoid and Degenerative Joint Diseases)

A small trial included 38 participants with degenerative rheumatic diseases involving joints or the spinal column, who were given either Phytodolor (30 drops three times daily) or placebo for three weeks. The primary end point was the amount of NSAIDs required by both groups to alleviate symptoms. The Phytodolor group required NSAIDs on three days compared to the placebo group, which required NSAIDs on 47 days. With the combination of treatments, clinical improvements (pain and flexibility) were similar for both groups. For example, the clinical measurements for those whose spinal columns were affected were the finger-to-floor assessment of mobility range and an evaluation of the pain when tapping the spinal column (Huber, 1991). A small crossover trial included 30 subjects with arthritis of the knee, hip, thumb, or shoulder, who were given either Phytodolor (40 drops three times daily) or placebo for one week. The subjects were allowed to take up to six (25 mg) tablets of diclofenac per day if necessary. In both phases of the crossover trial, the group

given placebo tended to require more diclofenac than the group given Phytodolor (Schadler, 1988).

A third study compared Phytodolor to both placebo and an injectable form of indomethacin (Amuno). This was a four-week trial that included 41 subjects with inflammatory or chronic degenerative diseases. After one week, mobility improved in the Phytodolor group compared with the placebo group. After two weeks, pain due to movement was improved in the Phytodolor group compared with the placebo group. The indomethacin group showed more relief from pain due to movement and continuous pain than the Phytodolor group after one week, but the improvements were similar after four weeks (Hahn and Hubner-Steiner, 1988).

According to our reviewer, Dr. John Hicks, none of the studies cited previously were large enough to support any definite conclusions regarding the benefit of Phytodolor. In addition, the trial methodology was deemed moderate to poor according to current standards.

SYSTEMATIC REVIEWS

A systematic review of double-blind, randomized clinical studies on Phytodolor included ten trials. Six trials were placebo-controlled, with three of these trials also including another active medication. Four other studies compared Phytodolor to another active medication without a placebo group. Three of the trials, which we were able to obtain in English or translated into English, were reviewed independently in the previous section. The trials included subjects with musculoskeletal problems, including osteoarthritis, epicondylitis, rheumatoid arthritis, and back pain. The studies evaluated various clinical symptoms, such as pain, grip strength, physical impairment, morning stiffness, swelling, and joint function, as well as the use of rescue medication, as outcome measures. The dose of Phytodolor ranged from 90 to 120 drops per day in liquid form and the equivalent of 200 drops in a tablet form. Treatment lasted from two to four weeks, and the trials ranged in size from 30 to 432 subjects, with a total of 1,135 in the ten trials. The author of the review concluded that Phytodolor is as effective as synthetic drugs (diclofenac, piroxicam, indomethacin) and more effective than placebo in treating musculoskeletal pain. Further, the author commented that data from these trials are sup-

ported by nine clinical studies that were not controlled and therefore not included in the review. The limitations of the studies, as stated by the author, were the heterogeneous nature of the patient groups, the use of subjective clinical end points, and the low dose of comparative therapeutic agents. In addition, several of the trial reports were unpublished and therefore not subjected to peer review (Ernst, 1999).

ADVERSE REACTIONS OR SIDE EFFECTS IN CLINICAL STUDIES

Neither the three individual studies nor the systematic review mentioned any significant side effects.

REFERENCES

Blumenthal M, Goldberg A, Brinkmann J, eds. (2000). *Herbal Medicine: Expanded Commission E Monographs.* Austin, TX: American Botanical Council.

Bruneton J (1999). *Pharmacognosy, Phytochemistry, Medicinal Plants,* Second Edition. Trans. CK Hatton. Paris, France: Lavoisier Publishing.

Ernst E (1999). The efficacy of Phytodolor for the treatment of musculoskeletal pain—A systematic review of randomized clinical trials. *Natural Medicine Journal* 2: 14-17.

Hahn S, Hubner-Steiner U (1988). The treatment of painful rheumatic diseases with Phytodolor in comparison to placebo and Amuno treatments. *Rheuma Schmerz & Entzündung* 8 (5): 55-58.

Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman-Gillman A (1996). *Goodman and Gillman's The Pharmacological Basis of Therapeutics,* Ninth Edition. New York: McGraw-Hill.

Huber B (1991). Therapy of degenerative rheumatic diseases: Requirement for additional analgesic medication under treatment with Phytodolor. *Fortschritte der Medizin* 109 (11): 248-250.

Schadler W (1988). Phytodolor for the treatment of activated arthrosis. *Rheuma: Therapeutic Guidelines Diagnostic Aids* 8: 280-290.

Schulz V, Hänsel R, Tyler VE (2001). *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine,* Fourth Edition. Trans. TC Telger. Berlin: Springer-Verlag.

DETAILS ON PHYTODOLOR PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Phytodolor™

Manufacturer	**Steigerwald Arzneimittel GmbH, Germany**
U.S. distributor	**None**
Formula Botanicals	**Common ash bark** (*Fraxinus excelsior* L.) **aspen leaves and bark** (*Populus tremula* L.) **goldenrod aerial parts** (*Solidago virgaurea* L.)
Quantity	Ash
Processing	Fresh plant aqueous alcoholic extracts Plant/extract ratios: ash 4.5:1; aspen 4.5:1; goldenrod 4.8:1
Standardization	Salicin 0.75 mg/ml; salicylic alcohol 0.042 mg/ml; isofraxidin 0.015 mg/ml; rutin 0.06 mg/ml
Formulation	Liquid

Recommended dose: Take 20 drops (1 ml) three to four times daily mixed in water or a favorite drink. For maximum support, double recommendation to 40 drops. Allow two to four weeks for best results.

DSHEA structure/function: Dietary supplement for optimum muscle and joint function.

Cautions: Do not take this product if sensitive to salicylates.

Other ingredients: Water, alcohol (45.6 percent)

Source(s) of information: Product package

Clinical Study: Phytodolor™ N

Extract name	None given
Manufacturer	Steigerwald GmbH, Germany

Indication	**Degenerative rheumatic diseases**
Level of evidence	**II**
Therapeutic benefit	**Trend**

Bibliographic reference
Huber B (1991). Therapy of degenerative rheumatic diseases: Requirement for additional analgesic medication under treatment with Phytodolor. *Fortschritte der Medizin* 109 (11): 248-250.

Trial design
Parallel. Pretrial washout lasting the half-life of the subjects' previous anti-inflammatory medication.

Study duration	3 weeks
Dose	30 drops 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	40
No. of subjects completed	38
Sex	Male and female
Age	50-80 years

Inclusion criteria
Inpatients with at least one rheumatological indication (in degenerative forms) for treatment with anti-inflammatory drugs.

Exclusion criteria
None mentioned.

End points
The condition of the most afflicted joint or the spinal column was measured prior to the study and after one, two, and three weeks. Circumference, maximum flexion in degrees, continuous pain while at rest, and pain during movement were recorded for joints. For the spinal column, finger-to-floor distance, assessment of the mobility range of the spinal column (small and big Schober index), and an evaluation of the pain by tapping on the spinal column were recorded. Patients were given diclofenac (an anti-inflammatory

drug) and at times paracetamol, in addition to Phytodolor or placebo, if the analgesic efficacy was insufficient. The amount of additional medication was noted. Laboratory parameters were assessed prior to the study and after three weeks of treatment.

Results
Clinical improvements were almost identical for both groups. Additional medication was required for 2 of 18 in the Phytodolor group, distributed on a total of three days, and 5 of 20 in the control group, distributed on a total of 47 days. The *p* value of the Wilcoxon test between the two groups was 0.17. Laboratory tests showed a insignificant decrease in leukocyte number in the Phytodolor group.

Side effects
None observed.

Author's comments
When administrating Phytodolor, significantly lower amounts of nonsteroidal anti-inflammatory drugs were required than with placebo. The tolerance of Phytodolor N is clearly better than the tolerance of nonsteroidal anti-inflammatory drugs.

Reviewer's comments
There was a trend toward less need for analgesics while taking Phytodolor. However, the study was not large enough to prove significant effects. Neither the blinding process nor the inclusion/exclusion criteria for the patients were described adequately. (3, 4)

Clinical Study: Phytodolor™

Extract name	None given
Manufacturer	Steigerwald GmbH, Germany
Indication	**Arthritis of various joints**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Schadler W (1988). Phytodolor for the treatment of activated arthrosis. *Rheuma: Therapeutic Guidelines Diagnostic Aids* 8: 280-290.

