HEALTH BENEFITS of NUTS and DRIED FRUITS

EDITED BY

Cesarettin Alasalvar
Jordi Salas-Salvadó
Emilio Ros
Joan Sabaté

CRC Press
Taylor & Francis Group

Health Benefits of Nuts and Dried Fruits

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Health Benefits of Nuts and Dried Fruits

Edited by
Cesarettin Alasalvar, Jordi Salas-Salvadó,
Emilio Ros, and Joan Sabaté


CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

International Standard Book Number-13: 978-1-138-04284-1 (Hardback)
International Standard Book Number-13: 978-1-315-17333-7 (eBook)

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Contents

PREFACE IX
EDITORS XI
CONTRIBUTORS XV

1 Health Benefits of Nuts and Dried Fruits: An Overview 1
CESARETTIN ALASALVAR, JORDI-SALAS SALVADÓ, EMILIO ROS, AND JOAN SABATÉ

SECTION I NUTS

2 Nuts: Nutrients, Natural Antioxidants, Fat-Soluble Bioactives, and Phenolics 13
CESARETTIN ALASALVAR, SUI KIAT CHANG, AND FEREIDOON SHAHIDI

3 Effect of Nut Consumption on Blood Lipids, Lipoproteins, and Apolipoproteins – Summary of the Evidence 59
JOAN SABATÉ, EDWARD BITOK, AND SUJATHA RAJARAM

4 Nuts and Cardio-Metabolic Syndrome (Endothelial Function, Inflammation, and Blood Pressure) 91
PABLO HERNÁNDEZ-ALONSO, MARTA GUASCH-FERRÉ, MÒNICA BULLÓ, AND JORDI SALAS-SALVADÓ

5 The Energetics of Nut Consumption: Oral Processing, Appetite, and Energy Balance 125
BREANNA M. MCARTHUR, KELLY A. HIGGINS, STEPHANIE R. HUNTER, AND RICHARD D. MATTES

6 Nut Consumption and Cardiovascular Disease **155**
TASNIM F. IMRAN AND LUC DJOUSSÉ

7 Nut Consumption and Adiposity **167**
MAIRA BES-RASTROLLO AND MIGUEL ÁNGEL MARTÍNEZ-GONZÁLEZ

8 Nuts in the Prevention and Management of Diabetes **181**
STEPHANIE K. NISHI, EFFIE VIGUILIOUK, SONIA BLANCO MEJIA, DAVID J.A. JENKINS, JOHN L. SIEVENPIPER, AND CYRIL W.C. KENDALL

9 Nut Consumption and Cancer **223**
HEINZ FREISLING AND HWAYOUNG NOH

10 Nut Consumption and All-Cause and Cause-Specific Mortality and Longevity: A Review of the Evidence **247**
DAGFINN AUNE

11 Nuts and Brain Health: Cognition, Depression, and Neurodegenerative Diseases **261**
EMILIO ROS AND ALEIX SALA-VILA

12 Nuts in Healthy Dietary Patterns and Dietary Guidelines **289**
ELIZABETH P. NEALE AND LINDA C. TAPSELL

13 Nuts: Gut Health and Microbiota **313**
SERENA GALIÈ, MÒNICA BULLÓ, ALESSANDRO ATZENI, PABLO HERNÁNDEZ-ALONSO, JANANEE MURALIDHARAN, AND JORDI SALAS-SALVADÓ

SECTION II DRIED FRUITS

14 Dried Fruits: Nutrients, Natural Antioxidants, and Phytochemicals **335**
CESARETTIN ALASALVAR, SUI KIAT CHANG, AND FEREIDOON SHAHIDI

15 Bioavailability of Nutrients and Phytochemicals from Dried Fruits **369**
ARIANNA CARUGHI, DANIEL GALLAHER, AND GIUSEPPINA MANDALARI

16 Effect of Dried Fruits on Lipid Profiles (Dose–Response, Effects on Different Groups and Different Dried Fruits, and Cardiovascular Diseases) 397
CHELSEA GARCIA AND CHRISTOPHER N. BLESSO

17 Dried Fruits and Cardio-Metabolic Syndrome (Endothelial Function, Inflammation, and Blood Pressure) 413
VALERIE SULLIVAN, KRISTINA PETERSEN, AND PENNY KRIS-ETHERTON

18 Dried Fruits in the Prevention and Control of Diabetes (Insulin Resistance and Prediabetes) 437
KRISTIE (KORBUA) SRICHAIKUL, MELODY ONG, ZOHA PRASLA, YAKUP KOHEN, IRIS MANDALOZANO, MELANIE PAQUETTE, SANDHYA SAHYE-PUDARUTH, DARSHNA PATEL, CYRIL W.C. KENDALL, JOHN L. SIEVENPIPER, AND DAVID J.A. JENKINS

19 Dried Fruit Consumption and Cancer 449
BRADLEY BOLLING, XIAOCAO LIU, AND JIYUAN LIU

20 Dried Fruits: Bone Health and Osteoprotection 469
BAHRAM H. ARJMANDI AND KELLI S. GEORGE

21 Dried Fruits: Gut Health and Microbiota 487
MARÍA MARHUENDA MUÑOZ AND ROSA M. LAMUELA RAVENTÓS

22 Other Health Benefits of Dried Fruits: Cognitive Function, Appetite, Satiety Control, Intestinal Health, and Hepatoprotection 497
JIE LIU, ZIYUAN WANG, AND MINGSI XIE

23 Dried Fruits as Components of Health Dietary Patterns 513
ANA PAULA SILVA CALDAS AND JOSEFINA BRESSAN

INDEX *527*

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Preface

Nuts and dried fruits are nutrient-rich foods and constitute an excellent means of delivering health-promoting bioactive compounds. As such, they serve as important healthful snack items, besides being part of many traditional and new recipes in gastronomy worldwide. Frequent consumption of nuts and/or dried fruits is highly recommended to obtain the full benefit of the nutrients, bioactives, and antioxidants that they contain, together with their desirable flavor (taste and aroma).

Consistent scientific evidence suggests that individuals who regularly consume sizable amounts of nuts (30 or 42.5 g/day, depending on recommendations by the European Food Safety Authority [EFSA] or the US Food and Drug Administration [FDA], respectively) and/or dried fruits (30–40 g/day, depending on the fruit) disclose lower rates of some chronic non-communicable diseases. The health effects of nuts encompass management of obesity and reduced incidence of cardiovascular diseases (CVD), type-2 diabetes, various types of cancers, and other diet-related chronic diseases. The strongest and most consistent beneficial effect of nut consumption is its association with reduced CVD rates. The salutary effects of nuts, together with the demonstration that, in spite of their high energy content, they do not promote adiposity and may help control body weight, has informed many lifestyle guidelines worldwide aimed at preventing CVD. Thus far, the FDA has approved three qualified health claims for nuts in general and walnuts and macadamias in particular, whereas the EFSA has approved one authorized health claim for walnuts.

Concerning dried fruits, the scientific evidence is more limited and less conclusive, but in recent years several studies have suggested their potential health benefits for glucose metabolism and other cardiovascular risk factors, as well as for osteoporosis, constipation, and other common disorders typically affecting people in developed countries. There is only one health claim approved by the EFSA for dried fruits, which refers to prunes and gastrointestinal health.

This book consists of 23 chapters divided into two sections preceded by an introductory chapter (Chapter 1). Section I includes 12 chapters on nuts (Chapters 2–13), and Section II includes 10 chapters on dried fruits (Chapters 14–23). The multifunctional health benefits of the most popular tree nuts (such as almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pistachios, and walnuts), peanuts (a legume that is included in the nut group because of a similar nutrient composition and health effects), and dried fruits (such as apricots, dates, figs, prunes, and raisins) are reviewed thoroughly. Where available, information on the health benefits of the least popular nuts and dried fruits is also covered. In addition, the

compositional and nutritional characteristics, natural antioxidants, and bioactives as well as phenolics/phytochemicals of nuts and dried fruits are comprehensively reviewed in Chapters 2 and 14, respectively.

We are most grateful to the contributors to this book, who are internationally renowned researchers, for their all-encompassing account of the the issues of concern on the health benefits of nuts and dried fruits. The book will serve as a major resource for those interested in the health aspects of nuts and dried fruits. Biochemists, food scientists, dietitians, nutritionists, and health professionals, including medical doctors, from academia, government, and nutrition clinics as well as industry should find the contents of this book of much interest. Although this book serves primarily as a reference manual, it also summarizes the current state of knowledge in key research areas and contains novel ideas for future research and development. In addition, it provides easy-to-read text suitable for teaching senior undergraduate and postgraduate students in the relevant areas. Nut and dried fruit growers, processors, exporters, and decision makers will obtain maximum benefit from this publication. Finally, we trust that this book will pave the way for a better appreciation of the concept, products, and opportunities in the field for professionals, public health regulators, processors, and consumers.

Cesarettin Alasalvar

Jordi Salas-Salvadó

Emilio Ros

Joan Sabaté

Editors

Cesarettin Alasalvar, Ph.D., FIFT, FISNFF, is the director of the Food Institute at TÜBİTAK Marmara Research Center (MRC) in Turkey and is also an Associate Professor of Food Science and Engineering. His research interests focus mainly on development of functional foods and nutraceuticals, nutritional and functional properties of foods, bioactive properties of phytochemicals, and separation and identification of bioactives as well as bioavailability of foods and human clinical trials. Dr. Alasalvar has been active in the Institute of Food Technologists (IFT) programs for many years and served as a past chair of the Nutraceuticals and Functional Foods Division. He was one of the co-founders of the International Society for Nutraceuticals and Functional Foods (ISNFF) and also served as a past president of ISNFF. Dr Alasalvar is an editor of *Food Chemistry* journal and serves as an editorial board member of *Journal of Functional Foods*, *Journal of Food Bioactives*, and *Food Production, Processing and Nutrition* journal. He is active in Horizon 2020 Programme and has served as Turkish Delegate of Societal Challenges II (Food Security, Sustainable Agriculture and Forestry, Marine, Maritime and Inland Water Research, and the Bio economy) of the Horizon 2020 Programme Committee since 2017. He is also the Scientific Advisory Board Member of PRIMA (Partnership for Research and Innovation in the Mediterranean Area – Horizon 2020) and serves on the Academic Committee and World Forum for Nutrition Research and Dissemination Committee Members of International Nut and Dried Fruit Council (INC). Dr Alasalvar is the editor of six books and holds five patents. His work has led to the publication of over 100 research articles in the form of peer-reviewed journals (*h*-index of 36) and book chapters. He has considerable experience in coordinating numerous national and European Union funded projects (FP7-NutraHEALTH and IPA-INNOFOOD). Dr Alasalvar has received a number of prestigious international awards, including the IFT-Fellow Award (2012), the TÜBİTAK MRC – Most Successful Researcher Award (2012), the ISNFF-Merit Award (2014), the Sabri Ülker International Science and Innovation Award on Food, Nutrition, and Health (2015), and the ISNFF-Fellow Award (2019) in recognition of his pioneering scientific achievements.

Jordi Salas-Salvadó**, M.D., Ph.D.,** is Professor of Nutrition, director of the Human Nutrition Research Unit at the Rovira i Virgili University (URV) and clinical head of the Nutrition Unit of the Internal Medicine Service of the Hospital Sant Joan de Reus, Spain. He is also the vice-president of the Pere i Virgili Health Research Institute, principal investigator of the Pathophysiology of Obesity and Nutrition Research Network at Instituto de Salud Carlos III, chairman of the World Forum for Nutrition

Research and Dissemination (INC), director of the Catalan Center of Nutrition (CCNIEC), and member of the Network of Experts of the Public Health Agency of Catalonia (ACSA). Previously, he was a member of the Scientific Committee of the Spanish Agency for Food Safety, president of the Spanish Federation of Societies of Nutrition, Food, and Dietetics (FESNAD), and vice-dean – head of studies in Human Nutrition and Dietetics (URV). His research interests focus mainly on human clinical trials evaluating the effect of diet and dietary components on obesity, type-2 diabetes mellitus, metabolic syndrome, and cardiovascular disease (CVD). He is one of the leaders of the PREDIMED study, a landmark trial evaluating the effect of the Mediterranean Diet on the primary prevention of CVD. He is now the director and chair of the Steering Committee of the PREDIMED-PLUS study, an ongoing multi-center, randomized, and primary prevention trial on 6,900 overweight/obese participants with metabolic syndrome. He has directed more than 30 research projects funded by public agencies and 25 projects in collaboration with pharmaceutical and food industries. He is principal investigator or co-principal investigator of other projects funded by the Instituto de Salud Carlos III, the European Commission, and National Institutes of Health (USA). He has published more than 550 original research articles in peer-reviewed journals, has been editor of six books, and has co-authored more than 65 other books (*h*-index of 63 and more than 18,000 citations). He has also received an award as a highly cited researcher 2018 by Clarivate Analytics.

Emilio Ros, M.D., Ph.D, is Emeritus Investigator, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Barcelona, Spain; founder and former head of the Lipid Clinic, Endocrinology, and Nutrition Department and Hospital Clinic, Barcelona; and former Principal Investigator of the research groups "Hypertension, Lipids, and Atherosclerosis" at IDIBAPS, Barcelona and "Nutrition, Lipids, and Cardiovascular Risk", CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain. He was founder and vice-president of Sociedad Española de Arteriosclerosis (SEA), founder and editor of the official journal of SEA "Clínica e Investigación en Arteriosclerosis," and founder and president of Sociedad Iberoamericana de Aterosclerosis. He underwent postgraduate training in the USA (New York and Boston, 1970–1976) and was certified by the American Board of Internal Medicine and the American Board of Internal Medicine, subspecialty Gastroenterology. He is active member of the editorial boards of *Metabolism* and *Nutrients*, and former associate editor of the *British Journal of Nutrition* and *Medicina Clínica* (Barcelona). His research interests include nutrition in the prevention of cardiovascular diseases, age-related cognitive decline, and dementia, with especial interest in the Mediterranean diet and walnuts, plant sterols, blood membrane fatty acids, genetic dyslipidemias, cardiovascular risk assessment, and vascular imaging techniques. He also led the nutritional intervention of the landmark PREDIMED trial of Mediterranean diet for primary cardiovascular prevention and serves on the steering committees of the PREDIMED and PREDIMED-PLUS studies. Dr Ros has received numerous research grants from public and private agencies. He has published more than 380 original papers, over 130 review papers, 30 editorials, and 90 scientific textbook chapters (*h*-index of 61). He has been speaker at many scientific conferences and professor of many

postgraduate courses in the fields of nutrition, lipid metabolism, atherosclerosis, and cardiovascular prevention. He received the award for best scientific career in Nutrition, Instituto Danone Spain 2013; the Grande-Covián Award for a life career in Nutrition, SEA 2014; the Excellence in Research Award, International Nut Council 2014; and the CCNIEC award for a life career in Nutrition, Barcelona 2015. He has also received an award as a highly cited researcher globally for the period 2006–2016 by Clarivate Analytics.

Joan Sabaté, M.D., Dr.PH, is professor of Nutrition and Epidemiology at Loma Linda University School of Public Health where he directs the Center for Nutrition, Lifestyle, and Disease Prevention. Originally from Spain, Dr Sabaté is a board-certified physician in Internal Medicine who moved to the USA to further train in Public Health Nutrition. He obtained a doctorate in Nutrition and a Fellowship in Nutritional Epidemiology. Dr Sabaté was the principal investigator of a nutrition intervention trial that directly linked the consumption of walnuts to significant reductions in serum cholesterol, published in the *New England Journal of Medicine* in 1993. The Archives of Internal Medicine later published his findings of a pooled analysis of 25 intervention trials establishing the benefits of nut consumption for blood lipid levels and lowering the risk of heart disease. He has been the principal investigator of over 30 clinical trials investigating the health effects of nuts and other plant foods, funded by public and private agencies. He enjoys conducting research and disseminating the findings. He has authored more than 200 research articles in the scientific literature, many of them in high-impact journals (*h*-index of 57 and more than 10,500 citations). Dr Sabaté is co-investigator of the Adventist Health Studies, prospective epidemiological studies relating dietary intake with health outcomes that have the largest cohorts of vegetarians. He is editor of the reference book *Vegetarian Nutrition* published by CRC Press, and was the principal architect of the Vegetarian Food Guide Pyramid released in 1987 at the 3rd International Congress on Vegetarian Nutrition and redesigned in 2008. He has been chair of the 4th–7th International Congress on Vegetarian Nutrition, and he edited the congress proceedings published in the *American Journal of Clinical Nutrition*. For the past 10 years, Dr Sabaté has directed the Environmental Nutrition research program at the Loma Linda University School of Public Health. This program focuses on sustainable diets and explores the interrelationships between the environmental and health impacts of food choices, and ultimately seeks to improve the sustainability, health, and equity of food systems. He is editor of the book *Environmental Nutrition: Connecting Health and Nutrition with Environmentally Sustainable Diets*, published by Elsevier.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Contributors

Cesarettin Alasalvar
TÜBİTAK Marmara Research Center
Food Institute
Gebze-Kocaeli, Turkey

Bahram H. Arjmandi
Department of Nutrition, Food, and Exercise Sciences
College of Human Sciences
Florida State University
Tallahassee, Florida

Alessandro Atzeni
Department of Biochemistry and Biotechnology
School of Medicine
Rovira i Virgili University
Reus, Spain

Dagfinn Aune
Department of Epidemiology and Biostatistics
School of Public Health
Imperial College London
London, United Kingdom

and

Department of Nutrition
Bjørknes University College
Oslo, Norway

and

Department of Endocrinology
Morbid Obesity and Preventive Medicine
Oslo University Hospital
Oslo, Norway

Maira Bes-Rastrollo
Department of Preventive Medicine and Public Health
University of Navarra
Pamplona, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

and

IdiSNA
Navarra Institute for Health Research
Pamplona, Spain

Edward Bitok
Center for Nutrition, Healthy Lifestyle, and Disease Prevention
School of Public Health
Loma Linda University
Loma Linda, California

and

Department of Nutrition and Dietetics
School of Allied Health Professions
Loma Linda University
Loma Linda, California

Christopher N. Blesso
Department of Nutritional Sciences
University of Connecticut
Storrs, Connecticut

Bradley Bolling
Department of Food Science
University of Wisconsin-Madison
Madison, Wisconsin

Josefina Bressan
Department of Nutrition and Health
Universidade Federal de Viçosa
Viçosa, Brazil

Mònica Bulló
Department of Biochemistry and Biotechnology
School of Medicine
Rovira i Virgili University
Reus, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

Ana Paula Silva Caldas
Department of Nutrition and Health
Universidade Federal de Viçosa
Viçosa, Brazil

Arianna Carughi
Sun-Maid Growers of California
Kingsburg, California

Sui Kiat Chang
Department of Nutrition and Dietetics
School of Health Sciences
International Medical University
Kuala Lumpur, Malaysia

Luc Djoussé
Department of Medicine
Division of Aging
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

and

Veterans Affairs Boston Healthcare System
Boston, Massachusetts

Heinz Freisling
Nutritional Methodology and Biostatistics Group
International Agency for Research on Cancer
Lyon, France

Serena Galiè
Department of Biochemistry and Biotechnology
School of Medicine
Rovira i Virgili University
Reus, Spain

Daniel Gallaher
Department of Food Science and Nutrition
University of Minnesota
St. Paul, Minnesota

Chelsea Garcia
Department of Nutritional Sciences
University of Connecticut
Storrs, Connecticut

Kelli S. George
Department of Nutrition, Food, and Exercise Sciences
College of Human Sciences
Florida State University
Tallahassee, Florida

Marta Guasch-Ferré
Department of Nutrition
Harvard TH Chan School of Public Health
Boston, Massachusetts

Pablo Hernández-Alonso
Department of Biochemistry and Biotechnology
School of Medicine
Rovira i Virgili University
Reus, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

Kelly A. Higgins
Department of Food Science
Purdue University
West Lafayette, Indiana

Stephanie R. Hunter
Department of Nutrition Science
Purdue University
West Lafayette, Indiana

Tasnim F. Imran
Department of Medicine
Cardiology Section
Boston Medical Center
Boston University School of Medicine
Boston, Massachusetts

and

Department of Medicine
Division of Aging
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

and

Veterans Affairs Boston Healthcare System
Boston, Massachusetts

David J.A. Jenkins
Department of Nutritional Sciences and Medicine
Faculty of Medicine
University of Toronto
Toronto, Ontario

and

Toronto 3D Knowledge Synthesis and Clinical Trials Unit
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

and

Li Ka Shing Knowledge Institute
St. Michael's Hospital
Toronto, Ontario

and

Division of Endocrinology and Metabolism
St. Michael's Hospital
Toronto, Ontario

Cyril W.C. Kendall
Toronto 3D Knowledge Synthesis and Clinical Trials Unit
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

and

Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ontario

and

College of Pharmacy and Nutrition
University of Saskatchewan
Saskatoon, Saskatchewan

Yakup Kohen
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

Penny Kris-Etherton
Department of Nutritional Sciences
The Pennsylvania State University
University Park, Pennsylvania

Jie Liu
Department of Food Science
School of Food and Health
Beijing Technology and Business University (BTBU)
Beijing, China

Jiyuan Liu
Department of Food Science
University of Wisconsin-Madison
Madison, Wisconsin

and

College of Food Science and Nutritional Engineering
China Agricultural University
Beijing, China

Xiaocao Liu
Department of Food Science
University of Wisconsin-Madison
Madison, Wisconsin

and

School of Food Science and Engineering
South China University of Technology
Guangzhou, China

Miguel Ángel Martínez-González
Department of Preventive Medicine and Public Health
University of Navarra
Pamplona, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

and

IdiSNA
Navarra Institute for Health Research
Pamplona, Spain

and

Department of Nutrition
TH Chan Harvard School of Public Health
Boston, Massachusetts

Giuseppina Mandalari
Department of Chemical, Biological, Pharmaceutical, and Environmental Science
University of Messina
Messina, Italy

Iris Mandalozano
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

Richard D. Mattes
Department of Nutrition Science
Purdue University
West Lafayette, Indiana

Breanna M. McArthur
Department of Food Science
Purdue University
West Lafayette, Indiana

Sonia Blanco Mejia
Toronto 3D Knowledge Synthesis and Clinical Trials Unit
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

and

Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ontario

María Marhuenda Muñoz
Department of Nutrition, Food Sciences, and Gastronomy
School of Pharmacy and Food Sciences
University of Barcelona
Barcelona, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

and

Nutrition and Food Safety Research Institute (INSA-UB)
University of Barcelona
Barcelona, Spain

Jananee Muralidharan
Department of Biochemistry and Biotechnology
School of Medicine
Rovira i Virgili University
Reus, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

Elizabeth P. Neale
School of Medicine
Faculty of Science, Medicine, and Health
University of Wollongong
Wollongong, Australia

Stephanie K. Nishi
Toronto 3D Knowledge Synthesis and Clinical Trials Unit
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

and

Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ontario

Hwayoung Noh
Nutritional Methodology and Biostatistics Group
International Agency for Research on Cancer
Lyon, France

Melody Ong
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

Melanie Paquette
Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ontario

and

Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

Darshna Patel
Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ontario

and

Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

Kristina Petersen
Department of Nutritional Sciences
The Pennsylvania State University
University Park, Pennsylvania

Zoha Prasla
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

Sujatha Rajaram
Center for Nutrition, Healthy Lifestyle, and Disease Prevention
School of Public Health
Loma Linda University
Loma Linda, California

Rosa M. Lamuela Raventós
Department of Nutrition, Food Sciences, and Gastronomy
School of Pharmacy and Food Sciences
University of Barcelona
Barcelona, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

and

Nutrition and Food Safety Research Institute (INSA-UB)
University of Barcelona
Barcelona, Spain

Emilio Ros
Endocrinology and Nutrition Service
Institut d'Investigacions Biomèdiques August Pi Sunyer
Hospital Clínic
Barcelona, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

Joan Sabaté
Center for Nutrition, Healthy Lifestyle, and Disease Prevention
School of Public Health
Loma Linda University
Loma Linda, California

Sandhya Sahye-Pudaruth
Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ontario

and

Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

Aleix Sala-Vila
Barcelonaβeta Brain Research Center (BBRC)
Pasqual Maragall Foundation
Barcelona, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

Jordi-Salas Salvadó
Department of Biochemistry and Biotechnology
School of Medicine
Rovira i Virgili University
Reus, Spain

and

CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

Fereidoon Shahidi
Department of Biochemistry
Memorial University of Newfoundland
St. John's, Newfoundland and Labrador

John L. Sievenpiper
Toronto 3D Knowledge Synthesis and Clinical Trials Unit
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

and

Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ontario

and

Division of Endocrinology and Metabolism
St. Michael's Hospital
Toronto, Ontario

and

Li Ka Shing Knowledge Institute
St. Michael's Hospital
Toronto, Ontario

Kristie (Korbua) Srichaikul
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

Valerie Sullivan
Department of Nutritional Sciences
The Pennsylvania State University
University Park, Pennsylvania

Linda C. Tapsell
School of Medicine
Faculty of Science, Medicine, and Health
University of Wollongong
Wollongong, Australia

Effie Viguiliouk
Toronto 3D Knowledge Synthesis and Clinical Trials Unit
Clinical Nutrition and Risk Factor Modification Center
St. Michael's Hospital
Toronto, Ontario

and

Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ontario

Ziyuan Wang
Department of Food Science
School of Food and Health
Beijing Technology and Business University (BTBU)
Beijing, China

Mingsi Xie
Department of Food Science
School of Food and Health
Beijing Technology and Business University (BTBU)
Beijing, China

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 1

Health Benefits of Nuts and Dried Fruits

An Overview

Cesarettin Alasalvar, Jordi-Salas Salvadó, Emilio Ros, and Joan Sabaté

1.1 Introduction 1
1.2 Health Benefits of Nuts 2
1.3 Health Benefits of Dried Fruits 4
1.4 Conclusion 5
References 5

1.1 Introduction

Nuts and dried fruits have been part of the human diet since prehistoric times [1,2]. They are key food categories in most plant-based diets, such as vegetarian diets [3], the Mediterranean diet, and other healthy regional diets [4].

According to the botanical definition, a nut is simply a dried fruit with one seed (rarely two) in which the ovary walls are very hard (stony or woody) at maturity, and the seed is unattached or free within the ovary wall. However, the word *nut* is commonly used to refer to any large, oily kernel in a shell that can be eaten as food. The most commonly consumed nuts are almonds, Brazil nuts, cashews, hazelnuts, macadamias, peanuts, pecans, pine nuts, pistachios, and walnuts. Peanuts are botanically legumes but, because of their similar nutrient composition and their proven

cardiovascular health benefits, they are considered as nuts by both nutritionists and consumers.

Fresh fruits are processed by various techniques to become dried fruits in order to extend their shelf life. Therefore, dried fruits are a concentrated form of fresh fruits with lower moisture content. Fruits can be dried whole, in halves, or in slices. In this form, they are easy to store and distribute, are available throughout the year, and are a healthier alternative to salty or sugary snacks. Apples, apricots, currants, dates, figs, peaches, pears, prunes, and raisins are referred to as traditional dried fruits, although other fruits such as blueberries, cranberries, and strawberries have also been included in this food category.

Nuts and dried fruits are nutrient-rich foods and constitute an excellent means to deliver health-promoting bioactive compounds. As such, they serve as important healthful snack items, besides being part of many traditional and new recipes of gastronomy worldwide. Frequent consumption of nuts and/or dried fruits is highly recommended to obtain the full benefit of the nutrients, bioactives, and antioxidants that they contain, together with their desirable flavor. The macronutrients, micronutrients, and other health-promoting bioactive compounds contained in nuts and dried fruits may synergistically interact to modulate the risk of cardiometabolic and other non-communicable diseases through various mechanisms.

Several prospective studies, clinical trials, and experimental investigations have reported beneficial effects on several outcomes after nut consumption [5]. The benefits of dried fruits, however, have been less explored [6].

This overview chapter summarizes the nutritional significance and health benefits of nuts and dried fruits and also discusses their great potential as salutary foods for a number of diseases afflicting humans.

1.2 Health Benefits of Nuts

Tree nuts are recognized as healthy foods because of their unique nutritional attributes. Tree nuts and peanuts are rich in monounsaturated fatty acids, with the exception of Brazil nuts, heartnuts, pine nuts, and walnuts, which are rich in polyunsaturated fatty acids [7]. They are good sources of dietary fiber [8,9] and provide macronutrients, micronutrients, fat-soluble bioactives, and phytochemicals [9–12].

Frequent nut consumption has especially been shown to have beneficial effects on the cardiovascular system. It has been well over two decades since nut consumption was first associated with a reduced risk of coronary heart disease (CHD) in the Adventist Health Study cohort [13] and its lipid-lowering effects shown in a randomized controlled trial [14]. In large epidemiologic studies, the frequency of nut consumption was consistently related to lower rates of CHD and total cardiovascular disease (CVD) incidence and mortality [15]. The frequency of nut consumption was also related to lower rates of sudden death in a large cohort of men, as well as lower rates of peripheral artery disease [16], atrial fibrillation [17], and all-cause and CVD mortality [15,18].

Nuts may exert a protective effect on CVD through different mechanisms. The most recognized is their lipid-lowering effect, which has consistently been demonstrated in several population groups using different types of nuts, study designs,

and comparator diets [19,20]. However, the magnitude of the reduced risk of CHD associated with nut consumption cannot be explained only by the cholesterol lowering effect.

Thus, nuts may protect against CVD through other potential mechanisms such as improving endothelial function, but no effect on inflammation [21] and oxidation [22], reducing postprandial glycaemia and insulin resistance while substituting other sources of carbohydrates [23], or increasing satiety [24]. Nut consumption has also recently been shown to change gut microbiota composition and metabolism with potential beneficial effects on cardiovascular risk factors [25].

Because nuts are an energy-dense food containing a high amount of fat, a widespread concern regarding their consumption is that it may lead to weight gain and obesity, and consequently increase the risk of type-2 diabetes (T2D) and other comorbidities. In addition, because nuts are frequently consumed salted, it is believed that they could contribute to an increased risk of hypertension. However, there is consistent evidence that frequent nut consumption does not lead to any appreciable weight gain or increase in the risk of abdominal obesity when incorporated into healthy diets [26,27]. Moreover, the evidence suggests that nut consumption does not increase insulin resistance in the long term and may even increase insulin sensitivity [28], and that it ameliorates endothelial function [21]. In addition, an inverse association was found between the frequency of nut consumption and the prevalence and incidence of metabolic syndrome (MetS) [29]. Finally, some clinical trials evaluated the effect of nuts in individuals with MetS and found that they may have benefited some of the components of the syndrome [29]. However, controversy exists as to the protective effect of nuts against T2D. Nuts may lower the risk of incident T2D in women, but the effect inconclusive in men [15]. Furthermore, limited evidence suggests that nuts might reduce blood pressure [30].

There is also incipient evidence that nut consumption may beneficially impact non-cardiovascular outcomes. Thus, nuts appear to reduce the risk of certain types of cancer [31,32], delay age-related cognitive decline [33], reduce the risk of depression [34], and improve sperm motility and other parameters of fertility [35].

In summary, a large body of scientific evidence suggests that individuals who regularly consume sizable amounts of nuts (30 or 42.5 g/day, depending on recommendation by European Food Safety Authority [EFSA] or the Food and Drug Administration [FDA], respectively) disclose lower rates of some chronic non-communicable diseases. Thus far, the FDA has approved three qualified health claims on nuts in general and walnuts and macadamias in particular [36,37,63], whereas the EFSA has approved one authorized health claim for walnuts [38]. Nuts have been included in the American Heart Association's (AHA) report on goals for health promotion and disease reduction for 2020 [39], in the recent AHA/American College of Cardiology Guidelines on lifestyle factors to reduce CVD risk, and in the Canadian Cardiovascular Society Guidelines and those of other National Institutes of Health and Scientific Societies. Nuts are also an important component of the Mediterranean diet [40], vegetarian diets [41], and any plant-based dietary pattern recommended for health [42].

Section I of this book provides a comprehensive overview on the nutritional profiles, health-promoting phytochemicals/bioactives, and health benefits of nuts when included in healthy dietary patterns.

1.3 Health Benefits of Dried Fruits

Dried fruits are a good source of energy due to their high carbohydrate content, contain small amounts of lipids and protein, and are rich sources of essential nutrients. Thus, dried fruits contain both water-soluble vitamins (betaine, choline, folate, niacin, pantothenic acid, pyridoxine, riboflavin, thiamine, and vitamin C) and fat-soluble vitamins (A, E, and K). Among them, vitamins A, C, and E are well known for their antioxidant properties. Dried fruits are also good sources of fiber and minerals [9]. In addition, they contain a wide array of bioactive phytochemicals, such as phenolic acids (hydroxycinnamic acids and hydroxybenzoic acids), flavonoids (anthocyanins, flavan-3-ols, flavonols, and flavones), phytoestrogens, carotenoids, tannins (proanthocyanins and hydrolysable tannins), stilbenes, and chalcones/dihydrochalcones, all powerful antioxidants. The positive health effects of the bioactive phytochemicals present in dried fruits are probably related to their strong antioxidant activities, among other mechanism [6,43].

With regard to health claims for dried fruits, the EFSA authorizes health claims provided that they are based on scientific evidence and can be easily understood by consumers. There has only been one health claim approved thus far by the EFSA for dry fruits, which refers to prunes and gastrointestinal health [44]. In order to obtain the claimed effect, about 100 g of prunes should be consumed daily. No health claim for dried fruits has been approved by the FDA.

Concerning dried fruits, the scientific evidence is more limited and not as conclusive as that available for nuts, but in the last decade it has suggested that individuals who regularly consume generous amounts of dried fruits experience favorable effects in terms of CVD, sudden cardiac death, stroke, cardiometabolic syndrome (endothelial function, inflammation, and blood pressure) [45–47], various types of cancer [48,49], T2D [23,50], obesity [51], and bone health [52,53], as well as gut health and microbiota [54–56], and other benefits for cognitive function, appetite, satiety control, and hepatoprotection [57], although for some outcomes controversies still exist. At any rate, daily consumption of dried fruits is recommended in order to obtain the full benefit of the nutrients and health-promoting phytochemicals, including antioxidants, that they contain, together with their desirable taste and aroma [58,59].

Because of the high sugar content of dried fruits, ranging from 38 g/100 g in prunes to 73 g/100 g in cranberries [9], they are expected to have a high glycemic index (70 and above) and thus promote high insulin responses. However, recent studies have shown that dried fruits have a low (55 and under) to moderate (56–69) glycemic and insulin index, and after consumption glycemic and insulin responses are comparable to those of fresh fruits [60]. This could be due to the presence of fiber and polyphenols, which are capable of modifying the glycemic response [6,61,62]. Frequent consumption of foods with a low glycemic index may help decrease the risk of T2D and help in the management of the established condition [43,58].

As mentioned, several studies have highlighted the health benefits of dried fruit consumption; however, there is no consensus in the literature about the portion size of dried fruit that should be consumed. In addition, in spite of the fact that there are no specific recommendations, the consumption of dried fruits has been encouraged as a strategy to improve diet quality and reach desirable levels of both fruit consumption and intake of some nutrients that are often deficitary in the usual diet [51].

Section II of this book provides a comprehensive overview on the nutritional profiles, health-promoting phytochemicals/bioactives, and health benefits of dried fruits when included in healthy dietary patterns.

1.4 Conclusion

In this book, we present the latest scientific evidence on the health effects of nuts and dried fruits and on how and why they occur. Consumption of both nuts and dried fruits has been associated with cardiometabolic and other health benefits. Although compared to nuts, the level of evidence on dried fruits is lower, the consumption of both food groups needs to be promoted for public health purposes. Nuts and dried fruits have a complementary nutritional profile. Both can be incorporated into a healthy diet as snacks, in salads, in sauces, and in other recipes. Future studies evaluating the health effects of combinations of nuts and dried fruits are warranted.

References

1. Casas-Agustench, P., Salas-Huetos, A., and Salas-Salvadó, J., Mediterranean nuts: Origins, ancient medicinal benefits and symbolism. *Public Health Nutr.*, 14, 2296–2301, 2011.
2. Salas-Salvadó, J., Casas-Agustench, P., and Salas-Huetos, A., Cultural and historical aspects of Mediterranean nuts with emphasis on their attributed healthy and nutritional properties. *Nutr. Metab. Cardiovasc. Dis.*, 21(Suppl. 1), S1–S6, 2011.
3. Haddad, E.H., Sabaté, J., and Whitten, C., Vegetarian food guide pyramid: A conceptual framework. *Am. J. Clin. Nutr.*, 70(Suppl.), 615S–619S, 1999.
4. Widmer, R.J., Flammer, A.J., Lerman, L.O., and Lerman, A., The Mediterranean diet, its components, and cardiovascular disease. *Am. J. Med.*, 128, 229–238, 2015.
5. de Souza, R.G.M., Schincaglia, R.M., Pimentel, G.D., and Mota, J.F., Nuts and human health outcomes: A systematic review. *Nutrients*, 12, 1311, 2017.
6. Chang, S.K., Alasalvar, C., and Shahidi, F., Review of dried fruits: Phytochemicals, antioxidant efficacies, and health effects. *J. Funct. Foods*, 21, 113–132, 2016.
7. Alasalvar, C., and Pelvan, E., Fat-soluble bioactives in nuts. *Eur. J. Lipid Sci. Technol.*, 113, 943–949, 2011.
8. Salas-Salvadó, J., Bulló, M., Pérez-Heras, A., and Ros, E., Dietary fibre, nuts and cardiovascular diseases. *Br. J. Nutr.*, 96(Suppl. 2), S46–S51, 2006.
9. U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed June 20, 2018).
10. Ros, E., Tapsell, L.C., and Sabaté, J., Nuts and berries for heart health. *Curr. Atheroscler. Rep.*, 12, 397–406, 2010.
11. Bolling, B.W., Oliver Chen, C.-Y., McKay, D.L., and Blumberg, J.B., Tree nut phytochemicals: Composition, antioxidant capacity, bioactivity, impact factors: A systematic review of almonds, Brazils, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts. *Nutr. Res. Rev.*, 24, 244–275, 2011.

12. Alasalvar, C., and Bolling, B.W., Review of nut phytochemicals, fat-soluble bioactives, antioxidant components and health effects. *Br. J. Nutr.*, 113(Suppl. 2), S68–S78, 2015.
13. Fraser, G.E., Sabaté, J., Beeson, W.L., and Strahan, T.M., A possible protective effect of nut consumption on risk of coronary heart disease: The Adventist Health Study. *Arch. Internal. Med.*, 152, 1416–1424, 1992.
14. Sabaté, J., Fraser, G.E., Burke, K., Knutsen, S.F., Bennett, H., and Lindsted, K.D., Effects of walnuts on serum lipid levels and blood pressure in normal men. *N. Engl. J. Med.*, 328, 603–607, 1993.
15. Kim, Y., Keogh, J., and Clifton, P.M., Nuts and cardio-metabolic disease: A review of meta-analyses. *Nutrients*, 10, 1935, 2018.
16. Heffron, S.P., Rockman, C.B., Gianos, E., Guo, Y., and Berger, J.S., Greater frequency of nut consumption is associated with lower prevalence of peripheral arterial disease. *Prev. Med.*, 72, 15–18, 2015.
17. Khawaja, O., Gaziano, J.M., and Djousse, L., Nut consumption and risk of atrial fibrillation in the Physicians' Health Study. *Nutr. J.*, 11, 17, 2012.
18. Aune, D., Keum, N., Giovannucci, E., Fadnes, L.T., Boffetta, P., Greenwood, D.C., Tonstad, S. et al., Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review and dose-response meta-analysis of prospective studies. *BMC. Med.*, 14, 207, 2016.
19. Sabaté, J., Oda, K., and Ros, E., Nut consumption and blood lipids: A pooled analysis of 25 intervention trials. *Arch. Int. Med.*, 170, 821–827, 2010.
20. Del Gobbo, L.C., Falk, M.C., Feldman, R., Lewis, K., and Mozaffarian, D., Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: Systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am. J. Clin. Nutr.*, 102, 1347–1356, 2015.
21. Neale, E.P., Tapsell, L.C., Guan, V., and Batterham, M.J., The effect of nut consumption on markers of inflammation and endothelial function: A systematic review and meta-analysis of randomised controlled trials. *BMJ. Open*, 7, e016863, 2017.
22. López-Uriarte, P., Bulló, M., Casas-Agustench, P., Babio, N., and Salas-Salvadó, J., Nuts and oxidation: A systematic review. *Nutr. Rev.*, 67, 497–508, 2009.
23. Hernandez-Alonso, P., Camacho-Barcia, L., Bullo, M., and Salas-Salvado, J., Nuts and dried fruits: An update of their beneficial effects on type 2 diabetes. *Nutrients*, 9, 673, 2017.
24. Tan, S.Y., Dhillon, J., and Mattes, R.D., A review of the effects of nuts on appetite, food intake, metabolism, and body weight. *Am. J. Clin. Nutr.*, 100(Suppl. 1), 412S–422S, 2014.
25. Lamuel-Raventos, R.M., and Onge, M.S., Prebiotic nut compounds and human microbiota. *Crit. Rev. Food. Sci. Nutr.*, 57, 3154–3163, 2017.
26. Flores-Mateo, G., Rojas-Rueda, D., Basora, J., Ros, E., and Salas-Salvadó, J., Nut intake and adiposity: Meta-analysis of clinical trials. *Am. J. Clin. Nutr.*, 97, 1346–1355, 2013.
27. Jackson, C.L., and Hu, F.B., Long-term associations of nut consumption with body weight and obesity. *Am. J. Clin. Nutr.*, 100(Suppl. 1), 408S–411S, 2014.
28. Kim, Y., Keogh, J.B., and Clifton, P.M., Benefits of nut consumption on insulin resistance and cardiovascular risk factors: Multiple potential mechanisms of actions. *Nutrients*, 9, 1271, 2017.
29. Salas-Salvadó, J., Guasch-Ferré, M., Bulló, M., and Sabaté, J., Nuts in the prevention and treatment of metabolic syndrome. *Am. J. Clin. Nutr.*, 100(Suppl. 1), 399S–407S, 2014.

30. Mohammadifard, N., Salehi-Abargouei, A., Salas-Salvadó, J., Guasch-Ferré, M., Humphries, K., and Sarrafzadegan, N., The effect of tree nut, peanut, and soy nut consumption on blood pressure: A systematic review and meta-analysis of randomized controlled clinical trials. *Am. J. Clin. Nutr.*, 101, 966–982, 2015.
31. Wu, L., Wang, Z., Zhu, J.J., Murad, A.L., Prokop, L.J., and Murad, M.H., Nut consumption and risk of cancer and type 2 diabetes: A systematic review and meta-analysis. *Nutr. Rev.*,73, 409–425, 2015.
32. van den Brandt, P.A., and Nieuwenhuis, L., Tree nut, peanut, and peanut butter intake and risk of postmenopausal breast cancer: The Netherlands Cohort Study. *Cancer Causes Control*, 29, 63–75, 2018.
33. Klimova, B., Kuca, K., Valis, M., and Hort, J., Role of nut consumption in the management of cognitive decline—A mini-review. *Curr. Alzheimer Res.*, 15, 877–882, 2018.
34. Arab, L., Guo, R., and Elashoff, D., Lower depression scores among walnut consumers in NHANES. *Nutrients*, 11, 275, 2019.
35. Salas-Huetos, A., Moraleda, R., Giardina, S., Anton, E., Blanco, J., Salas-Salvadó, J., and Bulló, M., Effect of nut consumption on semen quality and functionality in healthy men consuming a Western-style diet: A randomized controlled trial. *Am. J. Clin. Nutr.*, 108, 953–962, 2018.
36. Food and Drug Administration (FDA), *Qualified Health Claims: Letter of Enforcement Discretion – Nuts and Coronary Heart Disease, Docket No 02P-0505*, Food and Drug Administration, Washington, DC, 2003.
37. Food and Drug Administration (FDA), *Qualified Health Claims: Letter of Enforcement Discretion – Walnuts and Coronary Heart Disease (Docket No 02P-0292)*, Food and Drug Administration, Washington, DC, 2004.
38. European Food Safety Authority (EFSA), Scientific opinion on the substantiation of health claims related to walnuts and maintenance of normal blood LDL-cholesterol concentrations (ID 1156, 1158) and improvement of endothelium-dependent vasodilation (ID 1155, 1157) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J.*, 9(4), 2074, 2011.
39. Lloyd-Jones, D.M., Hong, Y., Labarthe, D., Mozaffarian, D., Appel, L.J., Van Horn, L., Greenlund, K. et al., American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*, 121, 586–613, 2010.
40. Bach-Faig, A., Berry, E.M., Lairon, D., Reguant, J., Trichopoulu, A., Dimini, S., Medina, F.X. et al., Mediterranean diet pyramid today: Science and cultural updates. *Public Health Nutr.*, 14, 2274–2284, 2011.
41. Sabaté, J., Nut consumption, vegetarian diets, ischemic heart disease risk, and all-cause mortality: Evidence from epidemiological studies. *Am. J. Clin. Nutr.*, 70(Suppl.), 500S–503S, 1999.
42. U.S. Department of Health and Human Services and U.S. Department of Agriculture, *Dietary Guidelines for Americans*, 7th ed., U.S. Government Printing Office, Washington, DC, 2010.
43. Alasalvar, C., and Shahidi, F., Composition, phytochemicals, and beneficial health effects of dried fruits: An overview, in *Dried Fruits: Phytochemicals and Health Effects*, Alasalvar, C. and Shahidi, F., Eds., John Wiley & Sons, Oxford, UK, 2013, pp. 1–18.

44. European Food Safety Authority (EFSA), Scientific opinion on the substantiation of a health claim related to prunes and contribution to normal bowel function pursuant to Article 14 of Regulation (EC) No 1924/2006. *EFSA J.*, 12(11), 3892, 2014.
45. Vayalil, P.K., Date fruits (*Phoenix dactylifera* Linn): An emerging medicinal food. *Crit. Rev. Food Sci. Nutr.*, 52, 249–271, 2012.
46. Anderson, T.J., Grégoire, J., Hegele, R.A., Couture, P., Mancini, G.B., McPherson, R., Francis, G.A. et al., 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can. J. Cardiol.*, 29, 151–167, 2013.
47. Carughi, A., Feeney, M.J., Kris-Etherton, P., Fulgoni, V., Kendall, C.W.C., Bulló, M., and Webb, D., Pairing nuts and dried fruit for cardiometabolic health. *Nutr. J.*, 15, 23–36, 2015.
48. Kundu, J.K., and Surh, Y.-J., Cancer chemopreventive effects of selected dried fruits, in *Dried Fruits: Phytochemicals and Health Effects*, Alasalvar, C. and Shahidi, F., Eds., John Wiley & Sons, Oxford, UK, 2013, pp. 19–51.
49. Williamson, G., and Carughi, A., Polyphenol content and health benefits of raisins. *Nutr. Res.*, 30, 511–519, 2010.
50. Esfahani, A., Lam, J., and Kendall, C.W., Acute effects of raisin consumption on glucose and insulin reponses in healthy individuals. *J. Nutr. Sci.*, 3, e1, 2014.
51. Keast, D.R., O'Neil, C.E., and Jones, J.M., Dried fruit consumption is associated with improved diet quality and reduced obesity in US adults: National Health and Nutrition Examination Survey, 1999–2004. *Nutr. Res.*, 31, 460–467, 2011.
52. Arjmandi, B.H., Johnson, S.A., Pourafshar, S., Navaei, N., George, K.S., Hooshmand, S., Chai, S.C. et al., Bone-protective effects of dried plum in postmenopausal women: Efficacy and possible mechanisms. *Nutrients*, 9, 496, 2017.
53. Hooshmand, S., Kern, M., Metti, D., Shamloufard, P., Chai, S.C., Johnson, S.A., Payton, M.E. et al., The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: A randomized, controlled trial. *Osteoporos. Int.*, 27, 2271–2279, 2016.
54. Lever, E., Cole, J., Scott, S.M., Emery, P.W., and Whela, K., Systematic review: The effect of prunes on gastrointestinal function. *Aliment. Pharm. Ther.*, 40, 750–758, 2014.
55. Mandalari, G., Chessa, S., Bisignano, C., Chand, L., and Carughie, A., The effect of sun-dried raisins (*Vitis vinifera* L.) on the *in vitro* composition of the gut microbiota. *Food Funct.*, 7, 4048–4060, 2016.
56. Carughi, A., Raisins as a source of prebiotic compounds in the diet. *FASEB J.*, 23, 716.9, 2009.
57. Farajian, P., Katsagani, M., and Zampelas, A., Short-term effects of a snack including dried prunes on energy intake and satiety in normal-weight individuals. *Eat. Behav.*, 11, 201–203, 2010.
58. International Nut and Dried Fruit Council (INC), Traditional dried fruits: Valuable tools to meet dietary recommendations for fruit intake, presented at the XXX World Nut and Dried Fruit Congress, Budapest, Hungary, May 20–22, 2011. Dried Fruit Round Table.
59. Martinez-Gonzalez, M.A., and Bes-Rastrollo, M., Dietary patterns, Mediterranean diet, and cardiovascular disease. *Curr. Opin. Lipidol.*, 25, 20–26, 2014.

60. Kim, Y., Hertzler, S.R., Byrne, H.K., and Mattern, C.O., Raisins are a low to moderate glycemic index food with a correspondingly low insulin index. *Nutr. Res.*, 28, 304–308, 2008.
61. Zunino, S.J., Type 2 diabetes and glycemic response to grapes or grape products. *J. Nutr.*, 139 (Suppl.), 1794S–1800S, 2009.
62. Widanagamage, R.D., Ekanayake, S., and Welihinda, J., Carbohydrate-rich foods: Glycemic indices and the effect of constituent macronutrients. *Int. J. Food Sci. Nutr.*, 60, 215–223, 2009.
63. Food and Drug Administration (FDA), *Petition for a Qualified Health Claim for Macadamia Nuts and Reduced Risk of Coronary Heart Disease (Docket No. FDA-2015-Q-4850)*, Food and Drug Administration, Washington, DC, 2017.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Section I

NUTS

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 2

Nuts

Nutrients, Natural Antioxidants, Fat-Soluble Bioactives, and Phenolics

Cesarettin Alasalvar, Sui Kiat Chang, and Fereidoon Shahidi

2.1 Introduction 14
2.2 Nutrient Profiles of Nuts 16
2.2.1 Proximate Composition 16
2.2.1.1 Lipids 16
2.2.1.2 Carbohydrates 20
2.2.1.3 Proteins 20
2.2.2 Minerals 21
2.2.3 Vitamins 21
2.2.4 Amino Acids 21
2.2.5 Health Claims for Nuts 22
2.2.6 Daily Intake Values of Minerals from Nuts 23
2.2.7 Daily Intake Values of Vitamins from Nuts 23
2.3 Total Phenolics and Phytates in Nuts 23
2.4 Natural Antioxidants in Nuts 29
2.5 Antioxidant Activities of Nuts 29
2.6 Fat-Soluble Bioactives in Nuts 31
2.6.1 Fatty Acids 31
2.6.2 Tocols (Tocopherols and Tocotrienols) 34
2.6.3 Phytosterols (Sterols and Stanols) 35
2.6.4 Sphingolipids 35
2.6.5 Carotenoids 36

2.6.6 Chlorophylls 36
2.6.7 Alkylphenols 36
2.7 Phenolics in Nuts 37
2.7.1 Flavonoids 37
2.7.1.1 Anthocyanins 37
2.7.1.2 Flavan-3-ols 37
2.7.1.3 Flavonols 45
2.7.1.4 Flavanones 46
2.7.1.5 Flavones 46
2.7.1.6 Flavanonols 46
2.7.1.7 Isoflavones 46
2.7.2 Phenolic Acids 46
2.7.3 Tannins 47
2.7.4 Stilbenes 50
2.7.5 Other Phenolics 50
2.8 Conclusion 50
References 51

2.1 Introduction

Nuts are dry fruits with generally one seed in which the wall becomes hard at maturity. The most popular tree nuts include almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios, and walnuts. In addition, acorns, beech nuts, betel nuts, butter nuts, chestnuts, coconuts, heartnuts, ginkgo nuts, hickory nuts, and pili nuts, among others, are also known as edible tree nuts. Peanuts, which are botanically legumes, have nutrient profiles similar to those of tree nuts and are thus also addressed in this chapter.

Considering the production of world's most popular nuts (Table 2.1), peanuts rank first on a global basis, with a production of 42,707,000 metric tons (MT) in-shell basis, followed by almonds (1,262,131 MT shell basis), walnuts (866,820 MT shell basis), cashews (786,068 MT shell basis), pistachios (587,507 in-shell basis), and hazelnuts (509,325 MT shell basis) in 2017–2018. Production of the remaining four nuts (Brazil nuts, macadamias, pecans, and pine nuts) was around 231,597 MT shell basis for the same year [1]. Moreover, world's chestnut production was 2,261,589 MT in-shell basis in 2016 [2]. Little information about the production of acorns, beech nuts, butter nuts, coconuts, hickory nuts, heart nuts, and pili nuts is available.