Trial design
Crossover. Patients were allowed to take up to six tablets (25 mg each) diclofenac per day if necessary.

Study duration	1 week
Dose	40 drops 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	30
No. of subjects completed	30
Sex	Male and female
Age	45-81 years (mean: 66)

Inclusion criteria
Subjects with arthrosis of the knee, hip-joint arthrosis, saddle-joint arthrosis of the thumb, and shoulder-joint arthrosis.

Exclusion criteria
None mentioned.

End points
Amount of diclofenac tablets consumed by each group.

Results
In the first week of treatment, all placebo patients used more diclofenac than during the first day of that treatment, whereas the Phytodolor patients used less. After the crossover, the additional consumption of diclofenac diminished in the Phytodolor group, and the consumption in the placebo group remained the same.

Side effects
No side effects were observed.

Author's comments
The effect of Phytodolor is largely the same as described for "chemical" anti-inflammatory agents. This gives the treating physician several possibilities to use Phytodolor for the benefit of his patients. In numerous cases Phytodolor

alone should be sufficient to improve the complaints of the patient adequately. In other cases, it is possible to reduce consumption of nonsteroidal anti-inflammatory drugs by administering them on an occasional basis.

Reviewer's comments
This study was too small to draw any conclusions. Neither the randomization nor the blinding were described adequately. In addition, the inclusion/exclusion criteria were not described in sufficient detail. (0, 2)

Clinical Study: Phytodolor™

Extract name	None given
Manufacturer	Steigerwald GmbH, Germany
Indication	**Degenerative rheumatic diseases**
Level of evidence	**III**
Therapeutic benefit	**Trend**

Bibliographic reference
Hahn S, Hubner-Steiner U (1988). The treatment of painful rheumatic diseases with Phytodolor in comparison to placebo and Amuno treatments. *Rheuma Schmerz & Entzündung* 8 (5): 55-58.

Trial design
Parallel. Three-arm study. Phytodolor and placebo were packaged in identical form. Amuno (indomethacin) (3 × 1 tsp daily) was administered as suspension. Phytodolor and placebo were double-blind, and administration of Amuno was open.

Study duration	1 month
Dose	30 drops three times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	Yes
Drug name	Amuno
Site description	Medical practice
No. of subjects enrolled	45

No. of subjects completed	41
Sex	Male and female
Age	28-84 years

Inclusion criteria
Patients suffering from inflammatory and chronic degenerative diseases.

Exclusion criteria
Patients with complaints of other causes.

End points
Improvement in disease symptoms after two and four weeks of treatment were compared to symptoms before treatment. Symptoms of pain due to movement, continuous pain, and limited mobility were evaluated on a scale of severe, medium-severe, mild, or nonexistent.

Results
After randomized assignment to treatment groups, the Amuno groups and Phytodolor groups were different in structure with regard to mobility (Amuno group had more pronounced limited mobility than Phytodolor group). Also, patients in the Phytodolor group most often suffered from arthrosis deformans, whereas patients in the Amuno group most often suffered from vertebra syndrome. The disease in the Phytodolor group had most often not persisted for longer than one year, whereas in the Amuno group, most patients had been suffering between one and eight years. After the first week of treatment, reductions in severity of pain due to movement and of continuous pain were more pronounced in the Amuno group than in the Phytodolor group. After four weeks of treatment, Phytodolor and Amuno showed similar success. (These results must be taken with reservations since the two groups were not equal at baseline.) Compared to placebo, the Phytodolor group showed significant improvement in "limited mobility" ($p < 0.01$) after one week and "pain due to movement" after two weeks ($p < 0.05$). In both groups, the symptom "continuous pain" was only mildly pronounced, and statistical differences could not be found.

Side effects
None observed with Phytodolor.

Authors' comments
Phytodolor was significantly more efficient than placebo in the treatment of degenerative and inflammatory rheumatic diseases. Phytodolor and Amuno both showed similar healing effects after a four weeks, though two thirds of the patients treated with indomethacin developed side effects. Because of the insufficient equality between the two patient groups, the results can be compared to a limited degree only.

Reviewer's comments

Compared to placebo, Phytodolor seemed to have more efficacy. However, the flawed randomization and small study size prevents any firm conclusions. No explanations for withdrawal were given for the three subjects who dropped out of the study. (2, 3)

Prostane®

Ingredients:
Salep orchid (*Orchis mascula* L.) tuber
Hygrophila (*Astercantha longifolia* Nees.) seed
Lettuce (*Lactuca scariola* L.) seed
Cow-itch (*Mucuna pruriens* (L.)DC.) seed
Elephant creeper (*Argyreia speciosa* [L. f.] Sweet) root
Small caltrops (*Tribulus terrestris* L.) fruit
Jeevanti (*Leptandenia reticulata* W. & A.) whole
Stone flower [*Parmelia perlata* (Huds.) Ach.] whole

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Prostane® is manufactured by The Himalaya Drug Company in India and distributed in the United States by Himalaya USA. Each tablet contains 600 mg of a proprietary blend of eight herbs. Prostane is also sold as ProstaCare®. The product is called "Speman" in the clinical trial we reviewed. Unfortunately that trial did not include any details on the product, so we were unable to compare the material used in the trial to the current product.

SUMMARY OF REVIEWED CLINICAL STUDIES

We reviewed one study with Prostane for treatment of acute and chronic urinary retention due to prostate enlargement. A nonmalignant enlargement of the prostate that is common in men older than 40 years of age is called benign prostatic hyperplasia (BPH). Symptoms of BPH include increased urinary urgency and frequency, urinary hesitancy, intermittency, sensation of incomplete voiding, and decreased force of the urine stream.

PROSTANE® SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Prostane®	The Himalaya Drug Company, India/ Himalaya USA	Blend of 8 ingredients	2 tablets 3 times daily	Benign prostatic hyperplasia	1	Undetermined (III-1)

Prostane

Benign Prostatic Hyperplasia

An open, placebo-controlled study with Prostane included 55 men with acute and chronic urinary retention due to prostate enlargement. Forty-seven participants had BPH, six had fibrotic disease, and two had prostate cancer. Forty-five of the patients were treated with Prostane and ten served as controls. Approximately 74 percent (28 of 38) of those in the treatment group with BPH had improved symptoms and decreases in prostate size and urinary congestion after 10 to 14 days of treatment with two tablets three times daily. The other ten in the treatment group with BPH required surgery (prostatectomy). All men that served as controls required surgery (Mukherjee, Ghosh, and De, 1986). The clinical efficacy of Prostane in this study was rated as undetermined due to poor study design.

ADVERSE REACTIONS OR SIDE EFFECTS

No side effects were reported in a clinical trial with 45 subjects given two tablets three times daily for a month (Mukherjee, Ghosh, and De, 1986).

REFERENCES

Mukherjee S, Ghosh TK, De D (1986). Effect of Speman on prostatism—A clinical study. *PROBE* 25 (3): 237-240. (Reprinted from *Indian Medical Journal* 1984; 78: 183.)

DETAILS ON PROSTANE PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Prostane®

Manufacturer	**The Himalaya Drug Company, India**
U.S. distributor	**Himalaya USA**
Formula botanicals	**Salep orchid tuber** (*Orchis mascula* L.); **hydrophila seed** (*Astercantha longifolia* Nees.); **lettuce seed** (*Lactuca scariola* L.); **cow-itch seed** (*Mucuna pruriens* (L.) DC.); **elephant creeper root** (*Argyreia speciosa* [L. f.] Sweet); **small caltrops fruit** (*Tribulus terrestris* L.); **Jeevanti, whole** (*Leptadenia reticulata* W. & A.), **stone flower, whole** [*Parmelia perlata* (Huds.) Ach.]
Quantity	600 mg
Processing	No information
Standardization	No information
Formulation	Tablet

Recommended dose: Take one or two tablets two times per day with meals.

DSHEA structure/function: Natural prostate support. Helps maintain a healthy prostate, and promotes normal urinary flow for optimum comfort.

Other ingredients: Tin sulfide, magnesium stearate, sodium carboxymethylcellulose, microcrystalline cellulose, crospovidone, aerosil.

Comments: Also sold as Speman and ProstaCare®.

Source(s) of information: Product label.

Clinical Study: Speman

Extract name	N/A
Manufacturer	The Himalaya Drug Company, India
Indication	**Benign prostatic hyperplasia; fibrotic disease; prostate cancer**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Mukherjee S, Ghosh TK, De D (1986). Effect of Speman on prostatism—A clinical study. *PROBE* 25 (3): 237-240. (Reprinted from *Indian Medical Journal* 1984; 78: 183.)

Trial design
Parallel. Ten patients acted as control and 45 were given Speman for 10 to 14 days. Patients in the study group were continued on Speman for a further 14 days, after which the dose was decreased to one tablet three times daily. Both groups were given antibiotics, antiseptics, and vitamins as necessary. Patients who presented with chronic retention of urine (29 cases) were fitted with a catheter, and the bladder was drained continuously for 10 to 14 days.

Study duration	10 to 14 days
Dose	2 tablets 3 times daily
Route of administration	Oral
Randomized	No
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	No
Drug comparison	No
Site description	Medical college hospital
No. of subjects enrolled	55
No. of subjects completed	55
Sex	Male
Age	Not given

Inclusion criteria
Patients with prostatism.

Exclusion criteria
None mentioned.

End points
Clinical observations included the magnitude of urinary symptoms (urinary flow and frequency), prostate status (benign, fibrotic, and malignant), and the presence or absence of acute or chronic retention of urine. Efficacy was determined according to whether patients' conditions improved and whether operation was necessary.

Results
Twenty-eight of 38 patients in the treatment group with benign hypertrophy of the prostate improved satisfactorily (decrease urinary frequency both day and night, increased urinary flow, reduction in the size of prostate, and decreased congestion as measured by cystoscopic examination). Of these 38 patients in the treatment group who had benign hypertrophy, only ten needed prostatectomy. In 18 of 29 patients who had been fitted with a catheter, retention of urine recurred after the catheter was removed (14 in Speman group, four in control group). All of these patients were subjected to prostatectomy, in addition to the other six cases from the control group.

Side effects
None mentioned.

Authors' comments
The majority of the patients in the study group who had benign hypertrophy of the prostate had highly satisfactory results with Speman.

Reviewer's comments
Because of the poor study design and confounding factors, little can be determined of the benefits of this agent. Ten to 14 days of treatment is also a short duration. The trial was neither randomized nor blinded. (1, 2)

Resistex™

Ingredients:

Astragalus [*Astragalus membranaceus* (Fisch. ex Link) Bunge] root
Eleuthero (Siberian ginseng) [*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.] root
Asian ginseng (*Panax ginseng* C.A. Meyey) root
Stephania (*Stephania tetrandra* S. Moore) root
Echinacea [*Echinacea purpurea* (L.) Moench] root
Barrenwort (*Epimedium grandiflorum* C. Morren) leaf and flower
Dong quai [*Angelica sinensis* (Oliv.) Diels] root

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Resistex® is manufactured and distributed by Botanica BioScience Corporation. Each capsule contains 450 mg of a proprietary blend of *Echinacea purpurea* root and extracts of astragalus, eleuthero (Siberian ginseng), Asian ginseng, stephania, barrenwort, and dong quai.

SUMMARY OF REVIEWED CLINICAL STUDIES

The Resistex formula was developed with the intention of providing resistance to infection with colds or flu. The initial cause of a cold or flu is a viral infection. Colds are caused most commonly by a rhinovirus and less often by a coronavirus. The influenza viruses cause the flu. In theory, bolstering the immune system can prevent disease or reduce symptoms. A number or herbal preparations have been promoted as immunostimulants for this purpose, including those containing echinacea and/or eleuthero (Wagner, 1997). Other herbs have been described as adaptogenic, i.e., substances that assist

RESISTEX® SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Resistex™	Botanica BioScience Corporation/Botanica BioScience Corporation	Herbal blend of 7 ingredients	2 (450 mg) tablets per day	Cold and flu (prevention)	1	Undetermined (III-1)

in nonspecific heightened resistance to stress. The adaptogenic properties of these herbs may be due, in part, to antioxidant and/or immunomodulatory activity (Davydov and Krikorian, 2000). Herbs with adaptogenic activity ascribed to them include eleuthero, Asian ginseng, ashwaganda, astragalus, and schisandra (Davydov and Krikorian, 2000; Wagner, Nörr, and Winterhoff, 1992; Wallace, 1998).

Resistex

Cold and Flu (Prevention)

An open, placebo-controlled clinical trial with 61 participants found Resistex to significantly reduce the incidence of colds and flu compared to recall of the previous season. Subjects were divided into three groups and given one or two tablets of Resistex or placebo. Treatment was initially for four weeks, followed by a one-week intermission, which was followed by several two-week treatment periods, each separated by one-week intermissions. The total trial length was four and a half months. As a result, the group that received two tablets Resistex (900 mg daily) had a 67 percent reduction in the incidence of colds and flu compared to the previous season. In comparison, the group that received one tablet (450 mg daily) had a 43 percent reduction, and the placebo group had a 14 percent reduction (Wang, 1998). Methodological flaws, such as the dependence on recall for the previous season's incidence of colds and flu, and lack of detail in the trial report led our reviewer, Dr. Richard O'Connor, to rate the clinical outcome of this trial as undetermined.

ADVERSE REACTIONS OR SIDE EFFECTS

No side effects were reported in a controlled clinical trial with 61 patients that used a dose of 900 mg per day (Wang, 1998).

REFERENCES

Davydov M, Krikorian AD (2000). *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliacaeae) as an adaptogen: A closer look. *Journal of Ethanopharmacology* 72 (3): 345-393.

Wagner H (1997). Herbal immunostimulants for the prophylaxis and therapy of colds and influenza. *The European Journal of Herbal Medicine* 3 (1): 22-30.

Wagner H, Nörr H, Winterhoff H (1992). Drugs with adaptogenic effects for strengthening the powers of resistance. *Zeitschrift für Phytotherapie* 13: 42-54

Wallace EC (1998). Adaptogenic herbs: Nature's solution to stress. *Nutrition Science News* 3 (5): 244-249.

Wang RT (1998). Outcomes study to evaluate the effects of Resistex on colds and flu in humans. China Academy of Preventative Medicine. Unpublished study.

DETAILS ON RESISTEX PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clniical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Resistex™

Manufacturer	**Botanica BioScience Corporation**
U.S. distributor	**Botanica BioScience Corporation**
Formula Botanicals	***Astragalus membranaceus*** (std. root extract); **Siberian ginseng** (*Eleutherococcus senticosus;* std. root extract); ***Panax ginseng*** (std. root extract); ***Stephania tetrandra*** (extract from root); ***Echinacea purpurea*** (root); ***Epimedium grandiflorum*** (extract from leaves and flowers); ***Angelica sinensis*** (std. root extract).
Quantity	450 mg
Processing	No information
Standardization	No information
Formulation	Capsule

Recommended dose: Take two capsules once a day before or between meals, one week on and one week off. Dosage can be increased up to four capsules, three times a day, at the onset of cold or flu symptoms.

DSHEA structure/function: Cold season defense. Enhances T-cell and antibody production.

Cautions: In case of accidental overdose, seek professional advice immediately. If you are taking prescription medicine or are pregnant or lactating, consult with your doctor before taking.

Other ingredients: Cellulose, magnesium stearate (vegetable grade), silica.

Source(s) of information: Product package (© 1999 Botanica BioScience Corporation).

Clinical Study: Resistex™

Extract name	None given
Manufacturer	Botanica Bioscience Corporation
Indication	**Cold and flu** (prevention)
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Wang RT (1998). Outcomes study to evaluate the effects of Resistex on colds and flu in humans. China Academy of Preventative Medicine. Unpublished study.

Trial design
Parallel. Patients took either Resistex or placebo every day for four weeks, then had a one-week break. This week was followed by two-week periods of taking either Resistex or placebo with one-week intermissions. This pattern was continued for several months. The trial began in November and concluded in March.

Study duration	4.5 months
Dose	1 or 2 (450 mg) tablets per day
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Open
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	61
No. of subjects completed	61
Sex	Male and female
Age	60-80 years

Inclusion criteria
Healthy elderly subjects between the ages of 60 and 80 with normal clinical chemistry profile and physician clearance.