Nuts contain numerous health-promoting bioactive components. They are highly nutritious and provide macronutrients (fats, proteins, and carbohydrates), micronutrients (minerals and vitamins), fat-soluble bioactives (monounsaturated fatty acids [MUFA], polyunsaturated fatty acids [PUFA], monoacylglycerols, diacylglycerols, triacylglycerols, phospholipids, sterol esters, tocopherols, tocotrienols, phytosterols, phytostanols, squalene, terpenoids, sphingolipids, carotenoids, chlorophylls, alkyl phenols, and essential oils, among others), and other phytochemicals belonging to the polyphenol class, such as phenolic acids (hydroxybenzoic and hydroxycinnamic), flavonoids [flavonols, flavones, flavanols (flavan-3-ols or catechins), flavanonols, flavanones, anthocyanins, and isoflavanes], stilbenes, lignans,

Table 2.1 World Nut Production, Kernel (Shell) Basis (Metric Tons)

Production	*2010/2011*	*2011/2012*	*2012/2013*	*2013/2014*	*2014/2015*	*2015/2016*	*2016/2017*	*2017/2018*
Almonds	922,113	1.125,266	1,072,174	1,094,714	1,064,050	1,094,578	1,185,905	1,262,131
Brazil nuts	26,450	23,673	28,880	26,850	28,500	27,850	27,600	12,200
Cashews	469,079	576,431	549,692	601,642	716,682	724,556	754,700	786,068
Hazelnuts	417,950	374,600	469,908	449,380	357,240	497,150	397,160	509,325
Macadamias	28,714	29,484	36,907	37,497	41,687	47,256	48,544	50,334
Pecans	91,214	91,215	115,768	110,670	122,340	119,726	118,213	137,013
Peanuts[a]	33,320,000	35,796,300	37,170,000	39,833,000	38,892,000	40,827,000	41,475,000	42,707,000
Pine nuts	20,600	34,295	11,550	11,480	39,950	19,550	23,550	32,050
Pistachios[a]	632,500	475,700	600,635	467,155	557,850	521,495	762,129	587,507
Walnuts	553,972	535,816	563,709	575,367	651,477	713,198	854,459	866,820

Source: Adapted from International Nut and Dried Fruit Council (INC), Nuts and Dried Fruits, Statistical Yearbook 2017/2018 and Nutfruit Magazine July 2018, INC, Reus, Spain, 2018.

[a] In-shell basis.

naphthoquinones, hydrolyzable tannins (ellagitannins and gallotannins), condensed tannins or proanthocyanidins, ellagic acid, and phenolic aldehydes, among other phytochemicals such as alkaloids, coumestan, phytates, terpenes, and phytoestrogens [3–12].

Based on United States Department of Agriculture (USDA) available data, total nut consumption (tree nuts and peanuts) in the United States is rather low (162 mg/day). In the EU, 5.0 g of peanuts/day are consumed, contributing 71.5 mg of polyphenols. Tree nuts have 86.9 mg of polyphenols, and thus the nut contribution to polyphenols in the EU diet amounts to 158 mg/day, which is very similar to the US diet [13].

This chapter provides a comprehensive overview of nutrients, natural antioxidants, fat-soluble bioactives, and phenolics in nuts. Percentages of recommended dietary allowances (RDA) or adequate intake (AI) of vitamins and minerals provided by nuts in adult men and women (aged 19–50 years) are also provided.

2.2 Nutrient Profiles of Nuts

Nuts are rich sources of essential nutrients. The compositional and nutritional characteristics of 18 nuts (acorns, almonds, beech nuts, Brazil nuts, butter nuts, cashews, chestnuts, coconuts, ginkgo nuts, hazelnuts, hickory nuts, macadamias, peanuts, pecans, pili nuts, pine nuts, pistachios, and walnuts) are compared and presented in Table 2.2. Nutrient profiles of heartnuts are not available in the USDA database or elsewhere, therefore they are not discussed in this section.

2.2.1 Proximate Composition

Nuts are a nutrient-dense component of the diet. Their proximate composition varies considerably depending on the nut type being considered. Based on the data provided in Table 2.2, lipid (fat) is the predominant component (2.00–79.55 g/100 g, being lowest in ginkgo nuts and highest in pili nuts), followed by carbohydrate (3.98–77.31 g/100 g, being lowest in pili nuts and highest in chestnuts), protein (6.20–25.80 g/100 g, being lowest in beech nuts and highest in peanuts), moisture (water) (1.36–12.40 g/100 g, being lowest in macadamias and highest in ginkgo nuts), and ash (1.14–3.70 g/100 g, being lowest in macadamias and highest in beech nuts). Nuts are characterized by a high lipid content and are thus considered an excellent source of energy (348–719 kcal/100 g, being lowest in ginkgo nuts and highest in pili nuts) [12]. Low moisture content is important for the extended shelf life and sensory quality of nuts, as it helps to reduce microbial growth and various associated undesirable biochemical changes [14].

2.2.1.1 Lipids

Most nuts are rich in lipids (ranging from 31.41 g/100 g in acorns to 79.55 g/100 g in pili nuts) with a few exceptions, such as ginkgo nuts (2.00 g/100 g) and chestnuts (4.45 g/100 g); these lipids make up the major portion of the energy obtained from these nuts (Table 2.2). Again, cultivar type, geographical location, and growing conditions influence the lipid content of mature kernels [14].

Table 2.2 Compositional and Nutritional Characteristics of Nuts (per 100 g)

Nutrient	*Unit*	*Acorns*[a]	*Almonds*	*Beech nuts*[b]	*Brazil nuts*	*Butter nuts*[c]	*Cashews*	*Chestnuts*[d]	*Coconuts*[e]	*Ginkgo nuts*[f]	*Hazelnuts*	*Hickory nuts*[g]	*Macadamias*	*Peanuts*	*Pecans*	*Pili nuts*[h]	*Pine nuts*	*Pistachios*	*Walnuts*
Proximate composition																			
Water	g	5.06	4.41	6.60	3.42	3.34	5.20	9.45	3.0	12.40	5.31	2.65	1.36	6.50	3.52	2.77	2.28	4.37	4.07
Energy	kcal	509	579	576	659	612	553	374	660	348	628	657	718	567	691	719	673	560	654
Protein	g	8.10	21.15	6.20	14.32	24.90	18.22	6.39	6.88	10.35	14.95	12.72	7.91	25.80	9.17	10.80	13.69	20.16	15.23
Lipid (fat)	g	31.41	49.93	50.00	67.10	56.98	43.85	4.45	64.53	2.00	60.75	64.37	75.77	49.24	71.97	79.55	68.37	45.32	65.21
SFA	g	4.08	3.80	5.72	16.13	1.31	7.78	0.84	57.22	0.38	4.47	7.04	12.06	6.28	6.18	31.18	4.90	5.91	6.13
MUFA	g	19.90	31.55	21.89	23.88	10.43	23.80	1.54	2.75	0.74	45.65	32.61	58.88	24.43	40.80	37.23	18.76	23.26	8.93
PUFA	g	6.05	12.33	20.09	24.40	42.74	7.85	1.76	0.71	0.74	7.92	21.89	1.50	15.56	21.61	7.61	34.07	14.38	47.17
Ash	g	1.78	2.97	3.70	3.43	2.73	2.54	2.40	1.94	2.80	2.29	2.0	1.14	2.33	1.49	2.91	2.59	2.99	1.78
Carbohydrate	g	53.66	21.55	33.50	11.74	12.05	30.19	77.31	23.65	72.45	16.70	18.25	13.82	16.13	13.86	3.98	13.08	27.17	13.71
Dietary fibre	g	na	12.5	na	7.5	4.7	3.3	11.7	16.3	na	9.7	6.4	8.6	8.5	9.6	na	3.7	10.6	6.7
Sugars	g	na	4.35	na	2.33	na	5.91	na	7.35	na	4.34	na	4.57	4.72	3.97	na	3.59	7.66	2.61
Starch	g	na	0.72	na	0.25	na	23.49	na	na	na	0.48	na	1.05	na	0.46	na	1.43	1.67	0.06
Minerals																			
Calcium	mg	54	269	1.0	160	53	37	67	26	20	114	61	85	92	70	145	16	105	98
Copper	mg	0.82	1.03	0.67	1.74	0.45	2.20	0.65	0.80	0.54	1.73	0.74	0.76	1.14	1.20	0.96	1.32	1.30	1.59
Fluoride	µg	na	na	na	na	na	na	na	na	na	na	na	na	na	10	na	na	3.4	na
Iron	mg	1.04	3.71	2.46	2.43	4.02	6.68	2.38	3.32	1.60	4.70	2.12	3.69	4.58	2.53	3.53	5.53	3.92	2.91
Magnesium	mg	82	270	na	376	237	292	74	90	53	163	173	130	168	121	302	251	121	158
Manganese	mg	1.36	2.18	1.34	1.22	6.56	1.66	1.30	2.75	0.22	6.18	4.61	4.13	1.93	4.50	2.31	8.80	1.20	3.41
Phosphorus	mg	103	481	0.0	725	446	593	175	206	269	290	336	188	376	277	575	575	490	346
Potassium	mg	709	733	1017	659	421	660	986	543	998	680	436	368	705	410	507	597	1025	441
Selenium	µg	na	4.1	na	1917	17.2	19.9	1.8	18.5	na	2.4	8.1	3.6	7.2	3.8	na	0.7	7.0	4.9
Sodium	mg	0.0	1.0	38	3.0	1.0	12	37	37	13	0.0	1.0	5.0	18	0.0	3.0	2.0	1.0	2.0
Zinc	mg	0.67	3.12	0.36	4.06	3.13	5.78	0.35	2.01	0.67	2.45	4.31	1.30	3.27	4.53	2.97	6.45	2.20	3.09

(*Continued*)

Table 2.2 (Continued) Compositional and Nutritional Characteristics of Nuts (per 100 g)

Nutrient	*Unit*	*Acorns*[a]	*Almonds*	*Beech nuts*[b]	*Brazil nuts*	*Butter nuts*[c]	*Cashews*	*Chestnuts*[d]	*Coconuts*[e]	*Ginkgo nuts*[f]	*Hazelnuts*	*Hickory nuts*[g]	*Macadamias*	*Peanuts*	*Pecans*	*Pili nuts*[h]	*Pine nuts*	*Pistachios*	*Walnuts*
Vitamins																			
Betaine	mg	na	0.5	na	0.4	na	na	na	na	na	0.4	na	na	0.6	0.7	na	0.4	na	0.3
Choline	mg	na	52.1	na	28.8	na	na	na	22.1	na	45.6	na	na	52.5	40.5	na	55.8	na	39.2
Folate (DFE)	µg	115	44	113	22	66	25	109	9.0	106	113	40	11	240	22	60	34	51	98
Niacin	mg	2.41	3.62	0.88	0.30	1.05	1.06	0.85	0.60	11.73	1.80	0.91	2.47	12.07	1.17	0.52	4.39	1.30	1.13
Pantothenic acid	mg	0.94	0.47	0.93	0.18	0.63	0.86	0.90	0.80	1.35	0.92	1.75	0.76	1.77	0.86	0.48	0.31	0.52	0.57
Pyridoxine (B-6)	mg	0.70	0.14	0.68	0.10	0.56	0.42	0.66	0.30	0.64	0.56	0.19	0.28	0.35	0.21	0.12	0.09	1.70	0.54
Riboflavin	mg	0.15	1.14	0.37	0.04	0.15	0.06	0.36	0.10	0.18	0.11	0.13	0.16	0.14	0.13	0.09	0.23	0.16	0.15
Thiamin	mg	0.15	0.21	0.30	0.62	0.38	0.42	0.30	0.06	0.43	0.64	0.87	1.20	0.64	0.66	0.91	0.36	0.87	0.34
Vitamin A (RAE)	µg	0.0	0.0	0.0	0.0	6.0	0.0	0.0	0.0	55	1.0	7.0	0.0	0.0	3.0	2.0	1.0	26	1.0
Vitamin C	mg	0.0	0.0	15.5	0.7	3.2	0.5	15	1.5	29.3	6.3	2.0	1.2	0.0	1.1	0.6	0.8	5.6	1.3
Vitamin E (ATE)	mg	na	25.63	na	5.65	na	0.90	na	0.44	na	15.03	na	0.54	8.33	1.40	na	9.33	2.86	0.70
Vitamin K	µg	na	0.0	na	0.0	na	34.1	na	0.30	na	14.2	na	na	0.0	3.5	na	53.9	na	2.70
Amino acids																			
Alanine	g	0.461	0.999	0.414	0.609	1.372	0.837	0.427	0.352	0.591	0.730	0.662	0.388	1.025	0.397	0.509	0.684	0.973	0.696
Arginine	g	0.623	2.465	0.443	2.140	4.862	2.123	0.457	1.130	1.005	2.211	2.086	1.402	3.085	1.177	0.516	2.413	2.134	2.278
Aspartic acid	g	0.837	2.639	1.071	1.325	3.096	1.795	1.103	0.673	1.298	1.679	1.368	1.099	3.146	0.929	1.222	1.303	1.884	1.829
Cystine	g	0.144	0.215	0.197	0.306	0.484	0.393	0.202	0.136	0.055	0.277	0.271	0.006	0.331	0.152	0.189	0.289	0.292	0.208
Glutamic acid	g	1.299	6.206	0.800	3.190	6.084	4.506	0.824	1.574	2.001	3.710	2.885	2.267	5.390	1.829	2.393	2.926	4.300	2.816
Glycine	g	0.376	1.429	0.319	0.733	1.508	0.937	0.329	0.326	0.554	0.724	0.708	0.454	1.554	0.453	0.650	0.691	1.009	0.816
Histidine[i]	g	0.224	0.539	0.172	0.409	0.808	0.456	0.177	0.158	0.244	0.432	0.389	0.195	0.652	0.262	0.255	0.341	0.512	0.391
Isoleucine[i]	g	0.376	0.751	0.245	0.518	1.179	0.789	0.252	0.270	0.500	0.545	0.576	0.314	0.907	0.336	0.483	0.542	0.917	0.625
Leucine[i]	g	0.644	1.473	0.367	1.190	2.199	1.472	0.378	0.511	0.755	1.063	1.027	0.602	1.672	0.598	0.890	0.991	1.604	1.170

(*Continued*)

Table 2.2 (Continued) Compositional and Nutritional Characteristics of Nuts (per 100 g)

Nutrient	*Unit*	*Acorns*[a]	*Almonds*	*Beech nuts*[b]	*Brazil nuts*	*Butter nuts*[c]	*Cashews*	*Chestnuts*[d]	*Coconuts*[e]	*Ginkgo nuts*[f]	*Hazelnuts*	*Hickory nuts*[g]	*Macadamias*	*Peanuts*	*Pecans*	*Pili nuts*[h]	*Pine nuts*	*Pistachios*	*Walnuts*
Lysine[i]	g	0.505	0.568	0.367	0.490	0.770	0.928	0.378	0.304	0.494	0.420	0.497	0.018	0.926	0.287	0.369	0.540	1.138	0.424
Methionine[i]	g	0.136	0.157	0.146	1.124	0.611	0.362	0.151	0.129	0.133	0.221	0.300	0.023	0.317	0.183	0.395	0.259	0.360	0.236
Phenylalanine[i]	g	0.354	1.132	0.262	0.639	1.442	0.951	0.270	0.349	0.408	0.663	0.713	0.665	1.377	0.426	0.497	0.524	1.092	0.711
Proline	g	0.324	0.969	0.326	0.706	1.236	0.812	0.336	0.284	0.830	0.561	0.571	0.468	1.138	0.363	0.471	0.673	0.938	0.706
Serine	g	0.344	0.912	0.310	0.676	1.640	1.079	0.319	0.356	0.695	0.735	0.806	0.419	1.271	0.474	0.599	0.835	1.283	0.934
Threonine[i]	g	0.312	0.601	0.221	0.365	0.940	0.688	0.228	0.251	0.640	0.497	0.422	0.370	0.883	0.306	0.407	0.370	0.684	0.596
Tryptophan[i]	g	0.098	0.211	0.069	0.135	0.366	0.287	0.071	0.081	0.170	0.193	0.139	0.067	0.250	0.093	0.189	0.107	0.251	0.170
Tyrosine	g	0.246	0.450	0.172	0.416	0.977	0.508	0.177	0.213	0.146	0.362	0.454	0.511	1.049	0.215	0.381	0.509	0.509	0.406
Valine[i]	g	0.455	0.855	0.346	0.760	1.541	1.094	0.357	0.417	0.677	0.701	0.730	0.363	1.082	0.411	0.701	0.687	1.249	0.753

Source: Adapted from the U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed June 20, 2018).

Note: Some numbers are rounded to the second digit after decimal point.

Abbreviations: ATE, alpha-tocopherol equivalents; DFE, dietary folate equivalents; MUFA, monounsaturated fatty acids; na, not available; PUFA, polyunsaturated fatty acids; RAE, retinol activity equivalents; SFA, saturated fatty acids.

[a] Acorns, dried.
[b] Beech nuts, dried.
[c] Butter nuts, dried.
[d] Chestnuts, European, dried, unpeeled.
[e] Coconuts, dried (desiccated), not sweetened.
[f] Ginkgo nuts, dried.
[g] Hickory nuts, dried.
[h] Pili nuts, dried.
[i] Indispensable amino acids.

The lipid composition of nuts is beneficial because most of the fatty acids are unsaturated (MUFA and PUFA) rather than saturated fatty acids (SFA) [5]. Among the 18 nuts listed in Table 2.2, only coconuts contain higher levels of SFA (57.22 g/100 g) than MUFA (2.75 g/100 g) and PUFA (0.71 g/100 g). MUFA is predominant in most nuts, except Brazil nuts, butter nuts, chestnuts, pine nuts, and walnuts [12] as well as heartnuts [15], which are rich in PUFA. The fatty acids of coconuts are mostly saturated in nature, with lauric acid (12:0) being the predominant SFA (14.9 g/100 g) [14].

Based on the data in Table 2.2, both MUFA and PUFA vary between 58.98% in pili nuts and 97.60% in butter nuts with respect to the total fatty acids present. In the most commonly consumed nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamias, peanuts, pecans, pine nuts, pistachios, and walnuts), heart-healthy unsaturated fatty acids (MUFA and PUFA) range from 74.96% in Brazil nuts to 92.30% in hazelnuts among the total fatty acids present (Table 2.2). Due to their high proportion of unsaturated fatty acids, nut oils have a more favorable composition than most vegetable oils. The fatty acid profiles of nut oils are given in detail in Section 2.6.1.

2.2.1.2 Carbohydrates

Carbohydrates are essentially composed of fiber, sugars, and starches. Acorns, chestnuts, and gingko nuts contain higher amounts of carbohydrates (53.66, 77.31, and 72.45 g/100 g, respectively) compared to other nuts (ranging from 3.98 g/100 g in pili nuts to 33.50 g/100 g in beech nuts). In addition, almonds, chestnuts, coconuts, and pistachios have a higher content of dietary fiber (12.5, 11.7, 16.3, and 10.6 g/100 g, respectively) than other nuts listed in Table 2.2 [12]. It is important to note that the high content of dietary fiber found in nuts helps meet dietary recommendations (14 g of fiber for every 1000 calories of food consumed). This becomes 25 g/day for adult women and 38 g/day for adult men, depending on age [16]. Based on the data provided in Table 2.2, at the suggested consumption level (1.5 ounces = ~42.5 g of nuts), nuts deliver 5.6%–27.7% of the daily recommendation of fiber for adult women and 3.7%–18.2% of that for adult men.

In terms of sugar content, pistachios contain the highest level (7.66 g/100 g), followed by coconuts (7.35 g/100 g) and cashews (5.91 g/100 g) (Table 2.2). Other nuts contain less than 5 g/100 g of sugar; hence data on the sugar content of most nuts is not presented due to their low content. Sucrose is the major simple sugar in nuts, accounting for >95% of the total sugars present. Other sugars include fructose, glucose, maltose, and galactose. The sugar content of nuts also varies considerably depending on the growing conditions, drying methods, nut maturity, cultivar, and growth/cultivation location [12,14].

Nuts, unlike other plant foods such as cereals and tubers, do not contain large amounts of starch, except for chestnuts. According to the USDA [12] database, cashews contain 23.49 g/100 g starch. In addition, recently Hao et al. [17] measured the total starch content of six chestnut cultivars from China and found that their content ranged from 58.33 to 63.58 g/100 g (on a dry weight basis). The average starch content of 47 chestnut cultivars grown in Spain was 57 g/100 g [18].

2.2.1.3 Proteins

Almonds, butter nuts, peanuts, and pistachios appear to have the highest protein content (21.15, 24.90, 25.80, and 20.16 g/100 g, respectively), whereas acorns, beech

nuts, chestnuts, coconuts, macadamias, and pecans contain the lowest amounts (less than 10 g/100 g) (Table 2.2). Nuts, in general, are a good source of plant protein, especially for people who do not include animal protein in their diet.

2.2.2 Minerals

A total of 11 minerals have been reported in nuts by USDA [12]. In general, potassium is the most abundant mineral, followed by phosphorus, calcium, and/or magnesium. Among the 18 nuts listed in Table 2.2, all contain 11 minerals, albeit to a different extent, except for fluoride, which is only reported in pecans and pistachios. The antioxidant mineral selenium in Brazil nuts (1917 μg/100 g) is much higher than other nuts (range from 0.7 μg/100 g in pine nuts to 19.9 μg/100 g in cashews). The daily requirement of minerals at the suggested consumption level of nuts is discussed in detail in Section 2.2.6.

2.2.3 Vitamins

Nuts contain both water-soluble vitamins (betaine, choline, folate, niacin, pantothenic acid, pyridoxine, riboflavin, thiamine, and vitamin C) and fat-soluble vitamins (A, E, and K), albeit to different extents. Among them, vitamins A, C, and E are known as antioxidant vitamins [3]. Beechnuts, chestnuts, and ginkgo nuts have the highest amounts of vitamin C (15.5, 15.0, and 29.3 mg/100 g, respectively) among the 18 nuts listed in Table 2.2. Almonds and hazelnuts are excellent sources of vitamin E [25.63 and 15.03 mg alpha-tocopherol equivalents (ATE)/100 g, respectively]. Pine nuts and cashews are the richest sources of vitamin K (53.9 and 34.1 μg/100 g, respectively), whereas vitamin A is most abundant in ginkgo nuts (55 μg retinol activity equivalents [RAE]/100 g). Peanuts contain almost ~2-fold higher folate than those of acorns, beech nuts, chestnuts, ginkgo nuts, hazelnuts, and walnuts. Nuts, in general, are poor sources of betaine, choline, vitamin A, vitamin C, and vitamin K, with some exceptions [12,14]. The daily requirement of vitamins at the suggested consumption level of nuts is discussed in detail in Section 2.2.7.

2.2.4 Amino Acids

The amino acid compositions of nuts are summarized in Table 2.2. Glutamic acid is the most abundant (0.800–6.206 g/100 g) amino acid, followed by arginine (0.443–4.862 g/100 g) and aspartic acid (0.673–3.146 g/100 g). These three amino acids contribute from nearly 35.56% (in acorns) to 50.11% (in almonds) to the total amino acids present. The quality of proteins is related mainly to their indispensable amino acid composition and digestibility. Although nuts contain all indispensable amino acids, nut proteins are incomplete proteins, similar to other plant proteins. The ratio of indispensable to total amino acids in nuts ranges from 29.85% for almonds to 43.18% for acorns (Table 2.2).

Considering the recommendations of the Food and Agriculture Organization (FAO)/World Health Organization (WHO) for indispensable amino acid intake for adults (>18 years old) [19], lysine is a limiting amino acid in macadamias, whereas

methionine is the limiting one in almonds, ginkgo nuts, hazelnuts, macadamias, peanuts, and walnuts (data in Table 2.2 were calculated based on reference protein). The other indispensable amino acids were all present above the reference values.

Ruggeri et al. [20] reported that lysine was the first indispensable limiting amino acid in almonds, hazelnuts, pecans, pine nuts, pistachios, and walnuts. Later on, Venkatachalam and Sathe [21] studied 10 commercially available nuts (almonds, cashews, hazelnuts, macadamias, pecans, peanuts, pine nuts, pistachios, and walnuts) and found that compared to the FAO/WHO recommended indispensable amino acid intake for adults, only almonds and peanuts were deficient in sulfur-containing amino acids (methionine + cystine), whereas all other tree nuts contained adequate amounts of all of the indispensable amino acids.

2.2.5 Health Claims for Nuts

So far, the Food and Drug Administration (FDA) has three qualified health claims on nuts in general and walnuts and macadamias in particular, whereas the European Food Safety Authority (EFSA) has only one authorized health claim for walnuts.

In 2003, the FDA approved the first qualified health claim, which states that "*scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease*" [22]. The FDA evaluated the data and determined that, although there was scientific evidence supporting this claim, the evidence was not conclusive. For a food to qualify for the qualified health claim, the product must contain 11 g or more of whole or chopped nuts per preference amount customarily consumed (a standard serving size). Any nuts labelled with the claim must contain less than 4 g saturated fat per 50 g. Eligible nuts for the claim include almonds, hazelnuts, pecans, some pine nuts, pistachios, walnuts, and peanuts [22,23].

In 2004, the FDA also approved another qualified health claim for nuts, specifically for walnuts and heart disease. The claim states that "*supportive but not conclusive research shows that eating 1.5 ounces per day of walnuts, as part of a low saturated fat and low cholesterol diet and not resulting in increased caloric intake, may reduce the risk of coronary heart disease*" [24]. The eligible foods must be whole or chopped walnuts.

In 2017, the FDA announced that the Agency would permit the use of a qualified health claim regarding the relationship between consumption of macadamias and a reduced risk of CHD despite the nuts being above the typically permitted level of fat and below the typically required levels of nutrients. The claim permitted for use by the FDA is that "*supportive but not conclusive research shows that eating 1.5 ounces per day of macadamia nuts, as part of a diet low in saturated fat and cholesterol and not resulting in increased intake of saturated fat or calories may reduce the risk of coronary heart disease*" [109].

The EFSA authorizes health claims provided that they are based on scientific evidence and can be easily understood by consumers. As of today, there is only one health claim approved by the EFSA with regard to nuts, which refers to walnuts and endothelial function. The claim, which states that "*walnuts contribute to the improvement of the elasticity of blood vessels*," can be used only in foods that provide a daily intake of 30 g of walnuts. In order to bear the claim, the consumer must be informed that the beneficial effect is obtained with a daily intake of 30 g of walnuts [25].

The daily values of minerals and vitamins in nuts are calculated and presented based on the FDA qualified health claim (1.5 ounces = ~42.5 g) in the following two sections.

2.2.6 Daily Intake Values of Minerals from Nuts

With respect to the nutritional aspects of nuts, the percentages of RDA or AI of minerals for adult men and women (aged 19–50 years) are given in Table 2.3 [12,26–30]. Consuming 42.5 g (one and one-half servings) of nuts [22] supplies 21.3%–104% (men and women) of copper, 5.5%–35.5% (men) and 2.5%–15.8% (women) of iron, 5.5%–39% (men) and 7.2%–50.7% (women) of magnesium, 4.1%–163% (men) and 5.2%–208% (women) of manganese, 6.3%–44% (men and women) of phosphorus, and 0.5%–1481% (men and women) of selenium for RDA or AI, respectively. With regard to selenium, Brazil nuts serve as an excellent source of this mineral. Only one kernel of Brazil nuts (5 g) supplies 174% of the RDA of selenium for adults. Based on RDA or AI values among the 18 nuts listed in Table 2.3, cashews are the richest source of copper and iron, whereas Brazil nuts are the richest source of selenium, phosphorus, and magnesium. In addition, pine nuts are rich in manganese and zinc. Nuts, in general, contribute to small amounts of daily intake values of potassium, while they contain little sodium.

2.2.7 Daily Intake Values of Vitamins from Nuts

With respect to the nutritional aspects of nuts, the percentages of RDA or AI of vitamins for adult men and women (aged 19–50 years) are given in Table 2.4 [12,27–29]. Consuming 42.5 g (one and one-half servings) of nuts [22] supplies 1.0%–25.5% (men and women) of folate, 0.8%–32.1% (men) and 0.9%–36.6% (women) of niacin, 1.5%–15% (men and women) of pantothenic acid, 2.9%–55.6% (men and women) of pyridoxine, 1.3%–37.3% (men) and 1.5%–44% (women) of riboflavin, 2.1%–42.5% (men) and 2.3%–46.4% (women) of thiamin, 1.2%–72.6% (men and women) of vitamin E for RDA or AI, respectively. Based on RDA or AI values among the nuts listed in Table 2.4, peanuts are the richest source of folate, niacin, and pantothenic acid, whereas almonds are the richest source of riboflavin and vitamin E. Vitamin E is the most abundant in both almonds and hazelnuts. In addition, cashews and pine nuts are good sources of vitamin K, while ginkgo nuts are rich in vitamin C. Nuts, in general, contribute to small amounts of daily intake values of choline and vitamins such as A, C, and K.

2.3 Total Phenolics and Phytates in Nuts

Phenolics are the major group of phytochemicals. With respect to total phenolic profiles of 12 nuts (Table 2.5), pecans have the highest total phenolics (2016 mg gallic acid equivalents (GAE) and total flavonoids (34.01 mg/100 g), whereas pistachios have the highest total isoflavones (177 μg/100 g), total lignans (199 μg/100 g), and total phytoestrogens (383 μg/100 g). In addition, hazelnuts contain the highest total content of proanthocyanidins (491 mg/100 g) [10,31–34]. Phytates have been reported in most nuts, ranging from 150 mg/100 g in macadamias to 350 mg/100 g

Table 2.3 Percentage of RDA or AI Values of Minerals in Nuts (for adults aged 19–50 years; based on 42.5 g or 1.5 ounces serving basis)

Mineral	*RDA or AI**	*Acorns*[a]	*Almonds*	*Beech nuts*[b]	*Brazil nuts*	*Butter nuts*[c]	*Cashews*	*Chestnuts*[d]	*Coconuts*[e]	*Ginkgo nuts*[f]	*Hazelnuts*	*Hickory nuts*[g]	*Macadamias*	*Peanuts*	*Pecans*	*Pili nuts*[h]	*Pine nuts*	*Pistachios*	*Walnuts*	*References*
Men																				
Calcium	1000 mg/day*	2.3	11.4	0.0	6.8	2.3	1.6	2.8	1.1	0.9	4.8	2.6	3.6	3.9	3.0	6.2	0.7	4.5	4.2	[12,26]
Copper	0.9 mg/day	38.7	48.6	31.6	82.2	21.3	104	30.7	37.8	25.5	81.7	34.9	35.9	53.8	56.7	45.3	62.3	61.4	75.1	[12,29]
Fluoride	4000 µg/day*	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	0.04	na	[12,26]
Iron	8 mg/day	5.5	19.7	13.1	12.9	21.4	35.5	12.6	17.6	8.5	25.0	11.3	19.6	24.3	13.4	18.8	29.4	20.8	15.5	[12,29]
Magnesium	400–420 mg/day	8.5	28.0	na	39.0	24.6	30.3	7.7	9.3	5.5	16.9	17.9	13.5	17.4	12.5	31.3	26.0	12.5	16.4	[12,26]
Manganese	2.3 mg/day*	25.1	40.3	24.8	22.5	121	30.7	24.0	50.8	4.1	114	85.2	76.3	35.7	83.2	42.7	163	22.2	63.0	[12,29]
Phosphorus	700 mg/day	6.3	29.2	0.0	44.0	27.1	36.0	10.6	12.5	16.3	17.6	20.4	11.4	22.8	16.8	34.9	34.9	29.8	21.0	[12,26]
Potassium	4700 mg/day	6.4	6.6	9.2	6.0	3.8	6.0	8.9	4.9	9.0	6.1	3.9	3.3	6.4	3.7	4.6	5.4	9.3	4.0	[12,30]
Selenium	55 µg/day	na	3.2	na	1481	13.3	15.4	1.4	14.3	na	1.9	6.3	2.8	5.6	2.9	na	0.5	5.4	3.8	[12,28]
Sodium	1500 mg/day	0.0	0.0	1.1	0.1	0.0	0.3	1.0	1.0	0.4	0.0	0.0	0.1	0.5	0.0	0.1	0.1	0.0	0.1	[12,30]
Zinc	11 mg/day	2.6	12.1	1.4	15.7	12.1	22.3	1.4	7.8	2.6	9.5	16.7	5.0	12.6	17.5	11.5	24.9	8.5	11.9	[12,29]
Women																				
Calcium	1000 mg/day*	2.3	11.4	0.0	6.8	2.3	1.6	2.8	1.1	0.9	4.8	2.6	3.6	3.9	3.0	6.2	0.7	4.5	4.2	[12,26]
Copper	0.9 mg/day	38.7	48.6	31.6	82.2	21.3	104	30.7	37.8	25.5	81.7	34.9	35.9	53.8	56.7	45.3	62.3	61.4	75.1	[12,29]
Fluoride	3000 µg/day*	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	0.05	na	[12,26]
Iron	18 mg/day	2.5	8.8	5.8	5.7	9.5	15.8	5.6	7.8	3.8	11.1	5.0	8.7	10.8	6.0	8.3	13.1	9.3	6.9	[12,29]
Magnesium	310–320 mg/day	11.1	36.4	na	50.7	32.0	39.4	10.0	12.1	7.2	22.0	23.3	17.5	22.7	16.3	40.7	33.9	16.3	21.3	[12,26]
Manganese	1.8 mg/day*	32.1	51.5	31.6	28.8	155	39.2	30.7	64.9	5.2	146	109	97.5	45.6	106	54.5	208	28.3	80.5	[12,29]
Phosphorus	700 mg/day	6.3	29.2	0.0	44.0	27.1	36.0	10.6	12.5	16.3	17.6	20.4	11.4	22.8	16.8	34.9	34.9	29.8	21.0	[12,26]
Potassium	4700 mg/day	6.4	6.6	9.2	6.0	3.8	6.0	8.9	4.9	9.0	6.1	3.9	3.3	6.4	3.7	4.6	5.4	9.3	4.0	[12,30]

(*Continued*)

Table 2.3 (Continued) Percentage of RDA or AI Values of Minerals in Nuts (for adults aged 19–50 years; based on 42.5 g or 1.5 ounces serving basis)

Mineral	*RDA or AI**	*Acorns*[a]	*Almonds*	*Beech nuts*[b]	*Brazil nuts*	*Butter nuts*[c]	*Cashews*	*Chestnuts*[d]	*Coconuts*[e]	*Ginkgo nuts*[f]	*Hazelnuts*	*Hickory nuts*[g]	*Macadamias*	*Peanuts*	*Pecans*	*Pili nuts*[h]	*Pine nuts*	*Pistachios*	*Walnuts*	*References*
Selenium	55 µg/day	na	3.2	na	1481	13.3	15.4	1.4	14.3	na	1.9	6.3	2.8	5.6	2.9	na	0.5	5.4	3.8	[12,28]
Sodium	1500 mg/day	0.0	0.0	1.1	0.1	0.0	0.3	1.0	1.0	0.4	0.0	0.0	0.1	0.5	0.0	0.1	0.1	0.0	0.1	[12,30]
Zinc	8 mg/day	3.6	16.6	1.9	21.6	16.6	30.7	1.9	10.7	3.6	13.0	22.9	6.9	17.4	24.1	15.8	34.3	11.7	16.4	[12,29]

Abbreviations: AI*, adequate intake; na, not available; RDA, recommended dietary allowances.

[a] Acorns, dried.
[b] Beech nuts, dried.
[c] Butter nuts, dried.
[d] Chestnuts, European, dried, unpeeled.
[e] Coconuts, dried (desiccated), not sweetened.
[f] Ginkgo nuts, dried.
[g] Hickory nuts, dried.
[h] Pili nuts, dried.

Table 2.4 Percentage of RDA or AI Values of Vitamins in Nuts (for adults aged 19–50 years; based on 42.5 g or 1.5 ounces serving basis)

Vitamin	*RDA or AI**	*Acorns*[a]	*Almonds*	*Beech nuts*[b]	*Brazil nuts*	*Butter nuts*[c]	*Cashews*	*Chestnuts*[d]	*Coconuts*[e]	*Ginkgo nuts*[f]	*Hazelnuts*	*Hickory nuts*[g]	*Macadamias*	*Peanuts*	*Pecans*	*Pili nuts*[h]	*Pine nuts*	*Pistachios*	*Walnuts*	*References*
Men																				
Choline	550 mg/day*	na	4.0	na	2.2	na	na	na	1.7	na	3.5	na	na	4.1	3.1	na	4.3	na	3.0	[12,27]
Folate (DFE)	400 µg/day	12.2	4.7	12.0	2.3	7.0	2.7	11.6	1.0	11.3	12.0	4.3	1.2	25.5	2.3	6.4	3.6	5.4	10.4	[12,27]
Niacin	16 mg/day	6.4	9.6	2.3	0.8	2.8	2.8	2.3	1.6	31.2	4.8	2.4	6.6	32.1	3.1	1.4	11.7	3.5	3.0	[12,27]
Pantothenic acid	5 mg/day*	8.0	4.0	7.9	1.5	5.4	7.3	7.7	6.8	11.5	7.8	14.9	6.5	15.0	7.3	4.1	2.6	4.4	4.8	[12,27]
Pyridoxine	1.3 mg/day	22.9	4.6	22.2	3.3	18.3	13.7	21.6	9.8	20.9	18.3	6.2	9.2	11.4	6.9	3.9	2.9	55.6	17.7	[12,27]
Riboflavin	1.3 mg/day	4.9	37.3	12.1	1.3	4.9	2.0	11.8	3.3	5.9	3.6	4.3	5.2	4.6	4.3	2.9	7.5	5.2	4.9	[12,27]
Thiamin	1.2 mg/day	5.3	7.4	10.6	22.0	13.5	14.9	10.6	2.1	15.2	22.7	30.8	42.5	22.7	23.4	32.2	12.8	30.8	12.0	[12,27]
Vitamin A (RAE)	900 µg/day	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	2.6	0.05	0.3	0.0	0.0	0.1	0.1	0.0	1.2	0.0	[12,29]
Vitamin C	90 mg/day	0.0	0.0	7.3	0.3	1.5	0.2	7.1	0.7	13.8	3.0	0.9	0.6	0.0	0.5	0.3	0.4	2.6	0.6	[12,28]
Vitamin E (ATE)	15 mg/day	na	72.6	na	16.0	na	2.6	na	1.2	na	42.6	na	1.5	23.6	4.0	na	26.4	8.1	2.0	[12,28]
Vitamin K	120 µg/day*	na	0.0	na	0.0	na	12.1	na	0.1	na	5.0	na	na	0.0	1.2	na	19.1	na	1.0	[12,29]
Women																				
Choline	425 mg/day*	na	5.2	na	2.9	na	na	na	2.2	na	4.6	na	na	5.3	4.1	na	5.6	na	3.9	[12,27]
Folate (DFE)	400 µg/day	12.2	4.7	12.0	2.3	7.0	2.7	11.6	1.0	11.3	12.0	4.3	1.2	25.5	2.3	6.4	3.6	5.4	10.4	[12,27]
Niacin	14 mg/day	7.3	11.0	2.7	0.9	3.2	3.2	2.6	1.8	35.6	5.5	2.8	7.5	36.6	3.6	1.6	13.3	3.9	3.4	[12,27]
Pantothenic acid	5 mg/day*	8.0	4.0	7.9	1.5	5.4	7.3	7.7	6.8	11.5	7.8	14.9	6.5	15.0	7.3	4.1	2.6	4.4	4.8	[12,27]
Pyridoxine	1.3 mg/day	22.9	4.6	22.2	3.3	18.3	13.7	21.6	9.8	20.9	18.3	6.2	9.2	11.4	6.9	3.9	2.9	55.6	17.7	[12,27]
Riboflavin	1.1 mg/day	5.8	44.0	14.3	1.5	5.8	2.3	13.9	3.9	7.0	4.3	5.0	6.2	5.4	5.0	3.5	8.9	6.2	5.8	[12,27]
Thiamin	1.1 mg/day	5.8	8.1	11.6	24.0	14.7	16.2	11.6	2.3	16.6	24.7	33.6	46.4	24.7	25.5	35.2	13.9	33.6	13.1	[12,27]

(*Continued*)

Table 2.4 (Continued) Percentage of RDA or AI Values of Vitamins in Nuts (for adults aged 19–50 years; based on 42.5 g or 1.5 ounces serving basis)

Vitamin	*RDA or AI**	*Acorns*[a]	*Almonds*	*Beech nuts*[b]	*Brazil nuts*	*Butter nuts*[c]	*Cashews*	*Chestnuts*[d]	*Coconuts*[e]	*Ginkgo nuts*[f]	*Hazelnuts*	*Hickory nuts*[g]	*Macadamias*	*Peanuts*	*Pecans*	*Pili nuts*[h]	*Pine nuts*	*Pistachios*	*Walnuts*	*References*
Vitamin A (RAE)	700 µg/day	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	3.3	0.06	0.4	0.0	0.0	0.2	0.1	0.1	1.6	0.1	[12,29]
Vitamin C	75 mg/day	0.0	0.0	8.8	0.4	1.8	0.3	8.5	0.9	16.6	3.6	1.1	0.7	0.0	0.6	0.3	0.5	3.2	0.7	[12,28]
Vitamin E (ATE)	15 mg/day	na	72.6	na	16.0	na	2.6	na	1.2	na	42.6	na	1.5	23.6	4.0	na	26.4	8.1	2.0	[12,28]
Vitamin K	90 µg/day*	na	0.0	na	0.0	na	16.1	na	0.1	na	6.7	na	na	0.0	1.7	na	25.5	na	1.3	[12,29]

Abbreviations: AI*, adequate intake; ATE, alpha-tocopherol equivalents; DFE, dietary folate equivalents; na, not available; RAE, retinol activity equivalents; RDA, recommended dietary allowances.

[a] Acorns, dried.
[b] Beech nuts, dried.
[c] Butter nuts, dried.
[d] Chestnuts, European, dried, unpeeled.
[e] Coconuts, dried (desiccated), not sweetened.
[f] Ginkgo nuts, dried.
[g] Hickory nuts, dried.
[h] Pili nuts, dried.

Table 2.5 Total Phenolics and Phytates in Nuts (100 g edible portion)

	Unit	*Almonds*	*Brazil nuts*	*Cashews*	*Chestnuts*[a]	*Hazelnuts*	*Heartnuts*[b]	*Macadamias*	*Peanuts*	*Pecans*	*Pine nuts*	*Pistachios*	*Walnuts*	*References*
Total phenolics	mg GAE/100 g	418	310	274	5–33	835	196	156	396	2016	68	1657	1556	[31,32,34]
Total flavonoids	mg/100 g	11.0	na	1.98	0.02	11.96	na	na	0.66	34.01	0.49	15.24	2.71	[10]
Total proanthocyanidins	mg/100 g	153	na	2.02	0.03	491	na	na	10.51	477	na	226	60.32	[11,98]
Total isoflavones	µg/100 g	18	na	22.1	21.2	30.2	na	na	7.3	3.5	na	177	53.3	[33]
Total lignans	µg/100 g	112	na	99.4	187	77.1	na	na	27.1	25	na	199	85.7	[33]
Total phytoesterogens	µg/100 g	131	na	122	210	108	na	na	34.5	28.8	na	383	140	[33]
Phytates	mg/100 g	350	190	290	na	230	na	150	170	180	200	290	200	[21]

Abbreviations: GAE, gallic acid equivalents; na, not available.

[a] Chestnuts are from three provinces in Turkey (Aydın, Bursa, and Zonguldak)

[b] Average of three heartnut varieties (Campbell CW1, Campbell CW3, and Imshu).

in almonds [21]. The corresponding values for other nuts (acorns, beech nuts, betel nuts, butter nuts, coconuts, ginkgo nuts, hickory nuts, and pili nuts) are not available in the literature. Detailed information on phenolics in nuts is given in Section 2.7.

2.4 Natural Antioxidants in Nuts

Comprehensive reviews on natural antioxidants in nuts have already been reported by Alasalvar and Shahidi [3], Alasalvar and Bolling [7], and Chang et al. [9]. Therefore, natural antioxidants in nuts are not discussed in detail in this chapter. Briefly, natural antioxidants present in nuts are in the form of nutrient and non-nutrient antioxidants. In addition to well-known nutrient antioxidants, namely vitamins A, C, and E, as well as the mineral selenium, there are numerous non-nutrient antioxidants, namely phenolics (such as resveratrol and quercetin) and carotenoids (such as β-carotene and lycopene) in plant foods. Thus, as mentioned earlier in this chapter (Sections 2.2.2 and 2.2.3), nuts are good sources of vitamin E and selenium. Among the antioxidant vitamins A, C, and E, vitamin E is the most abundant in most nuts. Vitamin E is a dominant and the most powerful lipid-soluble antioxidant in the body and serves as the primary defence against lipid peroxidation [35] by protecting the body's cells from free radical damage [36,37]. Although selenium has several health benefits, it is an essential constituent of a number of enzymes, some of which have antioxidant function [38].

With regards to non-nutrient antioxidants, thousands of phytochemicals, some with strong antioxidant activities, such as catechin, quercetin, tannins, ellagic acid, chlorogenic acid, cyanidin, carotenoids, and resveratrol, have been reported. Several studies have also reported that phenolic compounds possess much stronger antioxidant activities than nutrient antioxidants [3,4,6–9].

2.5 Antioxidant Activities of Nuts

Comprehensive review on *in vitro* and biological assays of natural (raw) and roasted nuts (almonds, Brazil nuts, cashews, chestnuts, hazelnuts, macadamias, peanuts, pecans, pine nuts, pistachios, and walnuts) have already been reported by Chang et al. [9]. The *in vitro* chemical assays employed included ferric reducing antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC), total antioxidant activity (TAA), thiobarbituric acid reactive substances (TBARS), reducing power, β-carotene bleaching assay, trolox equivalent antioxidant capacity (TEAC), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, among others. The biological-based assays commonly used include low-density lipoprotein (LDL) oxidation inhibition, LDL + very low-density lipoprotein (VLDL) oxidation inhibition, haemolysis inhibition, retention of supercoiled DNA, hydroxyl, superoxide, and hydrogen peroxide radical inhibitory assays [9].

Table 2.6 compares antioxidant activities (both *in vitro* and biological assays) of 12 nuts using three different *in vitro* assays (ORAC, DPPH, and FRAP) and one biological assay (LDL+VLDL). While pecans have the highest ORAC value [17,940 μmol trolox equivalents (TE)/100 g], walnuts possess the highest antioxidant activity in DPPH (12,000 μmol TE/100 g), FRAP (23.1 mmol Fe^{+2}/100 g), and LDL+VLDL

Table 2.6 Antioxidant Activities of Nuts (100 g edible portion)

	Unit	*Almonds*	*Brazil nuts*	*Cashews*	*Chestnuts*	*Hazelnuts*	*Heartnuts*	*Macadamias*	*Peanuts*	*Pecans*	*Pine nuts*	*Pistachios*	*Walnuts*	*References*
ORAC	μmol TE/100 g	4454	1419	1997	na	9645	na	1695	3166	17940	719	7983	13541	[31]
DPPH	μmol TE/100 g	120	260	300	620	420	na	450	590	5800	na	390	12000	[39]
FRAP	mmol Fe^{+2}/100 g	0.41	0.15	4.67	na	0.7	na	0.42	1.61	8.33	na	1.27	23.1	[40,41]
LDL + VLDL inhibition	IC_{50} (μM)	3.4	6.8	2.2	na	3.2	na	4.1	7.9	3.4	na	5.8	1.8	[13]

Abbreviations: DPPH, 2,2-diphenyl-1-picrylhydrazyl; FRAP, ferric-reducing ability of plasma; IC_{50}; the half maximal inhibitory concentration; LDL, low-density lipoprotein; na, not available; ORAC, oxygen radical absorbance capacity; TE, trolox equivalents; VLDL, very low-density lipoprotein.

oxidation inhibition (1.8 μM [IC_{50}]). In LDL+VLDL oxidation inhibition, the lowest value indicates the highest antioxidant activity [13,31,39–41]. The antioxidant activities of different nuts vary widely based on the assay type employed. This suggests the need to perform more than one type of antioxidant activity measurement to consider the various mechanisms of antioxidant action and the limitations of each assay [42].

Remarkably, in all nuts, most of the antioxidants are located in the skin (pellicle) and less than 10% is retained in the nut when the skin is removed [40]. In other words, the removal of the skin from nuts considerably reduces antioxidant activity [43]. In most other cases, nuts without the skin contain less than 50% of total antioxidants compared to nuts with skin [40,44,45]. This fact, rarely taken into consideration in prior feeding trials with nuts, should not be overlooked in future studies. Walnuts are an exception, because they are almost always consumed as a raw product with the skin. Over the past few years, much attention has been paid to the skins of nut kernels. Nut skins are rich sources of phenolic compounds and possess stronger antioxidant activities than those of their kernels [9].

Vinson and Chai [13] also measured the total polyphenols and antioxidant efficacies of nine nuts. The order of decreasing antioxidant efficacy (increasing IC_{50}) for raw nuts was reported as walnuts > cashews > hazelnuts > pecans > almonds > macadamias > pistachios > Brazil nuts > peanuts. Roasting caused a decline in efficacy [13].

In a recent study reported by Schlörmann et al. [46], the hydrophilic antioxidant activity (expressed as mmol TE/100 g fresh weight) of nuts decreased in the order of walnuts (11.0) > hazelnuts, pistachios (3.3) > almonds, macadamias (2.1), while the lipophilic antioxidant activity (expressed as μmol tocopherol equivalents/100 g fresh weight) of nuts decreased in the order of pistachios (29.5) > walnuts (26) > almonds (18) > hazelnuts (14.1) > macadamias (2.8).

2.6 Fat-Soluble Bioactives in Nuts

Fat is the predominant component in nuts (Table 2.2). There has been an increasing interest in functional characteristics of nut oils as they seem to be an interesting source of bioactive constituents. The benefits of including nuts in the human diet are partly related to their fat components. The levels of fat-soluble bioactives such as fatty acids (SFA, MUFA, and PUFA), tocols, vitamin E, phytosterols, sphingolipids, carotenoids, chlorophylls, and alkyl phenols present in 12 commonly consumed nut oils (almonds, Brazil nuts, cashews, chestnuts, hazelnuts, heartnuts, macadamias, peanuts, pecans, pine nuts, pistachios, and walnuts) are reported and compared in Table 2.7 [7,47–49]. Comprehensive reviews by Alasalvar and Pelvan [5] and Alasalvar and Bolling [7] on fat-soluble bioactives are available in the literature for further reading. The chemical structures of the major fat-soluble bioactives (carotenoids, fatty acids, sphingolipids, alkyl phenols, and chlorophylls) present in nuts are given in Figure 2.1.

2.6.1 Fatty Acids

Among the 12 nut oils listed in Table 2.7, heartnut, walnut, and macadamia oils contain the lowest proportion of SFA (3.66%), MUFA (15.28%), and PUFA (4.39%),

Table 2.7 Fat-soluble Bioactives in Nut Oils (100 g oil)

	Unit	*Almonds*	*Brazil nuts*	*Cashews*	*Chestnuts*[a]	*Hazelnuts*	*Heartnuts*	*Macadamias*	*Peanuts*[b]	*Pecans*	*Pine nuts*	*Pistachios*	*Walnuts*	*References*
SFA	%	9.09	25.35	21.12	17.36	7.79	3.66	18.18	15.95	8.35	24.10	14.24	11.76	[7]
MUFA	%	61.60	29.04	61.68	34.97	83.24	15.34	77.43	68.69	66.73	27.55	51.47	15.28	[7]
PUFA (ω = 6)	%	29.21	45.43	16.87	42.02	8.85	71.12	1.81	15.38	23.68	46.84	33.43	59.79	[7]
PUFA (ω = 3)	%	0.10	0.18	0.32	5.65	0.12	10.09	2.58	0.00	1.24	1.51	0.86	13.17	[7]
Tocols	mg/100 g	28.60	20.15	7.10	59.60	51.31	22.50	6.15	29.72	49.11	45.80	39.77	43.72	[7]
Vitamin E	ATE	26.35	3.14	1.13	5.88	41.92	2.24	0.92	17.01	6.55	20.03	33.28	7.58	[7]
Phytosterols	mg/100 g	271	208	199	na	165	na	128	284	283	164	184	307	[7]
Sphingolipids	mg/100 g	240	290	na	na	20	na	na	na	320	280	330	290	[47]
Carotenoids	mg/100 g	na	na	0.09	na	na	na	na	na	0.014	na	6.70	na	[7]
Chlorophylls	mg/100 g	na	na	na	na	na	na	na	na	na	0.007	24.09	na	[7]
Alkyl phenols	mg/100 g	na	na	146–242	na	na	na	na	na	na	na	44	na	[7,48,49]

Notes: Tocols includes tocopherols and tocotrienols.

Abbreviations: ATE, alpha-tocopherol equivalents; MUFA, monounsaturated fatty acids; na, not available; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

[a] European chestnuts.

[b] Runner peanuts.