Exclusion criteria
Acute or serious chronic diseases, receiving prescription medication or nonsteroidal anti-inflammatory drugs, taking vitamins or mineral supple-

ments during the least three months, alcohol or drug abuse, marked sleep disturbance, serious allergies, salient emotional or mood problems, or recent history of systemic infection, bone fracture, or surgery.

End points
Comparison of previous season's cold and flu histories with current season after supplementation with Resistex. Prior to random assignment, patients were questioned about their cold and flu history in the preceding year. During the study period, number of times cold or flu occurred and duration of illness were recorded.

Results
Patients in the high-dose treatment group showed a 67 percent reduction in the instance of cold and flu symptoms compared to 43 percent in the low-dose group and 14 percent for the placebo group. The difference between the high-dose group and placebo group was significant ($p < 0.01$).

Side effects
None mentioned.

Author's comments
The results support the comprehensive approach to boosting the body's immune system in the reduction of duration and severity of cold and flu symptoms in the active treatment group compared to the control group.

Reviewer's comments
This is a poorly conceived and poorly conducted study. The trial is apparently unblinded, and patient recalls were used as baseline. The author concludes that the product enhanced the immune system but no tests of immunity were performed. (0, 3)

Sinupret®

Ingredients:

Gentian (yellow gentian) (*Gentiana lutea* L.) root
Cowslip (primrose) (*Primula veris* L.) flower
Sorrel (sour dock) (*Rumex acetosa* L.) aerial parts
European elder (*Sambucus nigra* L.) flower
European vervain (vervain wort) (*Verbena officinalis* L. ssp. *officinalis*) aerial parts

PREPARATIONS USED IN REVIEWED CLINICAL STUDIES

Sinupret® is manufactured in Germany by Bionorica Arzneimittel GmbH. It contains a blend of five powdered plant materials: gentian root, European elder flower, European vervain aerial parts, cowslip flower, and sorrel aerial parts. Each tablet contains 78 mg of herbs. Sinupret is also sold in a liquid form: 100 g contains 29 g of aqueous alcoholic extracts (59 percent ethanol) of the herbs mentioned previously. Sinupret is distributed in the United States by Mediceutix, Inc.

SUMMARY OF REVIEWED CLINICAL STUDIES

Sinupret was approved as a drug to treat acute and chronic sinusitis by the federal authorities in Germany in 1997. Sinusitis is characterized by symptoms of nasal obstruction, discharge, postnasal drip, headache, and sore throat. It is often caused by a bacterial infection, and may follow a common cold or flu. Acute sinusitis may last for up to three weeks, but if it lasts for three months, it is considered chronic. Medical treatment is often aimed at eliminating the bacterial infection (if present) and reducing symptoms of sinus congestion and nasal discharge (Behr, 1998).

SINUPRET® SUMMARY TABLE

Product Name	Manufacturer/ U.S. Distributor	Product Characteristics	Dose in Trials	Indication	No. of Trials	Benefit (Evidence Level-Trial No.)
Sinupret®	Bionorica Arzneimittel GmbH, Germany/ Mediceutix, Inc.	Combination of gentian, European elder, European vervain, primrose, and sorrel	2 tablets, or 50 drops liquid, 3 times daily	Sinusitis	2	Yes (II-1) Undetermined (III-1)

Sinupret

Sinusitis

Two double-blind, placebo-controlled clinical studies on patients with acute or chronic sinusitis were reviewed. In a good-quality trial, 160 subjects with acute sinusitis were given either Sinupret (two 78 mg tablets three times daily) or placebo in addition to antibiotic and decongestant therapy. After two weeks, radiographic (X-ray) reports and patients' assessments showed significant improvement with Sinupret compared with placebo (Neubauer and März, 1994).

The other trial, with poor methodological ratings, included 31 subjects with chronic sinusitis and compared treatment with either the liquid or tablet form of Sinupret with two matching placebos. After one week of treatment, radiographic and ultrasound findings showed improvement with both forms of Sinupret compared with placebo. Complete recovery occurred in 12 of 16 subjects in the treatment group and in 6 of 15 subjects in the placebo group (Richstein and Mann, 1999).

Six additional controlled trials were conducted on Sinupret between 1980 and 1992. These trials were not obtained in English in their full form and so were not reviewed for their level of evidence for this book. They were summarized in an unpublished report written on behalf of the manufacturer (Bionorica), as well as in a published review (Behr, 1998; März, Ismail, and Popp, 1999). One study was double-blind and placebo-controlled, including 39 young subjects with asthma. As a result of treatment, radiographic findings showed improvement, and the frequency of asthma attacks was reduced (Lecheler and Mann, 1980). Another study compared Sinupret with antibiotics (doxycycline) to Esberitox (echinacea formula) with antibiotics to antibiotics alone in 90 subjects with acute bacterial sinusitis (Zimmer, 1985). Four other studies, including a total of 594 subjects with acute sinusitis, compared Sinupret to other expectorants: the volatile oil mytrol, acetylcysteine, or ambroxol Mucosolvan® (Kraus and März, 1992; Braum and März, 1990; Simm, Pape, and März, 1991; Wahls and März, 1990). In general the trials were positive, with Sinupret being similar to other active treatments for acute sinusitis.

POSTMARKETING SURVEILLANCE STUDY

A postmarketing surveillance study was conducted with 3,187 patients between 1 and 94 years old, with acute or chronic bronchitis. Sinupret was as effective as other expectorants, following ten days treatment with 150 drops or six tablets per day (Ernst, März, and Sieder, 1997).

ADVERSE REACTIONS OR SIDE EFFECTS

The two studies we reviewed reported no side effects. A small trial with 12 healthy participants, given either the usual or a fivefold dose of either the liquid or the tablet form for six weeks, found no adverse effects in numerous laboratory tests (Strobel, 1984). In a postmarketing surveillance study conducted with 3,187 patients in Germany, side effects were documented in 8 of the 1,013 patients who received Sinupret as their only therapy. The side effects were gastrointestinal intolerance with one instance of dizziness (Ernst, Sieder, and März, 1995).

A retrospective multicenter analysis of one thousand pregnant women who used Sinupret because of sinusitis or bronchitis, reported no evidence of risk for fetal malformations or adverse effects (Becker, Sieder, and März, 1997). Another study of 762 pregnant women also found no indication of teratogenic or embryotoxic effects (Queisser-Luft and Ismail, 2000).

REFERENCES

Becker MKF, Sieder C, März RW (1997). Sinupret in pregnancy—A retrospective study of 1,000 cases: Preliminary results. *Fact: Focus on Alternative and Complementary Therapies* 2 (4): 185. (Presented at the Fourth Annual Symposium on Complementary Healthcare, December 10-12, 1997, Exeter, United Kingdom.)

Behr B (1998). Sinupret: Efficacy and Safety Expert Report 1998. Unpublished.

Braum D, März RW (1990). Randomisierte vergleichsstudie Sinupret Dragees vs Fluimucil (Granulat) bei akuter und chronischer Sinusitis (N=160). Germany: Bericht Bionorica Arzneimittel GmbH, Neumarkt/Opf. Cited

in Behr B (1998). Sinupret: Efficacy and Safety Expert Report 1998. Unpublished.

Ernst E, Marz RW, Sieder Ch (1997). Acute bronchitis—Benefits of Sinupret: Comparative post-marketing surveillance study involving 3,187 patients. *Fortschritte der Medizin* 115 (11): 52-53.

Ernst E, Sieder Ch, Marz R (1995). Adverse drug reactions to herbal and synthetic expectorants. *International Journal of Risk and Safety in Medicine* 7: 219-225.

Kraus P, März RW (1992). Randomisierte vergleichsstudie Sinupret Dragees vs. Gelomytol f. bei akuter und chronischer Sinusitis (N=134). Klinischer und biometrischer Bericht, Bionorica GmbH, Neumarkt. Presented at the Fourth National and First International Congress on Phytomedicine, Munich. Cited in Behr B (1998). Sinupret: Efficacy and Safety Expert Report 1998. Unpublished.

Lecheler J, Mann R (1980). Sinupret Doppelblindstudie (bei jugendichen Asthmapatienten; N=39). Germany: Bericht Bionorica Arzneimittel GmbH, Neumarkt/Opf. Cited in Behr B (1998). Sinupret: Efficacy and Safety Expert Report 1998. Unpublished.

März RW, Ismail C, Popp MA (1999). Action profile and efficacy of a herbal combination preparation for the treatment of sinusitis. *Wiener Medezinische Wochenschrift* 149 (8-10): 202-208.