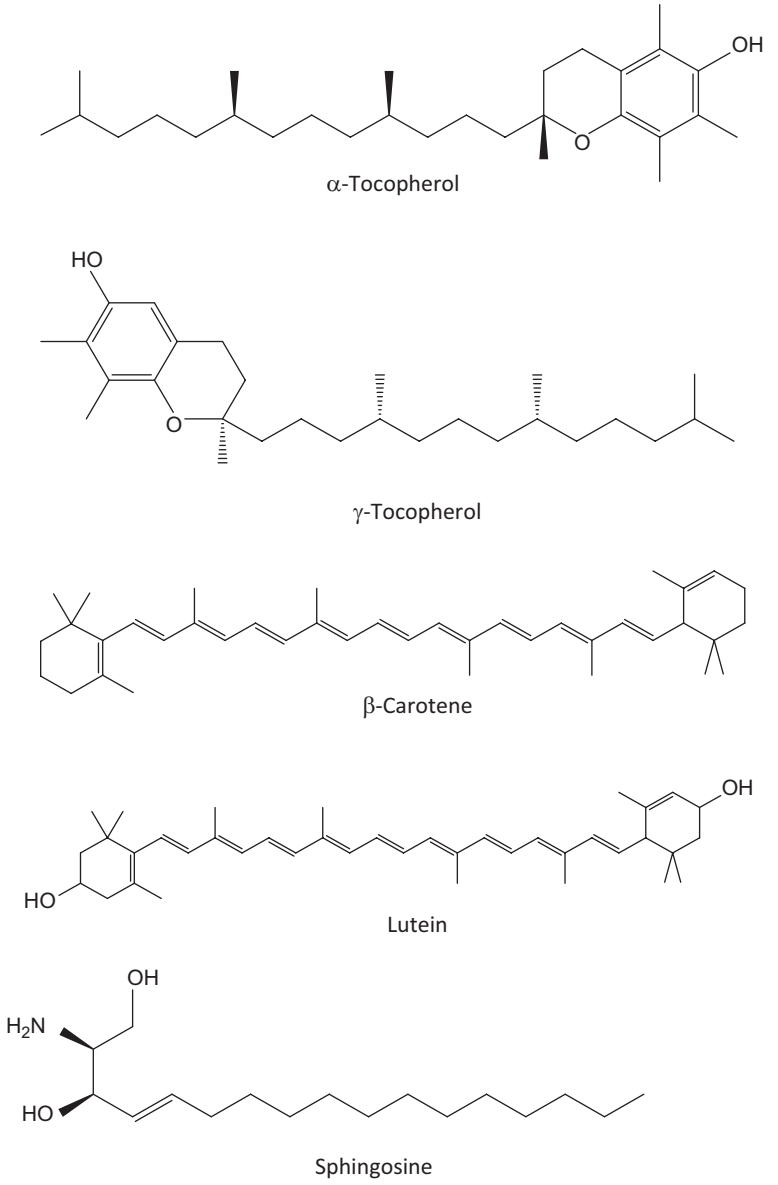
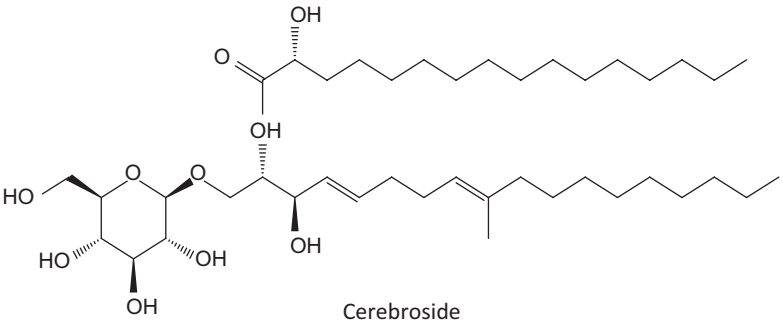
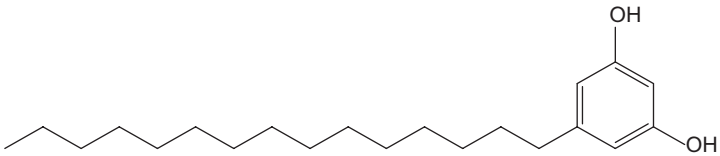


Figure 2.1 Chemical structures of the major fat-soluble bioactives (carotenoids, fatty acids, sphingolipids, alkyl phenols, and chlorophylls) present in nuts.

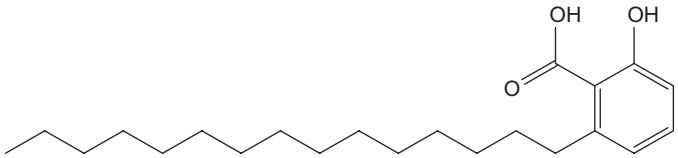
respectively, whereas oils from Brazil nuts, hazelnuts, and heartnuts contain the highest proportion of SFA (25.35%), MUFA (83.24%), and PUFA (81.21%), respectively. MUFA is predominant in most nut oils, except Brazil nuts, chestnuts, heartnuts, pine nuts, and walnuts, which are rich in PUFA. The heart-healthy fatty acids (MUFA + PUFA) vary between 74.65% in Brazil nut oil and 96.55% in heartnut oil of the total fatty acids present. In addition, heartnut and walnut oils are good sources



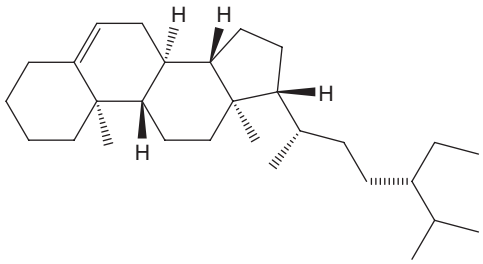
Cerebroside



Cardol



Anacardic acid



β-Sitosterol

Figure 2.1 (Continued) Chemical structures of the major fat-soluble bioactives (carotenoids, fatty acids, sphingolipids, alkyl phenols, and chlorophylls) present in nuts.

of omega-3 fatty acids (alpha-linolenic acid; 18:3ω-3) (10.09 and 13.17%, respectively) [5,7,15,21,50–52].

2.6.2 Tocols (Tocopherols and Tocotrienols)

Vitamin E refers to a group of fat-soluble compounds including four tocopherols and four tocotrienols, designated as α, β, γ, and δ. Nut oils contain different patterns and

amounts of tocols, predominantly α-tocopherol [5,7,12,53–55]. The mean content of total tocols ranges from 6.15 mg/100 g oil for macadamias to 59.60 mg/100 g oil for chestnuts (Table 2.7). Data on tocol levels and patterns in 12 nut oils (almonds, Brazil nuts, cashews, chestnuts, heartnuts, hazelnuts, macadamias, peanuts, pecans, pine nuts, pistachios, and walnuts) have been reported by Alasalvar and Pelvan [5]. Therefore, detailed profiles of nut oils are not provided in this chapter. As compared to other nut oils in Table 2.7, hazelnut oil serves as an excellent source of vitamin E (41.92 mg ATE/100 g oil), followed by pistachio oil (33.28 mg ATE/100 g), almond oil (26.35 mg ATE/100 g oil), pine nut oil (20.03 mg ATE/100 g oil), and peanut oil (17.01 mg ATE/100 g oil). Macadamia oil contains the lowest amount of vitamin E (0.92 mg ATE/100 g oil).

With regards to the RDA value of vitamin E, 42.5 g (one and one-half servings) of nuts recommended by the FDA [22] provide between 0.02% and 79.23% of the daily 15 mg of vitamin E recommended for adult men and women [28]. Hazelnut oil meets the highest RDA requirement among the 12 nut oils listed in Table 2.7.

2.6.3 Phytosterols (Sterols and Stanols)

Plant sterols and stanols (also known as phytosterols) are lipid-like compounds that occur naturally in many foods of plant origin. These include vegetable oils, nuts, seeds, cereals, vegetables, and fruits. They compete and inhibit the intestinal absorption of cholesterol. Plant stanols can be regarded as saturated plant sterols [56]. Systematic reviews and meta-analysis indicate that consumption of 2 g/day of sterols/stanols for 3–4 weeks lowers LDL cholesterol concentration by an average of 10% [57–59]. Both the FDA and EFSA have health claims on plant sterols and stanols. Therefore, both types of phytosterols are used in developing functional foods to reduce the risk of coronary heart disease [56].

The total phytosterol content of nut oils, expressed as mg/100 g oil, ranges from128 in macadamia oil to 307 in walnut oil (Table 2.7). Nut oils contain different patterns and amounts of phytosterols, predominantly β-sitosterol [5,7,47,52,54,60]. To the best of our knowledge, no data on phytosterols exist in the literature for chestnut and heartnut oils. Data for phytosterol levels and patterns in 10 nut oils (almonds, Brazil nuts, cashews, hazelnuts, macadamias, peanuts, pecans, pine nuts, pistachios, and walnuts) have been reported by Alasalvar and Pelvan [5]. Therefore, detailed patterns and profiles of nut oils are not provided in this chapter.

2.6.4 Sphingolipids

Sphingolipids in nut oils range from 20 to 330 mg/100 g, being lowest in hazelnut oil and highest in pistachio oil [47] (Table 2.7). Fang et al. [61] summarized the content of sphingolipids in five nuts (almonds, cashews, hazelnuts, peanuts, and walnuts) and found that the concentration of cerebroside (d18:2-C16:0h-Glu) ranged from 0.021 to 0.068 mg/g nut, being lowest in hazelnuts and highest in almonds. Studies about sphingolipids in nuts are quite sparse. However, two recent reviews discussing the sphingolipid characteristics of certain nuts have been published [5,62]. Thus, more efforts are needed to gain reliable data on the sphingolipid content of nuts. As

compared to other foods such as milk, eggs, soybeans, meats (chicken, beef, and pork), cereals (wheat), and nuts have relatively low sphingolipid content [7].

2.6.5 Carotenoids

Carotenoids are a group of pigments that occur widely and abundantly in nature. Fruits, vegetables and vegetable oils, dairy products, leaves, shrimp, lobster, crab, salmonid fish, and the plumage of exotic birds all contain carotenoids. They are responsible for bright red, orange, and yellow hues in many fruits and vegetables. In contrast to other plant foods, certain nuts contain limited amounts of carotenoids such as α- and β-carotene, β-cryptoxanthin, lutein, lycopene, and zeaxanthin [6,7,63–65]. Among the 12 nuts listed in Table 2.7, only cashew oil (0.09 mg/100 g oil), pecan oil (0.014 mg/100 g oil), and pistachio oil (6.70 mg/100 g oil) contain carotenoids [64–66].

Recently, Stuetz et al. [67] analyzed carotenoids in six raw (unroasted) and roasted nuts (almonds, cashews, hazelnuts, macadamias, pistachios, and walnuts). The concentrations of carotenoids were highest in pistachios with values for lutein/zeaxanthin of about 2757 μg/100 g raw nuts and for β-carotene of about 204 μg/100 g raw nuts. These levels were 16- and 8-fold higher than the concentrations of lutein/zeaxanthin and β-carotene in hazelnuts, respectively, with the highest content in carotenoids after pistachios. Roasted almonds and walnuts showed significantly lower lutein/zeaxanthin (34% and 39% at 160/170°C, $P < 0.001$) levels than the respective raw nuts, whereas the high concentrations of lutein/zeaxanthin in pistachios and hazelnuts were not affected by roasting [67].

2.6.6 Chlorophylls

Chlorophyll pigments are important quality parameters since they correlate with color, which is a basic attribute for evaluating oil quality. Among the commonly consumed nuts listed in Table 2.7, only pine nut oil (0.007 mg/100 g) and pistachio oil (24.09 mg/100 g) contain chlorophylls [7,64,68]. No data are available in the literature on the chlorophyll content of other nuts.

2.6.7 Alkylphenols

In general, alkylphenols are chemical compounds that consist of one or more alkyl chains bound to a phenol. Phenol consists of an aromatic ring and a hydroxyl group. Cashew oil contains between 146 and 242 mg/100 g anacardic acids and cardols, while pistachio oil has 16 different cardanols (44 mg/100 g) (Table 2.7) [7,48,49]. To the best of our knowledge, alkylphenols in other nuts have not been characterized and reported. A series of 12 components (anacardic acids, cardols, 2-methylcardols, and cardanols) in cashew shell oil have been isolated and reported [69].

Gómez-Caravaca et al. [70] measured alkyl phenols in raw and roasted cold pressed cashew nut oils. Anacardic acids were the major alkyl phenols contained in both oils (28.51 mg/100 g raw nut oil and 27.16 mg/100 g roasted nut oil), followed by cardol (15.42 mg/100 g raw nut oil and 20.37 mg/100 g roasted nut oil),

cardanol (0.70 mg/100 g raw nut oil and 1.67 mg/100 g roasted nut oil), and 2-methylcardol compounds (0.79 mg/100 g raw nut oil and 0.81 mg/100 g roasted nut oil). Raw and roasted oils did not show any different compositions except for cardanols. The oil produced from roasted cashew nuts had a higher concentration of cardanols. Trevisan et al. [48] also reported different levels and profiles of alkylphenols in various cashew products (such as apple, nut, cashew nutshell liquid, and fiber).

2.7 Phenolics in Nuts

Phytochemicals are defined as non-nutritive, naturally occurring, and biologically active compounds found in plants. They mainly consist of phenolics, carotenoids, organosulphur compounds, nitrogen-containing compounds, and alkaloids. Phenolics can be divided into flavonoids, phenolic acids, stilbenes, coumarins, lignans, and tannins, among others. They have been reported in nuts except coumarins [4]. Figure 2.2 shows selected simple phenolics (phenolic acids and flavonoids) present in nuts. Among them, flavonoids, phenolic acids, and tannins are the major groups of phenolics and are present in all nuts, albeit to different extents. Different classes and levels of phenolic compounds have been studied for different nuts and have also been reported in some databases such as the Phenol-Explorer and USDA databases [10,11,71]. Among nuts, almonds, chestnuts, hazelnuts, peanuts, pecans, pine nuts, pistachios, and walnuts have the most diverse phenolic profiles. However, limited studies have been carried out on the detailed phenolic profiles of Brazil nuts, cashews, heartnuts, and macadamias (Table 2.8). Detailed comparisons of phenolic profiles of 12 nuts are reviewed in detail here.

2.7.1 Flavonoids

Flavonoids are a group of phenolic compounds that can be classified into seven groups: anthocyanins, flavan-3-ols (flavanols or catechins), flavonols, flavanones, flavones, flavanonols, and isoflavones [4,42]. Flavonoids reported in nuts are predominantly conjugated with sugars or other polyols *via O*-glycosidic bonds or ester bonds.

2.7.1.1 Anthocyanins

Anthocyanins are only present in almonds (cyanidin, delphinidin, procyanidin B_2, and, procyanidin B_3), pistachios (cyanidin-3-*O*-galactoside and cyanidin-3-*O*-glucoside), and walnuts (cyanidin) (Table 2.8) [72–76].

2.7.1.2 Flavan-3-ols

Numerous flavan-3-ols have been characterized in nuts, except for heartnuts and macadamias. Hazelnuts have the highest number of flavan-3-ols, followed by peanuts, walnuts, and pine nuts (Table 2.8). Catechin is the most abundant flavan-3-ols in nuts. In addition, epicatechin is present in all nuts, except Brazil nuts and pecans. Epigallocatechin has been reported in both cashews and pine nuts, while gallocatechin is only present in chestnuts and pine nuts. Gallocatechin is the most abundant

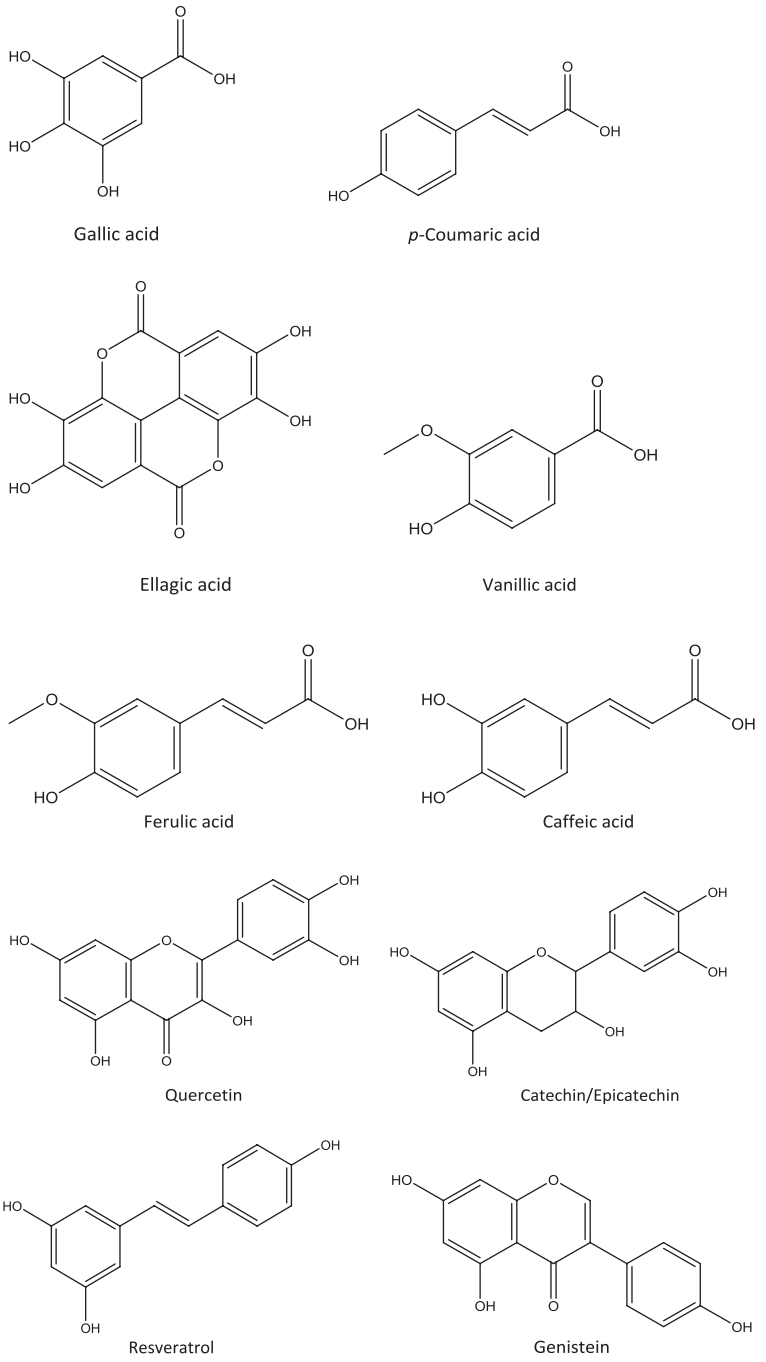


Figure 2.2 Selected simple phenolics (phenolic acids and flavonoids) present in nuts.

Table 2.8 Phenolics in Nuts

Nut	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
Almonds	Anthocyanins	Cyanidin	mg CE/g	1.76	[72]
		Delphinidin		0.05	
		Procyanidin B_2		1.24	
		Procyanidin B_3		3.16	
	Flavan-3-ols	(+)-Catechin	mg/100 g fw	0.2–2.4	[77,78]
		(-)-Epicatechin		0.2–0.8	
	Flavonols	Isorhamnetin	mg/g dw	0.04	[77]
		Isorhamnetin-3-*O*-glucoside		0.9	
		Isorhamnetin-3-*O*-rutinoside		0.9	
		Kaempferol		0.12	
		Kaempferol-3-*O*-glucoside		0.31	
		Kaempferol-3-*O*-rutinoside		0.28	
		Dihydroxykaempferol		0.3	
		Quercetin		0.12	
		Quercetin-3-*O*-galactoside		0.02	
		Quercetin-3-*O*-glucoside		0.01	
		Quercetin-3-*O*-rutinoside		0.3	
	Flavanones	Eriodictyol	mg/g dw	0.01–0.1	[77]
		Eriodictyol-7-*O*-glucoside		0.01	
		Naringenin		0.28	
		Naringenin-7-*O*-glucoside		0.03	
	Phenolic acids	Caffeic acid	mg/g dw	1.1–1.5	[77,78,88]
		Chlorogenic acid		1.6	
		o-Coumaric acid		0.2–0.7	
		p-Coumaric acid		0.12–0.6	
		trans-*p*-Coumaric acid		0.09	
		Ferulic acid		0.13–0.2	
		Gallic acid		0.1–0.45	
		5-Hydroxybenzoic acid		0.3–1.3	
		Protocatechuic acid		0.9–4.5	
		Vanillic acid		0.94–2.9	
		p-Hydroxybenzoic acid		0.15	
		p-Hydroxyphenylacetic acid		0.05	
		Phloretic acid		0.07	
		Sinapic acid		0.11	
		Syringic acid		0.08	
	Hydrolyzable tannins	Ellagitannins	mg/100 g fw	53–57	[103]
		Gallotannins		20–34	

(*Continued*)

Table 2.8 (Continued) Phenolics in Nuts

Nut	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
	Stilbenes	Resveratrol	mg/100 g fw	0.15	[78,107]
		Resveratrol-3-*O*-glucoside		7.72	
	Tyrosols	Hydroxytyrosol		0.20	
		Tyrosol		0.14	
		Vanillin		0.18	
Brazil nuts	Flavan-3-ols	Catechin	µg/g defatted meal	25.2	[79]
	Phenolic acids	Ellagic acid		11.4[a], 14.9[b]	
		Gallic acid		81.8[a], 52[b]	
		Protocatechuic acid		120[a], 33[b]	
		Vanillic acid		35[a], 8.8[b]	
Cashews	Flavan-3-ols	(+)-Catechin	mg/g of defatted meal	11.7	[80]
		(-)-Epicatechin		7.4	
		Epigallocatechin		4.5	
	Phenolic acids	*p*-Coumaric acid		0.1	
		Gallic acid		0.1	
		Syringic acid		0.6	
Chestnuts	Flavan-3-ols	(+)-Catechin	mg/100 g fw	0.01–0.3	[75,78]
		Epicatechin		0.3	
		(+)-Gallocatechin		0.01	
	Phenolic acids	Caffeic acid		0.08	
		o-Coumaric acid		0.09	
		Ferulic acid		0.13	
		Gallic acid		0.44	
		Sinapic acid		0.36	
		Syringic acid		0.07	
		Vanillic acid		0.07	
	Stilbenes	Resveratrol		0.08	
	Tyrosols	Hydroxytyrosol		0.12	
		Tyrosol		0.07	
Hazelnuts					
	Flavan-3-ols	Catechin	mg/100 g fw	1.08	[78,81]
		Epicatechin		0.15	
		Epicatechin-3-gallate		1.33	
		Procyanidin dimer 1	mg/kg dw	1.0–72.9	[81–83]
		Procyanidin dimer 2		1.25–25	
		Procyanidin dimer 3		1.84	
		Procyanidin trimer 1		0.24–7.4	
		Procyanidin trimer 2		0.5–3.0	
		Procyanidin trimer 3		0.7–12.3	
		Procyanidin trimer 4		10.2	
		Procyanidin trimer 5		12.0	
		Procyanidin trimer 6		1.9	
		Procyanidin tetramer 1		7.5	
		Procyanidin tetramer 2		3.3	
		Procyanidin tetramer 3		5.6	
		Procyanidin B_2		1.3–4.5	

(*Continued*)

Table 2.8 (Continued) Phenolics in Nuts

Nut	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
	Flavonols	Myricetin-3-*O*-rhamnoside		0.5–42.5	
		Quercetin pentoside		0.07–2.9	
		Quercetin-3-rhamnoside		0.5–47.0	
	Phenolic acids	Caffeic acid	mg/100 g fw	0.36	[45,78,81,82,94]
		Chlorogenic acid		1.7	
		Cinnamic acid		0.15	
		o-Coumaric acid		0.11	
		p-Coumaric acid		0.15–0.47	
		Ferulic acid		0.64	
		Gallic acid		0.13–1.3[a], 1.7–4.1[b]	
		p-Hydroxybenzoic acid		0.12	
		Protocatechuic acid		0.15–0.7[a], 2.5–7.8[b]	
		Syringic acid		0.08	
		Salicylic acid		0.06	
		Sinapic acid		0.13	
		Vanillic acid		0.03	
		4-Hydroxybenzoic acid		0.07	
	Hydrolysable tannins	B type dimer gallate	mg/kg dw	6.34	[83]
		Glansreginin A		21.3	
		Glansreginin B		56.1	
	Stilbenes	Resveratrol	mg/100 g fw	tr	[78]
	Tyrosols	Tyrosol		0.14	
		Vanillin		0.05	
	Dihydrochalcones	Phloretin-2-*O*-glucoside	mg/kg	1.04–4.6	[81]
Heartnuts	Phenolic acids	Ellagic acid	mg/100 g dw	55–70	[32]
		Valoneic acid dilactone		12–62	
Macadamias	Phenolic acids	2,6-Dihydroxybenzoic acid	mg/100 g dw	na	[96]
		3,5-Dimethoxy-4-hydroxycinnamic acid		na	
		2′-Hydroxy-4′-methoxyacetophenone		na	
		3′,5′-Dimethoxy-4′-hydroxyacetophenone		na	
Peanuts	Flavan-3-ols	Procyanidin monomers	mg CE/100 g	16.1	[84,85]
		A-type procyanidin dimers	mg/100 g dw	90.2	
		B-type procyanidin dimers		19.1	
		A-type procyanidin trimers		214	
		B-type procyanidin trimers		7.3	
		A-type procyanidin tetramers		296	
		B-type procyanidin tetramers		20.1	

(*Continued*)

Table 2.8 (Continued) Phenolics in Nuts

Nut	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
		Catechin	µg/g dw	tr	[85]
		Epicatechin		170	
	Flavonols	Kaempferol		1.6	[89]
		Quercetin		12.4	
	Phenolic acids	*cis*-Coutaric acid		296	[85,89]
		trans-Coutaric acid		139	
		Caftaric acid		17.3	
		Coumaroyl rhamnose		41.4	
		Ferulic acid		119	
		Feruloyl pentoside		29.7	
		p-Coumaric acid		31	
		p-Hydroxybenzoic pentoside		29.7	
		p-Hydroxybenzoic acid		157	
		Chlorogenic acid		2.42	
	Stilbenes	Resveratrol		0.1	
Pecans	Flavan-3-ols	Catechin	mg/100 g dw	0.3–0.4	[86]
	Phenolic acids	Caffeic acid	µg/g dw	96	[92,93]
		Chlorogenic acid		350	
		Gallic acid		45	
		p-Hydroxybenzoic acid		275	
		Protocatechuic acid		17.5	
		Ellagic acid	mg/g dw	3.4	
		Free phenolics	µg/g dw		[86,91]
		Caffeic acid hexoside		6.7	
		Gallic acid derivative		13.6	
		Breifolin carboxylic acid		5.2	
		Valoneic acid dilactone		9.4	
		Ellagic acid pentose		9.3	
		Methylellagic acid		7.4	
		Ellagic acid galloyl pentose		4.4	
		Methyl ellagic acid pentose		8.5	
		Dimethylellagic acid		3.1	
		Soluble esterified linked			
		Gallic acid derivative		79.3	
		Protocatechuic acid		21	
		p-Hydroxybenzoic acid		48.2	
		Valoneic acid dilactone		190	
		Ellagic acid		119	
		Methylellagic acid		7.0	
		Ellagic acid derivative		6.9	
		Sinapoylquinic acid		14.4	
		Soluble glycoside-bound			
		Caffeic acid hexoside		6.7	
		Gallic acid derivative		45.4	
		p-Hydroxybenzoic acid		30.9	
		Valoneic acid dilactone		262	

(*Continued*)

Table 2.8 (Continued) Phenolics in Nuts

Nut	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
		Ellagic acid		103	
		Syringic acid derivative		24	
		Gallic acid		86.2	
Pine nuts	Flavan-3-ols	Catechin	µg/g fw	3.9–36	[87]
		Epicatechin		1.5–16	
		Epicatechin-3-gallate		2.1–16	
		Epigallocatechin		2.8–18.5	
		Epigallocatechin-3-gallate		5.6–19	
		Gallocatechin		9.2–65	
	Flavonols	Quercetin		3.9–27	
	Flavanonols	Taxifolin		1.1–2.5	
	Phenolic acids	Ellagic acid		5.8–35.4	
		Gallic acid		2.9–26	
		Protocatechuic acid		1.2–1.7	
		Vanillic acid		2.8–21	
Pistachios	Anthocyanins	Cyanidin-3-*O*-galactoside	µg/g fw	0.2	[73,74]
		Cyanidin-3-*O*-glucoside		0.01	
	Flavan-3-ols	Catechin	mg/100 g fw	4.8	[73,74,88]
		Epicatechin		0.1–3.0	
		Procyanidin dimer		0.1–6.0	
	Flavanones	Eriodictyol-7-*O*-glucoside		4.1	
		Eriodictyol-3-*O*-hexoside		0.02–0.4	
		Eriodictyol		2.0–9.4	
		Naringenin		0.2	
		Naringenin-7-*O*-neohesperidoside		37.1	
	Flavones	Apigenin		0.6	
		Luteolin		0.08	
	Flavonols	Kaempferol		0.2	
		Myricetin		0.2	
		Quercetin		2.0	
		Quercetin-3-*O*-rutinoside		9.81	
		Quercetin-3-*O*-glucoside		3.0	
		Quercetin-3-*O*-hexoside		0.3	
		Rutin		3.0	
	Isoflavones	Daidzein		4.2	
		Genistein		6.9	
		Genistein-7-*O*-glucoside		4.7	
	Phenolic acids	Caffeic acid	mg/100 g fw	0.3–1.34	[78,88,95]
		Cinnamic acid		tr	
		o-Coumaric acid		16.8–65.6	
		p-Coumaric acid		13.5–39.0	
		Chlorogenic acid		0.75	
		Ferulic acid		4.2–7.2	
		Gallic acid		3.2–69.87	
		p-Hydroxybenzoic acid		0.1	

(*Continued*)

Table 2.8 (Continued) Phenolics in Nuts

Nut	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
		p-Hydroxyphenylacetic acid		0.05	
		Protocatechuic acid		2.1	
		Phloretic acid		0.05	
		Syringic acid		0.08	
		Vanillic acid		0.13	
	Stilbenes	Resveratrol	mg/100 g fw	0.14	[78]
	Tyrosols	Tyrosol	mg/100 g fw	0.13	[78]
		Hydroxytyrosol		0.21	
Walnuts	Anthocyanins	Cyanidin	mg/100 g fw	0.27	[75,76,105]
	Flavan-3-ols	Catechin	mg/kg fw	3.9–4.7	
		Epicatechin		0.8	
		Procyanidin dimer 1		252	
		Procyanidin dimer 2		2.11	
		Procyanidin trimer		278	
		Procyanidin tetramer		2.0	
	Flavonols	Q-galloyl pentoside 1		4.35	
		Q-galloyl pentoside 2		1.25	
		Q-galloyl pentoside		2.32	
		Unknown 429		16.0	
		Unknown 459		2.0	
		Quercetin	mg/100 g fw	0.75	[78]
	Phenolic acids	Caffeic acid	mg/100 g fw	0.18	[76,78]
		Chlorogenic acid		0.11	
		Cinnamic acid		0.05	
		o-Coumaric acid		0.34	
		p-Coumaric acid		0.21	
		Ferulic acid		0.15	
		p-Hydroxybenzoic acid		0.16	
		p-Hydroxyphenylacetic acid		0.05	
		Ellagic acid		4.4	
		Ellagic acid hexoside		2.9	
		Ellagic acid pentoside		31.8	
		3-*O*-Caffeoylquinic acid		1.8	
		3-*O*-*p*-Coumaroylquinic acid		1.2	
		Ferulic acid glucoside		0.32	
		Phloretic acid		0.05	
		Gallic acid		37.2	
		Protocatechuic acid		0.34	
		Sinapic acid		0.12	
		Syringic acid		0.15	
		Vanillic acid		0.14	
	Hydrolysable tannins	Galloyl bis HHDP glucose 1	mg/kg fw	185	[75,76,105]
		Galloyl bis HHDP glucose 2		57.6	
		Glansreginin B		28.2	
		Glansreginin A		484	

(*Continued*)

Table 2.8 (Continued) Phenolics in Nuts

Nut	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
		HHDP digalloyl glucose isomer 1		48.4	
		HHDP digalloyl glucose isomer 2		54.3	
		HHDP digalloyl glucose isomer 3		17.7	
		Di-galloylglucose		22	
		Di-HHDP glucose isomer 1		148	
		Di-HHDP glucose isomer 2		183	
		Di-HHDP glucose isomer 3		144	
		Di-HHDP glucose isomer 4		80.2	
		Vescalagin isomer 1		38.3	
		Vescalagin isomer 2		109	
		Vescalagin isomer 3		29.1	
		Vescalagin isomer 4		189	
		Vescalagin isomer 5		55.0	
		Vescalagin isomer 6		35.0	
		Ellagitanins	mg/100 g dw	1600	[105]
	Tyrosols	Hydroxytyrosol	mg/100 g fw	0.30	[76,78]
		Tyrosol		0.14	

Abbreviations: CE, catechin equivalents; dw, dry weight; fw, fresh weight; HHDP, hexahydroxydiphenoyl; na, not available; tr, trace.

[a] Phenolic compounds determined from free phenolic extracts.

[b] Phenolic compounds determined from bound phenolic extracts.

flavan-3-ol present among the six flavan-3-ols present in pine nuts. Procyanidin dimers and procyanidin trimers are present in both hazelnuts and walnuts, while procyanidin tetramers are present in hazelnuts, peanuts, and walnuts (Table 2.8) [73–88].

2.7.1.3 Flavonols

Flavonols have been reported in almonds, hazelnuts, peanuts, pine nuts, pistachios, and walnuts at varying concentrations. Lin et al. [77] reported 11 flavonols in almonds, among which isorhamnetin-3-*O*-glucoside and isorhamnetin-3-*O*-rutinoside predominated. Isorhamnetin, isorhamnetin-3-*O*-glucoside, isorhamnetin-3-*O*-rutinoside, and dihydroxykaempferol are only present in almonds among the 12 nuts reported in Table 2.8. Quercetin-3-*O*-rutinoside is the most abundant flavonol in pistachios [73]. Rutin has only been reported in pistachios. Kaempferol-3-*O*-glucoside is only present in almonds, while quercetin-3-*O*-glucoside and quercetin-3-*O*-rutinoside are reported in both almonds and pistachios. Some unique flavonols (such as Q-galloyl pentoside 1, Q-galloyl pentoside 2, Q-galloyl pentoside, unknown 429, and unknown 459) have only been reported in walnuts. Moreover, myricetin-3-*O*-rhamnoside, quercetin pentoside, and quercetin-3-rhamnoside are only present in hazelnuts (Table 2.8) [73–77,81–83,87–89].

2.7.1.4 Flavanones

Flavanones are another important group of flavonoids. Four flavanones in almonds (eriodictyol, eriodictyol-7-*O*-glucoside, naringenin, and naringenin-7-*O*-glucoside) and five flavanones in pistachios (eriodictyol-7-*O*-glucoside, eriodictyol-3-*O*-hexoside, eriodictyol, naringenin, and naringenin-7-*O*-neohesperidoside) have been identified (Table 2.8). Naringenin and naringenin-7-*O*-neohesperidoside are the most abundant flavanones reported in almonds and pistachios, respectively [73,74,77,88].

2.7.1.5 Flavones

Flavones, such as apigenin and luteolin, are present only in pistachios, where apigenin is the most abundant one (Table 2.8) [73,74,88].

2.7.1.6 Flavanonols

In terms of flavanonols, taxifolin is the only compound present in pine nuts, according to a study conducted by Hoon et al. [87] (Table 2.8).

2.7.1.7 Isoflavones

Four isoflavones (formononetin, daidzein, genistein, and glycitein), four lignans (matairesinol, lariciresinol, pinoresinol, and secoisolariciresinol), and one coumestan (coumestrol) are reported in nuts. Among nuts, pistachios are the richest source of total isoflavones, total lignans, and total phytoestrogens [33,90]. Tomaino et al. [73] identified three isoflavones in pistachios: daidzein, genistein, and genistein-7-O-glucoside (Table 2.8).

2.7.2 Phenolic Acids

Phenolic acids are the second largest group of phenolics after flavonoids. Phenolic acids in foods occur in free, esterified, glycosidic, and insoluble-bound forms. Free phenolic acids are known to contribute to the taste of foods. Two classes of phenolic acids, hydroxycinnamic acids and hydroxybenzoic acids, are present in nuts [9]. Pecans contain the highest number of phenolic acids (30) [86,91–93], followed by walnuts (20) [76,78], almonds (15) [77,78,88], hazelnuts (14) [45,78,81,82,94], pistachios (13) [78,88,95], and peanuts (10) [85,89]. Other nuts (Brazil nuts, cashews, chestnuts, heartnuts, macadamias, and pine nuts) contain between two and seven phenolic acids, being lowest in heartnuts and highest in chestnuts [32,75,78–80,87,96] (Table 2.8). All nuts contain phenolic acids, albeit to different extents.

Although phenolic acids have not been well characterized in some nuts (such as Brazil nuts, cashews, heartnuts, macadamias, and pine nuts), gallic acid is present in all nuts, except heartnuts, macadamias, and peanuts. Gallic acid is the most abundant phenolic acid reported in chestnuts, pistachios, and walnuts among the 12 nuts listed in Table 2.8. Chlorogenic acid [350 μg/g dry weight (dw)] is the most abundant phenolic acid identified in pecans, followed by *p*-hydroxybenzoic acid (275 μg/g dw) and caffeic acid (96 μg/g dw). Pecans are also a good source of ellagic acid together with Brazil nuts, heartnuts, pine nuts, and walnuts [32,76,78,79,87,92,93].

Moreover, protocatechuic acid is the most abundant phenolic acid present in almonds, Brazil nuts, and hazelnuts among phenolic acids identified for each nut. Although phloretic acid is reported only in almonds and pistachios, valoneic acid dilactone is present in heartnuts and pecans. In addition, *p*-hydroxyphenylacetic acid has been reported only in almonds, pistachios, and walnuts (Table 2.8).

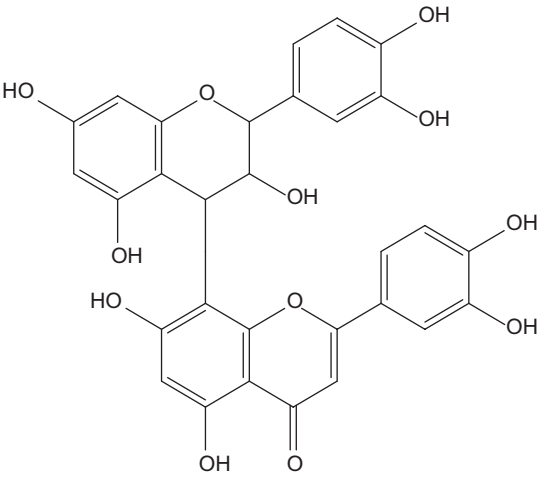
Some phenolic acid derivatives (such as brevifolincarboxylic acid, caffeic acid hexoside, protocatechuic acid hexoside, valoneic acid dilactone, methylellagic acid, dimethyl ellagic acid pentose, dimethyl ellagic acid galloyl pentose, dimethyl ellagic acid hexoside, digalloyl ellagic acid, ellagic acid galloyl pentose, and sinapoylquinic acid) have recently been reported for the first time in pecans [91,97]. Meanwhile, 3-*O*-*p*-coumaroylquinic and 3-*O*-caffeoylquinic acids are reported only in walnuts [83]. Recently, Pelvan et al. [94] have identified some new phenolic acids in Turkish Tombul hazelnuts, such as neochlorogenic acid, ellagic acid, 3-*p*-coumaroylquinic acid, digalloyl-glucose isomer, coutaric acid, and fertaric acid.

2.7.3 Tannins

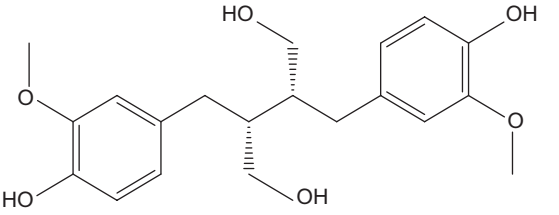
Proanthocyanidins (condensed tannins) and hydrolysable tannins are generally the most abundant polyphenols in most nuts. Depending on their structures, tannins are defined as proanthocyanidins (monomers, dimers, oligomers, and polymers of flavan-3-ols) or hydrolysable (gallotannins and ellagitannins). Selected complex phenolics (proanthocyanidins, gallotannins, and ellagitannins) present in nuts are given in Figure 2.3.

With regards to proanthocyanidins, the total proanthocyanidins contents of nuts are given in Table 2.5. Hazelnuts contain the highest total content of proanthocyanidins (491 mg/100 g) among nuts [11,98]. No proanthocyanidins are reported in Brazil nuts, heartnuts, macadamias, or pine nuts. The order of total proanthocyanidin concentrations in descending order of nuts is as follows: hazelnuts > pecans > pistachios > almonds > walnuts > cashews > chestnuts [98]. Lainas et al. [99] found that natural hazelnut extractable proanthocyanidins were 81% oligomers (4–9mers) and polymers (≥10mers). However, roasted hazelnut extractable proanthocyanidins were only monomers to trimers. This decrease was apparently due to skin loss during roasting. The majority of nut proanthocyanidins are highly polymerized (>10mers). However, cashews contain only the monomer and dimer of proanthocyanidins [100]. In addition, proanthocyanidins of pecans have also been determined where a majority of its proanthocyanidins were A- and B-type dimers. The proanthocyanidin monomers, trimers, tetramers, pentamers, and hexamers of pecans were also separated and characterized by the same authors [91,97]. Recently, B-type procyanidin hexamers have been reported in pecans [101]. The most common prodelphinidins reported in pecans are trimers [97,102], where tetramers to heptamers are also present [97,101].

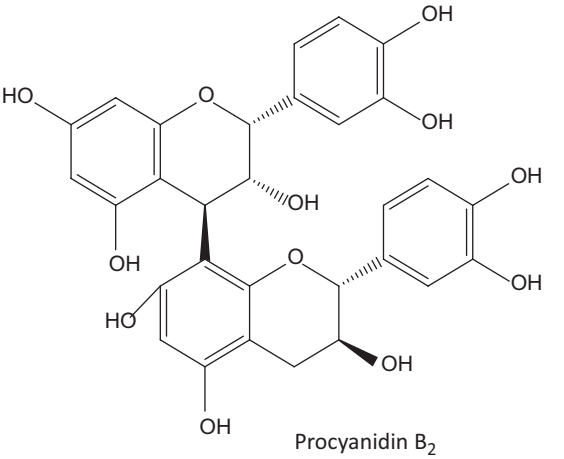
With respect to hydrolysable tannins, these have been well-documented in walnuts, hazelnuts, and almonds. Walnuts have been reported to contain the highest numbers of hydrolysable tannins, followed by hazelnuts and almonds (Table 2.8) [75,76,83,103,104]. Indeed, walnuts are the richest plant source of ellagitannins (~1600 mg/100 g), where the most abundant ellagitannin is pedunculagin [105,106]. Ellagitannins and gallotannins are present in almonds [103], whereas B type dimer gallete, glansreginin A, and glansreginin B are reported in hazelnuts [83]. Regueiro



Proanthocyanidin dimer

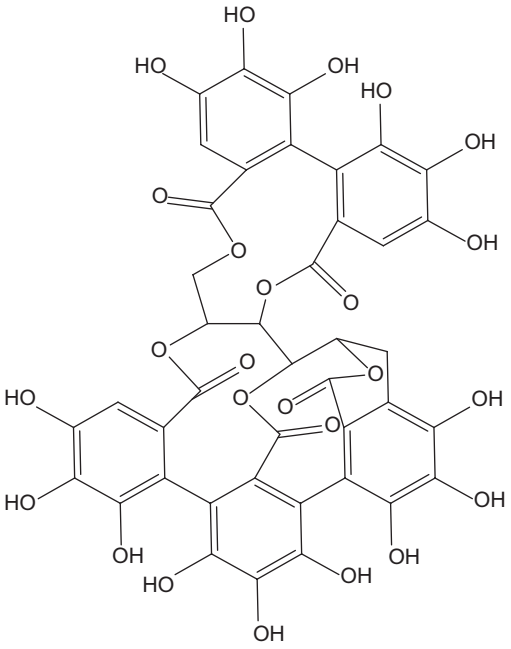


Secoisolariciresinol

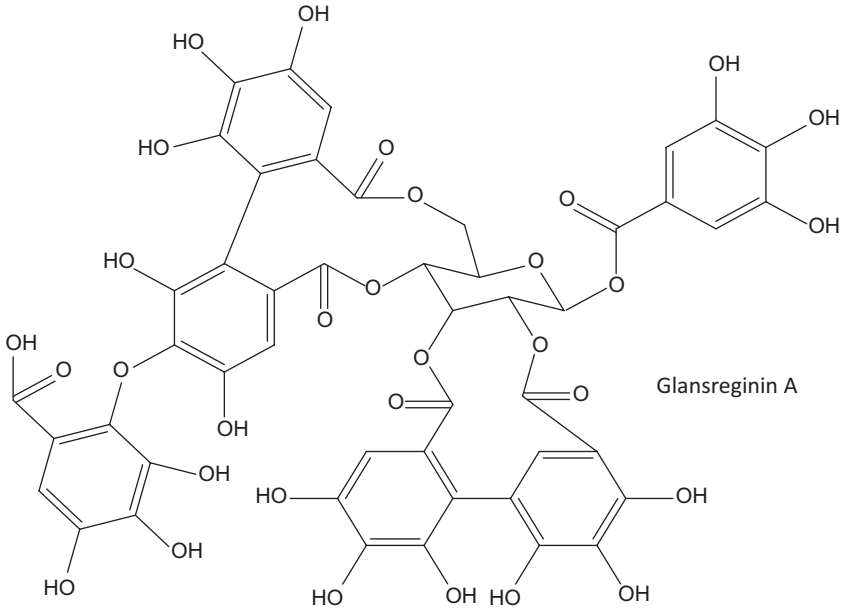


Procyanidin B_2

Figure 2.3 Selected complex phenolics (proanthocyanidins, gallotannins, and ellagitannins) present in nuts.



Vescalagin



Glansreginin A

Figure 2.3 (Continued) Selected complex phenolics (proanthocyanidins, gallotannins, and ellagitannins) present in nuts.

et al. [105] have identified and confirmed the identity of some polyphenols which had not earlier been reported in walnuts: stenophyllanin C, stenophyllanin A/B, malabathrin A, eucalbanin A, cornusiin B, heterophylliin E, pterocarinin B, pterocarinin A, oenothein B, reginin A, and alienanin B, and when compared to the results reported by Slatnar et al. [76]. Recently, Pelvan et al. [94] identified some new hydrolysable tannins in Turkish Tombul hazelnuts, namely flavogallonic acid dilactone isomer, valoneic acid dilactone, hexahydroxydiphenoyl (HHDP)-glucose isomer, ellagic acid pentoside isomer, and ellagic acid hexoside isomer. In addition, some new hydrolysable tannins, namely vescalagin isomers, di-hexahydroxydiphenoyl (Di-HHDP) glucose isomers, galloyl bis HHDP glucose, HHDP digalloyl glucose isomers, and di-galloylglucose, have been reported in walnuts (Table 2.8) [75,76]. HHDP detaches after acid hydrolysis and spontaneously lactonizes to ellagic acid. This group made up 60.8% of the hydrolysable tannins detected in walnuts. Glansreginin A and B are present in both hazelnuts and walnuts [75,76,83].

2.7.4 Stilbenes

The presence of stilbenes, such as resveratrol, has been reported in almonds, chestnuts, hazelnuts, peanuts, and pistachios. Hazelnuts contain trace amounts of stilbenes as compared to other reported nuts (Table 2.8) [8,78,85,89,107,108]. Stilbenes are predominantly located in the skins of nuts. Almonds also contain resveratrol-3-*O*-glucoside, predominantly concentrated in the skin [107]. The variability of resveratrol content among the 109 US peanut cultivars over 2 years was 0.003–0.026 mg/100 g peanuts [108].

2.7.5 Other Phenolics

Dihydrochalcones, such as phloretin-2-*O*-glucoside, are present only in hazelnuts [81]. Tyrosols, derivatives of phenethyl alcohol, are also reported in almonds, chestnuts, hazelnuts, pistachios, and walnuts. Three tyrosols (hydroxytyrosol, tyrosol, and vanillin) are present in nuts, among which vanillin is only reported in almonds and hazelnuts (Table 2.8) [78].

2.8 Conclusion

Nuts, which contain phytochemicals and fat-soluble minor components as well as nutrient and non-nutrient antioxidants, are an excellent choice for heart-healthy snack foods and food supplements. Nuts should be consumed with their skins (pellicles) and raw when possible, because of their high phytochemical content as well as antioxidant activity. A detailed and up-to-date summary and scientific review of the available data on nutrient and non-nutrient antioxidant components of nuts are reported in this chapter. The compiled results indicated that many of the fat-soluble bioactives and phytochemicals are yet to be fully identified and characterized in some nuts. Therefore, further research should focus on identifying and quantifying these health-promoting compounds in Brazil nuts, cashews, chestnuts, heartnuts, macadamias, and pine nuts.

References

1. International Nut and Dried Fruit Council (INC), *Nuts and Dried Fruits, Statistical Yearbook 2017/2018 and Nutfruit Magazine July 2018*, INC, Reus, Spain, 2018.
2. Food and Agricultural Organization (FAO), *Chestnut Production*. Published on line at: http://faostat.fao.org (accessed July 23, 2018).
3. Alasalvar, C., and Shahidi, F., Natural antioxidants in tree nuts. *Eur. J. Lipid Sci. Technol.*, 111, 1056–1962, 2009.
4. Alasalvar, C., and Shahidi, F., Tree nuts: Composition, phytochemicals, and health effects: An overview, in *Tree Nuts: Composition, Phytochemicals, and Health Effects*, Alasalvar, C. and Shahidi, F., Eds., CRC Press, Boca Raton, FL, 2009, pp. 1–10.
5. Alasalvar, C., and Pelvan, E., Fat-soluble bioactives in nuts. *Eur. J. Lipid Sci. Technol.*, 113, 943–949, 2011.
6. Bolling, B.W., Oliver Chen, C.-Y., McKay, D.L., and Blumberg, J.B., Tree nut phytochemicals: Composition, antioxidant capacity, bioactivity, impact factors: A systematic review of almonds, Brazils, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts. *Nutr. Res. Rev.*, 24, 244–275, 2011.
7. Alasalvar, C., and Bolling, B.W., Review of nut phytochemicals, fat-soluble bioactives, antioxidant components and health effects. *Br. J. Nutr.*, 113(Suppl. 2), S68–S78, 2015.
8. Bolling, B.W., Almond polyphenols: Methods of analysis, contribution to food quality, and health promotion. *CRFSFS*, 16, 346–368, 2017.
9. Chang, S.K., Alasalvar, C., Bolling, B.W., and Shahidi, F., Nuts and their co-products: The impact of processing (roasting), phenolics, bioavailability, and health benefits – A comprehensive review. *J. Funct. Foods*, 26, 88–122, 2016.
10. U.S. Department of Agriculture (USDA), USDA Database for the Flavonoid Content of Selected Foods, Release 3.3 – March 2018. Published on line at: http://www.ars.usda.gov/nutrientdata (accessed October 28, 2018).
11. U.S. Department of Agriculture (USDA), USDA Database for the Proanthocyanidin Content of Selected Foods, Release 2.1 – March 2018. Published on line at: http://www.ars.usda.gov/nutrientdata (accessed October 28, 2018).
12. U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed June 20, 2018).
13. Vinson, J.A., and Cai, Y., Nuts, especially walnuts, have both antioxidant quantity and efficacy and exhibit significant potential health benefits. *Food Funct.*, 3, 134–140, 2012.
14. Sathe, S.K., Monaghan, E.K., Kshirsagar, H.H., and Venkatachalam, M., Chemical composition of edible nut seeds and its implications in human health, in *Tree Nuts: Composition, Phytochemicals, and Health Effects*, Alasalvar, C. and Shahidi, F., Eds., CRC Press, Boca Raton, FL, 2009, pp. 11–35.
15. Li, L., Tsao, R., Yang, R., Kramer, J.K.G., and Hernandez, M., Fatty acid profiles, tocopherol contents, and antioxidant activities of heartnut (*Juglans ailanthifolia* var. *cordiformis*) and Persian walnut (*Juglans regia* L.). *J. Agric. Food Chem.*, 55, 1164–1169, 2007.
16. U.S. Department of Agriculture (USDA), *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*, The National Academies Press, Washington, DC, 2005.

17. Hao, H., Li, Q., Bao, W., Wu, Y., and Ouyang, J., Relationship between physicochemical characteristics and *in vitro* digestibility of chestnut (*Castanea mollissima*). *Food Hydrocoll.*, 84, 193–199, 2018.
18. Pereira-Lorenzo, S., Ramos-Cabrer, A.M., Díaz-Hernández, M.B., Ciordia-Ara, M., and Ríos-Mesa, D., Chemical composition of chestnut cultivars from Spain. *Sci. Hortic.*, 107, 306–314, 2006.
19. FAO/WHO/UNU, *Energy and Protein Requirement*, *Report of a Joint FAO/WHO/UNU Expert Consultation*, *World Health Organization* Technical Report Series 724, WHO, Geneva, Switzerland, 1985.
20. Ruggeri, S., Cappelloni, M., Gambelli, L., and Carnovale, E., Chemical composition and nutritive value of nuts grown in Italy. *Ital. J. Food Sci.*, 10, 243–252, 1998.
21. Venkatachalam, M., and Sathe, S.K., Chemical composition of selected edible nut seeds. *J. Agric. Food Chem.*, 54, 4705–4714, 2006.
22. Food and Drug Administration (FDA), *Qualified Health Claims: Letter of Enforcement Discretion – Nuts and Coronary Heart Disease, Docket No 02P-0505*, Food and Drug Administration, Washington, DC, 2003.
23. King, J.C., Rechkemmer, G., and Geiger, C.J., Second international nuts and health symposium, 2007: Introduction. *J. Nutr.*, 138(Suppl.), 1734S–1735S, 2008.
24. Food and Drug Administration (FDA), *Qualified Health Claims: Letter of Enforcement Discretion – Walnuts and Coronary Heart Disease (Docket No 02P-0292)*, Food and Drug Administration, Washington, DC, 2004.
25. European Food Safety Authority (EFSA), Scientific opinion on the substantiation of health claims related to walnuts and maintenance of normal blood LDL-cholesterol concentrations (ID 1156, 1158) and improvement of endothelium-dependent vasodilation (ID 1155, 1157) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J.*, 9(4), 2074, 2011.
26. DRIs., *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*, The National Academies Press, Washington, DC, 1997.
27. DRIs., *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, The National Academies Press, Washington, DC, 1998.
28. DRIs., *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*, The National Academies Press, Washington, DC, 2000.
29. DRIs., *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, The National Academies Press, Washington, DC, 2001.
30. DRIs., *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*, The National Academies Press, Washington, DC, 2004.
31. Wu, X., Beecher, G.R., Holden, J.M., Haytowitz, D.B., Gebhardt, S.E., and Prior, R.L., Lipophilic and hydrophilic antioxidant capacities of common foods in the United States. *J. Agric. Food Chem.*, 52, 4026–4037, 2004.
32. Li, L., Tsao, R., and Yang, R., Polyphenolic profiles and antioxidant activities of heartnut (*Juglans ailanthifolia* var. *cordiformis*) and Persian walnut (*Juglans regia* L.). *J. Agric. Food Chem.*, 54, 8033–8040, 2006.
33. Thompson, L.U., Boucher, B.A., Liu, Z., Cotterchio, M., and Kreiger, N., Phytoestrogen content of foods consumption in Canada, including isoflavones, lignans, and coumestan. *Nutr. Cancer*, 54, 184–201, 2006.
34. Otles, S., and Selek, I., Phenolic compounds and antioxidant activities of chestnut (*Castanea sativa* Mill.) fruits. *Qual. Assur. Saf. Crops Foods.*, 4, 199–205, 2012.