Neubauer N, März RW (1994). Placebo-controlled, randomized double-blind clinical trial with Sinupret sugar-coated tablets on the basis of a therapy with antibiotics and decongestant nasal drops in acute sinusitis. *Phytomedicine* 1 (3): 177-181.

Queisser-Luft A, Ismail Ch (2000). Safety of an herbal combination preparation in pregnancy—An example for using active detection systems for malformations. *Phytomedicine* Supplement II: 12.

Richstein A, Mann W (1999). Treatment of chronic rhino-sinusitis with Sinupret. *Schweizerische Zeitschrift für GanzheitsMedizin* 11 (6): 1-3. (Previously published as Richstein A, Mann W [1980]. Zur Behandlung der chronischen Sinusitis mit Sinupret®. *Therapie der Gegenwart* 119 [9]: 1055-1060.)

Simm KJ, Pape HG, März RW (1991). Doppelblindstudie Sinupret vs. Mucosovan mit/ohne Nasentropfen bei akuter Sinusitis (N=160). Clinical and biometrical report. Germany: Bionorica Arzneimittel GmbH, Neumarkt/Opf. Cited in Behr B (1998). Sinupret: Efficacy and Safety Expert Report 1998. Unpublished.

Strobel W (1984). The tolerance of Sinupret (the influences of long-term medication on clinical/chemical parameters in healthy participants). *Zeitschrift für Phytotherapie* 6: 2-6.

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Zimmer M (1985). Gezielte konservative Therapie der akuten Sinusitis in der HNO-Praxis. *Therapiewoche* 35: 4024-4028. Cited in Behr B (1998). Sinupret: Efficacy and Safety Expert Report 1998. Unpublished.

DETAILS ON SINUPRET PRODUCT AND CLINICAL STUDIES

A profile on the product is followed by details of the clinical studies associated with that product. Clinical studies are grouped by therapeutic indication, in accordance with the order in the Summary Table.

Product Profile: Sinupret®

Manufacturer	**Bionorica Arzneimittel GmbH, Germany**
U.S. distributor	Mediceutix, Inc.
Formula Botanicals	**Gentian root** (*Gentiana lutea* L.) 6 mg; **elder flower** (*Sambucus nigra* L.) 18 mg; **European vervain** aerial parts (*Verbena officinalis* L. ssp. *officinalis*), 18 mg; **cowslip flower** (*Primula veris* L.) 18 mg; **sorrel** aerial parts (*Rumex acetosa* L.), 18 mg
Quantity	78 mg
Processing	Herbs pulverized at low temperature
Standardization	No information
Formulation	Tablet

Other ingredients: Digestible carbohydrates (41.6 percent), and sorbitol (0.1 percent).

Source(s) of information: Neubauer and März, 1994; Physicians' Reference on Sinupret Dragées and Sinupret Drops, Bionorica GmbH Medical Scientific Information, 1991.

Clinical Study: Sinupret®

Extract name	N/A
Manufacturer	Bionorica Arzneimittel GmbH, Germany
Indication	**Acute sinusitis**
Level of evidence	**II**
Therapeutic benefit	**Yes**

Bibliographic reference

Neubauer N, März RW (1994). Placebo-controlled, randomized double-blind clinical trial with Sinupret sugar-coated tablets on the basis of a therapy with antibiotics and decongestant nasal drops in acute sinusitis. *Phytomedicine* 1 (3): 177-181.

Trial design

Parallel. Patients were given Sinupret or placebo in addition to antibiotic therapy, Vibramycin® (doxycycline), and decongestant therapy, Otriven® (xylometazoline).

Study duration	2 weeks
Dose	2 (78 mg) tablets 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	Yes
Blinding	Double-blind
Blinding adequate	Yes
Placebo	Yes
Drug comparison	No
Site description	Not described
No. of subjects enrolled	177
No. of subjects completed	160
Sex	Male and female
Age	Mean: 24.5 years

Inclusion criteria

Clinical diagnosis of an acute sinusitis in connection with an opacification of the plain sinus radiogram.

Exclusion criteria

Patients with extreme anatomical deviations of the nasal septum were excluded, as well as patients with known intolerance for doxycycline.

End points

Primary outcome criteria were radiographic findings (completely opaque, shadowed, nothing abnormal) and the patients' assessment of the therapy (three categories: asymptomatic, good effect, no effect). Secondary variables were clinical findings (mucosa findings, secretions, patency of the nose, headache). Evaluations took place before and after two weeks of treatment.

Results
Radiographic findings showed that the addition of Sinupret treatment to standard therapy was significantly more effective than standard therapy plus placebo ($p = 0.024$). Patient assessments at the end of therapy also indicated that Sinupret was more effective than placebo. The clinical variables showed that Sinupret was superior to placebo in reducing mucosal swelling, nasal obstruction, headache, and positive trends for nasal patency. No difference regarding secretion was found.

Side effects
None recorded.

Authors' comments
Conventional therapy for acute bacterial sinusitis can be markedly improved by including Sinupret in the therapeutic regimen. Furthermore, it can be deduced from our results that any negative interaction between the herbal preparation and the basic therapy was not observed.

Reviewer's comments
This is a well-described, well-designed study. The only criticism is that no mention is made of blinding the radiologist who interpreted the X-rays, a potential source of bias. This study suggests that the addition of Sinupret to standard therapy may improve therapeutic outcomes. The trial deserves to be replicated with blinding of the radiologist. (5, 5)

Clinical Study: Sinupret®

Extract name	N/A
Manufacturer	Bionorica Arzneimittel GmbH, Germany
Indication	**Chronic sinusitis**
Level of evidence	**III**
Therapeutic benefit	**Undetermined**

Bibliographic reference
Richstein A, Mann W (1999). Treatment of chronic rhino-sinusitis with Sinupret. *Schweizerische Zeitschrift für GanzheitsMedizin* 11 (6): 1-3. (Previously published as Richstein A, Mann W [1980]. Zur Behandlung der chronischen Sinusitis mit Sinupret®. *Therapie der Gegenwart* 119 [9]: 1055-1060.)

Trial design
Parallel. Two formulations (liquid and tablets) of Sinupret were compared with matching placebos.

Study duration	1 week
Dose	2 tablets or 50 drops of liquid formula 3 times daily
Route of administration	Oral
Randomized	Yes
Randomization adequate	No
Blinding	Double-blind
Blinding adequate	No
Placebo	Yes
Drug comparison	No
Site description	Medical school outpatients
No. of subjects enrolled	31
No. of subjects completed	31
Sex	Male and female
Age	6-73 years

Inclusion criteria
Patients suffering from chronic sinusitis, with symptoms such as headache, posterior nasal rhinorrhea, pressure sensation over the affected sinuses, and blocked nose.

Exclusion criteria
Patients for which sinus surgery is indicated as the primary mode of treatment.

End points
Assessment criteria were symptoms, endoscopic, radiologic, and ultrasonographic findings. Assessments were made at the beginning and end of the study, with a follow-up assessment on day 16 (nine days after the end of treatment).

Results
The radiologic (X-ray) and ultrasonographic findings of the paranasal sinuses and the symptoms of the patients showed considerable improvement and even complete recovery in 12 of 16 total patients in the verum group. In the placebo group, only 6 of 15 patients showed improvement. The therapeutic effect did not depend on the formulation (liquid or tablets). Statistical improvement was seen compared to placebo for headache and X-ray analy-

sis ($p = 0.025$ and $p = 0.001$, respectively). No difference existed between the two groups in posterior nasal secretion.

Side effects
None mentioned.

Authors' comments
This double-blinded prospective trial study of 31 patients with chronic sinusitis revealed that Sinupret has a positive effect on subjective and objective findings in patients with chronic rhino-sinusitis.

Reviewer's comments
This is a very small trial study whose inclusion criteria are not adequately described. The primary end points are also not described, and no mention of monitoring for adverse events is made. In their introduction, the authors describe a subset of patients who have symptoms but no significant radiologic abnormalities, but then in their inclusion criteria they include patients they describe as having radiologic abnormalities that change with therapy. This appears to be a bit of fuzzy logic. Neither Institutional Review Board (IRB) approval nor informed consent were obtained. Follow-up X-rays were taken with 11 of 16 subjects in the treatment group and 6 of 12 subjects in the placebo group. Neither the randomization nor the blinding were adequately described. (0, 2)

Appendix A

Products Listed by Manufacturer/Distributor

AB Cernelle, Sweden	
Cernilton®	Grass pollen
Access Business Group: Home of Nutrilite	
Nutrilite® Saw Palmetto with Nettle Root	Saw palmetto
Ardeypharm GmbH, Germany	
Devil's Claw	Devil's claw
Arkopharma Laboratoires Pharmaceutiques, France	
Arkojoint™	Devil's claw
Exolise™	Green tea
Harpadol®	Devil's claw
SPV_{30}™	Boxwood
Biofarm S.A., Romania	
Silimarina®	Milk thistle
Bioforce AG, Switzerland/Bioforce USA	
Aesculaforce	Horse chestnut
Echinaforce®	Echinacea
Geriaforce	Ginkgo
Ginkgoforce	Ginkgo
Hyperiforce	St. John's wort
Venaforce™	Horse chestnut
Bionorica Arzneimittel GmbH, Germany	
Mastodynon® N	Chaste tree
Sinupret®	Formula
Bluebonnet Nutrition Corporation	
Grape Seed Extract	Grape seed

Botanica BioScience Corporation

2nd Wind™	Formula
Resistex™	Formula

Bruschettini s.r.l., Italy

Procianidol	Grape seed

Chai-Na-Ta Corporation, Canada

American Ginseng	American ginseng

Dalidar Pharma Ltd., Israel

Zintona®	Ginger

Dansk Droge, Denmark

Gerimax Ginseng Extract	Ginseng

Ditta Farmigea S.p.A., Italy

FAR-1	Bilberry

Dr. Loges & Co. GmbH, Germany

Dysto-lux®	St. John's wort

Dr. Willmar Schwabe GmbH & Co., Germany

Crataegutt®	Hawthorn
Euvegal® forte	Valerian
Ginkgold®	Ginkgo
Ginkoba®	Ginkgo
HeartCare™	Hawthorn
Laitan®	Kava
Movana™	St. John's wort
Perika™	St. John's wort
ProstActive®	Saw palmetto
ProstActive® Plus	Saw palmetto
Prostagutt® forte	Saw palmetto
Neuroplant®	St. John's wort
Rökan®	Ginkgo
Tanakan®	Ginkgo
Tebonin® forte	Ginkgo
Valerian Nighttime™	Valerian
Extract: WS 1531	Devil's claw
Extract: WS 1540	Ginger

EcoNugenics Inc.

Padma® BASIC	Formula

Efamol Ltd., UK

Efamol®	Evening primrose

Enzymatic Therapy

Bilberry Extract	Bilberry
Ginkgo Biloba-24%	Ginkgo
Esberitox™	Echinacea
Herpilyn®	Lemon balm
Iberogast™	Formula
Saventaro®	Cat's claw
St. John's Wort Extract	St. John's wort

Essentially Pure Ingredients™

Pure-Gar®	Garlic

Eurovita A/S, Denmark

Eurovita Extract 33	Ginger

General Nutrition Corporation

Bowel Support Formula	Dragon's blood croton
Cycle Balance™	Chaste tree
St. John's Wort Ze 117™	St. John's wort

General Nutrition Research Laboratories

Garlic oil, cold pressed	Garlic

GlaxoSmithKline

Alluna™ Sleep	Valerian
Remifemin®	Black cohosh

Government Pharmaceutical Organization, Thailand

Spray-dried garlic	Garlic

Graminex L.L.C.

Cernilton®	Grass pollen

HBC Protocols, Inc.

Hypericum Perforatum II	St. John's wort

Health from the Sun/Arkopharma

Arkojoint™	Devil's claw
Exolise™	Green tea
SPV_{30}™	Boxwood

Hermes Arzneimittel GmbH, Germany

Tegra	Garlic

The Himalaya Drug Company, India/Himalaya USA

Cystone®	Formula
GastriCare®	Formula
Gastrim®	Formula
GeriCare®	Formula
Geriforte®	Formula
ProstaCare®	Formula
Prostane®	Formula
Speman	Formula
UriCare®	Formula

Indena S.p.A., Italy/Indena USA, Inc.

Extract: GinkgoSelect™	Ginkgo
Extract: LeucoSelect™	Grape seed
Leucoselect™-phytosome®	Grape seed
Extract: MirtoSelect™	Bilberry
Extract: PrunuSelect™	Pygeum
Extract: SabalSelect™	Saw palmetto
Extract: Siliphos®	Milk thistle
Extract: St. John Select™	St. John's wort

Inverni della Beffa, Italy (Indena S.p.A., Italy)

Pigenil	Pygeum
Silipide	Milk thistle
Tegens	Bilberry

Laboratoires Fournier, France

Tadenan®	Pygeum

Lichtwer Pharma AG, Germany

Cynara-SL™	Artichoke
Faros® 300	Hawthorn
Ginkai™	Ginkgo
Ginkyo®	Ginkgo
Hepar-SL forte®	Artichoke
Jarsin®	St. John's wort
Jarsin® 300	St. John's wort
Kaveri®	Ginkgo
Kira®	St. John's wort
Kwai®	Garlic
Sedonium™	Valerian

Lomapharm, Rudolf Lohmann GmbH KG, Germany

Herpilyn®	Lemon balm
Lomaherpan®	Lemon balm

Madaus AG, Germany

Agnolyt®	Chaste tree
Echinacin®	Echinacea
Echinagard®	Echinacea
EchinaGuard®	Echinacea
Escin gel	Horse chestnut
Legalon®	Milk thistle

Mitsui Norin Co., Ltd., Japan

Polyphenon E®	Green tea

Natrol, Inc.

Kavatrol™	Kava

Natural Wellness

Maximum Milk Thistle™	Milk thistle
UltraThistle™	Milk thistle

Nature's Way Products, Inc.

EchinaGuard®	Echinacea
Ginkgold®	Ginkgo
HeartCare™	Hawthorn
Perika™	St. John's wort
ProstActive®	Saw palmetto
ProstActive® Plus	Saw palmetto
Sambucol®	Elderberry
Valerian Nighttime™	Valerian

Novartis Consumer Health GmbH, Germany

Valverde Artischocke	Artichoke

Novogen Inc.

Promensil™	Red clover

Novogen Laboratories Pty Ltd., Australia

Promensil™	Red clover

Nutraceutical Corporation

CranActin®	Cranberry

Ocean Spray Cranberries, Inc.

Cranberry Juice Cocktail	Cranberry

Padma Inc., Switzerland

Padma® 28	Formula
Padma® BASIC	Formula

Pharmanex LLC/Pharmanex Natural Healthcare

Cholestin™	Red yeast rice
CordyMax® Cs-4	Cordyceps
JinShuiBao	Cordyceps
Tegreen 97®	Green tea

Pharmaton S.A., Switzerland/Pharmaton Natural Health Products

Gericomplex®	Ginseng
Gincosan®	Ginkgo
Ginkoba®	Ginkgo
Ginkoba M/E™	Ginkgo
Ginsana®	Ginseng
Ginsana® Gold Blend	Ginseng
Extract: GK501™	Ginkgo
Movana™	St. John's wort
Prostatonin®	Pygeum
Songha Night®	Valerian
Venastat™	Horse chestnut
Venostasin® retard	Horse chestnut

Pierre Fabre Médicament, France

Capistan	Saw palmetto
Liberprosta®	Saw palmetto
Permixon®	Saw palmetto
Sereprostat®	Saw palmetto

Razei Bar Industries, Ltd.

Sambucol®	Elderberry

Rexall Sundown, Inc.

St. John's Wort (Ze 117™)	St. John's wort

Sanofi-Synthelabo, France

Endotelon®	Grape seed

Schaper & Brümmer GmbH & Co. KG, Germany

Esberitox™	Echinacea
Remifemin®	Black cohosh
Strogen® uno	Saw palmetto

Scotia Pharmaceuticals Ltd., UK

Efamol Marine	Evening primrose
Epogam®	Evening primrose

Searle, UK

Efamast	Evening primrose

Shaman Pharmaceuticals, Inc./ShamanBotanicals.com

Bowel Support Formula	Dragon's blood croton
Provir™	Dragon's blood croton
SB-Normal Stool Formula™	Dragon's blood croton

Solaray, Inc.