35. Burton, G.W., Joyce, A., and Ingold, K.U., First proof that vitamin E is major lipid-soluble, chain-breaking antioxidant in human blood plasma. *Lancet*, 8292 ii, 327, 1982.
36. Azzi, A., and Stocker, A., Vitamin E: Non-antioxidant roles. *Prog. Lipid Res.*, 39, 231–255, 2000.
37. Eitenmiller, R., and Lee, J., *Vitamin E: Food Chemistry, Composition, and Analysis*, CRC Press, Boca Raton, FL, 2004.
38. Burk, R.F., Selenium, an antioxidant nutrient. *Nutr. Clin. Care*, 4, 47–49, 2002.
39. Abe, L.T., Lajolo, F.M., and Genovese, M.I., Comparison of phenol content and antioxidant capacity of nuts. *Ciênc. Tecnol. Aliment. Campinas*, 30, 254–259, 2010.
40. Blomhoff, R., Carlsen, M.H., Andersen, L.F., and Jacobs Jr, D.R., Health benefits of nuts: Potential role of antioxidants. *Br. J. Nutr.*, 96(Suppl. 2), S52–S60, 2006.
41. Ozer, H.K., Phenolic compositions and antioxidant activities of Maya nut (*Brosimum alicastrum*): Comparison with commercial nuts. *Int. J. Food Proper.*, 20, 2772–2781, 2017.
42. Shahidi, F., and Ambigaipalan, P., Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects – A review. *J. Funct. Foods*, 18, 820–897, 2015.
43. Arcan, I., and Yemenicioğlu, A., Antioxidant activity and phenolic content of fresh and dry nuts with or without seed coat. *J. Food Comp. Anal.*, 22, 184–188, 2009.
44. Samaranayaka, A.G.P., John, J.A., and Shahidi, F., Antioxidant activity of English walnut (*Juglans regia* L.). *J. Food Lipids*, 15, 384–397, 2008.
45. Pelvan, E., Alasalvar, C., and Uzman, S., Effects of roasting on the antioxidant status and phenolic profiles of commercial Turkish hazelnut varieties (*Corylus avellana* L.). *J. Agric. Food Chem.*, 60, 1218–1223, 2012.
46. Schlörmann, W., Birringer, M., Böhm, V., Löber, K., Jahreis, G., Lorkowski, S., Muller, A.K. et al., Influence of roasting conditions on health-related compounds in different nuts. *Food Chem.*, 180, 77–85, 2015.
47. Miraliakbari, H., and Shahidi, F., Antioxidant activity and minor components of tree nut oils. *Food Chem.*, 111, 421–427, 2008.
48. Trevisan, M.T.S., Pfundstein, B., Haubner, R., Wurtele, G., Spiegelhalder, B., Bartsch, H., and Owen, R.W., Characterization of alkyl phenols in cashew (*Anacardium occidentale*) products and assay of their antioxidant capacity. *Food Chem. Toxicol.*, 44, 188–197, 2006.
49. Saitta, M., Giuffrida, D., La Torre, G.L., Potorti, A.G., and Dugo, G., Characterisation of alkylphenols in pistachio (*Pistacia vera* L.) kernels. *Food Chem.*, 117, 451–455, 2009.
50. Shin, E.-C., Pegg, R.B., Phillips, R.D., and Eitenmiller, R.R., Commercial Runner peanut cultivars in the USA: Fatty acid composition. *Eur. J. Lipid Sci. Technol.*, 112, 195–207, 2010.
51. Barreira, J.C.M., Casal, S., Ferreira, I.C.F.R., Oliveira, M.B.P.P., and Pereira, J.A., Nutritional, fatty acids and triacylglycerols profiles of *Castanea sativa* Mill. cultivars: A compositional and chemometric approach. *J. Agric. Food Chem.*, 57, 2836–2842, 2009.
52. Alasalvar, C., Amaral, J.S., and Shahidi, F., Functional lipid characteristics of Turkish Tombul hazelnut (*Corylus avellana* L.). *J. Agric. Food Chem.*, 54, 10177–10183, 2006.
53. Maguire, L.S., O'Sullivan, S.M., Galvin, K., O'Connor, T.P., and O'Brien, N.M., Fatty acid profile, tocopherol, squalane and phytosterol content of walnuts, almonds, peanuts, hazelnuts and the macadamia nut. *Int. J. Food Sci. Nutr.*, 3, 171–178, 2004.

54. Ryan, E., Galvin, K., O'Connor, T.P., Maguire, A.R., and O'Brien, N.M., Fatty acid profile, tocopherol, squalene and phytosterol content of Brazil, pecan, pine, pistachio and cashew nuts. *Int. J. Food Sci. Nutr.*, 57, 219–228, 2006.
55. Shin, E.-C., Huang, Y.-Z., Pegg, R.B., Phillips, R.D., and Eitenmiller, R.R., Commercial Runner peanut cultivars in the United States: Tocopherol composition. *J. Agric. Food Chem.*, 57, 10289–10295, 2009.
56. Zawistowski, J., Applications of plant sterols and stanols in functional beverages, in *Handbook of Functional Beverages and Human Health*, Shahidi, F. and Alasalvar, C., Eds., CRC Press, Boca Raton, FL, 2016, pp. 785–800.
57. Han, S.F., Jiao, J., Xu, J.Y., Zimmermann, D., Actis-Goretta, L., Guan, L., Zhao, Y.Y. et al., Effects of plant stanol and sterol-enriched diets on lipid profiles in patients treated with statins: Systematic review and meta-analysis. *Sci. Rep.*, 6, 31337, 2016.
58. Genser, B., Silbernagel, G., De Backer, G., Bruckert, E., Carmena, R., Chapman, M.J., Deanfield, J. et al., Plant sterols and cardiovascular disease: A systematic review and meta-analysis. *Cardiology*, 125, 53–53, 2013.
59. Ras, R.T., Geleijnse, J.M., and Trautwein, E.A., LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: A meta-analysis of randomised controlled studies. *Br. J. Nutr.*, 112, 214–219, 2014.
60. Nórmen, L., Ellegård, L., Brants, H., Dutta, P., and Andersson, H., A phytosterol database: Fatty foods consumed in Sweden and the Netherlands. *J. Food Comp. Anal.*, 20, 193–201, 2007.
61. Fang, F., Ho, C.-T., Sang, S., and Rosen, R.T., Determination of sphingolipids in nuts and seeds by a single quadrupole liquid chromatography-mass spectrometry method. *J. Food Lipids*, 12, 327–343, 2005.
62. Wang, Y., Tan, D., and Ho, C.-T., Sphingolipids in tree nuts, in *Tree Nuts: Composition, Phytochemicals, and Health Effects*, in *Tree Nuts: Composition, Phytochemicals, and Health Effects*, Alasalvar, C. and Shahidi, F., Eds., CRC Press, Boca Raton, FL, 2009, pp. 85–93.
63. Kornsteiner, M., Wagner, K.-H., and Elmadfa, I., Tocopherols and total phenolics in 10 different nut types. *Food Chem.*, 98, 381–387, 2006.
64. Bellomo, M.G., and Fallico, B., Anthocyanins, chlorophylls and xanthophylls in pistachio nuts (*Pistacia vera*) of different geographic origin. *J. Food Comp. Anal.*, 20, 352–359, 2007.
65. Trox, J., Vadivel, V., Vetter, W., Stuetz, W., Scherbaum, V., Gola, U., Nohr, D. et al., Bioactive compounds in cashew nut (*Anacardium occidentale* L.) kernels: Effect of different shelling methods. *J. Agric. Food Chem.*, 58, 5341–5346, 2010.
66. Bouali, I., Trabelsi, H., Abdallah, I.B., Albouchi, A., Martine, L., Gregoire, S., Bouzaien, G. et al., Changes in fatty acid, tocopherol and xanthophyll contents during the development of Tunisian-grown pecan nuts. *J. Am. Oil Chem. Soc.*, 90, 1869–1876, 2013.
67. Stuetz, W., Schlörmann, W., and Glei, M., B-vitamins, carotenoids and α-/γ-tocopherol in raw and roasted nuts. *Food Chem.*, 221, 222–227, 2017.
68. Cheikh-Rouhou, S., Hentati, B., Besbes, S., Blecker, C., Deroanne, C., and Attia, H., Chemical composition and lipid fraction characteristics of Aleppo pine (*Pinus halepensis* Mill.) seeds cultivated in Tunisia. *Food Sci. Technol. Int.*, 15, 407–416, 2006.
69. Kubo, I., Komatsu, S., and Ochi, M., Molluscicides from cashew *Anacardium occidentale* and their large-scale isolation. *J. Agric. Food Chem.*, 34, 970–973, 1986.

70. Gómez-Caravaca, A.M., Verardo, V., and Caboni, M.F., Chromatographic techniques for the determination of alkyl-phenols, tocopherols and other minor polar compounds in raw and roasted cold pressed cashew nut oils. *J. Chromatogr. A*, 1217, 7411–7417, 2010.
71. Pérez-Jiménez, J., Neveu, V., Vos, F., and Scalbert, A., Identification of the 100 richest dietary sources of polyphenols: An application of the Phenol-Explorer database. *Eur. J. Clin. Nutr.*, 64(Suppl.), S112–S120, 2010.
72. Amarowicz, R., Troszyńska, A., and Shahidi, F., Antioxidant activity of almond seed extract and its fractions. *J. Food Lipids*, 12, 344–358, 2005.
73. Tomaino, A., Martorana, M., Arcoraci, T., Monteleone, D., Giovinazzo, C., and Saija, A., Antioxidant activity and phenolic profile of pistachio (*Pistacia vera* L., variety Bronte) seeds and skins. *Biochimie*, 92, 1115–1122, 2010.
74. Fabani, M.P., Luna, L., Baroni, M.V., Monferran, M.V., Ighani, M., Tapia, A., Wunderlin, D.A. et al., Pistachio (*Pistacia vera* var Kerman) from Argentinean cultivars. A natural product with potential to improve human health. *J. Funct. Foods*, 5, 1347–1356, 2013.
75. Harnly, J.M., Doherty, R.F., Beecher, G.R., Holden, J.M., Haytowitz, D.B., Bhagwat, S., and Gebhardt, S., Flavonoid content of US fruits, vegetables, and nuts. *J. Agric. Food Chem.*, 54, 9966–9977, 2006.
76. Slatnar, A., Mikulic-Petkovsek, M., Stampar, F., Veberic, R., and Solar, A., Identification and quantification of phenolic compounds in kernels, oil and bagasse pellets of common walnut (*Juglans regia* L.). *Food Res. Int.*, 67, 255–263, 2015.
77. Lin, J.T., Liu, S.C., Hu, C.C., Shyu, Y.S., Hsu, C.Y., and Yang, D.J., Effects of roasting temperature and duration on fatty acid composition, phenolic composition, Maillard reaction degree and antioxidant attribute of almond (*Prunus dulcis*) kernel. *Food Chem.*, 190, 520–528, 2016.
78. Kalogeropoulos, N., Chiou, A., Ioannou, M.S., and Karathanos, V.T., Nutritional evaluation and health promoting activities of nuts and seeds cultivated in Greece. *Int. J. Food Sci. Nutr.*, 64, 757–767, 2013.
79. John, J.A., and Shahidi, F., Phenolic compounds and antioxidant activity of Brazil nut (*Bertholletia excelsa*). *J. Funct. Foods*, 2, 196–209, 2010.
80. Chandrasekara, N., and Shahidi, F., Effect of roasting on phenolic content and antioxidant activities of whole cashew nuts, kernels, and testa. *J. Agric. Food Chem.*, 59, 5006–5014, 2011.
81. Schmitzer, V., Slatnar, A., Veberic, R., Stampar, F., and Solar, A., Roasting affects phenolic composition and antioxidative activity of hazelnuts (*Corylus avellana* L.). *J. Food Sci.*, 76, S14–S19, 2011.
82. Ciemniewska-Żytkiewicz, H., Verardo, V., Pasini, F., Bryś, J., Koczoń, P., and Caboni, M.F., Determination of lipid and phenolic fraction in two hazelnut (*Corylus avellana* L.) cultivars grown in Poland. *Food Chem.*, 168, 615–622, 2015.
83. Slatnar, A., Mikulic-Petkovsek, M., Stampar, F., Veberic, R., and Solar, A. eHPLC-MS^n identification and quantification of phenolic compounds in hazelnut kernels, oil and bagasse pellets. *Food Res. Int.*, 64, 783–789, 2014.
84. Yu, J., Ahmedna, M., Goktepe, I., and Dai, J., Peanut skin procyanidins: Composition and antioxidant activities as affected by processing. *J. Food Compost. Anal.*, 19, 364–371, 2006.
85. de Camargo, A.C., Bismara Regitano-d'Arce, M.A., and Shahidi, F., Phenolic profile of peanut by-products: Antioxidant potential and inhibition of alpha-glucosidase and lipase activities. *J. Am. Oil Chem. Soc.*, 94, 959–971, 2017.

86. Flores-Cordova, M., Muñoz-Márquez, E., Muñoz-Márquez, E., Ojeda-Barrios, D.L., Soto-Parra, J.M., and Preciado-Rangel, P., Phytochemical composition and antioxidant capacity in Mexican pecan nut. *Emir. J. Food Agric.*, 29, 346–350, 2017.
87. Hoon, L.Y., Choo, C., Watawana, M.I., Jayawardena, N., and Waisundara, V.Y., Evaluation of the total antioxidant capacity and antioxidant compounds of different solvent extracts of Chilgoza pine nuts (*Pinus gerardiana*). *J. Funct. Foods*, 18, 1014–1021, 2014.
88. Gültekin-Özgüven, M., Davarcı, F., Paslı, A.A., Özçelik, B., and Demir, N., Determination of phenolic compounds by ultra-high liquid chromatography-tandem mass spectrometry: Applications in nuts. *LWT-Food Sci. Technol.*, 64, 42–49, 2015.
89. Win, M.M., Abdul-Hamid, A., Baharin, B.S., Anwar, F., Sabu, M.C., and Pak-Dek, M.S., Phenolic compounds and antioxidant activity of peanut's skin, hull, raw kernel and roasted kernel flour. *Pak. J. Bot.*, 43, 1635–1642, 2011.
90. U.S. Department of Agriculture (USDA), USDA Database for the Isoflavones Content of Selected Foods, Release 2.1 – November 2015. Published on line at: http://www.ars.usda.gov/nutrientdata (accessed October 28, 2018).
91. Robbins, K.S., Gong, Y., Wells, M.L., Greenspan, P., and Pegg, R.B., Investigation of the antioxidant capacity and phenolic constituents of US pecans. *J. Funct. Foods*, 15, 11–22, 2015.
92. de la Rosa, L.A., Vazquez-Flores, A.A., Alvarez-Parrilla, E., Rodrigo-García, J., Medina-Campos, O.N., Ávila-Nava, A., Gonzáles-Reyes, S. et al., Content of major classes of polyphenolic compounds, antioxidant, antiproliferative, and cell protective activity of pecan crude extracts and their fractions. *J. Funct. Foods*, 7, 219–228, 2014.
93. Yang, J., Zhou, F., Xiong, L., Mao, S., Hu, Y., and Lu, B., Comparison of phenolic compounds, tocopherols, phytosterols and antioxidant potential in Zhejiang pecan (*Carya cathayensis*) at different stir-frying steps. *LWT-Food Sci. Technol.*, 62, 541–548, 2015.
94. Pelvan, E., Olgun, E.Ö., Karadağ, A., and Alasalvar, C., Phenolic profiles and antioxidant activity of Turkish Tombul hazelnut samples (natural, roasted, and roasted hazelnut skin). *Food Chem.*, 244, 102–108, 2018.
95. Garavand, F., Madadlou, A., and Moini, S., Determination of phenolic profile and antioxidant activity of pistachio hull using high-performance liquid chromatography-diode array detector–electro-spray ionization–mass spectrometry as affected by ultrasound and microwave. *Int. J. Food Prop.*, 20, 19–29, 2017.
96. Quinn, L.A., and Tang, H.H., Antioxidant properties of phenolic compounds in macadamia nuts. *J. Am. Oil Chem. Soc.*, 73, 1585–1588, 1996.
97. Robbins, K.S., Ma, Y., Wells, M.L., Greenspan, P., and Pegg, R.B., Separation and characterization of phenolic compounds from US pecans by liquid chromatography-tandem mass spectrometry. *J. Agric. Food Chem.*, 62, 4332–4341, 2014.
98. Gu, L., Kelm, M.A., Hammerstone, J.F., Beecher, G., Holden, J., Haytowitz, D., Gebhardt, S. et al., Concentrations of proanthocyanidins in common foods and estimations of normal consumption. *J. Nutr.*, 134, 613–617, 2004.
99. Lainas, K., Alasalvar, C., and Bolling, B.W., Effects of roasting on proanthocyanidins contents of Turkish Tombul hazelnut and its skin. *J. Funct. Foods*, 23, 647–653, 2016.

100. Neveu, V., Perez-Jimenez, J., Vos, F., Crespy, V., du Chaffaut, L., Mennen, L., Knox, C. et al., Phenol-Explorer: An online comprehensive database on polyphenol contents in foods. *Database*, bap024, 2010.
101. Gong, Y., and Pegg, R.B., Separation of ellagitannin-rich phenolics from US pecans and Chinese hickory nuts using fused-core HPLC columns and their characterization. *J. Agric. Food Chem.*, 65, 5810–5820, 2017.
102. Lerma-Herrera, M.A., Núñez-Gastélum, J.A., Ascacio-Valdés, J., Aguilar, C.N., Rodrigo-García, J., Díaz-Sánchez, A.G., Alvarez-Parrilla, E. et al., Estimation of the mean degree of polymerization of condensed tannins from the kernel and shell of *Carya illinoinensis* by HPLC/MS and spectrophotometric methods. *Food Anal. Method*, 10, 3023–3031, 2017.
103. Xie, L.Y., Roto, A.V., and Bolling, B.W., Characterization of ellagitannins, gallotannins, and bound proanthocyanidins from California almond (*Prunus dulcis*) varieties. *J. Agric. Food Chem.*, 60, 12151–12156, 2012.
104. Ros, E., Izquierdo-Pulido, M., and Sala-Vila, A., Beneficial effects of walnut consumption on human health: Role of micronutrients. *Curr. Opin. Clin. Metab. Care*, 21, 498–504, 2018.
105. Regueiro, J., Sánchez-González, C., Vallverdú-Queralt, A., Simal-Gándara, J., Lamuela-Raventós, R., and Izquierdo-Pulido, M., Comprehensive identification of walnut polyphenols by liquid chromatography coupled to linear ion trap – Orbitrap Mass Spectrometry. *Food Chem.*, 152, 340–348, 2014.
106. Sánchez-González, C., Ciudad, C.J., Noe, V., and Izquierdo-Pulido, M., Health benefits of walnut polyphenols: An exploration beyond their lipid profile. *Crit. Rev. Food Sci. Nutr.*, 57, 3373–3383, 2017.
107. Xie, L., and Bolling, B.W., Characterisation of stilbenes in California almonds (*Prunus dulcis*) by UHPLC-MS. *Food Chem.*, 148, 300–306, 2014.
108. Wang, M.L., Chen, C.Y., Tonnis, B., Barkley, N.A., Pinnow, D.L., Pittman, R.N., Davis, J. et al., Oil, fatty acid, flavonoid, and resveratrol content variability and FAD2A functional SNP genotypes in the US peanut mini-core collection. *J. Agric. Food Chem.*, 61, 2875–2882, 2013.
109. Food and Drug Administration (FDA), *Petition for a Qualified Health Claim for Macadamia Nuts and Reduced Risk of Coronary Heart Disease (Docket No. FDA-2015-Q-4850)*, Food and Drug Administration, Washington, DC, 2017.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 3

Effect of Nut Consumption on Blood Lipids, Lipoproteins, and Apolipoproteins – Summary of the Evidence

Joan Sabaté, Edward Bitok, and Sujatha Rajaram

3.1 Introduction 60
3.2 Effect of Nut Consumption on Blood Lipids and Lipoproteins 60
3.2.1 Total Cholesterol 61
3.2.2 LDL-C 62
3.2.3 HDL-C 63
3.2.4 Triacylglycerols 63
3.2.5 Apolipoproteins 64
3.2.6 ApoB:ApoA1 Ratio 65
3.2.7 Newer Markers of Blood Lipids 65
3.3 Mechanisms for the Beneficial Effect of Nut Consumption on Blood Lipids and Apolipoproteins 66
3.3.1 Fatty Acid Compositions 66
3.3.2 Other Nutrients/Non-Nutrients 71
3.3.2.1 Fiber 71
3.3.2.2 Phytosterols 72
3.3.2.3 Polyphenols 72
3.3.3 Changes in Gut Microbiome Induced by Nutrient Compounds of Nuts 73

3.4 Strength of the Evidence Regarding Nut Intake and Blood Lipids 73
3.5 Tree Nuts *versus* Peanuts 73
3.6 Walnuts *versus* Other Tree Nuts 74
3.7 Dose–Response Effect of Nut Diets 75
3.8 Populations That Benefit Most from Nut Intake with Respect to Improvement in Blood Lipids 76
3.9 Nut Form 77
3.10 Conclusion 78
References 79

3.1 Introduction

The history of nut effects on blood lipids dates back to the early 1990s, when we published data from the Adventist Health Study, an epidemiologic investigation of 26,473 California Seventh-day Adventists, which for the first time showed a protective effect of higher nut consumption on coronary heart disease (CHD) [1]. Consequently, in an attempt to understand the underlying mechanisms for protection against CHD, we designed and conducted a feeding trial which showed that moderate intake of walnuts improved the lipid profiles of young normolipidemic men [2]. This landmark finding led us to believe that the apparent protective effect of nut consumption against CHD observed among California Adventists might have been mediated in part through improvement in blood lipids. Ever since, many other trials with a variety of nuts and designs were conducted to test this hypothesis. We have previously reported pooled results of 25 trials that examined the effect of nut intake on blood lipids [3]. The results were not only confirmatory of our earlier findings, but also indicated that nut consumption lowered blood lipids in a dose-related manner. Presently, the lipid lowering-effect of nuts is the most extensively studied mechanism explaining the beneficial effects of nut consumption on cardiovascular disease (CVD) prevention (see detail in Chapter 6).

This chapter presents a summary of the evidence regarding the lipid, lipoprotein, and apolipoprotein changes induced by nut-enriched diets; it is not intended to be a comprehensive review. Areas of discussion include the efficacy of tree nuts *versus* peanuts, and walnuts *versus* other tree nuts, in modifying blood lipids and lipoproteins; the dose effect of nut consumption; and the clinical relevance (with respect to improvement in blood lipids) of nut studies conducted among various populations. More importantly, the potential mechanisms for improvement in blood lipids following nut consumption are discussed.

3.2 Effect of Nut Consumption on Blood Lipids and Lipoproteins

The causal role of an elevated serum cholesterol level in the genesis of atherosclerosis and its main clinical manifestation, CVD, is well established [4], as are lifestyle practices that have a marked impact in prevention [5]. Briefly, the pathological basis of CVD stems primarily from abnormalities in lipid and lipoprotein metabolism [6] that result in elevated low-density lipoprotein cholesterol (LDL-C) and total

cholesterol (TC) and low levels of high-density lipoprotein cholesterol (HDL-C). Results of pooled data from over 1 million individuals indicate that for every 38.7 mg/dL increment in TC, the risk of CHD increases by 20% in women and by 24% in men [4,7]. Decades ago, data from the Multiple Risk Factor Intervention Trial indicated that a marked reduction in LDL-C significantly decreased CHD risk [8]. Indeed, cholesterol reduction stands as a most important CHD preventive measure. Concerning nutritional effects on lipids, saturated fatty acids (SFAs) have been shown to have the greatest potential for raising LDL-C [9], while monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) have either a neutral or a lowering effect on LDL-C [10]. The latter two fatty acids are the predominant type of unsaturated fatty acids found in nuts and, together with other bioactive constituents, confer beneficial effects on blood lipids. We now review the evidence concerning nut effects on individual blood lipids and lipoproteins.

3.2.1 Total Cholesterol

As reported earlier, the beneficial effect of nut consumption on blood lipids was first demonstrated in a group of young normolipidemic men [2]. This pioneering study conducted in Loma Linda University demonstrated that an additional 10% decrease in TC could be realized with the incorporation of walnuts (20% of energy) into the National Cholesterol Education Program (NCEP)–recommended cholesterol-lowering diet. Over several years, dozens of other nut trials were conducted among different populations and with varying degrees of dietary control. The first meta-analysis on 13 walnut studies (n = 365) conducted through 2008 confirmed our earlier findings, with results indicating significantly greater decrease (weighted mean difference = -10.3 mg/dL) in TC in walnut diets compared to various control diets [11]. Shortly thereafter, we published a pooled analysis of 25 nut trials that encompassed 583 normolipidemic and hypercholesterolemic men and women with an age range of 19–86 years. Nut consumption ranged from 23 to 132 g/day (mean, 67 g). Collectively, nut intake achieved a 10.9 mg/dL [5.1%] reduction in TC [3]. Consistent with our findings, a systematic review and meta-analysis of 61 nut trials [12] (walnuts, n = 21; almonds, n = 16; pistachios, n = 7; hazelnuts, n = 6; macadamias, n = 4, pecans, n = 2; mixed tree nuts, n = 2; and Brazil nuts, n = 1) with 2,582 unique participants estimated an average reduction of 4.7 mg/dL (95% CI, –5.3, –4.0) in TC for every serving (28 g/day) of nuts. Comparably, other recent systematic reviews and meta-analyses that included studies on almonds [13], hazelnuts [14], pistachios [15], and walnuts [16] also reported significant decreases in TC with nut intake. With respect to the meta-analysis of walnut studies, results indicate that walnut-enriched diets lowered TC by 6.99 mg/dL (95% CI: –9.39, –4.58 mg/dL; $P < 0.001$) compared with control diets [16]. More pronounced effects were observed when walnuts accounted for 10%–25% of total energy compared with lower doses (< 10% of total energy).

We examined studies that were reported after the above systematic reviews and meta-analyses were published and found that they were consistent with earlier findings. For example, a 90-day study conducted among dyslipidemic and hypertensive patients to examine the effect of a healthful diet with partially defatted Brazil nut flours (13 g/day) compared to placebo (dried cassavas) showed a significant reduction in TC (–20.5 mg/dL) in the Brazil nut group [17]. Also, the consumption

of cashews (11% of total energy) as part of an average American diet significantly reduced TC by 3.9% in adults with or at risk of hyperlipidemia [18]. Contrastingly, a more recent study showed that the isocaloric incorporation of cashews into the diet of healthy subjects had little effect on TC [19]. An 8-week study conducted among healthy adults > 50 years showed that the walnut-enriched (43 g/day) diet significantly lowered TC compared to a control diet (walnut *versus* control: −8.5 ± 37.2 *versus* −1.1 ± 35.4 mg/dL) [20]. Mazidi et al. [21] also reported in a meta-analysis of 20 randomized clinical trials (RCTs) that nut consumption significantly reduced TC (mean difference = −0.82 mg/dL). Mirroring these findings are those of a systematic review and meta-analysis of 18 almond studies undertaken to determine the effects of almond supplementation on blood lipid levels. The average daily intake of almonds ranged from 20 to 113 g/day, and the duration of the almond consumption period ranged from 4 weeks to 18 months. Pooled results indicated that on average, almond-enriched diets significantly reduced TC by ~6 mg/dL [13]. The collective evidence from human intervention studies convincingly shows that nuts are effective in lowering TC. The benefits were observed despite differences in study design, sample size, nature of participants, and degree of dietary control, as well as amount or type of nut consumed.

3.2.2 LDL-C

Most cholesterol in the circulation is carried by LDL particles, and LDL-C has been shown by many prospective studies and RCTs to be responsible to a large extent for the association with CHD risk [22,23]. Nut trials have yielded trends for LDL-C that parallels those of TC. In our first walnut trial, we observed an 8.2 mg/dL decrease in LDL-C in the walnut diet compared to the control diet, representing a reduction of 16.3% [2]. Further, in our pooled analysis of 25 nut RCTs, we found that nut-enriched diets decreased LDL-C by 10.2 mg/dL (7.4% change) [3]. Since then, several systematic reviews and meta-analyses of studies encompassing various nut diets have also reported reductions in LDL-C, with mean estimates ranging from 0.69 to 9.2 mg/dL [11,13,14]. The most comprehensive report to date on nuts and blood lipids is a report comprising of 61 trials [12], 38 of which were RCTs and 23 nonrandomized trials. The overall effect of nut diets was a 4.8 mg/dL decrease in LDL-C for every 28 g/day serving of nuts. Further analysis showed a positive association between the dose of phytosterols (4.8 to 279 mg/day) and LDL-lowering effect, although this relationship was driven by the total daily dose of nuts, rather than by the differences in phytosterol content between types of nuts [24]. We found a few newer studies that were published after the most recent meta-analyses. Two studies, one with cashews [18] and another with walnuts [20], reported significant reductions in LDL-C. However, three others, two with cashews [19,25] and one with almonds [26], showed no significant changes in LDL-C. This is likely due to the low dose of nuts consumed and recruitment of subjects whose TC was elevated at baseline. We have previously discussed how the relationship between nut intake and blood lipids is modified by body mass index (BMI) [3]. As with TC, the evidence concerning nut consumption and lowering of LDL-C convincingly shows that the inclusion of a variety of nuts in the diet for periods as short as 3 weeks can result in significant reductions in LDL-C. The beneficial effects would be apparent regardless of study design, comparison diets, and degree of dietary control. However, the magnitude of

effect seems to be influenced by the dose rather than the type of nut, as highlighted in the meta-analysis by Del Gobbo et al. [12] Stronger effects were observed in randomized [27–40] and nonrandomized [41–50] trials providing ≥ 60 g/day (about 2 ounces or 2 servings) of nuts. Those providing 100 g nuts/day [43,46,49,50] lowered LDL-C concentrations by up to 35 mg/dL, an effect comparable to some statins [51]. It would be of interest for future studies to investigate whether higher nut doses would elicit even greater responses in LDL-C.

3.2.3 HDL-C

Prospective cohorts have reported an inverse relationship between serum HDL-C and risk for cardiovascular events in diverse populations [52]. Although the link between low HDL-C and increased CHD risk is well established, findings on the effect of nut-enriched diets on HDL-C are mixed and inconclusive. Several systematic reviews and meta-analyses of nut feeding trials, including studies with mixed tree nuts [12], almonds [13], hazelnuts [14], and walnuts [16], all showed that HDL-C was not significantly changed after nut consumption. One possible explanation for the neutral findings is that most trials recruited predominantly healthy individuals whose baseline HDL-C was not particularly low. Nonetheless, few studies have reported what would be considered clinically meaningful changes in HDL-C following nut consumption. These studies were either conducted in subjects with apparent risk factors or involved dietary restrictions/modifications. For example, a low dose of almonds (10 g/day) consumed before breakfast increased HDL-C by 12%–16% in CHD patients [53]. Likewise, substituting almonds for a carbohydrate-rich snack within a lower saturated-fat diet improved HDL-C in normal-weight hyperlipidemic individuals [54]. Remarkably, cashews, which were exempted in the 2003 Federal Drug Administration (FDA) "heart healthy" claim due to their high saturated fat content, were recently shown to increase HDL-C in adults with type-2 diabetes (T2D) [25]. To date, clinical outcome trials of pharmacological agents aimed at raising HDL-C have failed to show a reduction in atherosclerotic CVD events [55]. However, there is no reason to believe that raising HDL-C by natural means is not beneficial. In this case, nut consumption may present a cost-effective strategy for addressing low HDL-C, even if the benefits are minimal. Hence, further investigations with various populations (particularly those with low HDL-C) and varying doses of nuts are warranted to further examine a possible beneficial effect on HDL-C. Overall, based on the available evidence, no definitive conclusions can be drawn on the effect of nut consumption on HDL-C.

3.2.4 Triacylglycerols

Elevated serum triacylglycerols (TAG) are an established independent risk factor for atherosclerosis and CHD, but the risk associated with TAG is more pronounced in the presence of high LDL-C and/or low HDL-C levels [56]. In our pooled analysis of 25 nut trials, we reported that, overall, nut consumption had no significant effect on TAG levels – except in individuals with hypertriglyceridemia (≥ 150 mg/dL) [3], in whom TAG levels were reduced by 20.6 mg/dL (10.2%). A systematic review and meta-analysis of 61 nut trials conducted 5 years later [12] reported a

modest (–2.2 mg/dL) but significant reduction in TAG per serving of tree nuts (28.4 g/day). Reductions were greater in nonrandomized (-4.6 mg/dl) *versus* randomized trials (–1.6 mg/dL), with no significant between-group differences. Also, a recent systematic review and meta-analysis of 26 walnut trials [16] showed significantly greater reduction in TAG concentration (-4.69 mg/dL) in participants consuming walnut-enriched diets compared with those following control diets. However, in contrast to the results of our pooled analysis [3], no differences in effects were observed for trials enrolling hypercholesterolemic compared with normocholesterolemic individuals. In a previous meta-analysis of 13 walnut trials published by the same group [11], there was only a tendency towards decreased TAG with walnut-enriched diets. We examined studies published after the above reports and found four newer nut studies [19,26,57,58] that reported nonsignificant changes in TAG with various nut-enriched diets, and one with almonds that reported a significant decrease in TAG [59]. With respect to the almond study, it is highly likely that the observed effect on TAG was due to subjects having high TAG levels at baseline. Altogether, the evidence for a beneficial effect of nut consumption on TAG leans towards walnut and, to some extent, almond-enriched diets. The hypotriglyceridemic effect of nuts is amplified when baseline TAG levels are elevated, suggesting a possible therapeutic effect in this group. Nevertheless, more dose-response investigations are needed to shed light on the effect of nut consumption on TAG, especially in individuals with hypertriglyceridemia.

3.2.5 Apolipoproteins

Plasma apolipoproteins have been shown to be more informative predictors of future cardiovascular risk than lipoproteins [60]. Briefly, apolipoprotein B (ApoB) is the primary protein component of LDL, whereas apolipoprotein A1 (ApoA1) is the primary protein associated with HDL [61]. A systematic review and meta-analysis of 61 nut trials [12], 19 of which examined apolipoproteins, showed that inclusion of nuts in the diet did not affect ApoA1 concentration, but significantly lowered ApoB in a dose related manner (–3.7 mg/dL; 95% CI: –5.2, –2.3 mg/dL). Stronger effects were observed in individuals with T2D (–11.5 mg/dL; 95% CI: –16.2, –6.8 mg/dL) than in nondiabetic healthy populations (–2.5 mg/dL; 95% CI: –4.7, –0.3 mg/dL). In a recent meta-analysis of 26 RCTs [16], a diet rich in walnuts significantly reduced ApoB (mg/dL) (weighted mean difference = –3.74 [95% CI: –6.51, –0.97]) and marginally reduced ApoA1 (weighted mean difference = –2.91 [95% CI: –5.98, 0.08]). These results correspond to a 1.1% greater decrease in apoA1 and 4.2% greater decrease in ApoB for the walnut diet groups compared with the control diet groups.

Recent trials continue to elicit mixed findings on the effect of nut consumption on apolipoproteins. For example, a 4-week RCT comparing the individual and combined effects of consumption of dark chocolate, cocoa, and almonds on CVD risk factors [62] reported a –6.6 ± 2.6% decrease in ApoB in the almond-enriched diet compared to –2.1 ± 2.6% in the reference diet (average American diet). The decrease in ApoB was significantly greater when almonds were combined with dark chocolate (–7.2 ± 2.6% compared with –2.1 ± 2.6%). This study found no treatment effect of almonds on ApoA1. Similarly, a short trial with Brazil nuts resulted in no change in ApoA1 and a slight nonsignificant increase in ApoB [63,64]. Whereas many nut studies reported no change or slight reductions in ApoA1, a study with hazelnuts [65]

reported a significant increase in ApoA1, which was seen as reflecting an increase in HDL-C. Overall, in spite of the diversity in participant characteristics, comparison diets, and study design, nut feeding trials consistently demonstrated reductions in ApoB while ApoA1 remained largely unchanged. The beneficial effects of nuts on ApoB were observed over a wide spectrum of intake, ranging from 5 to 126 g of nuts per day. Still, more randomized studies of high-dose nut consumption will help clarify their benefit on apolipoproteins, especially among the diabetic population. Also, since ApoB resides on all atherogenic lipoproteins, mechanistic studies are needed to elucidate whether improvement in blood lipids is the result of decreased production or increased clearance of ApoB or both.

3.2.6 ApoB:ApoA1 Ratio

The ratio between ApoB and ApoA1 (ApoB:Apo-1) has been suggested to be a powerful and more accurate predictor of future CVD risk than TC and HDL-C [60,66]. In our previous almond study, we showed that the isoenergetic incorporation of ~68 g/day of almonds (20% of energy) into an 8368 kJ (2000 kcal) NCEP Step I diet significantly decreased the ApoB:ApoA1 ratio in a dose-related manner [36]. Reduction in the ApoB:ApoA1 ratio following nut consumption has also been observed in overweight and obese persons [62], patients with T2D [64,67] or at high CVD risk [68], and in mildly hypercholesterolemic individuals [69]. The above studies involved ingestion of 30–60 g/day of nuts (almonds, hazelnuts) for periods of 4–12 weeks. Although few studies have examined this outcome, the results strongly suggest that the inclusion of a variety of nuts in the diet may favorably change ApoB:ApoA1 ratio.

3.2.7 Newer Markers of Blood Lipids

Small dense LDL (sdLDL) and oxidized LDL (oxLDL) have been shown to play a significant role in atherosclerotic plaque formation [70–73]. The sdLDL and LDL particle phenotype associated with increased TAG-rich lipoprotein, are more susceptible to oxidation than large LDL [72]. The oxLDL on the other hand have been shown to favor the intracellular accumulation of cholesterol esters and generation of foam cells [73], which are the hallmark of early atherosclerotic lesion formation [74]. Several studies have examined oxidation markers following nut consumption. In a study of healthy individuals, Berry et al. [75] showed that participants were less prone to oxidation of plasma and LDL lipids after an almond diet than after a low-fat diet. Similarly, a walnut-enriched diet was associated with nonsignificant decreases in serum oxLDL [76]. In a large feeding trial involving older subjects at high cardiovascular disease risk, a Mediterranean diet (MedDiet) enriched with 30 g raw, unpeeled, mixed nuts (50% walnuts) given for 3 months was associated with a significant 10% reduction in circulating oxLDL concentrations [77]. Also, Hudthagosol et al. [78] examined postprandial changes following 3 sequences of test meals composed of whole pecans, blended pecans, and a formulation of refined ingredients of equivalent macronutrient composition. Results of this investigation indicated significant decrease in oxLDL by 30%, 33%, and 26% at 2, 3, and 8 hours respectively after the consumption of whole pecans. Likewise, a diet enriched with pistachios was modestly associated with decreases in oxLDL

[79], whereas hazelnut-enriched diets [44,48] resulted in a significant decrease in plasma oxLDL. However, not all studies disclosed inverse associations. Hyson et al. [80] failed to show any improvement in the susceptibility of LDL-C to oxidative stress after feeding either whole almonds or almond oil to healthy individuals. Unchanged oxLDL levels were also reported in two other intervention studies, one with walnuts [81] and another with hazelnuts [82]. The studies were conducted in hyperlipidemic adults and hyperlipidemic children respectively.

With respect to sdLDL, a MedDiet enriched with nuts (30 g/day) consumed for one year resulted in significant reductions of medium-small LDL and very-small LDL (10% and 11%, respectively) [83]. Also, replacing carbohydrate consumption with mixed nuts (75 g/day) for 3 months resulted in a significant reduction in sdLDL in men and postmenopausal women with T2D [64]. Elsewhere, Almario et al. [84] reported that a walnut-supplemented diet increased serum levels of alpha-linolenic acid (ALA), while decreasing total and LDL-C. The cholesterol lowering was largely confined to a significant reduction in sdLDL. In another trial, a diet providing 20% of energy from pistachios significantly reduced sdLDL levels in individuals with elevated LDL-C [85]. Further, a 4-week hazelnut-enriched diet (1 g/kg/day) increased the ratio of large to small LDL in normolipidemic individuals [48]. Another pistachio-enriched diet showed reduced sdLDL in subjects with pre-diabetes [86]. In contrast, the addition of almonds (100 g/day) to statin therapy for 4 weeks resulted in a rather unexpected finding, that is, a statistically significant shift from larger, buoyant LDL-C particles to smaller, dense LDL-C particles [87].

HDL particles have been shown to be cardioprotective due to their role in reverse cholesterol transport [88]. HDL may be separated into particles which contain ApoA-I (LpA-I) and those which contain both ApoA-I and ApoA-II (LpAI/AII) [89,90]. In a comparison of subjects with and without CHD, LpA-I has been shown to be the protective sub-fraction [91]. We came across two studies that have examined the effect of nut consumption on HDL sub-particles. One showed that substituting almonds (42 g/day) for a carbohydrate-rich snack within a lower-saturated fat diet improves HDL subspecies, specifically by preventing decreases in LpA-I [54]. The other study reported that a pistachio-enriched diet (57 g/day) significantly increased the percentage of small HDL particles [86].

Taken together, the above findings indicate that nut consumption not only prevents the oxidation of LDL, but also could modify the lipoprotein particle size and subclass concentrations in a way that favors cardiovascular health. These changes can take place with or without a change in the lipid profiles. We noted the lack of systematic reviews and/or meta-analyses on these outcomes, probably due to insufficient data. Hence more studies are needed to examine these newer markers of blood lipids. Table 3.1 presents the summary of systematic reviews and meta-analyses that have examined the effect of nut consumption on blood lipids and lipoproteins.

3.3 Mechanisms for the Beneficial Effect of Nut Consumption on Blood Lipids and Apolipoproteins

3.3.1 Fatty Acid Compositions

Nuts have favorable effects on serum lipids primarily because of their high levels of unsaturated fatty acids (such as MUFAs and PUFAs) and low levels of saturated fatty

Table 3.1 Summary of Systematic Reviews and Meta-Analyses that Have Examined the Effect of Nut Consumption on Blood Lipids

		Results							
Design	*Aim*	*TC*	*LDL-C*	*HDL-C*	*TAG*	*Apo*	*TC:HDL*	*LDL:HDL*	*References*
Systematic review and meta-analysis of controlled trials	Walnut consumption on blood lipids and other CVD risk factors	−6.99 mg/dL; (95% CI −9.39, −4.58 mg/dL; *P* overall effect < 0.001; I^2= 0.0%; *P*-het = 0.64)	−5.51 mg/dL (95% CI −7.72, −3.29 mg/dL; *P* overall effect < 0.001; I^2= 0.0%; *P*-het = 0.49)	0.10 mg/dL (95% CI −0.78, 0.97 mg/dL; *P* overall effect = 0.83; I^2 = 0.0%; P-het = 0.85)	−4.69 mg/dL (95% CI −8.93, −0.45 mg/dL; *P* overall effect = 0.03; I^2 = 0.0%; *P*-het = 0.99)	ApoA1: −2.91 mg/dL (95% CI −5.98, 0.08 mg/dL; *P* overall effect = 0.057; I^2= 0.0%; *P*-het = 0.822) ApoB: −3.74 mg/dL; 95% CI −6.51, −0.97 mg/dL; *P* overall effect = 0.008; I^2= 0.0%; *P*-het = 0.793)			[16]
Systematic review and meta-analysis of prospective studies	Determine the effect of nut consumption (tree nuts, peanuts, and soy nuts) on serum CRP and blood lipids	−0.82 mg/dL (95% CI −1.53 mg/dL, −0.11; *P* overall effect < 0.05)	−0.69 mg/dL (95% CI −1.32, −0.07; *P* overall effect < 0.05)	0.54 mg/dL (95% CI 0.17, 0.90; *P* overall effect < 0.05)	−0.66 mg/dL (95% CI −1.34, 0.01; *P* overall effect > 0.05)	ApoA1: 1.38 mg/dL (95% CI 0.15, 2.61 mg/dL; *P* overall effect < 0.05)			[21]

(*Contined*)

TABLE 3.1 (Continued) Summary of Systematic Reviews and Meta-Analyses that Have Examined the Effect of Nut Consumption on Blood Lipids

		Results							
Design	*Aim*	*TC*	*LDL-C*	*HDL-C*	*TAG*	*Apo*	*TC:HDL*	*LDL:HDL*	*References*
Systematic review and meta-analysis of RCTs	Determine the impact of almond consumption on blood lipid levels	-5.92 mg/dL (95% CI -9.1, -2.7 mg/dL; *P* overall effect < 0.001)	−4.8 mg/dL (95% CI −7.6 mg/dL, −2 mg/dL; *P* overall effect = 0.001)	−0.65 mg/dL (95% CI −1.6 mg/dL, 0.34; *P* overall effect = 0.207)	−2.6 mg/dL (95% CI −5.1, −0.07 mg/dL; *P* overall effect = 0·042)		− 0.2 (95% CI −0.4, −0.05; *P* overall effect = 0.009)	−0.09 (95% CI −0.2, 0.03 ; *P* overall effect = 0.145)	[13]
Systematic review and a meta-analysis of randomized and non-RCTs	Assess the effect of hazelnuts on blood lipids and body weight outcomes	Δ-changes from baseline across treatment (MDΔ) = − 5 mg/dL (95% highest posterior density interval (95% HPD) −11, 0.54 mg/dL)	MDΔ = − 5.8 mg/dL (95% HPD −12 , −0.11)	MDΔ = 0.08 mg/dL (95% HPD −5.4, 5.7 mg/dL)	MDΔ = 1.74 mg/dL (95% HPD −7.5, 10.4)				[14]

(*Continued*)

TABLE 3.1 (Continued) Summary of Systematic Reviews and Meta-Analyses that Have Examined the Effect of Nut Consumption on Blood Lipids

		Results							
Design	*Aim*	*TC*	*LDL-C*	*HDL-C*	*TAG*	*Apo*	*TC:HDL*	*LDL:HDL*	*References*
Systematic review and a meta-analysis of controlled intervention trials	Assessing association impact of tree nuts on blood lipids	−4.7 mg/dL (95% CI −5.3, −4.0 mg/dL; I^2 > 30%; *P*-het = 0.001; *P* overall effect < 0.05)	−4.8 mg/dL (95% CI −5.5, −4.2 mg/dL; I^2 > 30%; *P*-het = 0.01; *P* overall effect < 0.05)	−0.3 mg/dL (95% CI −0.9, 0.4; I^2 > 30%; *P*-het = 0.33; *P* overall effect = NS)	−2.2 mg/dL (95% CI −3.8, −0.5mg/dL; I^2 > 30%; *P*-het = 0.16; *P* overall effect < 0.05)	ApoA1: −0.6 mg/dL (95% CI −1.9, 0.7 mg/dL; I^2 > 30%; *P*-het = 0.38; *P* overall effect = NS) ApoB: −3.7 mg/dL (95% CI −5.2, −2.3 mg/dL; I^2 > 30%; *P*-het = 0.17; *P* overall effect < 0.05)			[12]
Pooled analysis of 25 intervention trials	Assess the impact of nut intake on blood lipid levels	−10.9 mg/dL (95% CI −14.1, −7.8 mg/dL) (5.1% change; *P* < 0.001)	−10.2 mg/dL (95% CI −13.1, −7.4 mg/dL; 7.4% change; *P* overall effect < 0.001)	0.09 mg/dL (95% CI −1.00, 1.19 mg/dL; *P* overall effect = NS)	−20.6 mg/dL (10.2% change; (95% CI −30.7, −9.9 mg/dL; *P* overall effect < 0.05) in subjects with TAG of 150 mg/dL		−0.24 (5.6% change; *P* overall effect = 0.001)	−0.22 (8.3% change; *P* overall effect = 0.001)	[3]

(*Contined*)

TABLE 3.1 (Continued) Summary of Systematic Reviews and Meta-Analyses that Have Examined the Effect of Nut Consumption on Blood Lipids

		Results							
Design	*Aim*	*TC*	*LDL-C*	*HDL-C*	*TAG*	*Apo*	*TC:HDL*	*LDL:HDL*	*References*
Meta-analysis of RCTs	Impact of almonds on blood lipids	–7 mg/dL (95% CI – 13.1, – 0.8 mg/dL; I^2 = 0.0%; *P*-het = NS; *P* overall effect = 0.030)	– 5.8 mg/dL (95% CI –11.2, 0.004 mg/dL; I^2 = 0.0%; *P*-het = NS; *P* overall effect = 0.05)	–2 mg/dL (95% CI –3.9, 0.4 mg/dL; I^2 = 0.0%; *P*-het = NS; *P* overall effect= 0.08)	–1.5 mg/dL (95% CI –7.7, 4.2 mg/dL; I^2 = 0.0%; *P*-het = NS; *P* overall effect = 0.58)			0.04 (95% CI 0.21 to 0.14) I^2= 0.0%; *P*-het = NS; *P* overall effect = 0.670)	[92]
Systematic review and a meta-analysis of controlled intervention trials (randomized, crossover, and parallel)	Assess the effect of walnuts on blood lipids	–10.3 mg/dL (95% CI –14.76, –5.83 mg/dL; I^2 = 0.0%; *P*-het = 0.63; *P* overall effect < 0.001)	–9.2 mg/dL (95% CI –13.1, –5.36 mg/dL; I^2 = 0.0%; *P*-het = 0.65; *P* overall effect < 0.001)	–0.2 mg/dL (95% CI –1.79, 1.38 mg/dL; I^2 = 0.0%; *P*-het = 0.8; *P* overall effect = 0.8)	–3.9 mg/dL (95% CI –11.92, 4.20 mg/dL; I^2 = 0.0%; *P*-het = 0.99; *P* overall effect = 0.3)				[11]

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Apo, Apolipoprotein; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HPD, highest posterior density interval; LDL-C, low-density lipoprotein cholesterol; MDΔ, mean difference of change; NS, nonsignificant; *P*-het, *P*-value for heterogeneity; RCTs, randomized controlled trials; TAG, triacylglycerols; TC, total cholesterol.

acids (SFAs – only 4%–5%), and a host of plant-based bioactive compounds [11]. Their unique fatty-acid profiles composed of MUFAs contribute an average of 62% of the energy from fat, and, together with PUFAs, contribute a total of ~91% of the energy from fat [93]. The fatty-acid profiles of nuts facilitate a favorable shift in dietary fatty acids when nuts are substituted for foods that are high in SFAs or carbohydrates. Animal and human studies have shown that fats containing unsaturated fatty acids enhance hepatic receptor-dependent clearance of LDL and concomitantly reduce plasma LDL-C levels [94]. PUFAs specifically have been shown to reduce the levels of ApoB while MUFAs increase the levels of ApoA1, which mediates the efflux of cholesterol associated with HDL particles [95]. The unsaturated fatty acids in nuts may alter the activities of lipoprotein lipase and hepatic lipase [96–98] by decreasing Apo CIII, which is an inhibitor of lipoprotein lipase. It is well established that overexpression of plasma Apo CIII causes hypertriglyceridemia [99]. Additionally, PUFAs can mediate the expression of several genes involved in lipid metabolism *via* nuclear factors including the peroxisomal proliferator–activated nuclear receptors gamma (PPAR γ), liver X receptor (LXR), hepatocyte nuclear factor-(HNF)-4α, nuclear factor kappa B (NFκB), and sterol-regulatory element binding protein (SREBP) [98,100]. Further, unsaturated fat is considered a better substrate for acetyl coenzyme A (Acyl-CoA) transferase, which esterifies cholesterol to cholesterol ester, thus reducing intracellular cholesterol levels [99]. Unsaturated fat in nuts tends to increase membrane fluidity [101,102], which can improve the affinity of LDL receptors to the ligand apoB-100 with ensuing enhancement of LDL-C uptake [102]. Additionally, the n-3 PUFA in some nuts, such as walnuts, can up-regulate the enzyme cholesterol 7-α hydroxylase, the rate-limiting enzyme of bile acid synthesis [94], *via* activation of nuclear factor LXR [103].

3.3.2 Other Nutrients/Non-Nutrients

3.3.2.1 Fiber

Although the improvement in blood lipids is attributable primarily to the favorable fatty acid profile of nuts, other components of nuts, including dietary fiber [104] and plant sterols [105], play a significant role as well (see detail in Chapter 2). Nuts contain ~7 g/100 g dietary fiber, of which ~25% is soluble fiber [106]. In a meta-analysis of 67 controlled trials to quantify the cholesterol-lowering effect of major dietary fiber, Brown et al. [106] noted that 2–10 g/day of soluble fiber was associated with small but significant decreases in TC. The soluble fiber in nuts, comprising hemicellulose, pectin, and lignin, has a salutary effect on lipid metabolism primarily through enhanced colonic synthesis of short-chain fatty acids by gut bacteria, particularly propionate synthesis [107,108]. These short-chain fatty acids have been shown to lower 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase and consequently reduce de novo cholesterol synthesis. This feedback loop mechanism enhances LDL uptake into hepatocytes, thus lowering plasma LDL-C [98,107]. The fiber in nuts may also interfere with micelle formation and increase the excretion of stool fat and bile acids [37,109,110]. When bile acids are lost in the feces, cholesterol from the intracellular cholesterol pool is utilized to replace it, which further reduces the intracellular cholesterol pool. Lowering the intracellular cholesterol pool provides a feedback to up-regulate LDL receptor expression with ensuing increased uptake

of LDL-C, resulting in decreased plasma LDL-C [111]. Insoluble fiber also retains water and hydrates the fecal bolus leading to increased fecal bulk and decreased intestinal transit time [104,112].