CranActin®	Cranberry

Solvay Arzneimittel GmbH, Germany

Baldrian-Dispert	Valerian
Valdispert®	Valerian

Steigerwald Arzneimittel GmbH, Germany

Iberogast™	Formula
Phytodolor™	Formula

Steiner Arzneimittel, Germany

Extract: STEI 300	St. John's wort

Swanson Health Products

Ginkgo Biloba	Ginkgo

Therabel Pharma, Belgium

Prostaserene®	Saw palmetto

Thomas J. Lipton Co. (now **Unilever Bestfoods, North America**)

Lipton Research Blend	Green tea

Thorne Research

GB24™	Ginkgo
Hyper-Ex®	St. John's wort
O.P.C.-100	Grape seed
Serenoa Gelcaps	Saw palmetto
Vacimyr®	Bilberry

Traditional Medicinals, Inc.

Echinacea Plus®	Echinacea

Wakunaga of America Co., Ltd.

Kyolic® Aged Garlic Extract™, HI-PO™ Formula 100	Garlic
Kyolic® Liquid Aged Garlic Extract™	Garlic

WBL Peking University Biotech Co. Ltd., China

Zhitai	Red Yeast Rice

Weber & Weber International GmbH & Co. KG, Germany/Weber & Weber USA

Petadolex™	Butterbur, Purple

Wei-Xin Company, China

Xue-zhi-kang	Red yeast rice

Zeller AG, Switzerland

Alluna™ Sleep	Valerian
Cycle Balance™	Chaste tree
Esbericum forte	St. John's wort
IVEL®	Valerian
Rebalance	St. John's wort
ReDormin®	Valerian
Remotiv®	St. John's wort
St. John's Wort (Ze 117™)	St. John's wort
St. John's Wort Ze 117™	St. John's wort
Valverde Hyperval	St. John's wort
Extract: ZE 339	Butterbur

Appendix B

Manufacturer/Distributor Contact Information

Corporate addresses and contact information have been verified to the best of the editor's ability. However, some telephone numbers may be incomplete and may require the addition of international dialing codes for the country specified.

AB Cernelle, Sweden
Vegeholm 4320, S-262 94 Engelholm, Sweden
Web site: www.abcernelle.com

Access Business Group: Home of Nutrilite
5600 Beach Boulevard/ P.O. Box 5940, Buena Park, B62 CA 90622-5940
Phone: 714-562-6220
Web site: www.nutrilite.com

Ardeypharm GmbH, Germany
Loerfeldstr. 20, 58313 Herdecke, Germany
Phone: 49-2330-977-677
Fax: 49-2330-977-697
Web site: www.ardeypharm.de

Arkopharma Laboratoires Pharmaceutiques, France
BP 28—06511 CARROS Cedex—France
Phone: 33-4-93-29-11-28
Web site: www.arkopharma.com/english

Biofarm S.A., Romania
Logafat Tantra nr. 99 Street, Sector 3, Bucharest, Romania
Phone: 40-21-3010637, 40-21-3010633, 40-21-3010632
Fax: 40-21-3010605, 40-21-3010631
Web site: www.biofarm.ro

Bioforce AG, Switzerland
CH-9325 Roggwil TG, Switzerland
Phone: 41-71-454-61-61
Fax: 41-71-454-61-62
Web site: www.bioforce.ch/en

Bioforce USA
437 Route 295, Chatham, NY 12037
Phone: 800-641-7555
Fax: 800-798-7555
Web site: www.bioforceusa.com

Bionorica Arzneimittel GmbH, Germany
Kerschensteiner Strasse 11-15, 92318 Neumarkt, Germany / P.O. Box 1851, D-92308 Neumarkt, Germany
Phone: 49-9181-231-90
Fax: 49-9181-231-265
Web site: www.bionorica.de

Bluebonnet Nutrition Corporation
12915 Dairy Ashford, Sugar Lsmf TX, 77478
Phone: 800-580-8866 / 281-240-3332
Fax: 281-240-3535
Web site: www.bluebonnetnutrition.com

Botanica BioScience Corporation
P.O. Box 1477, Ojai, CA 93024
Phone: 805-646-6062
Fax: 805-646-3026
Web site: www.botanica-bioscience.com

Bruschettini s.r.l., Italy
Via Isonzo, 6, 16147 Genova, Italy
Phone: 39-010-381222
Fax: 39-010-3993312
Web site: www.bruschettini.com

Chai-Na-Ta Corporation, Canada
5965 205A Street, Langley, British Columbia, Canada V2A8C4
Phone: 800-406-4668 (Canada & USA)/ 604-533-8883
Fax: 604-8-588-8891
Web site: www.chainata.com

Dalidar Pharma Ltd., Israel
c.o. Bio-Dar Ltd., Yavne Technology Park, P.O. box 344, Yavne 81103, Israel
Phone: 08-9420930
Fax: 08-9420928

Dansk Droge, Denmark
Industrigrenen 10, Ishøj 2635, Denmark
Phone: 435-65656
Fax: 435-65600
Email: info@danskdroge.dk

Ditta Farmigea S.p.A., Italy
No information available

Dr. Loges & Co. GmbH, Germany
P.O. Box 1262/ Schützenstrasse 5, 21423 Winsen, Germany
Phone: 49-4171-707-0
Fax: 49-4171-707-100
Web site: www.loges.de

Dr. Willmar Schwabe GmbH & Co., Germany
Willmar-Schwabe-Strasse 4, 76227 Karlsruhe, Germany
Phone: 49-721-4005-101
Fax: 49-721-4005-202
Web site: www.schwabe.de; www.schwabepharma.com

EcoNugenics Inc.
2208 Northpoint Parkway, Santa Rosa, CA 95407
Phone: 800-308-5518
Fax: 707-526-7689
Web site: www.econugenics.com

Efamol Ltd., UK
No information available

Enzymatic Therapy
825 Challenger Dr., Green Bay, WI 5431-8328
Phone: 920-469-1313/ 800-783-2286
Fax: 920-469-4400
Web site: www.enzy.com

Essentially Pure Ingredients™
21411 Prairie Street, Chatsworth, CA 91311
Phone: 818-739-6046
Fax: 818-739-6042
Web site: www.essentiallypure.com

Eurovita A/S, Denmark
Svejsegangen 4, 2690 Karlslunde, Denmark
Phone: 45-46-15-22-11
Fax: 45-46-15-32-11
Web site: www.eurovita.dk

General Nutrition Corporation
300 Sixth Avenue, Pittsburgh, PA 15222
Phone: 888-462-2548
Web site: www.gnc.com

General Nutrition Research Laboratories
Fargo, North Dakota
No further information available

GlaxoSmithKline Consumer Healthcare
5 Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 / One Franklin Plaza, Philadelphia, PA 19102 / Consumer Healthcare, P.O. Box 1467, Pittsburgh, PA 15230
Phone: 888-825-5249 (Remifemin® adverse events: 800-965-8804) (Alluna™ Sleep adverse events : 877-725-5862)
Web site: www.gsk.com; www.remifemin.com; www.allunasleep.com

Government Pharmaceutical Organization, Thailand
No information available

Graminex L.L.C.
95 Midland Rd., Saginaw, MI 48603
Phone: 877-472-6469/ 989-797-5502
Fax: 989-799-0020
Web site: www.graminex.com

HBC Protocols, Inc.
8205 Santa Monica Blvd., Suite 472, Los Angeles, CA 90046
Phone: 800-497-3742
Fax: 805-583-7717
Web site: www.hbcstore.com

Health from the Sun/Arkopharma
19 Crosby Drive, Bedford, MA 01730
Phone: 781-276-0505
Fax: 781-276-7335
Web site: www.healthfromthesun.com

Hermes Arzneimittel GmbH, Germany
Georg-Kalb Strasse 5-8, 82049 Grosshesselohe/Munich, Germany
Phone: 49-89-79102-0
Fax: 49-89-79102-280
Web site: www.hermes-arzneimittel.com

The Himalaya Drug Company, India
Makali, Bangalore—562123, India
Phone: 91-80-371-4444/ 91-80-371-4445/91-80-371-4446
Fax: 91-80-371-4468
Web site: www.himalayahealthcare.com

Himalaya USA
10440 Westoffice Drive, houston, Texas 77042
Phone: 713-863-1622/ 800-869-4640
Fax: 713-863-1686/ 800-577-6930
Web site: www.himalayausa.com