3.3.2.2 Phytosterols

Like all plant foods, nuts are cholesterol-free but contain chemically related phytosterols. The phytosterol content of nuts generally ranges from 72 to 272 mg/100 g in the form of campesterol, ergosterol, stigmasterol, and β-sitosterol [113,114]. In a systematic review and meta-analysis of 61 tree-nut trials, Del Gobbo et al. [24] showed that total phytosterol doses supplied by nuts in the different trials ranged from 4.8 to 279 mg/day. The detailed cholesterol-lowering mechanism of phytosterols is not completely understood, although it has been proposed that it is likely linked to their absorption, which in turn affects the absorption of cholesterol [115]. Both dietary cholesterol and plant sterols are transported to the cells of the intestinal mucosa by micelles. However, the high physiochemical affinity of plant sterols for micelles (because of a bulkier hydrocarbon molecule) induces competition with dietary cholesterol [116] which leads to decreased absorption of cholesterol in the duodenum and proximal jejunum. The displaced cholesterol is ultimately excreted with feces [115–117]. Also, phytosterols and cholesterol compete to be absorbed *via* the lipid-transporter protein, Niemann–Pick Type C1. In this process, phytosterols may down-regulate this transporter, thus decreasing cholesterol absorption [118]. The decrease in cholesterol absorption and re-absorption results in decreased cellular concentrations, which in turn upregulates the expression of the LDL receptor through activation of SREBP-2 [119]. Excretion of biliary cholesterol from hepatocytes is the last step in reverse cholesterol transport and may involve phytosterols as potential players [116]. Phytosterols may also exert hypocholesterolemic effects *via* interactions with intracellular enzymes, namely cholesterol acyltransferase (ACAT) and HMG-CoA reductase.

3.3.2.3 Polyphenols

Nuts are rich sources of highly bioactive polyphenols (see detail in Chapter 2), representing one of the richest food sources per serving [120,121]. The polyphenols present in nuts are mainly ellagitannins and proanthocyanidins, the former predominating in walnuts [122] and the latter in hazelnuts and almonds [123]. A study examining the acute effects of consuming a nut meal (75% of energy from walnuts or almonds) observed increased total plasma polyphenol levels, with peak concentration achieved approximately 90 minutes post-ingestion [124]. Similarly, a study designed to isolate, identify, and quantify phenolic compounds following walnut consumption (English *versus* black walnuts) observed the presence of various phenolic compounds including 5-caffeoylquinic acid, 3-caffeoylquinic acid (black walnut only), 4-caffeoylquinic acid, quercetin-3- rutinoside, quercetin-3-galactoside, quercetin- 3-pentoside, quercetin-3-arabinoside, quercetin-3-rhamnoside, and the aglycone quercetin (English walnut only) [125]. Catechins, which belong to the proanthocyanidins class, have been found in plasma after pecan consumption in humans [78] and almond ingestion by hamsters [126]. Polyphenols may exert cholesterol-lowering activity by inhibiting pancreatic cholesterol esterase, binding bile acids, and reducing the solubility of cholesterol in intestinal micelles with ensuing

cholesterol malabsorption [127]. A study performed in atherosclerosis-susceptible mice suggested that the combined presence of PUFAs and polyphenols is necessary for atheroprotective activity to occur [128], an observation that points to a novel mechanism for the anti-atherosclerotic effect of nuts.

3.3.3 Changes in Gut Microbiome Induced by Nutrient Compounds of Nuts

Prebiotic compounds in nuts may act collectively to stimulate growth of beneficial gut bacterial species, and at the same time inhibit growth of pathogenic ones [129]. Nuts are rich in polymerized polyphenols, representing one of the richest food sources of polymerized polyphenols per serving [120]. Polymerized polyphenols transit through the gut unabsorbed, arriving in the colon, where they act as substrates for the human gut microbiota. Data from the LifeLines-Deep study estimated that the gut microbiota composition can explain 4% of the variation in HDL-C [130]. Several of the microbes identified in this study, including *Bacteroidales* (phylum *Bacteroidetes*) and family *Clostridiaceae* (phylum *Firmicutes*) are known to be involved in bile acid metabolism [130]. Secondary bile acids derived from bacterial metabolism are absorbed in the colon [131], enter the circulation, and can modulate hepatic and/or systemic lipid metabolism through nuclear or G protein-coupled receptors (GPCRs) [132]. Short chain fatty acids (SCFAs) – acetate, butyrate, and propionate – are generated by gut bacterial fermentation of dietary fiber from nuts. SCFAs have been shown to suppress hepatic lipogenesis through activation of the hepatic cyclic adenosine 3', 5'-monophosphate (cAMP)/protein kinase A/cAMP-responsive element binding protein pathway and enhance oxidative metabolism in mice [133] and may thereby improve blood lipid levels. Altogether, nut consumption can positively alter the host microbiota to produce metabolites that may favorably modify blood lipids (see detail in Chapter 13). However, more human intervention studies administering different doses over a sufficiently long period of time should be performed to evaluate not only the prebiotic properties of nuts, but also the exact mechanisms by which the metabolites produced by gut microbiota promote healthy blood lipid levels.

3.4 Strength of the Evidence Regarding Nut Intake and Blood Lipids

Whereas the overall cholesterol-lowering effect of nuts is unequivocal, the evidence regarding nut effects on specific lipids/lipoproteins varies widely. Table 3.2 presents the summary of the level of evidence regarding the effect of nuts on individual lipid fractions.

3.5 Tree Nuts *versus* Peanuts

Peanuts, which botanically are groundnuts or legumes, are widely identified by consumers as part of the nut food group. Despite their diversity, peanuts share many common nutritional characteristics with tree nuts [134]. However, unlike tree nuts,

Table 3.2 Effects of Nut Consumption on Blood Lipids: Summary of Scientific Evidence

Particle	*Effect*	*Level of Evidence*	*References*
TC	Decrease	++	[1,2,9,10–16]
LDL-C	Decrease	++	[1,2,10,11,15,16]
HDL-C	Increase	+/–	[25,53,54]
*TAG	Decrease	+/–	[11,12,16,28,59]
ApoA1	Increase	+/–	[69]
ApoB	Decrease	+/–	[12,16,62]
ApoB : ApoA1	Decrease	+/–	[36,62,64,67–69]

Notes: ++, evidence from several studies; +, limited evidence from few studies; +/–, equivocal evidence. * Effect limited to individuals with elevated baseline levels.

Abbreviations: ApoA1, apolipoprotein A1; ApoB; apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TAG, triacylglycerols; TC, total cholesterol:

peanuts are more ubiquitous in the American diet owing to their high palatability and accessibility to lower-income shoppers [135]. Several studies have examined the effect of peanut consumption on blood lipids and lipoproteins. Results from individual studies are varied. For example, daily inclusion of 46 g peanuts and or/peanut butter in the diet of free-living adults with T2D resulted in clinically meaningful reduction in LDL-C:HDL-C and an increase in HDL-C [136]. A 12-week study showed that the incorporation of 42 g/day peanuts into the habitual diet led to significant reductions in TC and TAG only among participants with elevated baseline values [137]. At a much higher dose (500 kcal/day), peanut consumption resulted in a significant reduction in TC (7.2%) and TAG (20.0%) without significant changes in LDL-C or HDL-C [138]. According to the results of a systematic review and meta-analysis of 13 RCTs, peanuts had no significant effect on LDL-C weighted mean difference ([WMD: –3.31 mg/dL]), TAG (WMD: –7.59 mg/dL), and TC (WMD: 3.15 mg/dL) [139]. However, consumption of high-oleic peanuts and peanut sprouts had a positive significant effect on HDL-C when consumed for more than 12 weeks (WMD: 2.72 mg/dL) [139]. It is worth noting that previous peanut studies have reported lipid-lowering effects when MUFAs was substituted for SFAs [140,141], suggesting that the SFA content of the diet can modify the effect of peanuts (and tree nuts) on blood lipids and lipid ratios. Overall, the evidence suggests that peanuts are nearly as effective as tree nuts in lowering blood cholesterol and, to a smaller extent, apolipoproteins.

3.6 Walnuts *versus* Other Tree Nuts

Walnuts have a rather unique nutrient profiles compared to other nuts. The food composition database published by the U.S. Department of Agriculture indicates that 100 g of walnuts contain 15.2 g protein, 65.2 g fat, and 6.7 g dietary fiber [16].

Whereas most nuts are high in MUFAs, walnuts are composed largely of PUFAs (47.2 g), especially linoleic acid (18:2n-6; 38.1 g) and ALA (18:3n-3; 9.1 g) [16]. Walnuts have also the highest content of bioactive polyphenols of all nuts [122] and, unlike other nuts, contain sizable amounts of phytomelatonin [142], a molecule with antioxidant and anti-inflammatory properties, besides having a sleep-regulatory role. Several systematic reviews and meta-analyses investigating the effects of walnuts on blood lipids have been published. A recent meta-analysis of 26 RCTs with walnuts (15–108 g/day) representing 5%–24% of the total energy in prescribed diets showed that walnut diets significantly lowered TC (–6.99 mg/dL), LDL-C (–5.51 mg/dL) and TAG (–4.69 mg/dL) compared to control diets [16]. Another meta-analysis of 18 almond studies showed that TC, LDL-C, and TAG were significantly reduced by ~6 mg/dL, 4.8 mg/dL, and 5.9 mg/lL, respectively; and that HDL-C was not significantly affected (–0.66 mg/dL) with almond intake [13]. In reference to a previous meta-analysis and systematic review conducted by Banel and Hu [11], which found greater reduction in TC comparing walnuts with controls, Kim et al. [143] remarked that part of the reason could be the larger amount of walnuts consumed in these studies (30–108 g/day). This was also confirmed by Guasch-Ferré et al. [16], whose updated meta-analysis and systematic review of walnut studies showed pronounced effects in lowering of TC and LDL-C concentrations when walnuts accounted for 10%–25% of total energy compared with lower doses. Other tree nuts, including hazelnuts [14], pistachios [15], macadamias [42,144,145], and pecans [34,37], have equally showed beneficial effects on blood lipids, albeit with fewer RCTs. Hence, further studies are needed (especially with hazelnuts, macadamias, and pecans) to accurately distinguish how one nut type differs from the others in improving blood lipids. This is challenging considering that the relationship between nut consumption and blood lipids is confounded by many factors, including type of control diets, underlying disease conditions, and study design.

3.7 Dose–Response Effect of Nut Diets

Our previous pooled findings from intervention studies indicated that nut consumption improved blood lipids in a dose-related manner [3]. At 20% of dietary energy from nuts (equivalent to 71 g [2.5 ounces] for a 2000 kcal diet), blood lipid levels were reduced by 9.9 mg/dL (4.5% change) for TC and by 9.5 mg/dL (6.5% change) for LDL-C. At 12.2% of dietary energy from nuts (equivalent to 43 g [1.5 ounces]), blood lipid levels were reduced by 7.1 mg/dL (3.2% change) for TC and by 7.2 mg/dL (4.9% change) for LDL-C. At 10% of dietary energy from nuts (equivalent to 35 g [1.2 ounces]), blood lipid levels were reduced by 6.1 mg/lL (2.8% change) for TC and by 6.2 mg/dL (4.2% change) for LDL-C. Similar dose responses were estimated for the LDL-C:HDL-C ratio and for TAG levels in individuals with baseline TAG levels of at least 150 mg/dL [3]. More recently, Del Gobbo et al. [12] reported inverse relationships between tree nut intake and blood lipids. Specifically, linear dose–response relationships were observed between tree nut intake and ApoB ($r = -0.12$) and TAG ($r = -0.16$). However, the effect on TC and LDL-C was nonlinear, with stronger effects being observed in trials providing doses of ≥ 60 g nuts/day (≥ 2 servings/day). Results of a recent meta-analysis of 24 walnut studies ($n = 1059$) indicated that walnut intake significantly lowered TC in a dose-dependent manner; however, a nonsignificant trend between walnut intake and lower LDL-C was observed [16].

Del Gobbo et al. [12] recommended more RCTs with high doses of nuts (e.g., 100 g nuts/day - > 3 servings/day) to help clarify whether the benefits on blood lipids and apolipoproteins are indeed nonlinear.

3.8 Populations That Benefit Most from Nut Intake with Respect to Improvement in Blood Lipids

Tree nuts and peanuts have extensively been investigated in adults with hypercholesterolemia, obesity, metabolic syndrome, prediabetes, and diabetes, but less in individuals with established CVD and in pediatric populations. In addition, few studies have addressed the important question of which populations might obtain increased benefit from nut consumption in terms of lipid-profile improvement. A low dose of almonds (10 g/day) consumed before breakfast was shown to be effective in increasing HDL-C and lowering TC, LDL-C, TAG, and very low-density lipoprotein cholesterol (VLDL-C) in CHD patients on lipid-lowering medications [53]. Similarly, adding 100 g of almonds daily to chronic statin therapy for 4 weeks significantly reduced non-HDL-C [87]. Both these studies suggest that nuts may be effective as adjunctive treatment for patients on statin therapy. We have reported previously in our pooled analysis of 25 nut trials that the efficacy of nut consumption in improving lipid profiles was similar in men and women and across all age groups [3], although the effects were significantly modified by baseline LDL-C, BMI, and diet type. With respect to BMI, we noted that the cholesterol-lowering effects of nut consumption were more pronounced in individuals with lower BMI. This phenomena was also observed by Mukkudem-Petersen et al. [35], who reported that high consumption of neither walnuts nor cashews was associated with blood lipid changes in obese individuals or those with metabolic syndrome. Obese subjects have an attennuated cholesterol-lowering response to diets rich in unsaturated fat compared to lean individuals, probably because of underlying insulin resistance, which has been shown to favor de novo cholesterol syntheis [146]. This increased endogenous production of cholesterol is associated with reduced intestinal cholesterol absorption [147,148]. Nuts are rich in plant sterols that might contribute to cholesterol lowering by interfering with cholesterol absorption, but this effect would be blunted when cholesterol absoprtion rates are low. Another group that may benefit from nut intake are children and adolescents with primary hyperlipidemia [58]. In this 8-week RCT, 66 subjects were enrolled and randomized in 3 groups receiving 1) hazelnuts with skin; 2) hazelnuts without skin; and 3) dietary advices for hyperlipidemia only (controls). The amount of hazelnuts per portion was calculated based on the doses advised for adults, adjusted on the basis of the children's body weight (0.43 g/kg of body weight on average, corresponding to 15–30 g portions). Results of this study showed that hazelnuts significantly reduced the concentrations of LDL-C and increased the HDL-C:LDL-C ratio. However, in a separate analysis, hazelnut consumption had no significant effect on oxLDL levels [82].

According to the meta-analysis of Del Gobbo et al. [12], it is noteworthy that improvement in blood lipids following nut consumption has been observed without significant differences by disease condition, age, sex, background diet, intervention, or study duration. However, this meta-analysis concluded that tree nuts lowered ApoB to a 3–4-fold greater degree in trials conducted in diabetic individuals, suggesting that nuts may be important for lowering CVD risk in patients with T2D.

Table 3.3 Presence (Yes) or Absence (No) of Heterogeneity in 42 RCTs Examining Nut Intake and Blood Lipids/Apolipoproteins

Factor	*Lipid Fraction*					*P-value for Heterogeneity*
	TC	*LDL-C*	*HDL-C*	*ApoA1*	*ApoB*	
Age (mean)	No	No	No	No	No	all > 0.38
Gender	No	No	No	No	No	all > 0.18
Disease status	No	No	No	No	Yes $P = 0.018$ (diabetes)	all other > 0.28
Background diet	No	No	No	No	No	all > 0.18
Nut type	No	No	No	No	No	all > 0.10
Duration	No	No	No	No	No	all > 0.13

Source: Adapted from Del Gobbo, L.C. et al., *Am. J. Clin. Nutr.*, 102, 1347, 2015. With permission.

Notes: Results are based on weighted mean difference per serving nuts/day (28.4 g/day).

Age: < 40, 40–50, and > 50.

Gender: Male ≥ 50% and male ≤ 50%.

Disease status: Obese, metabolic syndrome, high cholesterol, type 2 diabetes, and apparently healthy.

Background diet: Habitual, American Heart Association diet, isoenergetic, low-fat, high-fat, and other healthy diets.

Nut type: Walnuts, pistachios, macademias, pecans, cashews, almonds, hazelnuts, mixed nuts.

Duration: 3–4 weeks, 4–5 weeks, and > 5 weeks.

Abbreviations: ApoA1, apolipoprotein A1; ApoB; apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized clinical trials; TC, total cholesterol.

More studies are needed to examine this assumption further. Table 3.3 indicates the presence or absence of heterogeneity among 42 RCTs of nuts and blood lipids/apolipoproteins based on supplementary data published [12].

3.9 Nut Form

It has been suggested that the cell wall of intact nuts may limit the release of lipids and other nutrients available for digestion [149]. Besides, short-term clinical trials report that whole-nut consumption increases fecal fat losses, suggesting that part of the fat passes therough the gastrointestinal tract undigested [149,150]. This has practical implications, since it could potentially diminish the cholesterol-lowering properties of whole nuts. Few studies have examined whether nut form (e.g., raw, roasted, whole, ground, or chopped) and processing may differentially impact blood lipids. A peanut trial [151] reported that there were no significant differences between peanut forms (raw unsalted, roasted unsalted, roasted salted, honey roasted peanuts, or peanut butter) with respect to changes in TC, LDL-C, HDL-C,

or TAG concentrations. Another study showed that the ingestion of three forms of hazelnuts (ground, sliced, or whole) improved the lipid and lipoprotein profiles in mildly hypercholesterolemic individuals regardless of nut form [69]. Another study comparing the effects of consuming dry roasted, lightly salted *versus* raw hazelnuts showed no significant differences in changes in blood lipids (TC and LDL-C) and apolipoprteins (ApoA1 and ApoB) bewteen the two nut forms, although HDL-C and TAG concentrations were significantly higher following the consumption of raw hazelnuts when compared to those that had been dry roasted and slightly salted [65]. These results are similar to those of of an almond study [50], which showed that unblanched almonds, whether raw or dry roasted, were equally effective in lowering TC and LDL-C. It is worth noting that previous research has reported that the nutrient composition of nuts remains largely unchanged when the roasting temperature is between 120 and 160 °C [152]. Roasting in this temperature range also resulted in a better sensory evaluation for nuts. Questions have arisen as to whether nut oils have differential effects on blood lipids compared to whole nuts. A study evaluating the effect of peanut oil on various outcomes, including blood lipids, reported an increase in HDL-C and significant reductions in LDL-C when a daily peanut oil load providing 30% of resting energy expenditure was given for 8 weeks [153]. In another study, overweight individuals with high LDL-C and TAG completed a randomized, controlled, four-period, postprandial feeding study [154]. During each of the four visits to the clinic, participants consumed one of four randomly assigned test diets: 85 g ground whole walnuts, 34 g ground de-fatted walnut meat, 51 g walnut oil, or 5.6 g ground defatted walnut skins. Results indicated that the ingestion of walnut oil significantly increased cholesterol efflux from foam cells by decreasing the expression of the lipogenic enzyme stearoyl CoA desaturase 1 (SCD1). Similarly, replacing one-half of the habititual fat intake with fat from whole almonds or almond oil had similar effects on plasma lipids in normolipidemic men and women, as both diets reduced TC, LDL-C, and TAG to the same extent and resulted in comparable increases in HDL-C [80].

Presently, there is little evidence to show that nut form and processing differentially affects blood lipids. Nonetheless, more studies are needed to further clarify this issue.

3.10 Conclusion

Although a considerable amount of research has been devoted to understanding the effect of nut consumption on blood lipids and lipoproteins, much remains to be learned. The level of evidence regarding the cholesterol (TC and LDL-C)-lowering effect of nuts is convincing. Correspondingly, their effect on apolipoproteins, HDL-C, and TAG concentrations remains unclear and warrants further investigation. As noted, the major determinant of the cholesterol-lowering effect of nuts appears to be nut dose (~42 g/day or 1.5 ounces) rather than nut type [12]. This highlights the need for quality feeding studies with varying doses, larger sample sizes, and longer duration to investigate this relationship. Notwithstanding the limitations of past studies, it should not be missed that nuts have many beneficial attributes. Key nutrients in nuts, including vegetable protein, unsaturated fat, dietary fiber, an array of vitamins and minerals, and other bioactive compounds such as polyphenols, work synergistically through multiple mechanisms not

only to promotefavorable lipid profiles, but also to induce other cardioprotective effects. In addition to its blood lipid–lowering effect, the inclusion of nuts in the diet has been shown to improve the overall nutrient profiles of the diet [155] without adversely affecting body weight [156,157]. Thus, the consumption of nuts as part of a healthy diet should be encouraged as a public health measure to promote cardiovascular health.

References

1. Fraser, G.E., Sabate, J., Beeson, W.L., and Strahan, T.M., A possible protective effect of nut consumption on risk of coronary heart disease: The Adventist Health Study. *Arch. Intern. Med.*, 152, 1416–1424, 1992.
2. Sabaté, J., Fraser, G.E., Burke, K., Knutsen, S.F., Bennett, H., and Lindsted, K.D., Effects of walnuts on serum lipid levels and blood pressure in normal men. *New. Eng. J. Med.*, 328, 603–637, 1993.
3. Sabaté, J., Oda, K., and Ros, E., Nut consumption and blood lipid levels: A pooled analysis of 25 intervention trials. *Arch. Intern. Med.*, 170, 821–827, 2010.
4. Peters, S.A., Singhateh, Y., Mackay, D., Huxley, R.R., and Woodward, M., Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis. *Atherosclerosis*, 248, 123–131, 2016.
5. Rippe, J.M., and Angelopoulos, T.J., Lifestyle strategies for cardiovascular risk reduction. *Curr. Atheroscler. Rep.*, 16, 444, 2014.
6. Hansson, G.K., Inflammation, atherosclerosis, and coronary artery disease. *New Eng. J. Med.*, 352, 1685–1695, 2005.
7. Carroll, M.D., Kit, B.K., Lacher, D.A., Shero, S.T., and Mussolino, M.E., Trends in lipids and lipoproteins in US adults, 1988–2010. *JAMA*, 308, 1545–1554, 2012.
8. Stamler, J., Wentworth, D., and Neaton, J.D., Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the multiple risk factor intervention trial (mrfit). *JAMA*, 256, 2823–2828, 1986.
9. Hu, F.B., Manson, J.E., and Willett, W.C., Types of dietary fat and risk of coronary heart disease: A critical review. *J. Am. Coll. Nutr.*, 20, 5–19, 2001.
10. Kris-Etherton, P.M., and Yu, S., Individual fatty acid effects on plasma lipids and lipoproteins: Human studies. *Am. J. Clin. Nutr.*, 65(Suppl. 5), 1628S–1644S, 1997.
11. Banel, D.K., and Hu, F.B., Effects of walnut consumption on blood lipids and other cardiovascular risk factors: A meta-analysis and systematic review. *Am. J. Clin. Nutr.*, 90, 56–63, 2009.
12. Del Gobbo, L.C., Falk, M.C., Feldman, R., Lewis, K., and Mozaffarian, D., Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: Systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am. J. Clin. Nutr.*, 102, 1347–1356, 2015.
13. Musa-Veloso, K., Paulionis, L., Poon, T., and Lee, H.Y., The effects of almond consumption on fasting blood lipid levels: A systematic review and meta-analysis of randomised controlled trials. *J. Nutr. Sci.*, 5, 1–15, 2016.
14. Perna, S., Giacosa, A., Bonitta, G., Bologna, C., Isu, A., Guido, D., and Rondanelli, M., Effects of hazelnut consumption on blood lipids and body weight: A systematic review and Bayesian meta-analysis. *Nutrients*, 8, 747, 2016.

15. Lippi, G., Cervellin, G., and Mattiuzzi, C., More pistachio nuts for improving the blood lipid profile: Systematic review of epidemiological evidence. *Acta Biomed.*, 87, 5–12, 2016.
16. Guasch-Ferré, M., Li, J., Hu, F.B., Salas-Salvadó, J., and Tobias, D.K., Effects of walnut consumption on blood lipids and other cardiovascular risk factors: An updated meta-analysis and systematic review of controlled trials. *Am. J. Clin. Nutr.*, 108, 174–187, 2018.
17. Carvalho, R.F., Huguenin, G.V., Luiz, R.R., Moreira, A.S., Oliveira, G.M., and Rosa, G., Intake of partially defatted Brazil nut flour reduces serum cholesterol in hypercholesterolemic patients-a randomized controlled trial. *Nutr. J.*, 14, 59, 2015.
18. Mah, E., Schulz, J.A., Kaden, V.N., Lawless, A.L., Rotor, J., Mantilla, L.B., and Liska, D.J., Cashew consumption reduces total and LDL cholesterol: A randomized, crossover, controlled-feeding trial. *Am. J. Clin. Nutr.*, 105, 1070–1078, 2017.
19. Baer, D.J., and Novotny, J.A., Consumption of cashew nuts does not influence blood lipids or other markers of cardiovascular disease in humans: A randomized controlled trial. *Am. J. Clin. Nutr.*, 109, 269–275, 2019.
20. Bamberger, C., Rossmeier, A., Lechner, K., Wu, L., Waldmann, E., Stark, R.G., Altenhofer, J. et al., A walnut-enriched diet reduces lipids in healthy Caucasian subjects, independent of recommended macronutrient replacement and time point of consumption: A prospective, randomized, controlled trial. *Nutrients*, 9, 1097, 2017.
21. Mazidi, M., Rezaie, P., Ferns, G.A., and Gao, H.-K., Impact of different types of tree nut, peanut, and soy nut consumption on serum C-reactive protein (CRP): A systematic review and meta-analysis of randomized controlled clinical trials. *Medicine*, 95, e5165, 2016.
22. Silverman, M.G., Ference, B.A., Im, K., Wiviott, S.D., Giugliano, R.P., Grundy, S.M., Braunwald, E. et al., Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. *JAMA*, 316, 1289–1297, 2016.
23. Grundy, S.M., Stone, N.J., Bailey, A.L., Beam, C., Birtcher, K.K., Blumenthal, R.S., Braun, L.T. et al., 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.*, 73, 3234–3237, 2019.
24. Del Gobbo, L.C., Falk, M.C., Feldman, R., Lewis, K., and Mozaffarian, D., Are phytosterols responsible for the low-density lipoprotein–lowering effects of tree nuts?: A systematic review and meta-analysis. *J. Am. Coll. Cardiol.*, 65, 2765–2767, 2015.
25. Mohan., V., Gayathri, R., Jaacks, L., Lakshmipriya, N., Anjana, R., Spiegelman, D., Jeevan, R.G. et al., Cashew nut consumption increases HDL cholesterol and reduces systolic blood pressure in Asian Indians with type 2 diabetes: A 12-week randomized controlled trial. *J. Nutr.*, 148, 63–69, 2018.
26. Bowen, J., Luscombe-Marsh, N.D., Stonehouse, W., Tran, C., Rogers, G.B., Johnson, N., Thompson, C.H. et al., Effects of almond consumption on metabolic function and liver fat in overweight and obese adults with elevated fasting blood glucose: A randomised controlled trial. *Clin. Nutr.*, 30, 10–18, 2019.
27. Chisholm, A., Mann, J., Skeaff, M., Frampton, C., Sutherland, W., Duncan, A., and Tiszavari, S., A diet rich in walnuts favourably influences plasma fatty acid

profile in moderately hyperlipidaemic subjects. *Eur. J. Clin. Nutr.*, 52, 12–16, 1998.
28. Colquhoun, D., Humphries, J., Moores, D., and Somerset, S., Effects of a macadamia nut enriched diet on serum lipids and lipoproteins compared to a low fat diet. *Food Aust.*, 48, 216–222, 1996.
29. Edwards, K., Kwaw, I., Matud, J., and Kurtz, I., Effect of pistachio nuts on serum lipid levels in patients with moderate hypercholesterolemia. *J. Am. Coll. Nutr.*, 18, 229–232, 1999.
30. Jambazian, P.R., Haddad, E., Rajaram, S., Tanzman, J., and Sabaté, J., Almonds in the diet simultaneously improve plasma α-tocopherol concentrations and reduce plasma lipids. *J. Am. Diet. Assoc.*, 105, 449–454, 2005.
31. Jia, X., Li, N., Zhang, W., Zhang, X., Lapsley, K., Huang, G, Blumber, J. et al., A pilot study on the effects of almond consumption on DNA damage and oxidative stress in smokers. *Nutr. Cancer.*, 54, 179–183, 2006.
32. Kocyigit, A., Koylu, A., and Keles, H., Effects of pistachio nuts consumption on plasma lipid profile and oxidative status in healthy volunteers. *Nutr. Metab. Cardiovasc. Dis.*, 16, 202–209, 2006.
33. Kurlandsky, S.B., and Stote, K.S., Cardioprotective effects of chocolate and almond consumption in healthy women. *Nutr. Res.*, 26, 509–516, 2006.
34. Morgan, W.A., and Clayshulte, B.J., Pecans lower low density lipoprotein cholesterol in people with normal lipid levels. *J. Am. Diet. Assoc.*, 100, 312–318, 2000.
35. Mukuddem-Petersen, J., Stonehouse, W., Jerling, J.C., Hanekom, S.M., and White, Z., Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: A controlled feeding trial. *Br. J. Nutr.*, 97, 1144–1153, 2007.
36. Sabaté, J., Haddad, E., Tanzman, J.S., Jambazian, P., and Rajaram, S., Serum lipid response to the graduated enrichment of a Step I diet with almonds: A randomized feeding trial. *Am. J. Clin. Nutr.*, 77, 1379–1384, 2003.
37. Rajaram, S., Burke, K., Connell, B., Myint, T., and Sabaté, J., A monounsaturated fatty acid–rich pecan-enriched diet favorably alters the serum lipid profile of healthy men and women. *J. Nutr.*, 131, 2275–2279, 2001.
38. Schutte, A.E., Van Rooyen, J.M., Huisman, H.W., Mukuddem-Petersen, J., Oosthuizen, W., Hanekom, S.M., and Jerling, J.C., Modulation of baroreflex sensitivity by walnuts *versus* cashew nuts in subjects with metabolic syndrome. *Am. J. Hypertens.*, 19, 629–636, 2006.
39. Sheridan, M.J., Cooper, J.N., Erario, M., and Cheifetz, C.E., Pistachio nut consumption and serum lipid levels. *J. Am. Coll. Nutr.*, 26, 141–148, 2007.
40. Spaccarotella, K.J., Kris-Etherton, P.M., Stone, W.L., Bagshaw, D.M., Fishell, V.K., West, S.G., Lawrence, F.R. et al., The effect of walnut intake on factors related to prostate and vascular health in older men. *Nutr. J.*, 7, 13, 2008.
41. Abbey, M., Noakes, M., Belling, G.B., and Nestel, P.J., Partial replacement of saturated fatty acids with almonds or walnuts lowers total plasma cholesterol and low-density-lipoprotein cholesterol. *Am. J. Clin. Nutr.*, 59, 995–999, 1994.
42. Garg, M.L., Blake, R.J., and Wills, R.B,. Macadamia nut consumption lowers plasma total and LDL cholesterol levels in hypercholesterolemic men. *J. Nutr.*, 133, 1060–1063, 2003.
43. Lovejoy, J.C., Most, M.M., Lefevre, M., Greenway, F.L, and Rood, J.C., Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. *Am. J. Clin. Nutr.*, 76, 1000–1006, 2002.

44. Orem, A., Yucesan, F.B., Orem, C., Akcan, B., Kural, B.V., Alasalvar, C., and Shahidi, F., Hazelnut-enriched diet improves cardiovascular risk biomarkers beyond a lipid-lowering effect in hypercholesterolemic subjects. *J. Clin. Lipidol.*, 2, 123–131, 2013.
45. Sari, I., Baltaci, Y., Bagci, C., Davutoglu, V., Erel, O., Celik, H., Ozer, O. et al., Effect of pistachio diet on lipid parameters, endothelial function, inflammation, and oxidative status: A prospective study. *Nutrition*, 26, 399–404, 2010.
46. Spiller, G., Jenkins, D., Cragen, L., Gates, J., Bosello, O., Berra, K., Rudd, C. et al., Effect of a diet high in monounsaturated fat from almonds on plasma cholesterol and lipoproteins. *J. Am. Coll. Nutr.*, 11, 126–130, 1992.
47. Wien, M., Sabaté, J., Ikle, D., Cole, S., and Kandeel, F., Almonds vs complex carbohydrates in a weight reduction program. *Int. J. Obes.*, 27, 1365–1372, 2003.
48. Yucesan, F.B., Orem, A., Kural, B.V., Orem, C., and Turan, İ., Hazelnut consumption decreases the susceptibility of LDL to oxidation, plasma oxidized LDL level and increases the ratio of large/small LDL in normolipidemic healthy subjects. *Anatol. J. Cardiol.*, 10, 28–36, 2010.
49. Aldemir, M., Okulu, E., Neşelioğlu, S., Erel, O., and Kayıgil, Ö., Pistachio diet improves erectile function parameters and serum lipid profiles in patients with erectile dysfunction. *Int. J. Impot. Res.*, 23, 32–38, 2011.
50. Spiller, G.A., Miller, A., Olivera, K., Reynolds, J., Miller, B., Morse, S.J, Dewell, A. et al., Effects of plant-based diets high in raw or roasted almonds, or roasted almond butter on serum lipoproteins in humans. *J. Am. Coll. Nutr.*, 22, 195–200, 2003.
51. Mihaylova, B., Emberson, J., Blackwell, L., Keech, A., Simes, J., Barnes, E., Voysey, M. et al., The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. *Lancet*, 380, 581–590, 2012.
52. Di Angelantonio, E., Sarwar, N., Perry, P., Kaptoge, S., Ray, K.K., Thompson, A., Wood, A.M. et al., Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*, 302, 1993–2000, 2009.
53. Jamshed, H., Sultan, F.A., Iqbal, R., and Gilani, A.H., Dietary almonds increase serum HDL cholesterol in coronary artery disease patients in a randomized controlled trial. *J. Nutr.*, 145, 2287–2292, 2015.
54. Berryman, C.E., Fleming, J.A., and Kris-Etherton, P.M., Inclusion of almonds in a cholesterol-lowering diet improves plasma HDL subspecies and cholesterol efflux to serum in normal-weight individuals with elevated LDL cholesterol. *J. Nutr.*, 147, 1517–1523, 2017.
55. Kingwell, B.A., Chapman, M.J., Kontush, A., and Miller, N.E., HDL-targeted therapies: Progress, failures and future. *Nat. Rev. Drug Discov.*, 13, 445–464, 2014.
56. Fruchart, J.-C., Duriez, P., and Luc, G., Triglycerides and risk for atherosclerotic disease, in *Comprehensive Management of High Risk Cardiovascular Patients*, Gotto, A.M. and Toth, P.P., Eds., CRC Press, Boca Raton, FL, 2016, pp. 367–414.
57. Butler, T., Confue, C., Guild, J., and Mushtaq, S., Effect of a single serving of pecan nuts on blood lipids and weight: A single blind randomised control trial. *Proc. Nutr. Soc.*, 77(OCE4), e164, 2018.
58. Deon, V., Del Bo, C., Guaraldi, F., Abello, F., Belviso, S., Porrini, M., Riso, P. et al., Effect of hazelnut on serum lipid profile and fatty acid composition of

erythrocyte phospholipids in children and adolescents with primary hyperlipidemia: A randomized controlled trial. *Clin Nutr.*, 37, 1193–1201, 2018.
59. Tahir, F.N., Shah, S.I.A., Danyal, M., and Qureshi, J.A., Effect of almond consumption on serum lipid profile in dyslipidemic adults. *Pak. J. Med Sci.*, 12, 799–801, 2018.
60. Sniderman, A., Junger, I., Holme, I., Aastveit, A., and Walldius, G., Errors that result from using the TC/HDL-C ratio rather than the apoB/apoA-I ratio to identify the lipoprotein-related risk of vascular disease. *J. Intern. Med.*, 259, 455–446, 2006.
61. Fredrickson, D.S., Lux, S.E., and Herbert, P.N., The apolipoproteins, in *Pharmacological Control of Lipid Metabolism*, Holmes, W.L., Paoletti, R., and Kritchevsky, D., Eds., Springer, Berlin, 1972, pp. 25–56.
62. Lee, Y., Berryman, C.E., West, S.G., Chen, C.Y.O., Blumberg, J.B., Lapsley, K.G., Preston, E.G. et al., Effects of dark chocolate and almonds on cardiovascular risk factors in overweight and obese individuals: A randomized controlled-feeding trial. *J. Am. Heart Assoc.*, 6, e005162, 2017.
63. Strunz, C.C., Oliveira, T.V., Vinagre, J.C., Lima, A., Cozzolino, S., and Maranhão, R.C., Brazil nut ingestion increased plasma selenium but had minimal effects on lipids, apolipoproteins, and high-density lipoprotein function in human subjects. *Nutr. Res.*, 28, 151–155, 2008.
64. Jenkins, D.J., Kendall, C.W., Banach, M.S., Srichaikul, K., Vidgen, E., Mitchell, S., Parker, T. et al., Nuts as a replacement for carbohydrates in the diabetic diet. *Diabetes Care*, 34, 1706–1711, 2011.
65. Tey, S.L., Robinson, T., Gray, A.R., Chisholm, A.W., and Brown, R.C., Do dry roasting, lightly salting nuts affect their cardioprotective properties and acceptability? *Eur. J. Nutr.*, 56, 1025–1036, 2017.
66. Andrikoula, M., and McDowell, I., The contribution of ApoB and ApoA1 measurements to cardiovascular risk assessment. *Diabetes Obes. Metab.*, 10, 271–278, 2008.
67. Li, S.-C., Liu, Y.-H., Liu, J.-F., Chang, W.-H., Chen, C.-M., and Chen, C.-Y.O., Almond consumption improved glycemic control and lipid profiles in patients with type 2 diabetes mellitus. *Metabolism*, 60, 474–479, 2011.
68. Solá, R., Fitó, M., Estruch, R., Salas-Salvadó, J., Corella, D., de La Torre, R., Munoz, M.M. et al., Effect of a traditional Mediterranean diet on apolipoproteins B, A1, and their ratio: A randomized, controlled trial. *Atherosclerosis*, 218, 174–180, 2011.
69. Tey, S., Brown, R., Chisholm, A., Delahunty, C., Gray, A., and Williams, S., Effects of different forms of hazelnuts on blood lipids and α-tocopherol concentrations in mildly hypercholesterolemic individuals *Eur. J. Clin. Nutr.*, 65, 117–124, 2011.
70. Koba, S., Yokota, Y., Sakai, K., Nakamura, Y., Tsunoda, F., Shoji, M., Ito, Y. et al., Small dense LDL cholesterol as strong predictors for secondary cardiovascular events compared with LDL cholesterol in elderly patients. *Atherosclerosis*, 263, e175–e176, 2017.
71. Di Pietro, N., Formoso, G., and Pandolfi, A., Physiology and pathophysiology of oxLDL uptake by vascular wall cells in atherosclerosis. *Vascul. Pharmacol.*, 84, 1–7, 2016.
72. Lamarche, B., Lemieux, I., and Despres, J., The small, dense LDL phenotype and the risk of coronary heart disease: Epidemiology, patho-physiology and therapeutic aspects. *Diabetes Metab.*, 25, 199–212, 1999.

73. Maiolino, G., Rossitto, G., Caielli, P., Bisogni, V., Rossi, G.P., and Calò, L.A., The role of oxidized low-density lipoproteins in atherosclerosis: The myths and the facts. *Mediators Inflamm.*, 714653, 2013.
74. Yu, X.-H., Fu, Y.-C., Zhang, D.-W., Yin, K., and Tang, C.-K., Foam cells in atherosclerosis. *Clin. Chim. Acta.*, 424, 245–252, 2013.
75. Berry, E.M., Eisenberg, S., Friedlander, Y., Harats, D., Kaufmann, N.A., Norman, Y., and Stein, Y., Effects of diets rich in monounsaturated fatty acids on plasma lipoproteins – the Jerusalem Nutrition Study. II Monounsaturated fatty acids vs carbohydrates. *Am. J. Clin. Nutr.*, 56, 394–403, 1992.
76. Ros, E., Núñez, I., Pérez-Heras, A., Serra, M., Gilabert, R., Casals, E, and Deulofeu, R., A walnut diet improves endothelial function in hypercholesterolemic subjects: A randomized crossover trial. *Circulation*, 109, 1609–1614, 2004.
77. Fitó, M., Guxens, M., Corella, D., Sáez, G., Estruch, R., de la Torre R, Francés, F. et al., Effect of a traditional Mediterranean diet on lipoprotein oxidation: A randomized controlled trial. *Arch. Intern. Med.*, 167, 1195–1203, 2007.
78. Hudthagosol, C., Haddad, E.H., McCarthy, K., Wang, P., Oda, K., and Sabaté, J., Pecans acutely increase plasma postprandial antioxidant capacity and catechins and decrease LDL oxidation in humans. *J. Nutr.*, 141, 56–62, 2010.
79. Kay, C.D., Gebauer, S.K., West, S.G., and Kris-Etherton, P.M., Pistachios increase serum antioxidants and lower serum oxidized-LDL in hypercholesterolemic adults. *J. Nutr.*, 140, 1093–1098, 2010.
80. Hyson, D.A., Schneeman, B.O., and Davis, P.A., Almonds and almond oil have similar effects on plasma lipids and LDL oxidation in healthy men and women. *J. Nutr.*, 132, 703–707, 2002.
81. Zambón, D., Sabaté, J., Munoz, S., Campero, B., Casals, E., Merlos, M., Laguna, J.C. et al., Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women: A randomized crossover trial. *Ann. Intern. Med.*, 132, 538–546, 2000.
82. Guaraldi, F., Deon, V., Del Bo, C., Vendrame, S., Porrini, M., Riso, P., and Guardamagna, O., Effect of short-term hazelnut consumption on DNA damage and oxidized LDL in children and adolescents with primary hyperlipidemia: A randomized controlled trial. *J. Nutr. Biochem.*, 57, 206–211, 2018.
83. Damasceno, N.R., Sala-Vila, A., Cofán, M., Pérez-Heras, A.M., Fitó, M., Ruiz-Gutiérrez, V., Martínez-González, M.-A. et al., Mediterranean diet supplemented with nuts reduces waist circumference and shifts lipoprotein subfractions to a less atherogenic pattern in subjects at high cardiovascular risk. *Atherosclerosis*, 230, 347–353, 2013.
84. Almario, R.U., Vonghavaravat, V., Wong, R., and Kasim-Karakas, S.E., Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. *Am. J. Clin. Nutr.*, 74, 72–79, 2001.
85. Holligan, S.D., West, S.G., Gebauer, S.K., Kay, C.D., and Kris-Etherton, P.M., A moderate-fat diet containing pistachios improves emerging markers of cardiometabolic syndrome in healthy adults with elevated LDL levels. *Br. J. Nutr.*, 112, 744–752, 2014.
86. Hernández-Alonso, P., Salas-Salvadó, J., Baldrich-Mora, M., Mallol, R., Correig, X., and Bulló, M., Effect of pistachio consumption on plasma lipoprotein subclasses in pre-diabetic subjects. *Nutr. Metab. Cardiovasc. Dis.*, 25, 396–402, 2015.
87. Ruisinger, J.F., Gibson, C.A., Backes, J.M., Smith, B.K., Sullivan, D.K., Moriarty, P.M., and Kris-Etherton, P., Statins and almonds to lower lipoproteins (the STALL Study). *J. Clin. Lipidol.*, 9, 58–64, 2015.

88. Fielding, C.J., and Fielding, P.E., Molecular physiology of reverse cholesterol transport. *J. Lipid Res.*, 36, 211–228, 1995.
89. Cheung, M.C., and Albers, J., Characterization of lipoprotein particles isolated by immunoaffinity chromatography: Particles containing AI and A-II and particles containing AI but no A-II. *J. Biol. Chem.*, 259, 12201–12209, 1984.
90. McVicar, J.P., Kunitake, S.T., Hamilton, RL., and Kane, J.P., Characteristics of human lipoproteins isolated by selected-affinity immunosorption of apolipoprotein AI. *Proc. Natl. Acad. Sci. USA.*, 81, 1356–1360, 1984.
91. Puchois, P., Kandoussi, A., Fievet, P., Fourrier, J., Bertrand, M., Koren, E., and Fruchart, J.C., Apolipoprotein AI containing lipoproteins in coronary artery disease. *Atherosclerosis*, 68, 35–40, 1987.
92. Phung, O.J., Makanji, S.S., White, C.M., and Coleman, C.I., Almonds have a neutral effect on serum lipid profiles: A meta-analysis of randomized trials. *J. Am. Diet. Assoc.*, 109, 865–873, 2009.
93. Kris-Etherton, P.M., Yu-Poth, S., Sabaté, J., Ratcliffe, H.E., Zhao, G., and Etherton, T.D., Nuts and their bioactive constituents: Effects on serum lipids and other factors that affect disease risk. *Am. J. Clin. Nutr.*, 70(Suppl. 3), 504S–511S, 1999.
94. Woollett, L.A., Spady, D.K., and Dietschy, J.M., Saturated and unsaturated fatty acids independently regulate low density lipoprotein receptor activity and production rate. *J. Lipid Res.*, 33, 77–88, 1992.
95. Mensink, R.P., Zock, P.L., Kester, A.D., and Katan, M.B., Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: A meta-analysis of 60 controlled trials. *Am. J. Clin. Nutr.*, 77, 1146–1155, 2003.
96. Campos, H., Dreon, D.M., and Krauss, R., Associations of hepatic and lipoprotein lipase activities with changes in dietary composition and low density lipoprotein subclasses. *J. Lipid Res.*, 36, 462–472, 1995.
97. Brousseau, M.E., Ordovas, J.M., Osada, J., Fasulo, J., Robins, S.J., Nicolosi, R.J., and Schaefer, E.J., Dietary monounsaturated and polyunsaturated fatty acids are comparable in their effects on hepatic apolipoprotein mRNA abundance and liver lipid concentrations when substituted for saturated fatty acids in cynomolgus monkeys. *J. Nutr.*, 125, 425–436, 1995.
98. Kim, Y., Keogh, J., and Clifton, P., Benefits of nut consumption on insulin resistance and cardiovascular risk factors: Multiple potential mechanisms of actions. *Nutrients*, 9, 1271, 2017.
99. Ito, Y., Azrolan, N., O'Connell, A., Walsh, A., and Breslow, J.L., Hypertriglyceridemia as a result of human apo CIII gene expression in transgenic mice. *Science*, 249, 790–793, 1990.
100. Sampath, H., and Ntambi, J.M., Polyunsaturated fatty acid regulation of genes of lipid metabolism. *Annu. Rev. Nutr.*, 25, 317–340, 2005.
101. Kinsella, J., Lipids, membrane receptors, and enzymes: Effects of dietary fatty acids. *J. Parenter. Enteral Nutr.*, 14, 200S–217S, 1990.
102. Kuo, P., Weinfeld, M., and Loscalzo, J., Effect of membrane fatty acyl composition on LDL metabolism in Hep G2 hepatocytes. *Biochemistry*, 29, 6626–6632, 1990.
103. Sampath, H., and Ntambi, J.M., Polyunsaturated fatty acid regulation of gene expression. *Nutr. Rev.*, 62, 333–339, 2004.
104. Salas-Salvadó, J., Bulló, M., Pérez-Heras, A., and Ros, E., Dietary fibre, nuts and cardiovascular diseases. *Br. J. Nutr.*, 96(Suppl. 2), S45–S51, 2006.

105. Segura, R., Javierre, C., Lizarraga, M.A., and Ros, E., Other relevant components of nuts: Phytosterols, folate and minerals. *Br. J. Nutr.*, 96(Suppl. 2), S36–S44, 2006.
106. Brown, L., Rosner, B., Willett, W.W., and Sacks, F.M., Cholesterol-lowering effects of dietary fiber: A meta-analysis. *Am. J. Clin. Nutr.*, 69, 30–42, 1999.
107. Wright, R.S., Anderson, J.W., and Bridges, S.R., Propionate inhibits hepatocyte lipid synthesis. *Proc. Soc. Exp. Biol. Med.*, 195, 26–29, 1990.
108. Wolever, T., Spadafora, P.J., Cunnane, S.C., and Pencharz, P.B., Propionate inhibits incorporation of colonic [1, 2–13C] acetate into plasma lipids in humans. *Am. J. Clin. Nutr.*, 61, 1241–1247, 1995.
109. Zemaitis, J., and Sabaté, J., Effect of almond consumption on stool weight and stool fat, presented at the Experimental Biology, Orlando, FL, March 31–April 4, 2001, Abstract A601.
110. Caimari, A., Puiggròs, F., Suárez, M., Crescenti, A., Laos, S., Ruiz, J.A., Alonso, V. et al., The intake of a hazelnut skin extract improves the plasma lipid profile and reduces the lithocholic/deoxycholic bile acid faecal ratio, a risk factor for colon cancer, in hamsters fed a high-fat diet. *Food Chem.*, 167, 138–144, 2015.
111. Anderson, J.W., and Chen, W.L., Plant fiber. Carbohydrate and lipid metabolism. *Am. J. Clin. Nutr.*, 32, 346–363, 1979.
112. Vahouny, G.V., Roy, T., Gallo, L., Story, J., Kritchevsky, D., and Cassidy, M., Dietary fibers III. Effects of chronic intake on cholesterol absorption and metabolism in the rat. *Am. J. Clin. Nutr.*, 33, 2182–2191, 1980.
113. Kornsteiner-Krenn, M., Wagner, K.-H., and Elmadfa, I., Phytosterol content and fatty acid pattern of ten different nut types. *Int. J. Vitam. Nutr. Res.*, 83, 263–270, 2013.
114. Escurriol, V., Cofán, M., Serra, M., Bulló, M., Basora, J., Salas-Salvadó, J., Corella, D. et al., Serum sterol responses to increasing plant sterol intake from natural foods in the Mediterranean diet. *Eur. J. Clin. Nutr.*, 48, 373–382, 2009.
115. Moreau, R.A., Nyström, L., Whitaker, B.D., Winkler-Moser, J.K., Baer, D.J., Gebauer, S.K., and Hicks, K.B., Phytosterols and their derivatives: Structural diversity, distribution, metabolism, analysis, and health-promoting uses. *Prog. Lipid. Res.*, 70, 35–61, 2018.
116. Racette, S.B., Lin, X., Lefevre, M., Spearie, C.A., Most, M.M., Ma, L., Ma, L. et al., Dose effects of dietary phytosterols on cholesterol metabolism: A controlled feeding study. *Am. J. Clin. Nutr.*, 91, 32–38, 2009.
117. Berryman, C.E., Preston, A.G., Karmally, W., Deckelbaum, R.J, and Kris-etherton, P.M., Effects of almond consumption on the reduction of LDL-cholesterol: A discussion of potential mechanisms and future research directions. *Nutr. Rev.*, 69, 171–185, 2011.
118. Jesch, E.D., Seo, J.M., Carr, T.P., and Lee, J.-Y., Sitosterol reduces messenger RNA and protein expression levels of Niemann-Pick C1-like 1 in FHs 74 Int cells. *Nutr. Res.*, 29, 859–866, 2009.
119. Costet, P., Molecular pathways and agents for lowering LDL-cholesterol in addition to statins. *Pharmacol. Ther.*, 126, 263–278, 2010.
120 Abe, L.T., Lajolo, F.M., and Genovese, M.I., Comparison of phenol content and antioxidant capacity of nuts. *Food Sci. Technol.*, 30, 254–259, 2010.
121. Pérez-Jiménez, J., Neveu, V., Vos, F., and Scalbert, A., Identification of the 100 richest dietary sources of polyphenols: An application of the Phenol-Explorer database. *Eur. J. Clin. Nutr.*, 64(Suppl. 3), S112–S120, 2010.