IMMODAL Pharmaka GmbH, Austria
Bundesstrasse 44, 6111 Volders/Tirol, Austria
Phone: 43-5224-57678
Fax: 43-5224-57646
Web site: www.immodal.com

Indena S.p.A., Italy
Viale Ortles, 12, 20139 Milano, Italy
Phone: 39-02-574961
Fax: 39-02-57404620
Web site: www.indena.it

Indena USA, Inc.
1001 Fourth Avenue Plaza, Suite 3714, Seattle, WA 98154
Phone: 206-340-6140
Fax: 206-340-0863
Web site: www.indena.com

Inverni della Beffa, Italy
Galleria Passarella 2, 20122 Milano, Italy
Phone: 39-02-574961

Laboratoires Fournier, France
42 re de Longvic, 21300 Chenove, France OR
153 rue de Buzenval, 92380 Garches, France
Phone: 33-3-80-44-70-00
Fax: 33-3-80-44-70-05
Web site: www.groupe-fournier.com

Lichtwer Pharma AG, Germany
Wallenroder Strasse 8-10, 13435 Berlin, Germany
Phone: 49-30-403-70-0
Fax: 49-30-403-70-103
Web site: www.lichtwer.de

Lomapharm, Rudolf Lohmann GmbH KG, Germany
Langes Feld 5, 31860 Emmerthal, Germany
Phone: 49-5155-63-200
Fax: 49-5155-63-240
Web site: www.lomapharm.de

Madaus AG, Germany
Ostmerheimer Strasse 198, D-51109 Köln, Germany
Phone: 49-221-8998-0
Fax: 49-221-8998-701
Web site: www.madaus.de

Mediceutix, Inc.
P.O. Box 21801, Eugene, OR 97402

Mitsui Norin Co., Ltd., Japan
Mitsui-Bekkan, 3-1-20 Muromachi, Nihonbashi, Chuo-ku, Tokyo 103, Japan
Phone: 81-3-3241-3114
Fax: 81-3-3241-6130
Web site: www.mitsui-norin.co.jp/

Natrol, Inc.
21411 Prairie Street, Chatsworth, CA 91311
Phone: 800-326-1520/ 818-739-6000
Fax: 818-739-6001
Web site: www.natrol.com

Natural Wellness
46 Main St./ P.O. Box 1139, Pine Bush, NY 12566
Phone: 800-364-5722
Fax: 845-744-5953
Web site: www.natural-wellness.com, www.liversupport.com

Nature's Way Products, Inc.
10 Mountain Springs Parkway, Springville, UT 84663
Phone: 800-489-1500
Fax: 800-489-1700
Web site: www.naturesway.com

Novartis Consumer Health GmbH, Germany
Zielstattstrasse 40, 81379 Munich, Germany
Phone: 49-89-7877-0
Fax: 49-89-7877-250
Web site: www.novartis-consumerhealth.de

Novogen Inc.
1 Landmark Square, Suite 240, Stamford, CT 06901
Phone: 203-327-1188
Fax: 203-327-0011
Web site: www.novogen.com

Novogen Laboratories Pty Ltd., Australia
140 Wicks Road, North Ryde NSW 2113, Australia
Phone: 61-2-9878-0088
Fax: 61-2-9878-0055
Web site: www.novogen.com

Nutraceutical Corporation
1400 Kearns Boulevard, Park City, UT 84060
Phone: 800-669-8877
Fax: 800-767-8514
Web site: www.nutraceutical.com

Ocean Spray Cranberries, Inc.
Ocean Spray Consumer Affairs Department, Ocean Spray Cranberries, Inc., One Ocean Spray Drive, Lakeville-Middleboro, MA 02349
Phone: 800-662-3263
Web site: www.oceanspray.com

Padma Inc., Switzerland
Wiesenstrasse 5, CH-8603 Schwerzenbach, Switzerland
Phone: 41-0-1-887-00-00
Web site: www.padma.ch/en/

Pharmanex, LLC
75 West Center Street, Provo, UT 84601
Phone: 801-345-1000
Fax: 801-345-9899
Web site: www.pharmanex.com

Pharmaton Natural Health Products
P.O. Box 368/ 900 Ridgebury Road, Ridgefield, CT 06877-0368
Phone: 800-451-6688
Fax: 203-798-5771
Web site: www.pharmaton.com

Pharmaton S.A., Switzerland
P.O. Box 6903 Lugano, Switzerland
Phone: 41-91-610-32-11
Fax: 41-91-610-32-09

Pierre Fabre Médicament, France
45, Place Abel Gance, 92654 Boulogne, France
Phone: 33-01-49-10-80-00
Web site: www.pierre-fabre.com

Razei Bar Industries, Ltd.
P.O. Box 8625, Jerusalem 91086, Israel

Rexall Sundown, Inc.
6111 Broken Sound Parkway, N.W., Boca Raton, FL 33487-3693
Phone: 888-776-5383/ 800-327-0908
Web site: www.rexallsundown.com

Sanofi-Synthelabo, France
174, av. De France, 75013 Paris, France
Phone: 33-1-5377-4000
Fax: 33-1-5377-4265
Web site: http://en.sanofi-synthelabo.com

Schaper & Brümmer GmbH & Co. KG, Germany
HRA 11133, Amtsgericht Braunschweig, 38251 Salzgitter, Germany
Phone: 49-5341-307-0
Fax: 49-53410307-124
Web site: www.schaper-bruemmer.de

Scotia Pharmaceuticals Ltd., UK
No information available

Searle, UK
No information available

ShamanBotanicals.com
Shaman.com, 213 E. Grand Avenue, South, San Francisco, CA 94080
Phone: 650-952-7070
Fax: 208-247-2533
Web site: www.shamanbotanicals.com

Solaray, Inc.
1400 Kearns Boulevard, Park City, UT 84060
Phone: 800-669-8877
Fax: 800-767-8514
Web site: www.nutraceutical.com

Solvay Arzneimittel GmbH, Germany
Hans-Böckler-Allee 20, D-30177 Hannover, Germany
Phone: 49-511-857-2400
Fax: 49-511-857-3120
Web site: www.solvay-arzneimittel.de

Steigerwald Arzneimittel GmbH, Germany
Havelstrasse 5, D-64295 Darmstadt, Germany/ P.O. Box 10 13 45,
D-64231 Darmstadt, Germany
Phone: 49-6151-3305-0
Fax: 49-6151-3305-410
Web site: www.steigerwald.de

Steiner Arzneimittel, Germany
P.O. Box 45020, 12175 Berlin, Germany
Web site: www.steinerarznei-berlin.de

Swanson Health Products
P.O. Box 2803, Fargo, ND 58108-2803
Phone: 800-437-4148/ 800-603-3198
Fax: 800-834-7197
Web site: www.swansonvitamins.com

Therabel Pharma, Belgium
Rue Egide Van Ophem 108, B-1180 Brussels, Belgium
Phone: 32-2-370-46-11
Fax: 32-2-370-46-90
Web site: www.therabel.com

Thomas J. Lipton Co. (now **Unilever Bestfoods, North America**)
Phone: 800-697-7887
Web site: www.lipton.com

Thorne Research
P.O. Box 25/ 25820 Highway 2 West, Dover, ID 83825
Phone: 208-263-1337
Fax: 208-265-2488
Web site: www.thorne.com

Traditional Medicinals, Inc.
4515 Ross Road, Sebastopol, CA 95472
Phone: 800-543-4372
Fax: 707-823-1599
Web site: www.traditionalmedicinals.com

Wakunaga of America Co., Ltd.
23501 Madero, Mission Viejo, CA 92691-2774
Phone: 800-421-2998/ 949-855-2776
Fax: 949-458-2764
Web site: www.kyolic.com

WBL Peking University Biotech Co. Ltd., China
No information available

Weber & Weber International GmbH & Co. KG, Germany
Herrchinger Str. 33, 82263 Inning/Ammersee, Germany
Phone: 49-8143-927-0
Fax: 49-8143-927-110
Web site: www.weber-weber.net

Weber & Weber USA
1245 Glen Heather
Windermere, FL 34786
Phone: 888-301-1084/ 888-989-3237
Web site: www.webernweber.com

Wei-Xin Company, China
No information available

Zeller AG, Switzerland
Seeblickstrasse 4, CH-8590 Romanshorn 1, Switzerland
Phone: 41-71-466-0500
Fax: 41-71-463-5007
Web site: www.zellerag.ch

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