122. Sánchez-González, C., Ciudad, C.J., Noé, V., and Izquierdo-Pulido, M., Health benefits of walnut polyphenols: An exploration beyond their lipid profile. *Crit. Rev. Food Sci. Nutr.*, 57, 3373–3383, 2017.
123. Monagas, M., Garrido, I., Lebrón-Aguilar, R., Gómez-Cordovés, M.C., Rybarczyk, A., Amarowicz, R., and Bartolomé, B., Comparative flavan-3-ol profile and antioxidant capacity of roasted peanut, hazelnut, and almond skins. *J. Agric. Food Chem.*, 57, 10590–10599, 2009.
124. Torabian, S., Haddad, E., Rajaram, S., Banta, J., and Sabaté, J. Acute effect of nut consumption on plasma total polyphenols, antioxidant capacity and lipid peroxidation. *J. Hum. Nutr. Diet.*, 22, 64–71, 2009.
125. Rorabaugh, J.M., Singh, A.P., Sherrell, I.M., Freeman, M.R., Vorsa, N., Fitschen, P., Malone, C. et al., English and black walnut phenolic antioxidant activity *in vitro* and following human nut consumption. *Food Nutr. Sci.*, 2, 193–200, 2011.
126. Chen, C.-Y., Milbury, P.E., Lapsley, K., and Blumberg, J.B., Flavonoids from almond skins are bioavailable and act synergistically with vitamins C and E to enhance hamster and human LDL resistance to oxidation. *J. Nutr.*, 135, 1366–1373, 2005.
127. Ngamukote, S., Mäkynen, K., Thilawech, T., and Adisakwattana, S., Cholesterol-lowering activity of the major polyphenols in grape seed. *Molecules*, 16, 5054–5061, 2011.
128. Zanotti, I., Dall'Asta, M., Mena, P., Mele, L., Bruni, R., Ray, S., and Del Rio, D., Atheroprotective effects of (poly) phenols: A focus on cell cholesterol metabolism. *Food Funct.*, 6, 13–31, 2015.
129. Sugizaki, C., and Naves, M., Potential prebiotic properties of nuts and edible seeds and their relationship to obesity. *Nutrients*, 10, 1645, 2018.
130. Fu, J., Bonder, M.J., Cenit, M.C., Tigchelaar, E.F., Maatman, A., Dekens, J.A., Brandsma, E. et al., The gut microbiome contributes to a substantial proportion of the variation in blood lipids. *Circ. Res.*, 117, 817–824, 2015.
131. Tomás-Barberán, F.A., Selma, M.V., and Espín, J.C., Interactions of gut microbiota with dietary polyphenols and consequences to human health. *Curr. Opin. Clin. Nutr. Metab. Care.*, 19, 471–476, 2016.
132. Watanabe, M., Houten, S.M., Mataki, C., Christoffolete, M.A., Kim, B.W., Sato, H., Messaddeq, N. et al., Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature*, 439, 484–489, 2006.
133. den Besten, G., Bleeker, A., Gerding, A., van Eunen, K., Havinga, R., van Dijk, T.H., Oosterveer, M.H. et al., Short-chain fatty acids protect against high-fat diet-induced obesity *via* a PPAR[gamma]-dependent Switch from lipogenesis to fat oxidation. *Diabetes*, 64, 2398–2408, 2015.
134. Ros, E., Health benefits of nut consumption. *Nutrients*, 2, 652–682, 2010.
135. Luu, H.N., Blot, W.J., Xiang, Y.-B., Cai, H., Hargreaves, M.K., Li, H., Yang, G. et al., Prospective evaluation of the association of nut/peanut consumption with total and cause-specific mortality. *JAMA Intern. Med.*, 175, 755–766, 2015.
136. Wien, M., Oda, K., and Sabaté, J., A randomized controlled trial to evaluate the effect of incorporating peanuts into an American Diabetes Association meal plan on the nutrient profile of the total diet and cardiometabolic parameters of adults with type 2 diabetes. *Nutr. J.*, 13, 1–10, 2014.
137. Jones, J.B., Provost, M., Keaver, L., Breen, C., Ludy, M.-J., and Mattes, R.D., A randomized trial on the effects of flavorings on the health benefits of daily peanut consumption. *Am. J. Clin. Nutr.*, 99, 490–496, 2014.

138. Lokko, P., Lartey, A., Armar-Klemesu, M., and Mattes, R.D., Regular peanut consumption improves plasma lipid levels in healthy Ghanaians. *Int. J. Food Sci. Nutr.*, 58, 190–200, 2007.
139. Azad, B.J., Daneshzad, E., and Azadbakht, L., Peanut and cardiovascular disease risk factors: A systematic review and meta-analysis. *Crit. Rev. Food Sci. Nutr.*, DOI: 10.1080/10408398.2018.1558395.
140. O'Byrne, D.J., Knauft, D.A., and Shireman, R.B., Low fat-monounsaturated rich diets containing high-oleic peanuts improve serum lipoprotein profiles. *Lipids*., 32, 687–695, 1997.
141. Kris-Etherton, P.M., Pearson, T.A., Wan, Y., Hargrove, R.L., Moriarty, K., Fishell, V., and Etherton, T.D., High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. *Am. J. Clin. Nutr.*, 70, 1009–1015, 1999.
142. Hayes, D., Angove, M.J., Tucci, J., and Dennis, C., Walnuts (*Juglans regia*) chemical composition and research in human health. *Crit. Rev. Food Sci. Nutr.*, 56, 1231–1241, 2016.
143. Kim, Y., Keogh, J., and Clifton, P., Nuts and cardio-metabolic disease: A review of meta-analyses. *Nutrients*, 10, 1935, 2018.
144. Curb, J.D., Wergowske, G., Dobbs, J.C., Abbott, R.D., and Huang, B., Serum lipid effects of a high–monounsaturated fat diet based on macadamia nuts. *Arch. Intern. Med.*, 160, 1154–1158, 2000.
145. Griel, A.E., Cao, Y., Bagshaw, D.D., Cifelli, A.M., Holub, B., and Kris-Etherton, P.M., A macadamia nut-rich diet reduces total and LDL-cholesterol in mildly hypercholesterolemic men and women. *J. Nutr.*, 138, 761–767, 2008.
146. Lefevre, M., Champagne, C.M., Tulley, R.T., Rood, J.C., and Most, M.M., Individual variability in cardiovascular disease risk factor responses to low-fat and low-saturated-fat diets in men: Body mass index, adiposity, and insulin resistance predict changes in LDL cholesterol. *Am. J. Clin. Nutr.*, 82, 957–963, 2005.
147. Simonen, P., Gylling, H., Howard, A.N., and Miettinen, T.A., Introducing a new component of the metabolic syndrome: Low cholesterol absorption. *Am. J. Clin. Nutr.*, 72, 82–88, 2000.
148. Knopp, R.H., Retzlaff, B., Fish, B., Walden, C., Wallick, S., Anderson, M., Aikawa, K. et al., Effects of insulin resistance and obesity on lipoproteins and sensitivity to egg feeding. *Arter. Thromb. Vasc. Biol.*, 23, 1437–1443, 2003.
149. Ellis, P.R., Kendall, C.W., Ren, Y., Parker, C., Pacy, J.F., Waldron, K.W., and Jenkins, D., Role of cell walls in the bioaccessibility of lipids in almond seeds. *Am. J. Clin. Nutr.*, 80, 604–613, 2004.
150. Hollis, J., and Mattes, R., Effect of chronic consumption of almonds on body weight in healthy humans. *Br. J. Nutr.*, 98, 651–656, 2007.
151. McKiernan, F., Lokko, P., Kuevi, A., Sales, R.L, Costa N.M., Bressan J., Alfenas, R.C.G. et al. Effects of peanut processing on body weight and fasting plasma lipids. *Br. J. Nutr.*, 104, 418–426, 2010.
152. Schlörmann, W., Birringer, M., Böhm, V., Löber, K., Jahreis, G., Lorkowski, S., Müller, A.K. et al., Influence of roasting conditions on health-related compounds in different nuts. *Food Chem.*, 180, 77–85, 2015.
153. Coelho, S.B., de Sales, R.L., Iyer, S.S., Bressan, J., Costa, N.M.B., Lokko, P., and Mattes, R., Effects of peanut oil load on energy expenditure, body composition, lipid profile, and appetite in lean and overweight adults. *Nutrition*, 22, 585–592, 2006.

154. Zhang, J., Grieger, J.A., Kris-Etherton, P.M., Thompson, J.T., Gillies, P.J., Fleming, J.A., and Heuvel, J.P.V., Walnut oil increases cholesterol efflux through inhibition of stearoyl CoA desaturase 1 in THP-1 macrophage-derived foam cells. *Nutr. Metab.*, 8, 61, 2011.
155. Bitok, E., Jaceldo-Siegl, K., Rajaram, S., Serra-Mir, M., Roth, I., Feitas-Simoes, T., Ros, E. et al., Favourable nutrient intake and displacement with long-term walnut supplementation among elderly: Results of a randomised trial. *Br. J. Nutr.*, 118, 201–209, 2017.
156. Bitok, E., Rajaram, S., Jaceldo-Siegl, K., Oda, K., Sala-Vila, A., Serra-Mir, M., Ros, E. et al., Effects of long-term walnut supplementation on body weight in free-living elderly: Results of a randomized controlled trial. *Nutrients*, 10, 1317, 2018.
157. Sabaté, J., Cordero-MacIntyre, Z., Siapco, G., Torabian, S., and Haddad, E., Does regular walnut consumption lead to weight gain? *Br. J. Nutr.*, 94, 859–864, 2005.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 4

Nuts and Cardio-Metabolic Syndrome (Endothelial Function, Inflammation, and Blood Pressure)

Pablo Hernández-Alonso, Marta Guasch-Ferré, Mònica Bulló, and Jordi Salas-Salvadó

4.1 Introduction 92
4.2 Health Benefits of Nut Consumption 93
4.2.1 Epidemiological Studies 93
4.2.2 *In Vitro* and *In Vivo* Animal Studies 96
4.2.2.1 Experimental Studies with Whole Nuts 96
4.2.2.2 Lipid Profiles of Nuts 97
4.2.2.3 Antioxidants in Nuts 97
4.2.2.4 Nut Extracts and Skins 98
4.2.2.5 Putative Mechanisms: Beneficial Effects of Nut Consumption on Inflammation and Endothelial Function/Blood Pressure Modulation 98
4.2.3 Human Intervention Studies 100
4.2.3.1 Acute Clinical Trials 100
4.2.3.2 Chronic Clinical Trials 105
4.3 Conclusion 116
References 117

4.1 Introduction

Nuts are a matrix of several bioactive compounds that exhibit a number of health benefits. Their unique nutritional profiles rich in mono- and polyunsaturated fatty acids (MUFA and PUFA), fiber, various minerals (e.g., potassium, calcium, and magnesium), vitamins (e.g., vitamin E), and phytochemicals with powerful antioxidant effects suggests a potential role in the modulation of inflammation (including oxidative-related processes), endothelial function (EF), and blood pressure (BP). In this regard, several cardio-metabolic disorders may benefit from their unique nutritional profiles. In this chapter, we focus on the health effects of nut consumption on parameters related to inflammation, EF, and BP, all of which are altered in the metabolic syndrome (MetS) [1].

Inflammation is a key early stage of many metabolic disorders and of the atherosclerotic process. Several inflammatory markers have been identified as independent predictors of different metabolic conditions in human prospective studies [2]. Chronic low-grade inflammation has been closely linked to the genesis and progression of insulin resistance (IR) and endothelial dysfunction (ED). The latter refers to the impairment of endothelium-dependent vasodilatation, implies widespread abnormalities in endothelial integrity and homeostasis, and is one of the mechanisms involved in the etiology and development of atherosclerosis. The endothelium maintains circulation and blood flow, regulates vascular tone, and modulates leukocyte and platelet adhesion to the endothelium and the transmigration of leukocytes into the sub-endothelial space. The most traditional and widely accepted view is that hypertension is a cause rather than a consequence of ED, although some authors suggest that the reverse may also be true.

Scientific evidence supports the hypothesis that dietary factors are important in modulating oxidation, inflammation, and EF. With this scenario, because several nut components have been shown to influence inflammation *in vivo*, the regular consumption of nuts could protect against the possible consequences of low-grade inflammation and ED.

In clinical practice and research studies, the most common technique used to evaluate EF is flow-mediated dilatation (FMD) of the brachial artery [3]. However, its application in practice requires a highly experienced operator, and comparability in different settings is challenging. Recently, peripheral arterial tonometry (PAT) provides an alternative option for non-invasive measurement of EF [4]. Placed on a fingertip, it measures pulse arterial volume changes induced by upper-arm cuff occlusion and generates the reactive hyperemia index (RHI) automatically. Unlike the FMD measurement, RHI is operator-independent and easy to perform. Brachial-ankle pulse wave velocity (baPWV) is usually monitored in some clinical trials as it reflects arterial elasticity [5].

Circulating biomarkers may also be measured to assess endothelial activation and inflammatory processes. Soluble cellular adhesion molecules are secreted by the endothelium together with immune cells such as macrophages. They comprise inter-cellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. These molecules are useful for monitoring EF because they are usually increased in patients with cardiovascular disease (CVD) [6]. Moreover, common evaluation of inflammatory-related processes is performed by measuring cytokines. Blood cells secrete cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β, whereas adipocytes secrete adipokines

such as adiponectin and leptin. High sensitivity C-reactive protein (CRP), which is secreted mainly by hepatocytes, is also a standard measure of systemic low-grade inflammation.

Available data from different epidemiological, *in vitro/in vivo*, and randomized clinical trials involving nut consumption, inflammation, and EF/BP are reviewed in this chapter.

4.2 Health Benefits of Nut Consumption

4.2.1 Epidemiological Studies

Several epidemiological studies have analyzed the associations between nut consumption and biomarkers related to inflammation, oxidation, and EF. Nut consumption has also been associated with a lower risk of hypertension in prospective cohort studies. Table 4.1 summarizes the evidence from epidemiological studies on nut consumption, inflammation, EF, and BP.

The EF biomarkers most commonly assessed in epidemiological studies include the circulating levels of VCAM-1, ICAM-1, and IL-6. Some clinical trials have included direct measurements of EF in the vascular bed, such as FMD of the brachial artery or PAT to obtain the RHI. As an illustration, in a cross-sectional study involving 772 individuals at high cardiovascular risk, participants in the highest tertile of mixed-nut consumption (hazelnuts, almonds, and walnuts) showed the lowest circulating levels of VCAM-1 and ICAM-1 together with lower concentrations of high-sensitivity CRP and IL-6 [7]. However, only ICAM-1 displayed a significant inverse association with a higher intake of nuts. Similarly, no significant associations between total nut consumption and the plasma biomarkers ICAM-1 and VCAM-1 were observed in a prospective study of 6,309 women from the Nurses' Health Study (NHS) followed for 22 years [8].

Most epidemiological studies usually include CRP, IL-6, fibrinogen, and adiponectin as inflammatory markers. The first epidemiological study examining these biomarkers was conducted in 2005 within the framework of the Multi-Ethnic Study of Atherosclerosis (MESA), a cross-sectional analysis of 6,080 participants which showed that total nut and seed consumption was inversely associated with circulating concentrations of CRP, IL-6, and fibrinogen [9]. After adjusting for potential confounders, mean concentrations of CRP decreased from 1.97 mg/L in subjects who rarely or never ate nuts and seeds to 1.71 mg/L in those consuming nuts and seeds ≥ 5 times/week (P for trend = 0.003). Corresponding adjusted mean concentrations of IL-6 and fibrinogen decreased from 1.25 to 1.14 pg/mL (P for trend = 0.003) and from 343 to 331 mg/dL (P for trend = 0.003), respectively [9]. However, these associations were attenuated when the models were further adjusted for body mass index (BMI). In another cross-sectional study involving 987 women with type-2 diabetes (T2D) from the NHS, greater adherence to the Mediterranean diet (MedDiet) was associated with higher concentrations of adiponectin, a potent anti-inflammatory cytokine originating in adipose tissue. Nuts, among other food groups, showed the strongest associations with adiponectin levels [10].

Thus far, five prospective cohort studies have evaluated the associations between nut consumption and the incidence of hypertension. Four studies found significant associations between nut consumption and a lower risk of hypertension

Table 4.1 Summary of Epidemiological Studies Evaluating Nut Consumption, Endothelial Function, Blood Pressure, and/or Inflammation

Study Name	*Number of Participants*	*Years of Follow-Up*	*Type of Nuts*	*Findings Related to EF, BP, and/or Inflammation*	*References*
CARDIA	4,304	15	Total nut consumption.	Total nut consumption was inversely associated with elevated BP (e.g., incident systolic BP > or = 130 mm Hg, diastolic BP > or = 85 mm Hg, or use of antihypertensive medication). HR for tertile 3 compared to tertile 1: HR (95% CI): 0.85 (0.72, 0.99); *P* for linear trend = 0.04.	[11]
MESA	6,080	Cross-sectional	Total nut & seed consumption.	Nut consumption was inversely associated with peripheral concentrations of CRP, IL-6, and fibrinogen.	[9]
NHS I	987 T2D women	Cross-sectional	Adherence to Mediterranean-type diet.	Greater adherence to a Mediterranean diet was associated with higher concentrations of plasma adiponectin (a potent anti-inflammatory cytokine originating in adipose tissue). Alcohol, whole grains, and nuts showed the strongest associations.	[10]
PREDIMED	339 men & 433 women	Cross-sectional	Adherence to Mediterranean-type diet.	Subjects in the highest tertile of nut consumption showed the lowest VCAM-1, ICAM-1, CRP, and IL-6 serum concentrations, although this association was only significant for ICAM-1.	[7]
Physicians' Health Study I	15,966	15	Total nut consumption.	Compared to subjects who did not consume nuts, multivariable adjusted HR (95% CI) for hypertension were 0.97 (0.91–1.03), 0.98 (0.92–1.05), 0.96 (0.89–1.03), and 0.82 (0.71–0.94) for nut consumption of 1–2 times/m and 1, 2–6, and > or = 7 times/week, respectively.	[12]

(*Continued*)

Table 4.1 (Continued) Summary of Epidemiological Studies Evaluating Nut Consumption, Endothelial Function, Blood Pressure, and/or Inflammation

Study Name	*Number of Participants*	*Years of Follow-Up*	*Type of Nuts*	*Findings Related to EF, BP, and/or Inflammation*	*References*
NHS	6,309	22	Total nut consumption.	No association of nut consumption with plasma biomarkers ICAM-1 and VCAM-1.	[8]
SUN	9,919	4.3	Total nut consumption.	No associations were observed between nut consumption and incidence of hypertension after adjusting for sex, age, and other dietary and non-dietary potential confounders (HR for those in the highest *versus* lowest nut consumption category = 0.77 [CI 95%: 0.46–1.30] P = 0.795).	[15]
ARIC study	9,913	9	Total nut consumption.	Nut consumption was inversely associated with incident hypertension (HR for those in the highest *versus* lowest nut consumption category = 0.87 [IC 95%: 0.77-0.97] P = 0.002).	[13]
NutriNet-Santé	80,426	3.4	Total nut consumption.	Nut consumption was inversely associated with hypertension. HR for quartile 4 compared to quartile 1: 0.72 (0.67, 0.89).	[14]

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults Study; CI, confidence interval; CRP, C-reactive protein; EF, endothelial function; HR, hazard ratios; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukine-6; MESA, Multi-Ethnic Study of Atherosclerosis; NHS, Nurses' Health Study; PREDIMED, Prevención con Dieta Mediterránea; SUN, Seguimiento Unidad de Navarra; T2D, type-2 diabetes; VCAM-1, vascular cell adhesion protein 1.

[11–14], while one study reported no relationship [15]. These prospective studies included large sample sizes ranging from 4,304 to 80,426 participants, with follow-up times ranging from 3.4 to 15 years. A 15%–28% lower risk of hypertension was observed in individuals in the highest nut-consumption categories compared to those in the lowest (Table 4.1).

In short, evidence from epidemiological studies suggests that nut consumption may have beneficial effects on EF and inflammatory biomarkers, but clearly, more prospective studies with large sample sizes are warranted to confirm these associations. In addition, consistent evidence from prospective cohort studies suggests that total nut consumption is inversely associated with the incidence of hypertension.

4.2.2 In Vitro *and* In Vivo *Animal Studies*

Results from *in vitro* and *in vivo* studies have provided a broad range of evidence regarding the beneficial effects of nut consumption on different health outcomes, such as hyperlipidemia and T2D [16]. However, the specific evaluation of the effect of nuts – or their components – in cell cultures or animal models on the modulation of parameters related to inflammation, EF, and BP is limited. Most of the published evidence has focused on inflammation and derives from assays using nut extracts or polyphenols (e.g., resveratrol or ellagic acid), which are present in nuts but also in other food groups. Almost all the available research on this topic has focused on extracts from non-edible parts, such as the peel, leaves, stems, and roots, and rarely on the kernel. An in-depth analysis of the healthful properties of non-edible parts of nuts is beyond the scope of this review, which focuses on studies that evaluate specific nutrients (e.g., polyphenols) or edible parts in traditional nuts in relation to inflammation, EF, and BP outcomes.

4.2.2.1 Experimental Studies with Whole Nuts

Two studies in rats found increased antioxidant enzymatic activity in animals fed pistachios for 8 weeks [17,18]. In the first study, the rats were divided into three groups of 12 animals and assigned to a control group, fed a standard diet; and two pistachio groups, fed a standard diet containing 20% or 40% energy from pistachios. A significant increase in the activities of paraoxonase/arylesterase 1 (PON1) and arylesterase – both markers of antioxidant capacity – was observed in the two groups with pistachio-supplemented diets compared to the control group after 10 weeks' intervention [17]. In the second study, the rats were assigned a control diet (standard commercial chow); a control diet supplemented with 1.26% energy intake in the form of pistachios; a control diet with 1.63% cholesterol, 0.41% cholic acid, and 16.3% sunflower oil (hyperlipidemic diet); or a hyperlipidemic diet supplemented with 1.26% energy intake in the form of pistachios. After 8 weeks, the rats on the hyperlipidemic diet supplemented with pistachios had higher total antioxidant activity, as determined by thiobarbituric acid-reactive substances (TBARS), compared to rats fed the hyperlipidemic diet alone [18].

Another study involving 19-month-old rats fed a 6% or 9% walnut diet, approximately equivalent to a human eating 28 g or 42 g, reported a significant inhibition of the activation or phosphorylation of P38-mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) in brain tissues. Because both molecules are

involved in the inflammatory response, these results suggest a potential attenuation of inflammatory genes mediated by nuts [19].

4.2.2.2 Lipid Profiles of Nuts

Several *in vitro* studies have suggested that the healthy properties of nuts can be attributed in part to their high content in dietary unsaturated fatty acids. Zhao et al. [20] showed that α-linolenic, linoleic, and docosahexaenoic acids were able to reduce the *Escherichia coli* lipopolysaccharide-stimulated production of IL-6, IL-1β, and TNF-α in a dose-dependent manner in THP-1 cells compared to palmitic acid. Contingent upon its content, walnut oil has shown both anti-inflammatory and pro-inflammatory properties in a monocytic cell line, depending on concentration and length of incubation, which suggests that it can diminish oxidative stress and modulate inflammation [21]. Importantly, oleic acid and peanut oil high in oleic acid were able to enhance insulin production in the INS-1 cell line, and oleic acid was able to reverse the inhibition of insulin production by TNF-α. These findings suggest that a diet high in oleic acid – easily achieved through consumption of peanuts, tree nuts other than walnuts, and olive oil – can have a beneficial effect reversing the negative effects of the inflammatory cytokines present in the circulation in metabolic disturbances [22].

4.2.2.3 Antioxidants in Nuts

As nuts are an antioxidant-rich matrix, research has focused on evaluating some of their most important antioxidants (see Chapter 2 for details). The efficacy of raw and roasted nut antioxidants to counteract oxidative stress was assessed by measuring the ability of free polyphenol nut extracts to inhibit the oxidation of lower density lipoproteins (low-density lipoprotein [LDL] plus very low-density lipoprotein [VLDL]). Walnut polyphenols showed the best efficacy of the nuts tested, as well as the highest lipoprotein-bound antioxidant activity [23]. A recent study investigated whether polyphenol extracts from natural raw shelled pistachios and roasted salted pistachio kernels have anti-inflammatory and antioxidant properties at lower doses than reported previously. The monocyte/macrophage cell line J774 was used to assess the extent of protection by raw shelled and roasted salted pistachios against lipopolysaccharide (LPS)-induced inflammation. The results demonstrated that pre-treatment with extracts from raw or roasted pistachios exerted significant protection against LPS-induced inflammation, as a reduction in TNF-α and IL-1β secretion was observed in a dose-dependent way. It was, therefore, shown that, at lower doses, the polyphenols present in pistachios do possess antioxidant and anti-inflammatory properties [24].

Specific polyphenols such as ellagic acid and resveratrol have been widely evaluated. Ellagic acid occurs naturally in fruits such as berries, nuts, and pomegranates, while resveratrol is mainly found in grapes and red wine, but also in some plants and fruits such as peanuts, pistachios, and cranberries [25]. Recently, researchers have begun to show a possible involvement of ellagic acid in the inflammatory cascade through the inhibition of cyclooxygenase (COX) protein expression, as well as anti-inflammatory effects *in vivo* in mice [26]. Moreover, resveratrol seems to protect against oxidative stress-induced ED in the aortas of diabetic mice by inhibiting TNF-α-induced activation [27]. Another phenolic compound, chlorogenic acid, which is found in coffee, apples, almonds, and artichokes, has also been

investigated. Chang et al. [28] showed that chlorogenic acid dose-dependently suppressed IL-1β-induced mRNA expression of VCAM-1, ICAM-1, and endothelial cell selectin in human umbilical vein endothelial cells (HUVEC). This anti-inflammatory activity of chlorogenic acid in HUVEC suggests that it could be useful in the prevention of atherosclerosis.

4.2.2.4 Nut Extracts and Skins

Gentile et al. [29] evaluated the effects of a hydrophilic nut extract (HPE) from *Pistacia vera* on the production of reactive oxygen species (ROS) in RAW 264.7 macrophage cells. A dose-dependent decrease in LPS-induced ROS production was observed when cells were incubated with different concentrations of HPE, suggesting that proanthocyanidins are bioactive components responsible for this effect. HPE suppressed nitric oxide (NO) and TNF-α production, inhibited prostaglandin E2 (PGE2) release, and decreased cyclooxygenase-2 (COX-2) content. Similarly, the incubation of RAW 264.7 murine macrophages with a pistachio oil extract for 24 hours decreased some LPS-induced inflammatory markers such as interferon-induced protein with tetratricopeptide repeats 2 (Ifit-2), TNF-α, and IL-6, together with the expression of TNFα, IL-6, and IL-1β [30].

Willis et al. [31] generated a methanolic extract of English walnuts (*Juglans regia*) and examined the effects of walnut extract exposure on LPS-induced activation in BV-2 microglial cells. They showed that walnut extract induced a decrease in TNF-α production, showing anti-inflammatory effects in microglia. THP-1 cell monocytes were incubated with peanut extract (24% phenolic acid, 37% flavanols, and 39% flavonols) for 1 hour and then stimulated with LPS for 4 hours. Polyphenol-rich peanut extract significantly reduced extracellular LPS-induced TNF-α protein secretion by inhibiting the c-Jun transcription factor, suggesting a potent anti-inflammatory effect [32]. In a recent study, gene expression profiles associated with inflammation (IL6, inducible nitric oxide synthase [iNOS], and COX-2) were characterized in LPS-stimulated RAW 264.7 macrophages after treatment with pistachio extracts. Skin and kernel polar extracts were the most potent components inhibiting the expression of COX-2. The skin non-polar extract had the strongest effect in decreasing the non-mitochondrial oxidative burst associated with inflammatory responses in macrophages [33].

4.2.2.5 Putative Mechanisms: Beneficial Effects of Nut Consumption on Inflammation and Endothelial Function/Blood Pressure Modulation

Nuts, as a complex food matrix, contain diverse macro- and micronutrients and other bioactive components that could have beneficial effects in several health outcomes. Through different mechanisms, certain components of nuts such as unsaturated fatty acids, minerals (e.g., magnesium, potassium, and calcium), fiber, L-arginine, antioxidants, and the low sodium content may synergically protect against inflammation and/or EF/BP (Figure 4.1).

There is a close connection between systemic markers of mild inflammation and the progression of ED, elevated BP, and atherosclerotic disease [34], and the set of bioactive compounds contained in nuts could partly explain their protective antioxidant and anti-inflammatory properties [16]. As described earlier, nuts are a

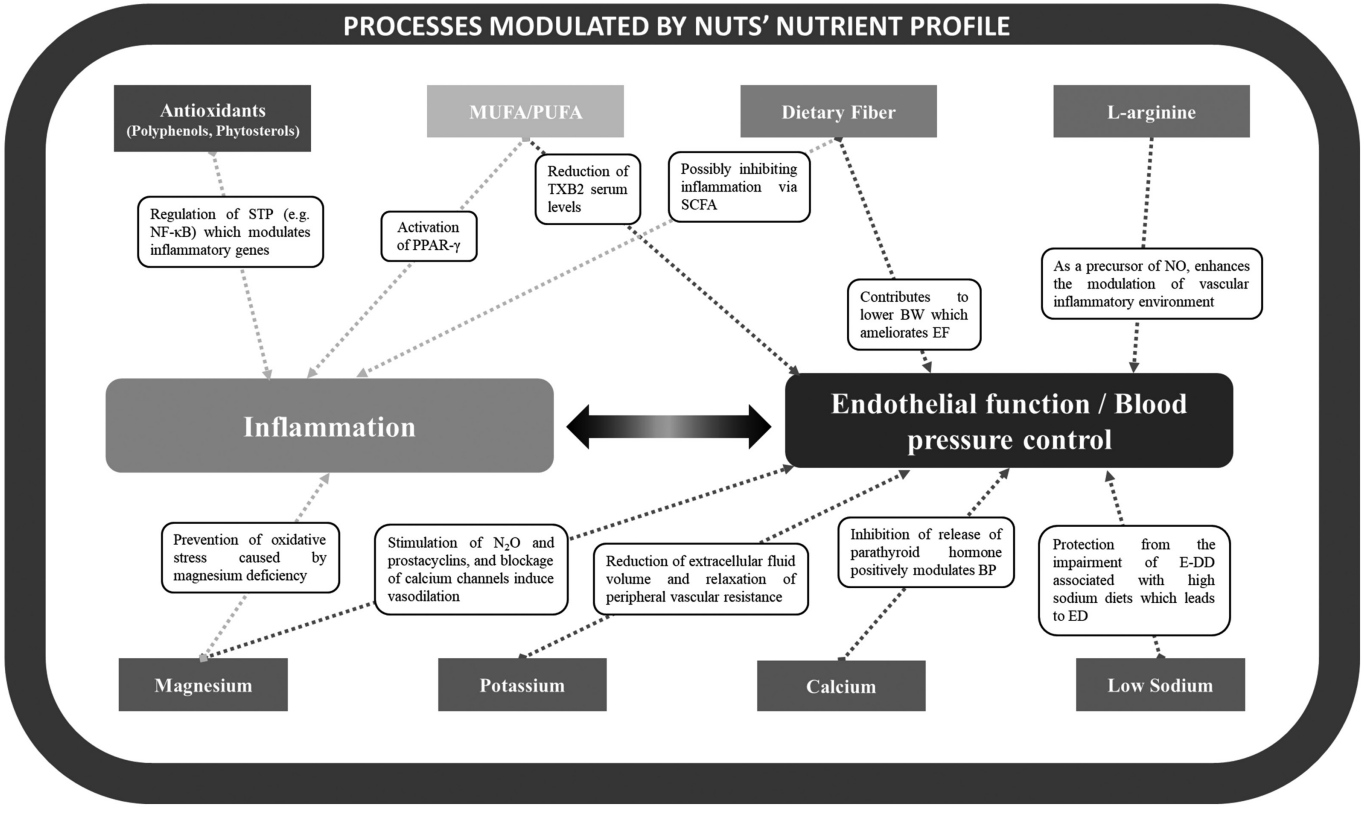


Figure 4.1 Mechanisms linking nut consumption to modulation of inflammation and endothelial function parameters. *Abbreviations*: BP, blood pressure; BW, body weight; ED, endothelial dysfunction; E-DD, endothelium-dependent dilation; EF, endothelial function; MUFA, monounsaturated fatty acids; NF-κB, nuclear factor kappa B; NO, nitric oxide; PPAR-γ, peroxisome proliferator-activated receptor-γ; PUFA, polyunsaturated fatty acids; SCFA, short-chain fatty acids; STP, signal transduction pathways; TXB2, thromboxane B2.

rich source of several types of antioxidants, such as polyphenols (e.g., flavonoids) and tocopherols. The intake of antioxidants may play a relevant role in modulating inflammation through both their antioxidant action and the modulation of signal transduction pathways such as the NF-κB and ensuring regulation of inflammatory genes in macrophages and endothelial cells [25].

Nuts are high in unsaturated fatty acids. Walnuts are rich in PUFA, while almonds and hazelnuts contain high levels of MUFA (see Chapter 2 for details). The beneficial anti-inflammatory effects of unsaturated fats have been widely described. For example, α-linolenic acid, an important component in walnuts, appears to elicit anti-inflammatory effects *via* activation of the peroxisome-proliferator activated receptor γ [35]. Both PUFA and MUFA were able to reduce serum levels of the vasoconstrictor thromboxane B2 (TXB2), which might influence BP regulation [36]. Regarding their mineral content, the low amount of sodium in nuts may protect against impairment of the endothelium-dependent dilation accompanying high sodium diets, which promote ED. Epidemiological data has shown that magnesium intake is inversely associated with systemic inflammation, ED, and metabolic conditions [37]. Magnesium intake stimulates the production of nitrous oxide (N_2O) and vasodilator prostacyclins and blocks calcium channels, thus inducing vasodilatation [37]. Moreover, potassium intake may decrease BP by reducing extracellular fluid volume, modulating the activity of the renin-angiotensin system, reducing angiotensin effects, relaxing vascular smooth muscle, and reducing peripheral vascular resistance [38]. Inadequate amounts of dietary calcium may cause blood calcium levels to drop and promote the release of parathyroid hormones that may negatively affect BP control [39].

The fiber content of nuts could lower postprandial glycemia and, through colonic fermentation, produce short-chain fatty acids that may inhibit inflammation. Furthermore, dietary fiber is purported to decrease BP by inducing satiety, decreasing energy intake, contributing to a lower body weight, and ameliorating EF [40]. The amino acid content of L-arginine, a precursor of NO, seems to modulate the vascular inflammatory and systemic hormonal environment, which, in turn, may have a positive effect on vascular EF [39].

To conclude, although the available evidence is still limited, a consistent beneficial effect of nut components in parameters related to inflammation, oxidation, and BP has been suggested. Further studies are needed in order to assay the nutrients from nuts in *in vitro/in vivo* models of ED and/or hypertension.

4.2.3 Human Intervention Studies

Results from human intervention studies consistently support previous findings derived from observational studies in large populations, studies conducted in experimental animals, and those obtained in *in vitro* assays.

4.2.3.1 Acute Clinical Trials

A total of seven acute crossover studies have evaluated the effects of nut consumption on EF/BP and/or inflammation in healthy, obese, MetS, or mild hypercholesterolemic subjects (Table 4.2). These studies mainly focused on walnuts [41–43], but evidence from almonds [44], pistachios [45], peanuts [46], and hazelnuts [47] is also

Table 4.2 Acute Studies Evaluating Nut Consumption, Endothelial Function, Blood Pressure, and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Type of Nut (Study Design)*	*Control Group*	*Intervention Group(s)*	*EF and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
Study group I: 12 (9/3) Healthy subjects (32 ± 8) Study group II: 12 (11/1) Hypercholesterolemic subjects (45 ± 13)	Walnuts Crossover	No control meal	25 g OO or walnuts added to an HF meal	In both study groups, FMD was worse after OO meal than after walnut meal.	Significantly lower E-selectin levels after the consumption of the walnut meal *versus* the OO meal.		[41][a]
20 (20/0) Healthy subjects (25 ± 4)	Almonds Crossover	CO	a) WA b) AO	Differences in peak reductions in peripheral augmentation index (measure of vascular tone) after the WA, AO, and CO meals were insignificant between meals.		Postprandial increase in plasma TAG was lower after the WA meal than after the AO and CO meals.	[44][b]
20 (20/0) ApoE3/E3 healthy subjects (nr)	Walnuts Crossover (1 breakfast meal after 4 weeks of intervention)	No control meal	Four weeks on: a) Western diet b) Mediterranean diet c) High CHO and vegetal n-3 FA diet Breakfasts: a) butter b) OO c) walnuts, respectively to each group		Significantly lower postprandial. IL-6 expression in PBMCs after consuming a walnut breakfast compared to OO or butter breakfasts. Butter breakfast increased TNF-α levels compared to OO and walnut breakfasts.		[42][c]

(*Continued*)

Table 4.2 (Continued) Acute Studies Evaluating Nut Consumption, Endothelial Function, Blood Pressure, and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Type of Nut (Study Design)*	*Control Group*	*Intervention Group(s)*	*EF and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
15 (9/6) Obese subjects with moderate hypercholesterolemia (49 ± 2)	Walnuts Crossover	No control group	a) 85 g whole walnuts b) 34 g de-fatted nutmeat c) 51 g walnut oil d) 5.6 g walnut skins	Walnut oil improved EF measured by PAT (RHI) and whole walnuts increased *in vitro* cholesterol efflux.		Postmeal FRAP response differed by treatment. 34 g defatted nutmeal treatment tended to lower mean FRAP compared to the oil and skin treatments.	[43][a]
20 (8/12) MetS subjects (Range: 40-65)	Pistachios Crossover	Study 1: 50 g of available CHOs a) WB1 b) WB, butter, and cheese Study 2: 12 g of available CHOs c) WB2	Study 1: white bread + 85 g PD1 Study 2: PD2	An intermediate change in EF measured by PAT (RHI) was observed after the WB plus pistachio meals that did not differ from the other 50 g available CHO meals. There was no difference in RHI between the two 12 g available CHO meals.		Both PD1 and PD2 meals significantly reduced postprandial glycaemia *versus* WB1 and WB2, respectively.	[45][a]
15 (15/0) Healthy obese subjects (Range: 20–65)	Peanuts Crossover	Control meal shake matched for energy and macronutrient content	Shake with peanuts (85 g)	Non-significant in FMD after the peanut shake.		Peanuts blunted serum TAG response at 120 and 240 min post-meal *versus* control meal.	[46][a]

(*Continued*)

Table 4.2 (Continued) Acute Studies Evaluating Nut Consumption, Endothelial Function, Blood Pressure, and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Type of Nut (Study Design)*	*Control Group*	*Intervention Group(s)*	*EF and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
22 Healthy subjects (31.2 ± 6.1)	Hazelnuts Crossover	NDT	a) HFM b) HFM + 40 g hazelnuts		Ox-LDL increased in HFM *versus* NDT and decreased in HFM + 40 g hazaelnuts *versus* McDM.		[47][c]

Abbreviations: AO, muffins with almond oil plus defatted almond flour; ApoE3, apolipoprotein E3; BP, blood pressure; CHO, carbohydrates; CO, muffins with 50 g sunflower oil blend; EF, endothelial function; F, female; FA, fatty acids; FMD, flow-mediated dilatation; FRAP, ferric reducing antioxidant potential; HF, high fat; HFM, high-fat diet; IL, interleukin; M, male; MetS, metabolic syndrome; NDT, no dietary treatment; nr, not reported; OO, olive oil; ox-LDL, oxidized low-density lipoprotein; PAT, peripheral arterial tonometry; PBMC, peripheral blood mononuclear cell; PD, pistachio diet; RHI, reactive hyperemia index; TAG, triacylglycerols; TNF-α, tumor necrosis factor-α; WA, muffins with almond macroparticles; WB, white bread.

[a] EF is the primary outcome.

[b] EF/BP and inflammation are secondary outcomes.

[c] Inflammation is primary outcome.

available. Four studies have evaluated EF/BP [41,43,45,46], and two others have analyzed inflammation [42,47] as primary outcomes. Another trial conducted with almonds investigated inflammation as a secondary outcome [44].

The study by Cortés et al. [41] compared the effects of high saturated fatty acid meals supplemented with either walnuts or olive oil (OO) on postprandial events in healthy or hypercholesterolemic subjects. They found a similar postprandial rise in inflammatory markers after the two meals, except for soluble E-selectin, which was lower after the walnut meal. They also reported that postprandial FMD was worse after the OO meal *versus* the walnut meal in both study groups. Berryman et al. [43] also evaluated acute walnut consumption in 15 obese and mildly hypercholesterolemic subjects. They reported that walnut oil favorably affected EF – as measured by an increase in both the RHI and the Framingham RHI – and whole walnut intervention increased *ex vivo* cholesterol efflux in J774 cells cultured with postprandial serum *versus* fasting baseline. On the other hand, two recent studies using other nuts and conducted in MetS and obese subjects found contradictory results [45,46]. Kendall et al. [45] reported an intermediate change in RHI after a meal with white bread plus 85 g of pistachios, even though it did not differ from the other available 50 g carbohydrate control meals. Liu et al. [46] found no significant modulation of FMD following a peanut shake (85 g peanuts) *versus* a control meal matched for energy and macronutrient content. Interestingly, both acute trials found further improvements in postprandial glycemia [45] and triacylglycerols (TAG) levels [46].

Studies evaluating acute nut consumption and inflammatory markers as the primary outcome have been conducted in healthy subjects [42,47], evaluating either walnuts or hazelnuts. Jiménez-Gómez et al. [42] conducted a trial in 20 healthy men consisting of 4 weeks following three different interventions (Western diet, Mediterranean diet, or high carbohydrate diet) and a vegetable n-3 fatty acid diet with a subsequent breakfast meal consisting of butter, OO or walnuts, respectively. The authors reported a significantly lower postprandial IL-6 expression in peripheral blood mononuclear cells (PBMC) after consuming a walnut breakfast compared to the OO and butter breakfasts. Moreover, the butter breakfast increased TNF-α levels compared to the OO and walnut breakfasts. Di Renzo et al. [47] recently evaluated the inclusion of 40 g hazelnuts in the context of a high-fat and high-saturated fat meal. They reported that oxidized low-density lipoprotein (ox-LDL) increased with the high-fat meal compared to no dietary treatment and decreased with the high-fat meal plus hazelnuts *versus* the high-fat meal alone.

Finally, Berry et al. [44] evaluated EF as a secondary outcome in a trial aiming to analyze postprandial lipid profiles after the consumption of almonds incorporated into muffins. Participants in treatment groups consumed almond microparticles or almond oil plus almond flour, while those in the control group consumed a muffin with a sunflower oil blend. The researchers failed to find any modulation in measures of vascular tone, but they did report that the postprandial increase in plasma TAG was lower after the meal with almond microparticles than after the other two test meals.

In conclusion, acute nut consumption seems to induce a reduction in the concentration of some inflammatory biomarkers, and walnut meals improve EF, but there is little evidence of any beneficial effect of other nuts. Even though there are several acute clinical trials involving EF/BP and/or inflammatory parameters in healthy or hypercholesterolemic individuals, there is a lack of studies evaluating

these outcomes in those with hypertension or T2D who might benefit more from the beneficial effect of different types of nuts on inflammatory and/or EF/BP markers.

4.2.3.2 Chronic Clinical Trials

Several clinical trials have evaluated the effect of different types of nuts or a combination of them on multiple parameters and/or biomarkers related to inflammation, EF, and BP (Table 4.3). The EF – measured as FMD, PAT, and/or circulating molecules – were the primary outcome in 15 randomized clinical trials (RCTs) [48–62], whereas biomarkers of inflammation were the primary outcome in 18 trials [50,56,57,62–76]. Additionally, another 17 trials have evaluated parameters related to EF, BP, and/or inflammation as secondary outcomes [77–93].

4.2.3.2.1 Clinical Trials Evaluating EF Several chronic RCTs have focused on EF parameters as primary or secondary outcomes (Table 4.3). The number of participants in these studies ranged from 15 to 372 and their baseline characteristics were variable, including healthy, obese, diabetic, and hypercholesterolemic individuals, and those with MetS and at high cardiovascular risk. Several types of nuts have been analyzed, such as pistachios, walnuts, peanuts, almonds, hazelnuts, and mixed nuts. Interventions ranged from 4 to 24 weeks, six studies were parallel, and 13 had a crossover design. Nut doses ranged from 10% to 20% of energy and were added to different types of diet and compared to control groups such as *ab libitum* diets, hypocaloric diets, low-fat diets, Western diets, average American diets, and lifestyle modifications.

Beneficial effects of nut consumption on EF were observed in five clinical trials [52–54,61,93]. FMD improved significantly after consumption of a walnut-enriched diet in three crossover studies, with diets being supplemented with 56 g/day, 16.4% of energy or 56 g/day of walnuts, respectively [53,54,58]. Importantly, significant improvements were also found in FMD following a walnut-supplemented diet with or without calorie regulation and compared to a walnut-free diet [93]. The intake of 80 g/day of in-shell pistachios plus lifestyle modification also showed significant improvements in baPWV and FMD compared to lifestyle modification alone [61].

Walnuts are the most studied nuts regarding effects on vascular reactivity, as assessed by FMD. For example, in a crossover feeding trial comparing a walnut-supplemented diet with an isoenergetic healthy MedDiet for 4 weeks each, Ros et al. [49] found improved EF through increased FMD and decreased VCAM-1 and ICAM-1 in 20 patients with hypercholesterolemia. Another crossover study conducted in normal to mildly hypercholesterolemic participants also showed that a walnut diet reduced ICAM-1 compared to a nut- and fish-free diet [57]. However, other RCTs observed no significant changes in EF after consumption of a walnut-enriched diet [56,89]. According to the authors, the differing results between studies are likely due to the length of the dietary interventions, differences in the baseline lipid profiles, and the fact that greater benefits in EF have been observed in hypercholesterolemic subjects as opposed to normocholesterolemic subjects. Biomarkers of EF, ICAM-1, and VCAM-1 were also slightly improved after the consumption of a walnut-enriched diet and a diet containing mixed nuts [52]. In fact, other RCTs evaluating different types of nuts, such as mixed nuts [50], almonds [67], and hazelnuts [71] have also observed beneficial effects of nut consumption on EF, measured as

Table 4.3 Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
40 (20/20) Healthy subjects (27 ± 5)	Walnuts Crossover (4 weeks per period)	Traditional Japanese meals provided.	12.5% energy from walnuts (52 g/day); traditional Japanese meals provided.	NS in BP.		Blood lipids were improved in the walnut diet.	[78][a]
27 (15/12) Hyperlipidemic subjects (64 ± 9)	Almonds Crossover (1 month per period)	147 g muffins.	a) 73 g almonds. b) 37 g almonds plus 75 g muffins.		Reduction of ox-LDL in the full-dose almond group *versus* control group. Failed to observe any effect on serum CRP levels.	Full dose of almonds exhibited the greatest lipid profile reduction.	[63][b]
65 (28/37) Overweight/obese subjects (53 ± 11)	Almonds Parallel (24 weeks)	Hypo-caloric isocaloric diet + complex carbohydrate-enriched formula.	Hypo-caloric isocaloric diet + 84 g/day almond supplement.	Decreased SBP in almond *versus* control group.			[48][c]
20 (8/12) Hypercholesterolemic subjects (Range: 26-75)	Walnuts Crossover (4 weeks per period)	Isocaloric MedDiet.	Isocaloric MedDiet + single dose of walnuts (18% of energy, 40–65 g/day).	NS on BP. Increased FMD in walnuts *versus* control group. Decreased VCAM-1 and ICAM-1 NS in walnuts *versus* control group.	Failed to observe any effect on serum CRP concentrations.	Blood lipids improved in intervention group.	[49][c]
28 (5/23) Healthy subjects (45 ± 7)	Walnuts Crossover (4 weeks per period)	Cholesterol-lowering meals provided low-fat diet plus canola oil cereal-enriched supplement.	20% of energy from walnuts (84 g/day); meals provided.	NS in BP.			[79][c]
34 (20/14) Hyperlipidemic subjects (58.4 ± 8.6)	Almonds Crossover (4 weeks per period)	Very low saturated fat diet.	a) Control diet plus 20 mg statin. b) Portfolio diet (14 g/1000 kcal of almonds).		No treatment reduced CRP levels. After subjects with high levels of CRP were excluded. CRP was reduced significantly in both statin and portfolio diets.		[64][b]

(*Continued*)

Table 4.3 (Continued) Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
772 (339/443) Subjects at high cardiovascular risk (Range: 55–80)	Mixed nuts Parallel (12 weeks)	*Ad libitum* low-fat diet.	a) *Ad libitum* MedDiet + mixed nuts (hazelnuts, almonds, and walnuts). b) *Ad libitum* MedDiet + olive oil.	Decreased VCAM-1 and ICAM-1 in MedDiet + nuts *versus* control group.	Decrease in plasma IL-6 concentrations in subjects randomized to both MedDiets compared to subjects in a low-fat diet group.		[50][b,c]
62 (28/34) MetS subjects (Range: 21–65)	Walnuts and cashews Parallel (8 weeks)	South-African isocaloric diet.	South-African isocaloric diet plus 20 of energy from: a) walnut supplement. b) cashew supplement (63–108 g/day).	NS in walnuts *versus* control group. NS in cashew *versus* control group.			[80][a]
372 (210/162) Subjects at high CHD risk (55–80)	Mixed nuts (hazelnuts, almonds, and walnuts) Parallel (12 weeks)	*Ab libitum* low-fat.	a) *Ad libitum* MedDiet + mixed nut supplement. b) *Ad libitum* MedDiet + VOO Supplement.	Decreased SBP and DBP in MedDiet + nuts or VOO *versus* control group.			[81][a]
17 (17/0) Hypercholesterolemic subjects (Mean: 54)	Macadamias Sequential feeding trial (4 weeks)	No control diet.	A dose of 40–90 g/day of macadamias (15% of energy intake).		Significant decreases in plasma concentrations of LTB_4 and oxidative stress (8-isoprostane).		[65][b]
15 (15/0) Hypercholesterolemic subjects (48 ± 8)	Hazelnuts Crossover (4 weeks per period)	Low fat, high-CHO diet.	Low-fat, high-CHO diet plus hazelnuts.	NS differences in FMD or aPWV.			[82][a]
64 (29/35) MetS subjects (45 ± 10)	Walnuts Parallel (8 weeks)	Control: meals provided percentage of energy from protein:carbohydrates:fat as follows: 20:47:33.	Meals provided 20% of energy from walnuts (63–108 g/day).	NS on BP.	No improvement in serum CRP concentrations.		[83][a]

(*Continued*)

Table 4.3 (Continued) Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
15 (11/4) Hypercholesterolemic subjects (60 ± 3)	Pistachios Crossover (4 weeks per period)	*Ab libitum*.	*Ab libitum* + pistachios (15% of energy) supplementation (57–85 g).	NS in BP.			[84][a]
23 (20/3) Hypercholesterolemic subjects (Range: 55–65)	Walnuts Crossover (6 weeks each period)	AAD: 2.3 g of ALA and 22.1 g of LA.	a) LA: diet high in LA (10.6 g of ALA and 37.6 g of LA). b) ALA: diet high in ALA (19.1 g of ALA and 30.8 g of LA). These were derived from walnuts, walnut oil, and flaxseed oil.		ALA diet inhibited the PBMC production of IL-6, IL-1β, and TNF-α and decreased serum TNF-α concentrations, compared to the AAD.		[66][b]
21 (21/0) Healthy subjects (Range: 55–75)	Walnuts Crossover (8 weeks per period)	American isocaloric diet.	American isocaloric diet + 75 g/day walnut supplement.	NS in BP.			[85][a]
54 (54/0) Hypercholesterolemic subjects (25–65)	Peanuts Crossover (4 weeks per period)	*Ab libitum* diet.	*Ab libitum* diet + 75 g peanuts (20% of energy; roasted and lightly salted).	NS on BP.		Blood lipids were improved after the peanut diet.	[51][c]
50 (28/22) MetS subjects (Range: 18–65)	Mixed nuts Parallel (12 weeks)	*Ab libitum* low fat.	*Ad libitum* low-fat diet + mixed nut supplement (walnuts + almonds + hazelnuts).	NS on BP. ICAM-1 decreased during nut diet but NS were observed among treatments. NS effects were shown in Endo-PAT measurements.		NS on oxidative stress.	[52][c]

(*Continued*)

Table 4.3 (Continued) Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
21 (9/12) T2D subjects (58 ± 9)	Walnuts Crossover (8 weeks per period)	*Ab libitum*.	*Ab libitum* + 56 g walnuts.	FMD improved significantly after consumption of the walnut-enriched diet. Increased SBP and DBP in walnuts *versus* control group.		Blood lipids were improved after the walnut diet.	[53][c]
25 (11/14) Healthy subjects (41 ± 13)	Almonds Crossover (4 weeks per period)	Nut-free heart-healthy diet.	Control diet with isoenergetic replacement of almonds: a) 10%, low-almond diet. b) 20%, high-almond diet.	Reduction of E-selectin as the percentage of energy from almonds increased.	CRP was lower in both almond diets *versus* control diet. No effect on IL-6.		[67][b]
20 (20/0) Hypercholesterolemic subjects (49±2)	Walnuts Crossover (18 weeks)	Average American diet.	Alfa-linolenic acid diet from walnuts and walnut oil (walnuts, 16.4% of energy).	Walnut diet reduced DBP. FMD increased (34%) compared to control.			[54][c]
65 (17/48) Subjects with pre-D (53 ± 10)	Almonds Parallel (16 weeks)	American Diabetic Association diet.	American Diabetic Association diet + 56 g almonds (raw or dry roasted).	NS on BP.			[55][c]
122 (53/69) MetS subjects (Range: 25–65)	Walnuts Parallel (12 weeks)	Lifestyle Counseling based on AHA guidelines.	Lifestyle Counseling based on AHA guidelines plus isocaloric bread of 100 g weight (30 g walnuts).	BP decreased from baseline in the walnut-enriched group.		Blood lipids were improved but glucose parameters were not affected.	[86][a]

(*Continued*)

Table 4.3 (Continued) Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
50 (28/22) MetS subjects (Range: 18–65)	Mixed nuts Parallel (3 months)	Prudent nut-free diet.	Prudent diet supplemented with 30 g/day of nuts (15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts).	Reduction of SBP and DBP in both interventions *versus* baseline.	Reduction of IL-6 in the nut group *versus* the control group.	Improvement in insulin resistance after nut consumption *versus* control diet.	[68][b]
18 (9/9) Hypercholesterolemic subjects (56 ± 13)	Walnuts/ almonds Crossover (4 weeks per period)	No control group.	Replacement of 40% of the fat in the background diet with VOO, walnuts, or almonds.	No changes in BP.	Inflammatory markers were unaffected.	Reduction of LDL-C in all the groups.	[87][a]
30 (30/0) Healthy subjects (23±3)	Walnuts Crossover (4 weeks per period)	*Ab libitum* diet.	*Ab libitum* diet + 15 g walnuts.	NS on BP.		Blood lipids were not affected by walnut diet.	[77][a]
15 (9/6) Obese and MetS subjects (58 ± 2.5)	Walnuts Crossover (4 days per period)	Isocaloric diet plus liquid meal.	48 g/day of walnuts incorporated into a liquid meal.	No significant changes in s-ICAM-1 and 3, VCAM-1, E-selectin, and P-selectin after nut consumption.	Nut intake did not alter levels of CRP, IL-6, and IL-8 or TNF-α.		[56][b,c]
113 (46/67) Pre-hypertensive and hypercholesterolemic subjects (54 ± 9.9)	Hazelnuts Parallel (4 weeks)	Cocoa cream (control) added to a low-SF diet.	Cocoa cream products added to a low-SF diet: a) cocoa + hazelnut cream (30 g/day hazelnuts). b) Diet a + phytosterols (2 g/day). c) Diet b + soluble fiber (20 g/day).	Diet (a) showed a reduction in SBP *versus* control diet.	Diet (c) reduced CRP and ox-LDL levels compared to control diet.	Lipid profiles were improved in diet (b) and (c) *versus* the control diet.	[69][b]

(*Continued*)

Table 4.3 (Continued) Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
25 (14/11) Normal to mildly hyperlipidemic subjects (Range: 23–65)	Walnuts Crossover (4 weeks per period)	Nut- and fish-free diet.	Nut group: 42.5 g walnuts per 2412 kcal 6 times/week. Fish group: 113 g fatty fish per 2412 kcal 2 times/week.	Walnut diet reduced s-ICAM-1 *versus* control diet.	No effect of nuts on IL-1β, IL-6, TNF-α, or CRP.	Walnut and fish diets inhibited concentrations of PGEM and TXB2 *versus* control diet.	[57][b,c]
40 (18-28) Overweight with MetS subjects (57 ± 12)	Walnuts Crossover (8 weeks per period)	*Ab libitum*.	*Ab libitum* + 56 g of walnuts provided.	FMD improved during walnut-enriched diet compared to control. Beneficial trends in SBP.		Blood lipids were not affected by walnut diet.	[58][c]
28 Healthy, normal, or mild hypertension subjects (Range: 35–61)	Pistachios Crossover (4 weeks per period)	Low-fat diet.	Low-fat diet + 30 g/day (10 of energy) Low-fat diet + 60 g (20% of energy) pistachios (50% raw and 50% roasted and salted).	Significant reduction in SBP.			[59][c]
20 (9/11) T2D subjects (58 ± 2)	Almonds Crossover (4 weeks per period)	Control NCEP step II.	Approximately 56 g/day of almonds to replace 20% of energy.	Serum ICAM-1 and VCAM-1 were unaffected.	Almond diet decreased IL-6, CRP, and TNF-α compared to control diet.		[70][b]
107 (46/61) Overweight/obese subjects (42.5 ± 12.4)	Hazelnuts Parallel (12 weeks)	Nut-free.	30 g/day or 60 g/day of hazelnuts.	Tendency to improve VCAM-1 in the 60 g/day nut group *versus* the nut-free group ($P = 0.07$).	Non-significant changes in inflammatory markers.		[71][b]

(*Continued*)

Table 4.3 (Continued) Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
21 (7/14) HC subjects (44 ± 10)	Hazelnuts (49–86) Crossover (4 weeks per period)	Isocaloric control.	Hazelnut, 49–86 g/day, 18%–20% of total energy.	Hazelnut diet significantly improved FMD (56.6%) and reduce sVCAM-1 levels.	Ox-LDL and CRP improved after hazelnut diet.		[88][a]
20 (4/16) Healthy lacto-ovo-vegetarians subjects (38 ± 3)	Walnuts Crossover (8 weeks per period)	Control diet: habitual diet supplemented with standard egg (6/week).	Habitual diet supplemented with walnuts (28.4 g/week) or n-3 FA enriched egg (6/week).		No differences in inflammatory markers.	Walnuts lowered TAG, TC, and Apo B compared to standard egg but not to n-3 FA enriched egg diet.	[72][b]
10 (6/4) Healthy subjects (24.7 ± 3.4)	Brazil nuts Crossover (30 days per period)	No nuts.	5, 20, or 50 g Brazil nuts.		Portions of 20 or 50 g Brazil nuts caused a significant decrease of IL-1, IL-6, TNF- α, and IFN-γ, and an increase of IL-10 at both 1 day and 30 days post-intake.		[73][b]
68 (37/31) MetS subjects (42.5 ± 8.2)	Pistachios Parallel (6 months)	Standard control diet according to dietary guidelines for Asian Indians with exercise protocol.	Standard diet with exercise protocol supplemented with unsalted pistachios (20% of daily energy).		CRP and TNF-α levels were reduced following nut-diet *versus* nut-free diet.	Improvement in lipid profiles.	[74][b]
40 (10/30) Healthy subjects (60 ± 1)	Walnuts Crossover (8 weeks per period)	Western-type diet.	43 g/day of walnuts.	No significant changes in postprandial EF measured by PAT.	ICAM-1, VCAM-1, and IL-6 were unaffected.	Reduction in non-HDL-C after nut diet *versus* nut-free diet.	[89][a]

(*Continued*)

Table 4.3 (Continued) Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
65 (65/0) Overweight/obese subjects (Range: 18–50)	Peanuts Parallel (4 weeks)	Nut-free diet.	56 g/day of conventional peanuts or high-oleic peanuts.	No significant changes in BP.	IL-10 increased significantly in all groups. TNF-α increased in nut-free and conventional peanut groups. NS changes between groups.	TAG reduced in both peanut periods.	[75][b]
54 (29/25) Subjects with pre-diabetes (Mean [95% CI] 55 [53.4–56.8])	Pistachios Crossover (4 months per period)	Nut-free diet.	Pistachio diet was supplemented with 57 g/day of pistachios.	BP was not modified during pistachio diet.	Expression of IL-6 in lymphocytes was reduced during pistachio compared to control diet. Circulating levels were unchanged.	FBG, insulin, and HOMA-IR decreased significantly after the chronic pistachio period compared to the nut-free period.	[90][a]
60 (0/60) MetS subjects (and BMI ≥ 23 kg/m^2) (Range: 35–65)	Mixed nuts Parallel (6 weeks)	Nut-free group.	30 g/day of mixed nuts (walnuts, peanuts, and pine nuts).	EF measured by PAT remained unchanged.	ICAM-1, VCAM-1, and ox-LDL were not improved.	Lipid profiles were improved in the nut group.	[91][a]
44 (11/33) T2D subjects (Mean: 51)	Pistachios Crossover (3 months per period)	Previous diet without pistachios.	Two snacks of 25 g pistachios/day.	There were no significant changes in BP.	CRP levels did not differ between interventions.	Marked decrease in HbA_{1c} and FBG concentrations in the pistachio diet group compared to the control group.	[92][a]
61 (29/32) Overweight/obese subjects (65 ± 7)	High-oleic peanuts Crossover (12 weeks per period)	Nut-free diet.	15%–20% of energy from high-oleic peanuts.		No differences in CRP levels.	No effect on lipid profiles, glucose, or insulin levels.	[76][b]

(*Continued*)

Table 4.3 (Continued) Chronic Clinical Trials Evaluating Nut Consumption and Outcomes Related to Endothelial Function/Blood Pressure Modulation and Inflammation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*EF- and BP-Related Outcomes*	*Inflammation-Related Outcomes*	*Other Outcomes*	*References*
45 (18/27) CAD subjects (61.8 ± 8.6)	Almonds Crossover (6 weeks each period)	Nut-free NCEP Step 1 diet.	NCEP Step 1 diet with 85 g/day of almonds.	Almond diet did not alter vascular function* or BP. Tended to decrease VCAM-1 (P = 0.064).	Almond diet did not improve CRP, TNF-α, or E-selectin levels.		[60][a]
60 (46/14) Moderate hypercholesterolemic subjects (Range: 25–60)	Pistachios Parallel (12 weeks)	Lifestyle modification.	Lifestyle modification + 80 g in-shell pistachios.	NS on BP. Significant improvements in baPWV and improvements in BAFMD.			[61][a]
112 (31/81) Subjects with high risk of T2D (Range: 25–75)	Walnuts Parallel (6 months)	Walnut-free *ad libitum* diet.	56 g/day of walnuts: a) Without calorie regulation (*ad libitum*), or b) With calorie regulation (isocaloric condition).	Significant improvement in FMD following both walnut diets. NS differences between them.		TC and LDL-C were improved in both walnut diets.	[93][a]
30 (15/15) T2D subjects (56.1 ± 7.8)	Pistachios Crossover (4 weeks each period)	Nut-free diet.	20% of energy from pistachios.	FMD and PAT were not different between intervention groups.	Inflammatory markers were unchanged.	Lipid profiles were improved in the pistachio diet. Glucose levels were unmodified.	[62][b,c]

Note: *Assessed by measurements of FMD, peripheral arterial tonometry, and pulse wave velocity.

Abbreviations: AAD, Average American Diet; AHA, American Heart Association; ALA, α-linolenic acid; Apo B, apolipoprotein B; aPWV, aortic pulse wave velocity; BAFMD, brachial artery flow-mediated vasodilation; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CHO, carbohydrates; CRP, C-reactive protein; DBP, diastolic blood pressure; EF, endothelial function; Endo-PAT, endothelial and peripheral arterial tone; F, female; FA, fatty acids; FBG, fasting blood glucose; FMD, flow-mediated dilation; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; ICAM-1, secretory intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL, interleukin; LA, linoleic acid; LDL-C, low-density lipoprotein-cholesterol; LTB_4, leukotriene B_4; M, male; MedDiet, Mediterranean diet; MetS, metabolic syndrome; n-3 FA, omega 3 fatty acids; NCEP, National Cholesterol Education Program; NS, non-significant; ox-LDL, oxidized low-density lipoprotein; PAT, peripheral arterial tonometry; PBMC, peripheral blood mononuclear cell; PGEM, prostaglandin E metabolite; SBP, systolic blood pressure; SF, saturated fats; T2D, type-2 diabetes; TAG, triacylglycerols; TC, total cholesterol; TNF-α, tumor necrosis factor-α; TXB2, thromboxane B2; VCAM-1, vascular cell adhesion molecule-1; VOO, virgin olive oil.

[a] EF/BP and/or inflammation are secondary outcomes.

[b] Inflammation is the primary outcome.

[c] EF is the primary outcome.

circulating biomarkers such as ICAM-1 and VCAM-1 in healthy individuals, obese individuals, or those at high cardiovascular risk.

4.2.3.2.2 Clinical Trials Evaluating Inflammation The effect of nut consumption on the modulation of chronic inflammation and oxidation as primary or secondary outcomes was evaluated in several RCTs (Table 4.3). In a dose-response RCT conducted in 25 hyperlipidemic subjects, an average consumption of 73 g of almonds per day significantly reduced ox-LDL concentrations compared to an isoenergetic control diet, which supports the protective effect of nuts on coronary heart disease (CHD). However, no significant changes were found for CRP [63]. Similar findings were obtained by the same research group in another clinical trial conducted in hyperlipidemic subjects following a portfolio diet rich in plant sterols, soy protein, viscous fibers, and almonds for 4 weeks. No significant treatment effect was observed on CRP concentrations. However, the proportion of CRP changes in the portfolio diet group was significantly greater than that of control group when subjects with CRP levels above the 75th percentile were excluded from the analysis [64]. The improvement in inflammatory status after nut consumption was also demonstrated in healthy subjects. In this case, a single ingestion of 20 g or 50 g of Brazil nuts caused a significant long-term decrease in circulating IL-1, IL-6, TNF-α, and interferon-γIFN-γ levels and increased IL-10 for up to 30 days after consumption, questioning the advantage of consuming a large portion of nuts intermittently or small portions chronically [73]. These anti-inflammatory effects were corroborated in a 24-week RCT conducted in 60 subjects with MetS. After consuming a diet providing 20% energy from unsalted pistachios, a significant reduction in CRP, TNF-α, leptin, and TBARS, together with increased adiponectin concentrations, was observed. Changes in other inflammatory markers were no longer significant [74]. Moreover, two crossover RCTs in healthy and T2D individuals whom were given different doses of almonds (ranging from 10% to 20% of energy) analyzed the effect of almond consumption of CRP levels. Both studies showed a significant decrease in CRP following almond diets compared to control diets [67,70]. Likewise, one parallel study involving prehypertensive and hypercholesterolemic participants [69] and one crossover trial with hypercholesterolemic participants [88] suggested beneficial effects through lowering CRP after the consumption of hazelnuts (30 g/day and 49–86 g/day, respectively). However, CRP concentrations remained unchanged after the intake of nuts (mixed nuts, pistachios, almonds, and walnuts) in several other controlled clinical trials [49,50,56,57,60,87,92,94]. Other biomarkers of inflammation including IL-6, IL-8, IL-10, TNF-α, and ox-LDL have also been investigated, although inconsistent results were found. Differences in the length of the trials, type of population, and the type and amount of nuts could partly explain the discrepancies. Some of these trials have also investigated other outcomes, such as lipid profiles and glucose parameters.

A systematic review and meta-analysis of 61 RCTs revealed no significant effects of tree nuts on inflammatory markers (e.g., CRP in 8 RCTs) [95]. Neale et al. [96] recently published another systematic review and meta-analysis of the effects of nut consumption on markers of inflammation and EF. A total of 32 randomized controlled studies were included. Results indicated a beneficial effect of nut consumption on FMD (weighted mean differences [WMD]: 0.79% [95% CI 0.35 to 1.23]) as a marker of EF, and a non-significant reduction of CRP levels (WMD:

−0.01 mg/L [95% CI −0.06 to 0.03]), or circulating molecules such as ICAM-1 and VCAM-1 as measures of inflammation. This meta-analysis points to a positive effect of nuts on EF but also to a lack of consistent evidence for a clear anti-inflammatory role.

4.2.3.2.3 Clinical Trials Evaluating Blood Pressure A large number of controlled feeding trials using nuts have evaluated the effect of different types of nuts on BP, always as a secondary outcome. The total doses of nuts used ranged from 30 to 108 g/day. In most of the studies, subjects consumed raw nuts in the context of a diet. Comparisons were made with nut-free diets or meals (Table 4.3).

Although several RCTs have observed no changes in BP after nut-supplemented diets, seven others have reported an improvement in BP after the consumption of mixed nuts [54,55,58,59,68,69,86]. Three of them showed beneficial effects in lowering systolic and diastolic BP in subjects following diets enriched with walnuts (30–56 g/day) [54,58,86], one with almonds (84 g/day) [55] and one with pistachios (30-60 g/day) [59]. The largest study involved 372 participants at high cardiovascular risk and showed that a MedDiet supplemented with mixed nuts (hazelnuts, almonds, and walnuts) for 12 weeks decreased both systolic and diastolic BP compared to a control diet recommending the reduction of all types of fat intake [81].

Along these lines, a recent meta-analysis of 21 RCTs evaluating the effect of tree nuts and peanuts on BP, always a secondary outcome of nut feeding studies, showed that total nut consumption lowered systolic BP in participants without T2D. Pistachios seemed to have the strongest effect on reducing both systolic and diastolic BP. Mixed nuts also reduced diastolic BP, but no significant effects were observed for overall nut consumption in the total population [97]. A subsequent meta-analysis of 17 RCTs assessing the lipid effects of nuts in which BP was a secondary outcome found a null effect on systolic or diastolic BP [95].

In summary, findings from chronic RCTs suggest potential benefits of nut consumption on EF, BP, and inflammatory biomarkers, although some evidence, particularly for the effects on BP, is still controversial and further investigation is needed.

4.3 Conclusion

In conclusion, evidence from epidemiological, *in vitro/in vivo*, and clinical studies generally supports the notion that nut consumption is associated with beneficial effects on EF and inflammation. In particular, several RCTs have demonstrated that consumption of nuts, particularly walnuts, improves EF as directly assessed by FMD or PAT. Some, but not all, RCTs with nuts have also reported lower concentrations of circulating EF molecules, particularly IL-6 and VCAM-1, and of inflammatory and oxidative markers, but not of CRP. The unique nutritional composition of nuts may explain their potential to favorably influence vascular reactivity. The knowledge gaps on the anti-inflammatory and endothelial-related effects of nuts observed in clinical studies using nut-enriched diets probably stem from the fact that most of them were not designed to evaluate these specific outcomes. Further research is clearly needed to pinpoint the role of nut consumption in cardiometabolic variables at the molecular and cellular levels and to replicate the results found in epidemiological and clinical studies especially designed for this purpose. As shown in

the present chapter, the ability of nuts to ameliorate EF, BP, and inflammation could partly explain the consistent inverse associations observed between the frequency of nut consumption and the risk of CVD.

References

1. International Diabetes Federation, The IDF consensus worldwide definition of the metabolic syndrome. *IDF Consens. Worldw. Defin. Metab. Syndr.*, 28, 1–7, 2006.
2. Kotas, M.E., and Medzhitov, R., Homeostasis, inflammation, and disease susceptibility. *Cell*, 160, 816–827, 2015.
3. Corretti, M.C., Anderson, T.J., Benjamin, E.J., Celermajer, D., Charbonneau, F., Creager, M.A., Deanfield, J. et al., Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the international brachial artery reactivity task force. *J. Am. Coll. Cardiol.*, 39, 257–265, 2002.
4. Deanfield, J.E., Halcox, J.P., and Rabelink, T.J., Endothelial function and dysfunction. *Circulation*, 115, 1285–1295, 2007.
5. Yamashina, A., Tomiyama, H., Arai, T., Hirose, K., Koji, Y., Hirayama, Y., Yamamoto, Y. et al., Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens. Res.*, 26, 615–622, 2003.
6. Ponthieux, A., Herbeth, B., Droesch, S., Haddy, N., Lambert, D., and Visvikis, S., Biological determinants of serum ICAM-1, E-selectin, P-selectin and L-selectin levels in healthy subjects: The Stanislas study. *Atherosclerosis*, 172, 299–308, 2004.
7. Salas-Salvadó, J., Garcia-Arellano, A., Estruch, R., Marquez-Sandoval, F., Corella, D., Fiol, M., Gómez-Gracia, E. et al., Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur. J. Clin. Nutr.*, 62, 651–659, 2008.
8. Li, T.Y., Brennan, A.M., Wedick, N.M., Mantzoros, C., Rifai, N., and Hu, F.B., Regular consumption of nuts is associated with a lower risk of cardiovascular disease in women with type 2 diabetes. *J. Nutr.*, 139, 1333–1338, 2009.
9. Jiang, R., Jacobs, D.R., Mayer-Davis, E., Szklo, M., Herrington, D., Jenny, N.S., Kronmal, R. et al., Nut and seed consumption and inflammatory markers in the Multi-Ethnic Study of Atherosclerosis. *Am. J. Epidemiol.*, 163, 222–231, 2006.
10. Mantzoros, C.S., Williams, C.J., Manson, J.E., Meigs, J.B., and Hu, F.B., Adherence to the Mediterranean dietary pattern is positively associated with plasma adiponectin concentrations in diabetic women. *Am. J. Clin. Nutr.*, 84, 328–335, 2006.
11. Steffen, L.M., Kroenke, C.H., Yu, X., Pereira, M.A., Slattery, M.L., Van Horn, L., Gross, M.D. et al., Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am. J. Clin. Nutr.*, 82, 1169–77–4, 2005.
12. Djousse, L., Rudich, T., and Gaziano, J.M., Nut consumption and risk of hypertension in US male physicians. *Clin. Nutr.*, 28, 10–14, 2009.

13. Weng, L.-C., Steffen, L.M., Szklo, M., Nettleton, J., Chambless, L., and Folsom, A.R., A diet pattern with more dairy and nuts, but less meat is related to lower risk of developing hypertension in middle-aged adults: The Atherosclerosis Risk in Communities (ARIC) study. *Nutrients*, 5, 1719–1733, 2013.
14. Lelong, H., Blacher, J., Baudry, J., Adriouch, S., Galan, P., Fezeu, L., Hercberg, S. et al., Individual and combined effects of dietary factors on risk of incident hypertension. *Hypertension*, 117, 09622, 2017.
15. Martinez-Lapiscina, E.H., Pimenta, A.M., Beunza, J.J., Bes-Rastrollo, M., Martinez, J.A., and Martinez-Gonzalez, M.A., Nut consumption and incidence of hypertension: The SUN prospective cohort . *Nutr. Metab. Cardiovasc. Dis.*, 20, 359–365, 2010.
16. Ros, E., Health benefits of nut consumption. *Nutrients*, 2, 652–682, 2010.
17. Aksoy, N., Aksoy, M., and Bagci, C., Pistachio intake increases high density lipoprotein levels and inhibits low-density lipoprotein oxidation in rats. *Tohoku J.*, 212, 43–48, 2007.
18. Alturfan, A.A., Emekli-Alturfan, E., and Uslu, E., Consumption of pistachio nuts beneficially affected blood lipids and total antioxidant activity in rats fed a high-cholesterol diet. *Folia Biol. (Praha)*, 55, 132–136, 2009.
19. Poulose, S.M., Bielinski, D.F., and Shukitt-Hale, B., Walnut diet reduces accumulation of polyubiquitinated proteins and inflammation in the brain of aged rats. *J. Nutr. Biochem.*, 24, 912–919, 2013.
20. Zhao, G., Etherton, T.D., Martin, K.R., Vanden Heuvel, J.P., Gillies, P.J., West, S.G., and Kris-Etherton, P.M., Anti-inflammatory effects of polyunsaturated fatty acids in THP-1 cells. *Biochem. Biophys. Res. Commun.*, 336, 909–917, 2005.
21. Laubertová, L., Koňariková, K., Gbelcová, H., Ďuračková, Z., and Žitňanová, I., Effect of walnut oil on hyperglycemia-induced oxidative stress and pro-inflammatory cytokines production. *Eur. J. Nutr.*, 54, 291–299, 2014.
22. Vassiliou, E.K., Gonzalez, A., Garcia, C., Tadros, J.H., Chakraborty, G., and Toney, J.H., Oleic acid and peanut oil high in oleic acid reverse the inhibitory effect of insulin production of the inflammatory cytokine TNF-alpha both *in vitro* and *in vivo* systems. *Lipids Health Dis.*, 8, 25, 2009.
23. Vinson, J.A., and Cai, Y., Nuts, especially walnuts, have both antioxidant quantity and efficacy and exhibit significant potential health benefits. *Food Funct.*, 3, 134–140, 2012.
24. Paterniti, I., Impellizzeri, D., Cordaro, M., Siracusa, R., Bisignano, C., Gugliandolo, E., Carughi, A. et al., The anti-inflammatory and antioxidant potential of pistachios (*Pistacia vera* l.) *in vitro* and *in vivo*. *Nutrients*, 9, 915, 2017.
25. Zhang, H., and Tsao, R., Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. *Curr. Opin. Food Sci.*, 8, 33–42, 2016.
26. Rogerio, A.P., Fontanari, C., Melo, M.C.C., Ambrosio, S.R., de Souza, G.E.P., Pereira, P.S., França, S.C. et al., Anti-inflammatory, analgesic and anti-oedematous effects of *Lafoensia pacari* extract and ellagic acid. *J. Pharm. Pharmacol.*, 58, 1265–1273, 2006.
27. Zhang, H., Zhang, J., Ungvari, Z., and Zhang, C., Resveratrol improves endothelial function: Role of TNF-α and vascular oxidative stress. *Arterioscler. Thromb. Vasc. Biol.*, 29, 1164–1171, 2009.
28. Chang, W.C., Chen, C.H., Lee, M.F., Chang, T., and Yu, Y.M., Chlorogenic acid attenuates adhesion molecules upregulation in IL-1β-treated endothelial cells. *Eur. J. Nutr.*, 49, 267–275, 2010.

29. Gentile, C., Allegra, M., Angileri, F., Pintaudi, A.M., Livrea, M.A., and Tesoriere, L., Polymeric proanthocyanidins from Sicilian pistachio (*Pistacia vera* L.) nut extract inhibit lipopolysaccharide-induced inflammatory response in RAW 264.7 cells. *Eur. J. Nutr.*, 51, 353–363, 2012.
30. Zhang, J., Kris-Etherton, P.M., Thompson, J.T., and Vanden Heuvel, J.P., Effect of pistachio oil on gene expression of IFN-induced protein with tetratricopeptide repeats 2: A biomarker of inflammatory response. *Mol. Nutr. Food Res.*, 54(Suppl. 1), S83–S92, 2010.
31. Willis, L.M., Bielinski, D.F., Fisher, D.R., Matthan, N.R., and Joseph, J.A., Walnut extract inhibits LPS-induced activation of Bv-2 microglia *via* internalization of TLR4: Possible involvement of phospholipase D2. *Inflammation*, 33, 325–333, 2010.
32. Catalán, Ú., Fernández-Castillejo, S., Anglès, N., Morelló, J.R., Yebras, M., and Solà, R., Inhibition of the transcription factor c-Jun by the MAPK family, and not the NF-κB pathway, suggests that peanut extract has anti-inflammatory properties. *Mol. Immunol.*, 52, 125–132, 2012.
33. Grace, M.H., Esposito, D., Timmers, M.A., Xiong, J., Yousef, G., Komarnytsky, S., and Lila, M.A., *In vitro* lipolytic, antioxidant and anti-inflammatory activities of roasted pistachio kernel and skin constituents. *Food Funct.*, 4285–4298, 2016.
34. Vallance, P., Collier, J., and Bhagat, K., Infection, inflammation, and infarction: Does acute endothelial dysfunction provide a link? *Lancet*, 349, 1391–1392, 1997.
35. Jiang, C., Ting, A.T., and Seed, B., PPAR-g agonists inhibit production of monocyte inflammatory cytokines. *Nature*, 391, 82–86, 1998.
36. Ferrara, L.A., Raimondi, A.S., d'Episcopo, L., Guida, L., Dello Russo, A., and Marotta, T., Olive oil and reduced need for antihypertensive medications. *Arch. Intern. Med.*, 160, 837–842, 2000.
37. Song, Y., Ridker, P.M., Manson, J.E., Cook, N.R., Buring, J.E., and Liu, S., Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. *Diabetes Care*, 28, 1438–1444, 2005.
38. Adrogué, H.J., and Madias, N.E., Sodium and potassium in the pathogenesis of hypertension. *N. Engl. J. Med.*, 356, 1966–1978, 2007.
39. Casas-Agustench, P., López-Uriarte, P., Ros, E., Bulló, M., and Salas-Salvadó, J., Nuts, hypertension and endothelial function. *Nutr. Metab. Cardiovasc. Dis.*, 21(Suppl. 1), S21–S33, 2011.
40. Alonso, A., Beunza, J.J., Bes-Rastrollo, M., Pajares, R.M., and Martínez-González, M.Á., Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch. Med. Res.*, 37, 778–786, 2006.
41. Cortés, B., Núñez, I., Cofán, M., Gilabert, R., Pérez-Heras, A., Casals, E., Deulofeu, R. et al., Acute effects of high-fat meals enriched with walnuts or olive oil on postprandial endothelial function. *J. Am. Coll. Cardiol.*, 48, 1666–1671, 2006.
42. Jiménez-Gómez, Y., López-Miranda, J., Blanco-Colio, L.M., Marín, C., Pérez-Martínez, P., Ruano, J., Paniagua, J.A. et al., Olive oil and walnut breakfasts reduce the postprandial inflammatory response in mononuclear cells compared with a butter breakfast in healthy men. *Atherosclerosis*, 204, e70–e76, 2009.
43. Berryman, C.E., Grieger, J.A., West, S.G., Chen, C.-Y.O., Blumberg, J.B., Rothblat, G.H., Sankaranarayanan, S. et al., Acute consumption of walnuts and

walnut components differentially affect postprandial lipemia, endothelial function, oxidative stress, and cholesterol efflux in humans with mild hypercholesterolemia. *J. Nutr.*, 143, 788–794, 2013.
44. Berry, S.E.E., Tydeman, E.A., Lewis, H.B., Phalora, R., Rosborough, J., Picout, D.R., and Ellis, P.R., Manipulation of lipid bioaccessibility of almond seeds influences postprandial lipemia in healthy human subjects. *Am. J. Clin. Nutr.*, 88, 922–929, 2008.
45. Kendall, C.W.C., West, S.G., Augustin, L.S., Esfahani, A., Vidgen, E., Bashyam, B., Sauder, K.A. et al., Acute effects of pistachio consumption on glucose and insulin, satiety hormones and endothelial function in the metabolic syndrome. *Eur. J. Clin. Nutr.*, 68, 370–375, 2014.
46. Liu, X., Hill, A.M., West, S.G., Gabauer, R.M., McCrea, C.E., Fleming, J.A., and Kris-Etherton, P.M., Acute peanut consumption alters postprandial lipids and vascular responses in healthy overweight or obese men. *J. Nutr.*, 147, 835–840, 2017.
47. Di Renzo, L., Merra, G., Botta, R., Gualtieri, P., Manzo, A., Perrone, M.A., Mazza, M. et al., Post-prandial effects of hazelnut-enriched high fat meal on LDL oxidative status, oxidative and inflammatory gene expression of healthy subjects: A randomized trial. *Eur. Rev. Med. Pharmacol. Sci.*, 21, 1610–1626, 2017.
48. Wien, M.A., Sabate, J.M., Ikle, D.N., Cole, S.E., and Kandeel, F.R., Almonds vs complex carbohydrates in a weight reduction program. *Int. J. Obes. Relat. Metab. Disord.*, 27, 1365–1372, 2003.
49. Ros, E., Núñez, I., Pérez-Heras, A., Serra, M., Gilabert, R., Casals, E., and Deulofeu, R., A walnut diet improves endothelial function in hypercholesterolemic subjects: A randomized crossover trial. *Circulation*, 109, 1609–1614, 2004.
50. Estruch, R., Martínez-González, M.A., Corella, D., Salas-Salvadó, J., Ruiz-Gutiérrez, V., Covas, M.I., Fiol, M. et al., Effects of a Mediterranean-style diet on cardiovascular risk factors: A randomized trial. *Ann. Intern. Med.*, 145, 1–11, 2006.
51. Ghadimi Nouran, M., Kimiagar, M., Abadi, A., Mirzazadeh, M., and Harrison, G., Peanut consumption and cardiovascular risk. *Public Health Nutr.*, 13, 1581–1586, 2010.
52. Lopez-Uriarte, P., Nogues, R., Saez, G., Bullo, M., Romeu, M., Masana, L., Tormos, C. et al., Effect of nut consumption on oxidative stress and the endothelial function in metabolic syndrome . *Clin. Nutr.*, 29, 373–380, 2010.
53. Ma, Y., Njike, V.Y., Millet, J., Dutta, S., Doughty, K., Treu, J.A., and Katz, D.L., Effects of walnut consumption on endothelial function in type 2 diabetic subjects: A randomized controlled crossover trial. *Diabetes Care*, 33, 227–232, 2010.
54. West, S.G., Krick, A.L., Klein, L.C., Zhao, G., Wojtowicz, T.F., McGuiness, M., Bagshaw, D.M. et al., Effects of diets high in walnuts and flax oil on hemodynamic responses to stress and vascular endothelial function. *J. Am. Coll. Nutr.*, 29, 595–603, 2010.
55. Wien, M., Bleich, D., Raghuwanshi, M., Gould-Forgerite, S., Gomes, J., Monahan-Couch, L., and Oda, K., Almond consumption and cardiovascular risk factors in adults with prediabetes. *J. Am. Coll. Nutr.*, 29, 189–197, 2010.
56. Aronis, K.N., Vamvini, M.T., Chamberland, J.P., Sweeney, L.L., Brennan, A.M., Magkos, F., and Mantzoros, C.S., Short-term walnut consumption increases circulating total adiponectin and apolipoprotein A concentrations, but does not

affect markers of inflammation or vascular injury in obese humans with the metabolic syndrome: Data from a double-blinded, randomized, *Metab. Clin. Exp.*, 61, 577–582, 2012.
57. Chiang, Y.-L., Haddad, E., Rajaram, S., Shavlik, D., and Sabaté, J., The effect of dietary walnuts compared to fatty fish on eicosanoids, cytokines, soluble endothelial adhesion molecules and lymphocyte subsets: A randomized, controlled crossover trial. *Prostaglandins, Leukot. Essent. Fat. Acids*, 87, 111–117, 2012.
58. Katz, D.L., Davidhi, A., Ma, Y., Kavak, Y., Bifulco, L., and Njike, V.Y., Effects of walnuts on endothelial function in overweight adults with visceral obesity: A randomized, controlled, crossover trial. *J. Am. Coll. Nutr.*, 31, 415–423, 2012.
59. West, S.G., Gebauer, S.K., Kay, C.D., Bagshaw, D.M., Savastano, D.M., Diefenbach, C., and Kris-Etherton, P.M., Diets containing pistachios reduce systolic blood pressure and peripheral vascular responses to stress in adults with dyslipidemia. *Hypertension*, 60, 58–63, 2012.
60. Chen, C.-Y.O., Holbrook, M., Duess, M.-A., Dohadwala, M.M., Hamburg, N.M., Asztalos, B.F., Milbury, P.E. et al., Effect of almond consumption on vascular function in patients with coronary artery disease: A randomized, controlled, cross-over trial. *Nutr. J.*, 14, 61, 2015.
61. Kasliwal, R.R., Bansal, M., Mehrotra, R., Yeptho, K.P., and Trehan, N., Effect of pistachio nut consumption on endothelial function and arterial stiffness. *Nutrition*, 31, 678–685, 2015.
62. Sauder, K.A., McCrea, C.E., Ulbrecht, J.S., Kris-Etherton, P.M., and West, S.G., Effects of pistachios on the lipid/lipoprotein profile, glycemic control, inflammation, and endothelial function in type 2 diabetes: A randomized trial. *Metabolism*, 64, 1521–1529, 2015.
63. Jenkins, D.J.A., Kendall, C.W.C., Marchie, A., Parker, T.L., Connelly, P.W., Qian, W., Haight, J.S., Faulkner, D. et al., Dose response of almonds on coronary heart disease risk factors: Blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: A randomized, controlled, crossover trial. *Circulation*, 106, 1327–1332, 2002.
64. Jenkins, D.J.A., Kendall, C.W.C., Marchie, A., Faulkner, D.A., Josse, A.R., Wong, J.M.W., de Souza, R., Emam, A. et al., Direct comparison of dietary portfolio vs statin on C-reactive protein. *Eur. J. Clin. Nutr.*, 59, 851–860, 2005.
65. Garg, M.L., Blake, R.J., Wills, R.B.H., and Clayton, E.H., Macadamia nut consumption modulates favourably risk factors for coronary artery disease in hypercholesterolemic subjects. *Lipids*, 42, 583–587, 2007.
66. Zhao, G., Etherton, T.D., Martin, K.R., Gillies, P.J., West, S.G., and Kris-Etherton, P.M., Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. *Am. J. Clin. Nutr.*, 85, 385–391, 2007.
67. Rajaram, S., Connell, K.M., and Sabaté, J., Effect of almond-enriched high-monounsaturated fat diet on selected markers of inflammation: A randomised, controlled, crossover study. *Br. J. Nutr.*, 103, 907–912, 2010.
68. Casas-Agustench, P., López-Uriarte, P., Bulló, M., Ros, E., Cabré-Vila, J.J., and Salas-Salvadó, J., Effects of one serving of mixed nuts on serum lipids, insulin resistance and inflammatory markers in patients with the metabolic syndrome. *Nutr. Metab. Cardiovasc. Dis.*, 21, 126–135, 2011.
69. Solà, R., Valls, R.M., Godàs, G., Perez-Busquets, G., Ribalta, J., Girona, J., Heras, M. et al., Cocoa, hazelnuts, sterols and soluble fiber cream reduces lipids and inflammation biomarkers in hypertensive patients: A randomized controlled trial. *PLoS One*, 7, e31103, 2012.

70. Liu, J.-F., Liu, Y.-H., Chen, C.-M., Chang, W.-H., and Chen, C.-Y.O., The effect of almonds on inflammation and oxidative stress in Chinese patients with type 2 diabetes mellitus: A randomized crossover controlled feeding trial. *Eur. J. Nutr.*, 52, 927–935, 2013.
71. Tey, S.L., Gray, A.R., Chisholm, A.W., Delahunty, C.M., and Brown, R.C., The dose of hazelnuts influences acceptance and diet quality but not inflammatory markers and body composition in overweight and obese individuals. *J. Nutr.*, 143, 2013.
72. Burns-Whitmore, B., Haddad, E., Sabaté, J., and Rajaram, S., Effects of supplementing n-3 fatty acid enriched eggs and walnuts on cardiovascular disease risk markers in healthy free-living lacto-ovo-vegetarians: A randomized, crossover, free-living intervention study. *Nutr. J.*, 13, 29, 2014.
73. Colpo, E., Dalton, D.A., Vilanova, C., Reetz, L.G.B., Duarte, M.M.M.F., Farias, I.L.G., Meinerz, D.F. et al., Brazilian nut consumption by healthy volunteers improves inflammatory parameters. *Nutrition*, 30, 459–465, 2014.
74. Gulati, S., Misra, A., Pandey, R.M., Bhatt, S.P., and Saluja, S., Effects of pistachio nuts on body composition, metabolic, inflammatory and oxidative stress parameters in Asian Indians with metabolic syndrome: A 24-wk, randomized control trial. *Nutrition*, 30, 192–197, 2014.
75. Moreira Alves, R.D., Boroni Moreira, A.P., Macedo, V.S., Bressan, J., de Cássia Gonçalves Alfenas, R., Mattes, R., and Brunoro Costa, N.M., High-oleic peanuts: New perspective to attenuate glucose homeostasis disruption and inflammation related obesity. *Obesity*, 22, 1981–1988, 2014.
76. Barbour, J., Howe, P., Buckley, J., Bryan, J., and Coates, A., Effect of 12 weeks high oleic peanut consumption on cardio-metabolic risk factors and body composition. *Nutrients*, 7, 7381–7388, 2015.
77. Din, J.N., Aftab, S.M., Jubb, A.W., Carnegy, F.H., Lyall, K., Sarma, J., Newby, D.E., and Flapan, A.D., Effect of moderate walnut consumption on lipid profile, arterial stiffness and platelet activation in humans. *Eur. J. Clin. Nutr.*, 65, 234–239, 2011.
78. Iwamoto, M., Imaizumi, K., Sato, M., Hirooka, Y., Sakai, K., Takeshita, A., and Kono, M., Serum lipid profiles in Japanese women and men during consumption of walnuts. *Eur. J. Clin. Nutr.*, 56, 629–637, 2002.
79. Chisholm, A., Mc Auley, K., Mann, J., Williams, S., and Skeaff, M., Cholesterol lowering effects of nuts compared with a Canola oil enriched cereal of similar fat composition. *Nutr. Metab. Cardiovasc. Dis.*, 15, 284–292, 2005.
80. Schutte, A.E., Van Rooyen, J.M., Huisman, H.W., Mukuddem-Petersen, J., Oosthuizen, W., Hanekom, S.M., and Jerling, J.C., Modulation of baroreflex sensitivity by walnuts *versus* cashew nuts in subjects with metabolic syndrome. *Am. J. Hypertens.*, 19, 629–636, 2006.
81. Fito, M., Guxens, M., Corella, D., Saez, G., Estruch, R., de la Torre, R., Frances, F. et al., Effect of a traditional Mediterranean diet on lipoprotein oxidation: A randomized controlled trial. *Arch. Intern. Med.*, 167, 1195–1203, 2007.
82. Mercanligil, S.M., Arslan, P., Alasalvar, C., Okut, E., Akgul, E., Pinar, A., Geyik, P.O. et al., Effects of hazelnut-enriched diet on plasma cholesterol and lipoprotein profiles in hypercholesterolemic adult men. *Eur. J. Clin. Nutr.*, 61, 212–220, 2007.
83. Mukuddem-Petersen, J., Stonehouse Oosthuizen, W., Jerling, J.C., Hanekom, S.M., and White, Z., Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: A controlled feeding trial. *Br. J. Nutr.*, 97, 1144–1153, 2007.

84. Sheridan, M.J., Cooper, J.N., Erario, M., and Cheifetz, C.E., Pistachio nut consumption and serum lipid levels. *J. Am. Coll. Nutr.*, 26, 141–148, 2007.
85. Spaccarotella, K.J., Kris-Etherton, P.M., Stone, W.L., Bagshaw, D.M., Fishell, V.K., West, S.G., Lawrence, F.R. et al., The effect of walnut intake on factors related to prostate and vascular health in older men. *Nutr. J.*, 7, 13, 2008.
86. Wu, H., Pan, A., Yu, Z., Qi, Q., Lu, L., Zhang, G., Yu, D. et al., Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome. *J. Nutr.*, 140, 1937–1942, 2010.
87. Damasceno, N.R.T., Pérez-Heras, A., Serra, M., Cofán, M., Sala-Vila, A., Salas-Salvadó, J., and Ros, E., Crossover study of diets enriched with virgin olive oil, walnuts or almonds. Effects on lipids and other cardiovascular risk markers. *Nutr. Metab. Cardiovasc. Dis.*, 21(Suppl.), S14–S20, 2011.
88. Orem, A., Yucesan, F.B., Orem, C., Akcan, B., Kural, B.V., Alasalvar, C., and Shahidi, F., Hazelnut-enriched diet improves cardiovascular risk biomarkers beyond a lipid-lowering effect in hypercholesterolemic subjects. *J. Clin. Lipidol.*, 7, 123–131, 2013.
89. Wu, L., Piotrowski, K., Rau, T., Waldmann, E., Broedl, U.C., Demmelmair, H., Koletzko, B. et al., Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: A randomized controlled cross-over clinical trial. *Metabolism*., 63, 382–391, 2014.
90. Hernández-Alonso, P., Salas-Salvadó, J., Baldrich-Mora, M., Juanola-Falgarona, M., and Bulló, M., Beneficial effect of pistachio consumption on glucose metabolism, insulin resistance, inflammation, and related metabolic risk markers: A randomized clinical trial. *Diabetes Care*, 37, 3098–3105, 2014.
91. Lee, Y.J., Nam, G.E., Seo, J.A., Yoon, T., Seo, I., Lee, J.H., Im, D. et al., Nut consumption has favorable effects on lipid profiles of Korean women with metabolic syndrome. *Nutr. Res.*, 34, 814–824, 2014.
92. Parham, M., Heidari, S., Khorramirad, A., Hozoori, M., Hosseinzadeh, F., Bakhtyari, L., and Vafaeimanesh, J., Effects of pistachio nut supplementation on blood glucose in patients with type 2 diabetes: A randomized crossover trial. *Rev. Diabet. Stud.*, 11, 190–196, 2014.
93. Njike, V.Y., Ayettey, R., Petraro, P., Treu, J.A., and Katz, D.L., Walnut ingestion in adults at risk for diabetes: Effects on body composition, diet quality, and cardiac risk measures. *BMJ Open Diabetes Res. Care*, 3, e000115, 2015.
94. Sari, I., Baltaci, Y., Bagci, C., Davutoglu, V., Erel, O., Celik, H., Ozer, O. et al., Effect of pistachio diet on lipid parameters, endothelial function, inflammation, and oxidative status: A prospective study. *Nutrition*, 26, 399–404, 2010.
95. Del Gobbo, L.C., Falk, M.C., Feldman, R., Lewis, K., and Mozaffarian, D., Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: Systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am. J. Clin. Nutr.*, 102, 1347–1356, 2015.
96. Neale, E.P., Tapsell, L.C., Guan, V., and Batterham, M.J., The effect of nut consumption on markers of inflammation and endothelial function: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*, 7, e016863, 2017.
97. Mohammadifard, N., Salehi-Abarghouei, A., Salas-Salvadó, J., Guasch-Ferré, M., Humphries, K., and Sarrafzadegan, N., The effect of tree nut, peanut, and soy nut consumption on blood pressure: A systematic review and meta-analysis of randomized controlled clinical trials. *Am. J. Clin. Nutr.*, 101, 966–982, 2015.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 5

The Energetics of Nut Consumption

Oral Processing, Appetite, and Energy Balance

Breanna M. McArthur, Kelly A. Higgins, Stephanie R. Hunter, and Richard D. Mattes

5.1 Introduction 126
5.1.1 Mastication of Whole, Raw Nuts, and Energy Extraction 130
5.1.2 Mastication of Processed Nuts and Energy Extraction 130
5.1.3 Mastication of Various Nut Types 131
5.1.4 Fecal Fat Excretion 132
5.1.5 The Role of Mastication on Energy Expenditure 132
5.1.6 Oral Processing of Nuts and Appetite 136
5.1.6.1 Nut Consumption, Gut Hormones, and Appetite 136
5.2 Non-Oral Effects of Nut Consumption on Appetite 137
5.2.1 Timing of Nut Consumption 137
5.2.2 Properties of Nuts that Affect Appetite 138
5.3 Nut Consumption and Dietary Compensation 139
5.3.1 Summary of RCTs 140
5.3.2 Impact of Study Design on Dietary Compensation 140
5.3.3 Impact of Nut Type and Load on Dietary Compensation 140
5.3.4 Dietary Compensation and Body Weight in RCTs 145
5.4 Nut Consumption Patterns 145
5.4.1 Nut Consumption and Diet Quality 146

5.5 Are There Differences between Nuts? 146
5.6 Conclusion 147
References 147

5.1 Introduction

Substantial epidemiological and clinical evidence indicates that tree and ground nut consumption is associated, correlatively or causally, with reduced risk for numerous chronic diseases. The mechanisms behind these associations have not been fully characterized. However, it is hypothesized that increased intake of phytochemicals, fiber, unsaturated fats, and selected micronutrients from nuts leads to reductions in low-density lipoprotein (LDL)-cholesterol, total cholesterol, triacylglycerols, and blood pressure, as well as moderating blood sugar and appetite. As a result, several regulatory bodies including the Food and Drug Administration, European Food Safety Authority, and Food Standards Australia New Zealand have approved health claims for nuts. The evidence behind these claims is reviewed in other chapters of this book (see Chapters 2 and 12 for details).

Despite the approved health claims and the high nutrient density of nuts, their consumption is hindered because they are viewed as energy dense and high in fat. These properties have been associated with positive energy balance, overweight, and obesity, conditions that contribute to chronic diseases such as cardiovascular disease, diabetes, and hypertension. Thus, concern about body weight remains a barrier to increased nut consumption [1]. However, evidence challenging this view has emerged over the past three decades. Energy intake and body weight measured in cross-sectional and prospective cohort studies are summarized in Table 5.1. Across numerous studies, body weight is lower among nut consumers than non-consumers despite the evidence indicating that nut consumers have higher energy intake. This seeming contradiction may be due to energy underreporting by nut non-consumers, differences in dietary and lifestyle patterns associated with body weight in nut consumers and non-consumers, or properties of nuts that affect energy balance. The latter is the focus of this review.

Research over the past two decades has revealed three mechanisms that collectively indicate that moderate nut consumption has a limited effect on body weight [2]:

1. The energy contained in nuts is not fully bioaccessible, leading to limited absorption efficiency.
2. Frequent nut consumption may enhance resting energy expenditure.
3. Nuts have strong effects on appetitive sensations leading to a high level of dietary energy compensation.

All three of these mechanisms have their origins in the oral cavity. It is here that initial appetitive signals are generated in response to the chemical and physical properties of nuts. These signals modulate the motivation to eat and perhaps also digestive, absorptive, and metabolic processes. Added to this, the mechanical reduction of nuts into digestible particles through mastication alters their physical state with implications for digestive and absorptive efficiency. Further, oral processing stimulates sympathetic nervous system activity that may contribute to energy expenditure.

Table 5.1 Energy Intake and Body Weight with Nut Consumption in Prospective Cohort and Cross-Sectional Studies

Study	*Sample Size*	*Follow-Up Duration (Years)*	*Assessment Method*	*Nut*	*Exposure*	*Body Weight*	*Energy Intake*	*References*
PHS	21,454[b]	1	FFQ	Nuts	Never, 1–3 × per month, 1 × per week, and >2 × per week	BMI of 24.9, 24.9, 25.0, and 24.7	nm	[92]
SUN	8,865	2.33	FFQ and food records	Walnuts, almonds, hazelnuts, and peanuts	Never, 1–3 × per month, 1 × per week, and >2 × per week	Odds ratio of weight gain ≥ 5 kg: 1.00, 0.93, 0.94, and 0.61 ($P < 0.001$)	2,172, 2,354, 2,510, and 2,674[c] kcal, respectively	[93]
NHS II	51,188[a]	8	FFQ	Peanut butter, peanuts, and tree nuts	Never, 1–3 × per month, 1 × per week, and >2 × per week	0.51 kg less weight gain between non-consumers and nut consumers ≥ 2x/week ($P < 0.001$)	1,673, 1,819, 1,939, and 2,083[c] kcal, respectively	[88]

(*Continued*)

Table 5.1 (Continued) Energy Intake and Body Weight with Nut Consumption in Prospective Cohort and Cross-Sectional Studies

Study	*Sample Size*	*Follow-Up Duration (Years)*	*Assessment Method*	*Nut*	*Exposure*	*Body Weight*	*Energy Intake*	*References*
CSFII/ DHKS	14,262	Cross-sectional	Food records	Peanuts (whole and butter)	Peanut users *versus* non-users	Men: 26.3 *versus* 26.6 ($P > 0.05$) Women: 25.7 *versus* 26.2 ($P < 0.05$)	Men: 2569 *versus* 2214 kcal ($P < 0.001$) Women: 1727 *versus* 1546 kcal ($P < 0.001$)	[89]
NHS	83,818[a]	16	FFQ and food records	Peanut butter, peanuts, and tree nuts	Never, < 1 × per week,1 –4 × per week, and ≥ 5 × per week	BMI of 24.7, 24.3, 24.0, and 23.4[c]	1471, 1541, 1668, 1882[c] kcal, respectively	[94]
PREDIMED	847	Cross-sectional	FFQ	Walnuts or other nuts	BMI quintiles	Standardized β-coefficient for nut intake on BMI = –0.12 ($P < 0.007$)	nm	[86]

(*Continued*)

Table 5.1 (Continued) Energy Intake and Body Weight with Nut Consumption in Prospective Cohort and Cross-Sectional Studies

Study	*Sample Size*	*Follow-Up Duration (Years)*	*Assessment Method*	*Nut*	*Exposure*	*Body Weight*	*Energy Intake*	*References*
AHS-2	803	Cross-sectional	FFQ	Tree nuts, peanuts, and peanut butter	High (> 2 × per week) *versus* low (<2 × per week)	29.8 low peanut/low tree nut, 28.7 high peanut/low tree nut, 27.2 high peanut/high tree nut, 26.6 low peanut/high tree nut	1635 kcal low peanut/low tree nut, 1983 kcal high peanut/low tree nut, 2343 kcal high peanut/high tree nut, 1913 kcal low peanut/high tree nut	[90]
NHANES (1999–2004)	13,292	Cross-sectional	Dietary recall	Tree nuts (whole and butter)	Consumer (≥ 7.1 g/day) or non-consumers	nm	2568 *versus* 2193 kcal ($P < 0.01$)	[83]
NHANES (2005–2010)	14,386	Cross-sectional	Dietary recall	Tree nuts (whole and butter)	Consumer (≥ 7.1 g/day) or non-consumers	nm	2247 *versus* 2042 kcal	[84]

Abbreviations: AHS, Adventist Health Study; BMI, body mass index; CSFII/DHKS, Continuing Survey of Food Intake by Individuals and Diet and Health Survey; FFQ, Food Frequency Questionnaire; nm, not measured; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; PHS, Physicians' Health Study; PREDIMED, Prevención con Dieta Mediterránea; SUN, Seguimeiento Universidad de Navarra.

[a] Only females enrolled in study.

[b] Only males enrolled in study.

[c] Measurement at baseline assessment.

There is increasing recognition that the oral cavity is a critical, integral component of the gastrointestinal (GI) tract rather than a distinct entity. "Taste" receptors, once thought to exist only in the mouth, have now been identified throughout the body [3,4]. At the same time, appetitive hormones previously believed to emanate from the stomach and small intestine are now known to be released by taste cells [5,6]. Thus, there is coordination and a continuum of processes starting with the entry of food into the oral cavity and ending with fecal excretion that determines the impact of consuming any given food, beverage, or diet. This chapter begins by critically evaluating the literature relating the oral processing of nuts to energy intake, energy expenditure, and appetite, elaborating on the role of nut type and degree of processing. This is followed by a broader consideration of the effects of nut consumption on total diet quality and energy balance.

5.1.1 Mastication of Whole, Raw Nuts, and Energy Extraction

Mastication is the initial step in digestion [7]. Its primary role is to mechanically break down solid foods, such as nuts, into smaller particles so that nutrients embedded within cellular compartments of the food matrix can be released (bioaccessible) and made potentially available for absorption in the intestine (bioavailable) [8]. At the cellular level, mastication results in cell separation, cell rupture, or a combination depending on the structure and composition of the cell walls [8,9]. *Cell separation* occurs when the forces holding the cells together are weaker than the cell walls and is associated with limited release of intracellular nutrients. *Cell rupture* occurs when the forces holding the cells together are stronger than the cell walls and their cellular contents are released under pressure. Generally, the cells of soft plant tissues, such as cooked legumes and ripe fruits, separate, whereas the cells of crisp/crunchy plant tissues, such as nuts, tend to rupture. For the latter foods, the number of ruptured cells created during mechanical processing affects digestion and absorption of intra-cellular lipids and potentially other nutrients [10]. However, even when mastication fails to fully rupture cell walls, fractures and fissures are created that can provide digestive enzymes access to enter cells for digestion [7,10,11] and facilitate the release of nutrients [8,12].

Inadequate mastication may lead to inefficient energy absorption [13]. In the case of nuts, lipid bioaccessibility depends on the proportion of ruptured to intact cells after mastication, and this is generally inversely related to the size of particles in the swallowed food bolus [12,14], as illustrated in Figure 5.1. Whole raw almonds, for example, are chewed into relatively large particles and their particles have a proportion of cells that are not disrupted, thus making them more resistant to lipid release [14,15]. Few trials to date have investigated how chewing affects particle size and lipid release from less brittle whole nuts (e.g., walnuts, pine nuts, and cashews). Presumably, the mastication of these nuts results in smaller bolus particles, although cells may separate rather than rupture, limiting lipid release/digestion. Further verification is required to support this hypothesis.

5.1.2 Mastication of Processed Nuts and Energy Extraction

Inherent desired properties of nuts may be augmented by how they are processed which can alter their digestibility. Roasting dehydrates nut tissues, causing them to

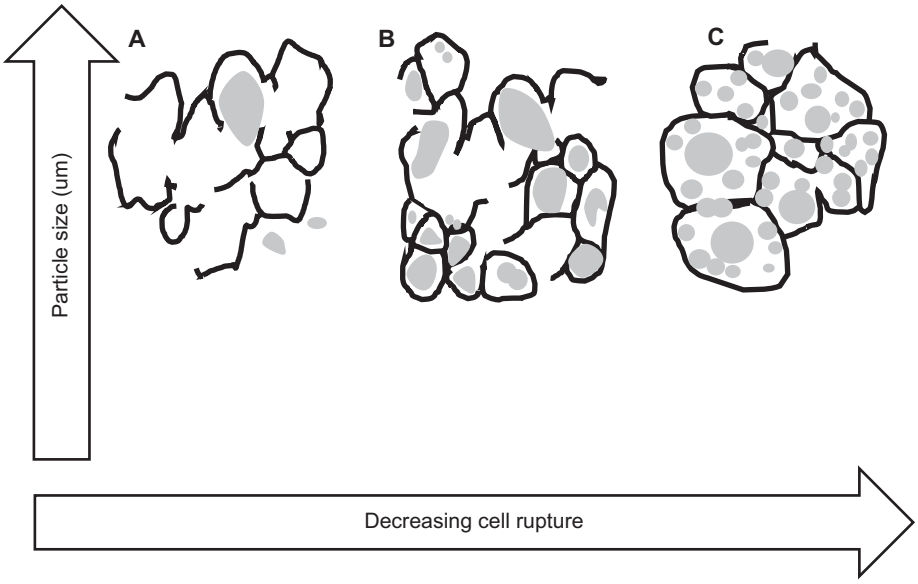


Figure 5.1 Structural changes in the microstructure of masticated nut particles of increasing size (*A*, *B*, and *C*). Note, cell wall structure is shown in black and intracellular lipids are in gray. *A* shows that cells within smaller bolus particles are ruptured and most of the cellular lipid has been extracted, and *B* and *C* illustrate limited cell wall rupturing within particles of larger sizes and cells.

become more brittle. This promotes their degradation during mastication and generally results in greater lipid bioaccessibility and bioavailability [16]. Additionally, roasting and nut form (e.g., whole, sliced, butter, oil, or flour) significantly modifies chewing behavior (e.g., bite force, number of masticatory cycles required before swallowing, and final particle size) [17]. The implications of processing remain poorly characterized. *In vitro* digestion of almonds demonstrates that roasting results in smaller particles when masticated but negligible changes in lipid release [12,14]. Randomized controlled trials (RCTs) have yielded different results. In one trial, roasted almonds yielded a greater number of particles with smaller sizes and greater available energy compared to whole raw almonds [18]. Conversely, another controlled trial reported particle sizes were significantly larger (> 3.35 mm) after mastication of sliced and roasted almonds compared to other almond varieties [19]. The variability in an individual's mastication patterns may, in part, contribute to the discrepancies in lipid availability across studies [20]. More research is necessary to understand the significance (or insignificance) of nut processing on nutrient bioavailability and energy extraction.

5.1.3 Mastication of Various Nut Types

Overall, the available data demonstrate that insufficient mechanical disruption of nut tissues results in incomplete nutrient release. Although most trials documenting this phenomenon have been conducted with almonds, trials with other nuts have

yielded similar findings [21–24]. However, energy yields do not conform to projections based on physical properties. Almonds and walnuts differ in hardness yet yield comparable energy [15,21]. Walnuts and pistachios are not markedly different in physical properties [21,22] but yield discrepant amounts of energy. It is presently not possible to predict energy yields across nut types; therefore, more information is needed to elucidate their contribution to energy balance. Further, nuts are eaten in many ways (e.g., boiled, steamed, or as ingredients), which can greatly affect their overall bioaccessibility. Generally, a better understanding of the relationship between nutrient extraction and the digestion of available energy in nuts would provide a basis for processing nuts to achieve different purposes. For individuals in positive energy balance, whole nut consumption may be recommended to lower energy bioaccessibility, whereas for individuals ingesting nuts with the goal of increasing intake of macro- and micronutrients, nut forms with higher nutrient bioavailability may be optimal (e.g., oil and butter).

5.1.4 Fecal Fat Excretion

The accepted energy values of nuts as reported in the United States Department of Agriculture (USDA) National Nutrient Database are based on the Atwater factors; a system commonly used to approximate the metabolizable energy of foods [25]. Evidence of the limited energy bioaccessibility of nuts is not reflected in these energy estimates. Recent studies indicate that almonds, walnuts, cashews, and pistachios provide approximately 24%, 21%, 16% and 5% less metabolizable energy, respectively, than predicted by Atwater factors [15,21,22,97]. Studies of peanuts [26,27] and pecans [23] also reveal inefficient energy absorption based on increased fecal fat loss, but the magnitude has not been quantified. Findings from these studies are summarized in Table 5.2. Indeed, nut form also impacts bioaccessibility and bioavailability, and thus fecal fat excretion varies depending on the physical food form consumed. This effect has been documented in trials with various peanut [24,26] and almond products (e.g., whole, sliced, butter, and oil) [18].

5.1.5 The Role of Mastication on Energy Expenditure

Another complementary explanation for the inverse or null association between nut consumption and body weight relates to enhanced energy expenditure with chronic nut consumption. Total energy expenditure is primarily comprised of three components: resting energy expenditure (REE) (the energy required to support the body at rest), thermogenic effect of feeding (TEF) (the energy cost of digesting, absorbing, and metabolizing food), and the energy expended during physical activity [28]. Several trials reveal an increase in thermogenesis with peanut consumption [27,29,30]. One study observed an increase in REE and TEF after providing 320 kcal of high-oleic peanuts to men with overweight or obesity in an acute feeding trail [29]. Another trial found that REE was elevated 11% after frequent peanut consumption in healthy adults for 19 weeks; however, no change in TEF was observed [27]. Similarly, another trial noted a 5% increase in REE in participants with overweight compared to normal weight participants following peanut oil ingestion for 8 weeks, and an 11% increase in REE was reported in overweight men only [30]. This increase

Table 5.2 Human Feeding Studies with Nuts Reporting Data on Fecal and Energy Loss

Nut Type	*Intervention*	*Time (Week)*	*Total Fecal Energy Loss*	*Fecal Fat Energy Loss*	*Comments*	*References*
Almonds	0 g/day *versus* 43 g/d *versus* 86 g/day + controlled diet	4	nm	2-Fold ↑ with 43 g/day and 86 g/day *versus* 0 g/day	Total energy of the diet not specified	[95]
Almonds	0 g/day *versus* 42 g/day *versus* 84 g/day + controlled diet	2	↑ With 42 g/day and 84 g/day *versus* 0 g/day	4-Fold ↑ with 42 g/day 6-Fold ↑ with 84 g/day	↓ Absorption of total CHO with 42 g/day *versus* 0 g/day. ↓ Absorption of CHO, fiber, and protein with 84 g/day *versus* 0 g/day. Dose response on change in fecal fat. Dose response on change in energy loss.	[15]
Almonds	42/g whole (R and RO) *versus* 42/g slice (R and RO) *versus* 42/g nut butter + controlled diet	3	↑ Whole (R and RO) and sliced R ↔ Nut butter	nm	70%, 75%, 78%, and 98% of energy from whole R, whole RO, sliced R, and butter was absorbed, respectively.	[18]
Almonds	55 g/day with different levels of controlled chewing (10 *versus* 25 *versus* 40 chews)	3	↑ After 10 chews *versus* 40 chews	↑ After 10 chews *versus* 25 and 40 chews	With lower levels of chewing, total energy and fat loss was greater than with higher levels of chewing. Control group not included.	[29]

(*Continued*)

Table 5.2 (Continued) Human Feeding Studies with Nuts Reporting Data on Fecal and Energy Loss

Nut Type	*Intervention*	*Time (Week)*	*Total Fecal Energy Loss*	*Fecal Fat Energy Loss*	*Comments*	*References*
Cashews	0 g/day *versus* 42 g/day + controlled diet	4	↑ With 42 g/day *versus* 0 g/day Increased from 129.6 to 186.3 kcal/day	↑ With 42 g/day *versus* 0 g/day Increased from 1.7 to 3.6 g/day	↓ Digestibility of fat, protein, and carbohydrate in the total diet with 42 g/day versus 0 g/day.	[97]
Peanuts	Control period *versus* 70 g/day P *versus* PB *versus* PO *versus* PF + controlled non-vegetarian diet	2	↑ With P, PB, and PF ↔ With PF	↑ With P *versus* control ↓ With PB and PF ↑ With P *versus* control ↓ With PB and PF	EI ↑ with P, PB, and PF.	[26]
Peanuts	76 g/day P *versus* PB *versus* PO + 20 g fiber/day HF *versus* 10 g fiber/day LF vegetarian diet	6	nm	↑ With P, PB, and PO on HF/LF	Fiber plus the large quantity of nuts likely resulted in the overestimation of the effects of nut form on stool fat excretion.	[24]
Pecans	0 g/day *versus* 71 g/day	4	↑ With 71 g/day *versus* 0 g/day	nm	Total energy content of the diet not specified. More energy from fat provided by pecan diet (43%) *versus* control (30%) that may introduce confounding.	[23]

(*Continued*)

Table 5.2 (Continued) Human Feeding Studies with Nuts Reporting Data on Fecal and Energy Loss

Nut Type	*Intervention*	*Time (Week)*	*Total Fecal Energy Loss*	*Fecal Fat Energy Loss*	*Comments*	*References*
Pistachio	0 g/day *versus* 42 g/day *versus* 84 g/day + controlled diet	2	3-Fold ↑ with 42 g/day *versus* 0 g/day 4-Fold ↑ with 84 g/day *versus* 0 g/day	2-Fold ↑ with 84 g/day	↑ EI with 84 g/day *versus* 42 g/day and 0 g/day. No dose response on change in fecal fat. Dose response on change in energy loss. 5% energy malabsorbed.	[22]
Walnuts	0 g/day *versus* 42 g/day + controlled diet	3	4-Fold ↑	2-Fold ↑	21% energy malabsorbed.	[69]

Abbreviations: CHO, carbohydrate; EI, energy intake; HF, high fiber; LF, low fiber; nm, not measured; P, whole peanuts; PB, peanut butter; PF, peanut flour; PO, peanut oil; R, raw; RO, roasted.

in REE was sustained after adjusting for body weight and heart rate. No differences in TEF were reported in groups that were either lean or overweight [30]. Other trials have failed to observe differences in energy expenditure among different types of nuts (e.g., walnuts [31], hazelnuts [32], or almonds [2,33]). To date, data do not indicate that nut consumption augments physical activity [2,27,30,32,33]. Only one study reported an increase in physical activity with regular nut consumption [34]. However, the study was not designed to assess changes in energy expenditure.

The mechanism by which nut consumption may increase energy expenditure is not clear but has been attributed to the combination of mono- and polyunsaturated fatty acids (MUFA and PUFA) and protein they provide. Protein is the most thermogenic macronutrient [35], and unsaturated fatty acids are oxidized more rapidly than saturated fatty acids (SFA) [36]. This would be expected to result in increased TEF, which has not been widely observed. Chewing can elevate REE [37–39], but not to the magnitude reported for nut intake. Taken together, a rise in energy expenditure associated with nut consumption has been reported, but not consistently. Verification or rejection of this proposed mechanism for energy dissipation would be worthwhile.

Collectively, these data provide a plausible mechanism to explain findings of higher daily energy intake coupled with neutral effects on body weight among nut consumers. Increased fecal energy loss and elevated energy expenditure would offset the greater energy consumption as measured by bomb calorimetry or calculations based on proximate analyses of nuts.

5.1.6 Oral Processing of Nuts and Appetite

5.1.6.1 Nut Consumption, Gut Hormones, and Appetite

The oral processing of nuts may promote satiety by various mechanisms [40,41]. First, mastication disrupts the cell walls of nuts, releasing the lipids and proteins from the cells [42], which, in turn, prompt the release of gut-derived hormones, such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), peptide YY (PYY), and leptin, that reportedly enhance satiation and satiety. However, the evidence is mixed regarding whether these hormones alter appetite or if they simply aid the digestive process of food components that promote satiety [43,44]. Studies that measured endocrine responses from nuts have yielded inconsistent results: one trial showed significantly increased PYY after peanut consumption compared to no peanuts [45], whereas other trials reported no significant difference in PYY concentration after consumption of walnuts [31] or pine nut oil [46] compared to no nuts. Similar discrepant results were observed for GLP-1. A significant increase in GLP-1 concentration has been noted after consumption of pine nut oil compared to no nut consumption [46], while others reported trends but no significant differences with nut consumption compared to no nut consumption [45]. Additional studies noted no significant difference in GLP-1 concentration after whole nut consumption compared to no nut consumption [31,47]. Other measured hormones (e.g., CCK, ghrelin, leptin, and GIP) also showed inconsistent findings after consumption of nuts compared to no nuts [31,45–47]. Therefore, the role of gut hormone responses in nut-induced satiety is not clear.

Second, the satiety effect of nuts may be partially attributed to their physical form and increased need for mastication. Studies comparing nut forms have isolated

the relative importance of oral processing on appetite (appetitive sensations defined in Table 5.3). One study reported that, when consumed as a preload, both peanuts and peanut butter led to suppression in hunger ratings, but the decline was less with peanut butter [48]. In another study that compared whole almonds, almond butter, almond flour, and almond oil, daylong fullness ratings were significantly higher after consuming whole almonds compared to almond flour and almond oil, and higher fullness ratings were reported for almond butter compared to almond flour [47]. Similar results have been reported with whole walnuts and walnut butter [107]. These results suggest that whole nuts have stronger satiation and hunger suppressing effects than forms that have been mechanically reduced. There may be a higher expected satiation with whole nuts that becomes self-fulfilling [49]. Thus, it appears that mechanical processing makes a stronger contribution to appetitive sensations than nutrient signaling, but a cognitive effect is also plausible [50].

5.2 Non-Oral Effects of Nut Consumption on Appetite

5.2.1 Timing of Nut Consumption

Over the past two decades, nuts have become a model food for appetite control: They have been shown to increase satiation [47] and satiety [31] and to decrease hunger [48,51] and desire-to-eat [51] ratings. The timing of nut consumption may alter their effects on appetite [51]. Several studies indicate a strong appetitive effect when nuts are consumed in the morning. Consumption of whole almonds in cereal at breakfast significantly increased daylong fullness ratings compared to cereal without almonds in adults who were overweight [47]. Similarly, walnut consumption as part of a shake at breakfast was associated with higher satiety and fullness ratings before consumption of lunch compared to when an energy, carbohydrate, and fat-matched placebo shake was consumed at breakfast [31]. Reported satiety remained significantly increased after 3 and 4 days of consuming the walnut shakes at breakfast [31]. When almonds were consumed with a meal at lunch, there was less hunger suppression than when almonds were consumed at breakfast [51]. Likewise, there

Table 5.3 Definitions of Indices of Appetite

Indices of Appetite	*Definition*
Hunger	The sensation that initiates an eating event based on a biological need for energy. It is not related to how much one can eat.
Fullness	The sensation that grows within an eating event and controls how much food one will eat.
Desire to eat	The sensation that is driven by cognitive influences, sensory properties of foods, and expectation. It provides motivation to seek out food independent of energy needs. It is not related to how much one can eat.
Prospective consumption	An estimate of how much one thinks they can eat at a given moment.
Satiation	The sensation that promotes the termination of an eating event.
Satiety	The sensation that influences the interval between eating events.

were no significant differences in appetite ratings when peanuts were consumed at lunch compared to an iso-energetic meal [52]. This suggests that if consumed with a meal, nuts paired with breakfast elicit optimal suppression of hunger and increased satiety ratings throughout the morning and day in acute feeding trials, although additional verification is required.

Snack consumption promotes excess energy intake and has been implicated in the obesity epidemic [53,54]. However, nuts consumed as a snack can exert marked suppressive effects on hunger and desire to eat ratings [51]. A 4-week, randomized, controlled parallel-arm study with participants at risk for type-2 diabetes contrasted almond consumption at breakfast, lunch, or as a morning or afternoon snack compared to no almond consumption. Participants who consumed almonds reported lower hunger and desire-to-eat ratings before the subsequent meals. However, participants that consumed almonds alone as a morning or afternoon snack reported significantly lower levels of hunger and desire to eat ratings 60 minutes post snack, compared to when almonds were consumed with meals. In that trial, there were no significant differences in fullness ratings [51]. In another study, normal weight women reported dose-dependent greater fullness and lower hunger after consumption of 0, 28, or 42 g of raw almonds as a mid-morning snack. Energy intake at lunch was also lower in a step-wise pattern. However, the appetite ratings were not suppressed throughout the day, as no significant group differences in appetitive ratings between lunch and dinner were observed [55]. Conversely, another study examining the effects of peanuts consumed with a meal or as an afternoon snack in healthy participants observed that average hunger and fullness ratings did not differ between snack groups with and without peanuts or with timing of consumption. However, there was greater energy compensation after consuming the peanut-only load and the snack mix with the peanut load compared to the energy-matched control snack [52]. Although not fully consistent, the preponderance of evidence indicates nuts consumed as a snack suppress hunger, augment fullness, and promote energy compensation at a subsequent eating event. If verified through further work, this would support a role for nuts by individuals who choose to snack while attempting to maintain or lose body weight. Collectively, nuts consumed with breakfast or as a snack have the most pronounced effects on appetite compared to other times of the day.

5.2.2 Properties of Nuts that Affect Appetite

While no single property of nuts has been shown to account for noted appetitive effects, there are multiple reasons for the decreased ratings of hunger and desire to eat and the increased ratings of fullness and satiety reported across studies. First, nuts provide 0.9–3.5 g of dietary fiber per 1 oz portion [56]. Fiber contributes to gastric distension and slows gastric emptying, transit time, and absorption of nutrients from the GI tract. These actions possibly increase feelings of fullness, but they do not explain the entire phenomenon. Secondly, nuts provide unsaturated fatty acids, including 2.5–16.7 g MUFA and 0.4–13.4 g PUFA per 1 oz serving [56]. Unsaturated fatty acids are more readily oxidized than SFA [57]. It has been hypothesized that fatty acid oxidation maintains satiety between meals and is documented to delay the onset of feelings of hunger in mice [57]. Therefore, the high unsaturated fatty acid content of nuts could contribute to satiety and longer intervals between eating events [57]. However, several trials failed to report differential appetitive effects

following nut loads varying in fatty acid composition [58,59]. Nuts are also rich in protein, with a content ranging from 2.2–6.0 g per oz [56]. Protein is reportedly the most satiating macronutrient [60], and consumption is associated with decreased energy intake compared to other macronutrients [61–63]. Protein consumption leads to the secretion of satiety hormones such as GIP, GLP-1, CCK, and PYY and the inhibition of ghrelin, all of which may promote satiety. However, as noted above, nut consumption does not have a robust effect on gut peptide secretion. Nevertheless, the composition of nuts (e.g., fiber, unsaturated fat, and protein) may contribute to their effects on appetite.

In addition to their chemical composition, there are physical attributes of nuts that could aid in modulating appetite. For example, consuming in-shell nuts may lower energy intake. A randomized, crossover, controlled-feeding trial in university students revealed that consumption of in-shell pistachios led to lower energy intake than shelled pistachio kernels [64]. It was hypothesized that not only does consumer manual shelling slow consumption time, but also that the empty shells provide a visual cue as to how many nuts were eaten, which may affect appetite and energy intake [65]. However, no significant differences in fullness or satisfaction ratings were reported in this study [64].

Overall, nuts have been shown to increase fullness and satiety and to decrease hunger and desire-to-eat ratings, especially when eaten at breakfast or as snacks. Multiple nutrient, cognitive, and physical properties of nuts likely act synergistically to impart these sensations, and isolation of these components does not yield the same effects. But even so, changes in appetitive sensations are just one mechanism by which nuts may prompt energy displacement.

5.3 Nut Consumption and Dietary Compensation

When nuts are consumed, they may be added to the diet or displace other energy-yielding foods or beverages to varying degrees. The latter is referred to as *dietary compensation* or *energy displacement*. Dietary compensation is calculated as the percentage of energy contributed by the nut that is offset by the reduction of free-feeding energy intake [61]. Compensation most commonly refers to energy intake but may be assessed for any nutrient or other food constituent.

The following dietary information is needed to calculate dietary energy or nutrient (i) compensation [27,62] in feeding trials: habitual or baseline energy intake (H_i), amount of energy in the supplemented food (S_i), and the observed energy intake on the supplemented diet (A_i). Percent dietary compensation equates to $\frac{(H_i + S_i) - A_i}{S_i} * 100$. Zero pearcent dietary compensation occurs when the supplemented food is *added* to the diet. This results in increased energy intake contributed by the nut supplement and theoretically increases body weight if consumed chronically. Varying degrees of dietary compensation can occur if nuts are *substituted* for other forms of energy in the diet, either intentionally or unintentionally. 100% dietary compensation occurs when all the energy provided by the nut supplement is displaced by an equal amount of energy from the free-feeding diet. Under this condition, no change in body weight would be expected. If nut supplementation leads to reduced total daily energy intake compared to the habitual diet, then dietary

compensation is greater than 100%. This would be expected to lead to weight loss. Partial compensation would lead to an intermediate level of weight gain if compensation is the only mechanism by which the energy from nuts is offset. As discussed above, this is not the case due to inefficiencies in energy extraction. This section discusses dietary compensation in response to nut consumption as a mechanism to explain the lack of change in body weight after incorporating nuts into the diet.

5.3.1 Summary of RCTs

Numerous studies have investigated energy intake and body weight changes with the incorporation of a variety of nuts to the diet. Dietary compensation studies have been summarized previously [43,61]. These and additional trials assessing the effect of nut consumption on energy intake, dietary compensation, and body weight are compiled in Table 5.4. When dietary compensation was not reported in the primary research article, an estimation was calculated based on the energy content of the nut load, habitual energy intake, and energy intake with the nut load (see formula above). Reported dietary compensation with nut consumption ranges from 19%–151%. Variability in calculated dietary compensation may be attributed to study design (e.g., free feeding, substitution, and addition to diet) and the nature of the nut load (e.g., nut type, physical form, and portion size).

5.3.2 Impact of Study Design on Dietary Compensation

Free-feeding studies supply nuts to participants with no additional dietary guidance and are the most ecologically valid approach to studying dietary compensation. In contrast, substitution studies direct participants to substitute the nuts for another source of energy in the diet. Addition trials require participants to adhere to their customary diet, purposefully prohibiting compensation with the addition of nuts. To understand the effect of the free-feeding, substitution, and addition consumption of peanuts on energy balance, one trial instructed participants to consume 50% of their energy as peanuts freely, in addition to, or substituted into an isoenergetic diet in a crossover design trial [27]. Dietary compensation in the substitution arm was 98%, which was expected, given this was the dietary instruction. Dietary compensation in the addition arm (theoretically 0% energy compensation) was 56%. Thus, participants did not comply with the dietary instruction – an observation that is consistent with a high satiety value for peanuts. When provided with peanuts to consume freely with no dietary advice, dietary compensation was 66%. These results suggest energy intake is at least partially compensated for with intake of peanuts in a free-feeding environment.

5.3.3 Impact of Nut Type and Load on Dietary Compensation

Both nut type and energy content of the nut load could influence dietary compensation. Few RCTs compare energy compensation between nuts. One acute study reported that peanuts and peanut butter preloads led to compensation of 151% and 104%, respectively, while compensation was 57% following consumption of almonds

Table 5.4 Summary of Randomized Controlled Trials with Nut Supplements

Study Design	*Free Feeding, Substitution, Addition*	*Nut*	*Dose (Per Day)*	*Control*	*Duration*	*Compensation*	*Change in Energy Intake*	*Change in Body Weight*	*References*
Crossover, 3 arms	Free feeding, addition, and substitution	Peanuts	89 g (505 kcal)	Free feeding, addition, and substitution	30 weeks and 3–10 weeks treatments	66% free feeding, 56% addition, and 98% substitution	NS	NS	[27]
Parallel arm, 2 arms	Free feeding	Walnuts	43 g/day (281 kcal)	No load	24 months	19%	IN	NR	[63]
Preload	Free feeding	Peanuts	300 kcal	Isocaloric load	300 min	50%–74%	NS	NR	[52]
Cohort	Free feeding	Almonds	15% of daily energy, 54.3 g (320 kcal)	0 kcal/day from nuts	6 months	54%–78%	IN	IN	[33]
Crossover, 2 arms	Free feeding	Almonds	344 kcal	No load	23 weeks	74%	D	NS	[2]
Crossover, 2 arms	Substitution	Walnuts	75 g/day (491 kcal)	No load	8 weeks	25%	IN	NS	[67]
Preload	Free feeding	Almonds	80.4 g (500 kcal)	No load and isoenergetic preload	180 min and 24 hours	57%	NS	NR	[48]
Preload	Free feeding	Peanuts	87.5 g (500 kcal)	No load and isoenergetic preload	180 min and 24 hours	104%	NS	NR	[48]
Preload	Free feeding	Peanut butter	70.8 g (500 kcal)	No load and isoenergetic preload	180 min and 24 hours	151%	NS	NR	[48]

(*Continued*)

Table 5.4 (Continued) Summary of Randomized Controlled Trials with Nut Supplements

Study Design	*Free Feeding, Substitution, Addition*	*Nut*	*Dose (Per Day)*	*Control*	*Duration*	*Compensation*	*Change in Energy Intake*	*Change in Body Weight*	*References*
Parallel, 4 arms	Free feeding	Peanut oil	~52 g/day (460 kcal)	Olive oil, safflower oil, or no load	8 weeks	46%	IN	NR	[96]
Parallel arm, 4 arms	Free feeding	Hazelnuts	42 g (263 kcal)	50 g chocolate, 50 g potato crisps, or no snack	12 weeks	68%	NS	NS	[68]
Parallel arm, 4 arms	Free feeding	Hazelnuts	42 g (263 kcal)	50 g chocolate, 50 g potato crisps, or no snack	12 weeks	61%	NS	NS	[63]
Crossover, 4 arms	Free feeding and dietary counseling	Walnuts	48 g (375 kcal)	No load	40 weeks	80%[c] with walnuts, 99%[c] with walnuts, and low fat diet	IN	NS	[66]
Prospective cohort	Free feeding	Macadamias	15% of daily energy, 40–90 g[b]	No load	4 weeks	69%–86%	NS	D	[98]
Cross-over, 3 arms	Free feeding	Almonds	28 or 42 g (173 and 259 kcals)	No load	3 days	72% with 28 g load and 115% with 42 g load[c]	NS	NR	[55]

(*Continued*)

Table 5.4 (Continued) Summary of Randomized Controlled Trials with Nut Supplements

Study Design	*Free Feeding, Substitution, Addition*	*Nut*	*Dose (Per Day)*	*Control*	*Duration*	*Compensation*	*Change in Energy Intake*	*Change in Body Weight*	*References*
Cohort	Free feeding	Almonds	52 g (307 kcal)	No load	6 months	54%[c] (report 7.7% from median)	IN	NR	[62]
Crossover, 3 arms	Substitution and low-fat dietary counseling	Almonds	11.1% of daily energy + 11.1% of daily energy, and 22.2% of daily energy	Isoenergetic muffin	4 weeks	76%[c] on half almond supplement and 68%[c] on full almond supplement	IN	NS	[99]
Preload	Free feeding and low fat dietary counseling	Peanuts	28 g (170 kcal)	Grain bar (140 kcal)	8 weeks	55%[c]	NS	IN compared to grain bar	[100]
Cohort	Substitution	Almonds	100 g (579 kcal[c])	No load	4 weeks	115%[c]	NS	IN	[101]
Parallel, 5 arms	Free feeding	Peanuts	56 g (313–335 kcal)	Isoenergetic nut form	4 weeks	99%[c]	NS	NS	[102]
Prospective cohort	Substitution and controlled feeding	Hazelnuts	11.6% of daily energy, 40 g (251 kcal)	Low-fat diet	4 weeks	–6.8%[c]	IN	NS	[103]
Parallel, 2 arms	Free feeding	Pecans	68 g (459 kcal)	No load	8 weeks	30%[c]	IN	NS	[104]

(*Continued*)

Table 5.4 (Continued) Summary of Randomized Controlled Trials with Nut Supplements

Study Design	*Free Feeding, Substitution, Addition*	*Nut*	*Dose (Per Day)*	*Control*	*Duration*	*Compensation*	*Change in Energy Intake*	*Change in Body Weight*	*References*
Crossover, 2 arms	Free feeding	Walnuts	12% of daily energy, 28–56 g (183–366 kcal)	No load	12 weeks	42%[c]	IN	IN	[69]
Parallel arm, 5 arms	Free feeding	Almonds	43 g (245 kcal)	No load	4 weeks	81%–129%[c]	NS	NS	[51]
Parallel arm, 3 arms	Dietary counseling[a]	Walnuts bread	30 g	No load	12 weeks	199%[c]	IN	NS	[105]
Prospective cohort	Free feeding	Hazelnuts	1 g/kg	No load	4 weeks	–48%[c] to 17%[c]	IN	NS	[106]
Parallel arm, 3 arms	Dietary counseling	Almonds	56 g (343 kcal)	Cereal bar (227 kcal) and no load	12 weeks	123% at 6 weeks and 131% at 12 weeks[c]	NS	NS	[70]

Abbreviations: D, decreased; IN, increased; NR, not reported; NS, difference not significant.

[a] Participants were instructed to replace a staple food with the bread supplement provided and received dietary counseling and written materials to adhere to American Heart Association Guidelines.

[b] Exact amount of energy in the supplement not provided.

[c] Calculated using formula if compensation was not provided in the study.

[48]. However, there is not enough evidence from RCTs to conclude that consumption of any one type of nut leads to greater dietary compensation than another. This is largely due to the wide variability in energy compensation across studies. For example, calculated energy compensation with walnut consumption was 19% in one study [63] and 80% in another study [66]. Some studies provide nut supplements based on the subjects' daily energy requirement; other studies use a specified energy load. Both methods have their advantages and disadvantages. Interpretation of weight change in interventions with nut loads based on energy requirements would equate the magnitude of metabolic challenge across individuals and thereby reduce variance. On the other hand, providing a specified load may be more relevant to free-feeding conditions, because nuts are often consumed in pre-portioned packages.

5.3.4 Dietary Compensation and Body Weight in RCTs

Despite incomplete compensation, body weight does not change significantly with chronic nut consumption [2,27,32,33,67–73]. Weight gain did occur in two free-feeding studies, although the gain was far less than expected if no dietary compensation had occurred [33,69]. With no dietary advice other than to add 12% of dietary energy as walnuts (on average 35 g), changes in body weight and fat mass were minimal (1.0 kg) [69]. Similarly, when 15% of daily energy was consumed as almonds (on average 54.3 g or 320 kcal), dietary compensation fell between 54% and 78% (based on estimates from dietary recalls and food diaries, respectively). Actual weight gain was only 0.40 kg [33]. Therefore, despite incomplete compensation of dietary energy, there is little evidence from RCTs that consumption of nuts promotes weight gain [43,61,74,75].

5.4 Nut Consumption Patterns

Before summarizing what food groups might be displaced with nut consumption, it is important to understand how nuts are typically consumed. The healthy fat trend, increased snack consumption, and desire for healthy convenience foods have led to increased nut sales since the late 1990s [76,77] as well as the increased inclusion of nuts in alternative food products [78]. In 2001–2004, candy was the top nut-containing food (46%), followed by baked items/desserts (24%), cookies (17%), ready-to-eat cereal (9%), and entrees (4%) [79]. In 2009–2010, approximately 80% of nuts in the United States were consumed as a single food item. The remaining 20% were consumed with grains (6.7%–8.5%) or candy (8.0%–8.5%) [80]. Nuts are now most commonly consumed as snacks (75%) [77]. However, nuts (particularly nut butters in sandwiches or nuts in confections) can also be consumed as part of a mixed meal. Peanuts can be consumed as peanut butter and jelly, a common convenient meal eaten by adolescents and adults in the United States. Consumption of nuts in this form is quite different than consumption of a walnut cookie or almonds out of hand, yet it is classified the same in the epidemiological assessment of National Health and Nutrition Examination Survey (NHANES) datasets and other dietary pattern databases. For example, an assessment of African American women with overweight or obesity found nuts were most commonly consumed as desserts, and consumption of nuts was associated with increased consumption of added sugars [81]. The consumption of nut-containing products has

not been evaluated extensively in either epidemiological studies or RCTs. Although nuts may contribute desired nutrients, ultimately their health impact will be determined by how they are included in the diet.

5.4.1 Nut Consumption and Diet Quality

Generally, nut consumption leads to a nutrient profile of the diet that reflects that of the nut itself (e.g., increased fiber, MUFA, PUFA, vitamin E, and potassium and magnesium, among others). Diet quality is commonly determined by compliance to the USDA Guidelines for Americans, assessed using the Healthy Eating Index (HEI). It has been proposed that replacing all snacks in the typical American diet (based on NHANES 2009–2012 data) iso-energetically with nuts would theoretically improve diet quality by reducing energy contributed by solid fats and added sugars [82]. Nut consumers (defined as consuming ≥ 7.09 g of nuts/day) had higher HEI-2010 scores than non-consumers in both NHANES 1999–2004 and 2005–2010 [32,83,84]. Similarly, nut consumers in Mediterranean countries typically have higher Mediterranean diet scores and overall metabolic health than non-nut consumers [85,86].

Although HEI is a validated method for assessing diet quality from dietary recalls [87], using this index to determine the effect of nut intake on diet quality is questionable in both RCTs and epidemiological studies. This is primarily because nuts themselves are a dimension of the HEI score formula, falling under "total protein foods" and "fatty acids." Therefore, by definition of the HEI, diet quality improves with nut consumption even if all other components of the diet stay the same. A better assessment of diet quality requires examination of intake of specific foods and nutrients, and how they change between nut consumer categories. Cross-sectional dietary pattern studies commonly report higher total fat [83,88], lower saturated fat [83,89], lower total grains [83,84], lower refined grains [88], and lower meat [83,88,90] consumption among nut consumers, suggesting that nuts may, in part, replace these items in the diet.

Improved diet quality associated with nut intake raises the question of whether nuts themselves reduce the risk of obesity or metabolic diseases or if nuts are simply consumed by individuals who practice a healthy diet and lifestyle; is it the nut or the person consuming the nut? Although it is likely that nuts are consumed by individuals who practice other healthy diet and lifestyle patterns, there is evidence that nut consumption improves diet quality. When provided with mixed nuts as part of the Mediterranean diet in the Prevención con Dieta Mediterránea (PREDIMED) study, nut consumers reported increased consumption of legumes and fish compared to the habitual diet [73]. In another study, participants consumed lower quantities of SFA, carbohydrates, and higher total fat, MUFA, and PUFA when provided with a daily serving of hazelnuts for 12 weeks than participants provided with iso-energetic chocolate, potato crisps, or no additional food. A replication of this study yielded similar results [68]. However, nut supplementation alone does not appear to improve diet quality beyond the nutritional benefits of the included nuts.

5.5 Are There Differences between Nuts?

Although all nuts are energy-dense and nutrient-rich, they vary on multiple dimensions such as macro- and micro-nutrient content, phytochemical content, structural

and sensory properties, consumption practices, and food forms. Evidence to date indicates that no nut yields 100% of their calculated energy content, although there is some variability between nut types and forms [15,21,22]. Despite these differences, all nuts have the same effect on energy balance. Since nuts are grouped into one category in most epidemiological trials, the ability to determine whether there are differences between nuts is limited. Epidemiological studies investigating the difference between the impact of peanuts and tree nuts on obesity reported greater weight maintenance benefits with the consumption of tree nuts than with peanuts [88,90]. However, this has not been evaluated in a RCT and remains uncertain [90]. Nuts are rarely compared between each other in RCTs. If multiple nuts are consumed, they are typically delivered as a mixture of nuts rather than separately to different groups. Overall, there is currently not enough evidence to determine if the various nuts have different effects on appetite or dietary compensation. The prevailing view is that nuts are more similar than different in their effects on body weight [43].

5.6 Conclusion

Obesity has risen markedly over the last several decades, and studies have shown a positive relationship between body weight and high-energy-dense foods [91]. Nuts are energy-dense and can make substantial contributions to daily energy intake, yet the literature indicates that frequent nut consumption does not undermine, and may even aid, weight loss/maintenance. Multiple mechanisms linked to the oral cavity, including incomplete energy bioaccessibility, a possible augmentation of thermogenesis, and superior satiety/satiation effects, have been proposed to explain the lack of association between nut consumption and weight gain. Based on the available evidence from RCTs, mastication seems to have an effect on the bioaccessibility and satiety properties of nuts. However, additional data are needed to make definitive conclusions concerning the specific role of mastication in the thermogenic and energy compensation effects of nuts. Future studies should determine whether different forms and types of nuts have distinct effects on nutrient bioaccessibility, appetite responses, and energy compensation.

In conclusion, nuts included in a healthy dietary pattern may be beneficial for weight management because they provide many important nutrients that are known to improve human health concurrent with appetitive sensations that drive strong energy compensation. However, the impact of nuts on health cannot be detached from the foods they displace in the diet. The degree to which the health benefits associated with nut consumption are altered by the foods they displace in the diet is not well understood. Additional data regarding the effects of nut consumption on overall diet quality are needed to further our understanding of the greater effect they exert on health.

References

1. Brown, R.C., Yong, L.C., Gray, A.R., Tey, S.L., Chisholm, A., and Leong, S.L., Perceptions and knowledge of nuts amongst health professionals in New Zealand. *Nutrients*, 9, 220, 2017.
2. Hollis, J., and Mattes, R., Effect of chronic consumption of almonds on body weight in healthy humans. *Br. J. Nutr.*, 98, 651–656, 2007.

3. Janssen, S., and Depoortere, I., Nutrient sensing in the gut: New roads to therapeutics? *Trends Endocrin. Met.*, 24, 92–100, 2013.
4. Depoortere, I., Taste receptors of the gut: Emerging roles in health and disease. *Gut*, 63, 179–190, 2014.
5. Cai, H., Maudsley, S., and Martin, B., What is the role of metabolic hormones in taste buds of the tongue. *Front. Horm. Res.*, 42, 134–146, 2014.
6. Calvo, S.S., and Egan, J.M., The endocrinology of taste receptors. *Nat. Rev. Endocrinol.*, 11, 213–227, 2015.
7. Kong, F., and Singh, R., Disintegration of solid foods in human stomach. *J. Food Sci.*, 73, R67–R80, 2008.
8. Grundy, M.M., Edwards, C.H., Mackie, A.R., Gidley, M.J., Butterworth, P.J., and Ellis, P.R., Re-evaluation of the mechanisms of dietary fibre and implications for macronutrient bioaccessibility, digestion and postprandial metabolism. *Br. J. Nutr.*, 116, 816–833, 2016.
9. Waldron, K.W., Parker, M., and Smith, A.C., Plant cell walls and food quality. *Compr. Rev. Food Sci. Food Saf.*, 2, 128–146, 2003.
10. Mandalari, G., Faulks, R.M., Rich, G.T., Lo Turco, V., Picout, D.R., Lo Curto, R.B., Bisignano, G. et al., Release of protein, lipid, and vitamin E from almond seeds during digestion. *J. Agric. Food Chem.*, 56, 3409–3416, 2008.
11. Grassby, T., Picout, D.R., Mandalari, G., Faulks, R.M., Kendall, C.W., Rich, G.T., Wickham, M.S. et al., Modelling of nutrient bioaccessibility in almond seeds based on the fracture properties of their cell walls. *Food Funct.*, 5, 3096–3106, 2014.
12. Mandalari, G., Grundy, M.M., Grassby, T., Parker, M.L., Cross, K.L, Chessa, S., Bisignano, C. et al., The effects of processing and mastication on almond lipid bioaccessibility using novel methods of *in vitro* digestion modelling and micro-structural analysis. *Br. J. Nutr.*, 112, 1521–1529, 2014.
13. Cassady, B.A., Hollis, J.H., Fulford, A.D., Considine, R.V., and Mattes, R.D., Mastication of almonds: Effects of lipid bioaccessibility, appetite, and hormone response. *Am. J. Clin. Nutr.*, 89, 794–800, 2009.
14. Grundy, M.M.L., Grassby, T., Mandalari, G., Waldron, K.W., Butterworth, P.J., Berry, S.E., Ellis, P.R. et al., Effect of mastication on lipid bioaccessibility of almonds in a randomized human study and its implications for digestion kinetics, metabolizable energy, and postprandial lipemia. *Am. J. Clin. Nutr.*, 101, 25–33, 2015.
15. Novotny, J.A., Gebauer, S.K., and Baer, D.J., Discrepancy between the Atwater factor predicted and empirically measured energy values of almonds in human diets. *Am. J. Clin. Nutr.*, 96, 296–301, 2012.
16. Grundy, M.M.L., Lapsley, K., and Ellis, P.R., A review of the impact of processing on nutrient bioaccessibility and digestion of almonds. *Int. J. Food Sci. Technol.*, 51, 1937–1946, 2016.
17. McKiernan, F., and Mattes R.D., Effects of peanut processing on masticatory performance during variable appetitive states. *J. Nutr. Metab.*, 487301, 2010.
18. Gebauer, S.K., Novotny, J.A., Bornhorst, G.M., and Baer, D.J., Food processing and structure impact the metabolizable energy of almonds. *Food Funct.*, 7, 4231–4238, 2016.
19. Frecka, J.M., Hollis, J.H., and Mattes, R.D., Effects of appetite, BMI, food form and flavor on mastication: Almonds as a test food. *Eur. J. Clin. Nutr.*, 62, 1231–1238, 2007.
20. Van der Bilt, A., Engelen, L., Pereira, L.J., van der Glas, H.W., and Abbink, J.H., Oral physiology and mastication. *Physiol. Behav.*, 89, 22–27, 2006.

21. Baer, D.J., Gebauer, S.K., and Novotny, J.A., Walnuts consumed by healthy adults provide less available energy than predicted by the Atwater factors. *J. Nutr.*, 146, 9–13, 2015.
22. Baer, D.J., Gebauer, S.K., and Novotny, J.A., Measured energy value of pistachios in the human diet. *Br. J. Nutr.*, 107, 120–125, 2012.
23. Haddad, E., and Sabaté, J., Effect of pecan consumption on stool fat. *FASEB J.*, 14, A294, 2000.
24. Levine, A.S., and Silvis, S.E., Absorption of whole peanuts, peanut oil, and peanut butter. *New Engl. J. Med.*, 303, 917–918, 1980.
25. Zou, M.L., Moughan, P.J., Awati, A., and Livesey, G.L., Accuracy of the Atwater factors and related food energy conversion factors with low-fat, high-fiber diets when energy intake is reduced spontaneously. *Am. J. Clin. Nutr.*, 86, 1649–1656, 2007.
26. Traoret, C., Lokko, P., Cruz, A., Oliveira, C.G., Costa, N., Bressan, J., Alfenas, R., and Mattes, R.D., Peanut digestion and energy balance. *Int. J. Obesity*, 32, 322–328, 2008.
27. Alper, C., and Mattes, R.D., Effects of chronic peanut consumption on energy balance and hedonics. *Int. J. Obesity*, 26, 1129–1137, 2002.
28. Hall, K.D., Heymsfield, S.B., Kemnitz, J.W., Klein, S., Schoeller, D.A., and Speakman, J.R., Energy balance and its components: Implications for body weight regulation. *Am. J. Clin. Nutr.*, 95, 989–994, 2012.
29. Alves, R.D.M., Moreira, A.P.B., Macedo, V.S., Costa, N.M.B., Alfenas, R.C.G., and Bressan, J., High-oleic peanuts increase diet-induced thermogenesis in overweight and obese men. *Nutrición Hospitalaria*, 29, 1024–1032, 2014.
30. Coelho, S.B., Sales, R.L., Iyer, S.S., Bressan, J., Costa, N.M.B., Lokko, P., and Mattes, R.D., Effects of peanut oil load on energy expenditure, body composition, lipid profile, and appetite in lean and overweight adults. *Nutrition*, 22, 585–592, 2006.
31. Brennan, A.M., Sweeney, L.L., Liu, X., and Mantzoros, C.S., Walnut consumption increases satiation but has no effect on insulin resistance or the metabolic profile over a 4-day period. *Obesity*, 18, 1176–1182, 2010.
32. Tey, S.L., Brown, R., Gray, A., Chisholm, A., and Delahunty, C., Nuts improve diet quality compared to other energy-dense snacks while maintaining body weight. *J. Nutr. Metab.*, 357350, 2011.
33. Fraser, G.E., Bennett, H.W., Jaceldo, K.B., and Sabaté, J., Effect on body weight of a free 76 kilojoule (320 calorie) daily supplement of almonds for six months. *J. Am. Coll. Nutr.*, 21, 275–283, 2002.
34. Agebratt, C., Strom, E., Romu, T., Dahlqvist-Leinhard, O., Borga, M., Leandersson, P., and Nystrom, F., A randomized study of the effects of additional fruit and nuts consumption on hepatic fat content, cardiovascular risk factors and basal metabolic rate. *PloS One*, 11, e0147149, 2016.
35. Westerterp, K., Wilson, S., and Rolland, V., Diet induced thermogenesis measured over 24h in a respiration chamber: Effect of diet composition. *Int. J. Obes. Relat. Metab. Disord.*, 23, 287–292, 1999.
36. Jones, P.J., and Schoeller, D.A., Polyunsaturated: Saturated ratio of diet fat influences energy substrate utilization in the human. *Metabolism*, 37, 145–151, 1988.
37. Kresge, D.L., and Melanson, K., Chewing gum increases energy expenditure before and after controlled breakfasts. *Appl. Physiol. Nutr. Metab.*, 40, 401–406, 2014.

38. Komai, N., Motokubota, N., Suzuki, M., Hayashi, I., Moritani, T., and Nagai, N., Thorough mastication prior to swallowing increases postprandial satiety and the thermic effect of a meal in young women. *J. Nutr. Sci. Vitaminol.*, 62, 288–294, 2016.
39. Paphangkorakit, J., Leelayuwat, N., Boonyawat, N., Parniangtong, A., and Sripratoom, J., Effect of chewing speed on energy expenditure in healthy subjects. *Acta Odontol. Scand.*, 72, 424–427, 2014.
40. Jordan, H.A., Voluntary intragastric feeding: Oral and gastric contributions to food intake and hunger in man. *J. Comp. Physiol. Psychol.*, 68, 498–506, 1969.
41. Lavin, J.H., French, S.J., and Read, N.W., Comparison of oral and gastric administration of sucrose and maltose on gastric emptying rate and appetite. *Int. J. Obes. Relat. Metab. Disord.*, 26, 80–86, 2002.
42. Mattes, R.D., and Dreher, M.L., Nuts and healthy body weight maintenance mechanisms. *Asia Pac. J. Clin. Nutr.*, 19, 137–141, 2010.
43. Tan, S.Y., Dhillon, J., and Mattes, R.D., A review of the effects of nuts on appetite, food intake, metabolism, and body weight. *Am. J. Clin. Nutr.*, 100(Suppl. 1), 412S–422S, 2014.
44. Mars, M., Stafleu, A., and de Graaf, C., Use of satiety peptides in assessing the satiating capacity of foods. *Physiol. Behav.*, 105, 483–488, 2012.
45. Reis, C.E., Ribeiro, D.N., Costa, N.M.B., Bressan, J., Alfenas, R.C.G., and Mattes, R.D., Acute and second-meal effects of peanuts on glycaemic response and appetite in obese women with high type 2 diabetes risk: A randomised cross-over clinical trial. *Br. J. Nutr.*, 109, 2015–2023, 2013.
46. Pasman, W.J., Heimerikx, J., Rubingh, C.M., van den Berg, R., O'Shea, M., Gambelli, L., Hendriks, H.F.J. et al., The effect of Korean pine nut oil on *in vitro* CCK release, on appetite sensations and on gut hormones in post-menopausal overweight women. *Lipids Health Dis.*, 7, 10, 2008.
47. Mori, A.M., Considine, R.V., and Mattes, R.D., Acute and second-meal effects of almond form in impaired glucose tolerant adults: A randomized crossover trial. *Nutr. Metab. (Lond)*, 8, 6, 2011.
48. Kirkmeyer, S.V., and Mattes, R.D., Effects of food attributes on hunger and food intake. *Int. J. Obes. Relat. Metab. Disord.*, 24, 1167–1175, 2000.
49. Brunstrom, J.M., Burn, J.F., Sell, N.R., Collingwood, J.M., Rogers, P.J., Wilkinson, L.L., Hinton, E.C. et al., Episodic memory and appetite regulation in humans. *PLoS One*, 7, e50707, 2012.
50. Farr, O.M., Tuccinardi, D., Upadhyay, J., Oussaada, S.M., and Mantzoros, C.S., Walnut consumption increases activation of the insula to highly desirable food cues: A randomized, double-blind, placebo-controlled, cross-over fMRI study. *Diabetes Obes. Metab.*, 20, 173–177, 2017.
51. Tan, S.Y., and Mattes, R.D., Appetitive, dietary and health effects of almonds consumed with meals or as snacks: A randomized, controlled trial. *Eur. J. Clin. Nutr.*, 67, 1205–1214, 2013.
52. Devitt, A.A., Kuevi, A., Coelho, S.B., Lartey, A., Lokko, P., Costa, N., Bressan, J. et al., Appetitive and dietary effects of consuming an energy-dense food (peanuts) with or between meals by snackers and nonsnackers. *J. Nutr. Metab.*, 928352, 2011.
53. Piernas, C., and Popkin, B.M., Snacking increased among U.S. adults between 1977 and 2006. *J. Nutr.*, 140, 325–332, 2010.

54. Berteus Forslund, H., Torgerson, J.S., Sjostrom, L., and Lindroos, A.K., Snacking frequency in relation to energy intake and food choices in obese men and women compared to a reference population. *Int. J. Obes. Relat. Metab. Disord.*, 29, 711–719, 2005.
55. Hull, S., Re, R., Chambers, L., Echaniz, A., and Wickham, M.S., A mid-morning snack of almonds generates satiety and appropriate adjustment of subsequent food intake in healthy women. *Eur. J. Nutr.*, 54, 803–810, 2015.
56. U.S. Department of Agriculture (USDA), *National Nutrient Database for Standard Reference* 27, National Technical Information Service, USDA, Springfield, VA, 2014.
57. Langhans, W., Leitner, C., and Arnold, M., Dietary fat sensing *via* fatty acid oxidation inssasenterocytes: Possible role in the control of eating. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 300, R554–R565, 2011.
58. Alfenas, R.C., and Mattes, R.D., Effect of fat sources on satiety. *Obes. Res.*, 11, 183–187, 2003.
59. Strik, C.M., Lithander, F.E., McGill, A.T., MacGibbon, A.K., McArdle, B.H., and Poppitt, S.D., No evidence of differential effects of SFA, MUFA or PUFA on post-ingestive satiety and energy intake: A randomised trial of fatty acid saturation. *Nutr. J.*, 9, 24, 2010.
60. Pesta, D.H., and Samuel, V.T., A high-protein diet for reducing body fat: Mechanisms and possible caveats. *Nutr. Metab. (Lond)*, 11, 53, 2014.
61. Mattes, R.D., Kris-Etherton, P.M., and Foster, G.D., Impact of peanuts and tree nuts on body weight and healthy weight loss in adults. *J. Nutr.*, 138(Suppl.), 1741S–1745S, 2008.
62. Jaceldo-Siegl, K., Sabaté, J., Rajaram, S., and Fraser, G.E., Long-term almond supplementation without advice on food replacement induces favourable nutrient modifications to the habitual diets of free-living individuals. *Br. J. Nutr.*, 92, 533–540, 2004.
63. Bitok, E., Jaceldo-Siegl, K., Rajaram, S., Serra-Mir, M., Roth, I., Feitas-Simoes, T., Ros, E. et al., Favourable nutrient intake and displacement with long-term walnut supplementation among elderly: Results of a randomised trial. *Br. J. Nutr.*, 118, 201–209, 2017.
64. Honselman, C.S., Painter, J.E., Kennedy-Hagan, K.J., Halvorson, A., Rhodes, K., Brooks, T.L., and Skwir, K., In-shell pistachio nuts reduce caloric intake compared to shelled nuts. *Appetite*, 57, 414–417, 2011.
65. Bullo, M., Juanola-Falgarona, M., Hernandez-Alonso, P., and Salas-Salvadó, J., Nutrition attributes and health effects of pistachio nuts. *Br. J. Nutr.*, 113(Suppl. 2), S79–S93, 2015.
66. Almario, R.U., Vonghavaravat, V., Wong, R., and Kasim-Karakas, S.E., Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. *Am. J. Clin. Nutr.*, 74, 72–79, 2001.
67. Kranz, S., Hill, A.M., Fleming, J.A., Hartman, T.J., West, S.G., and Kris-Etherton, P.M., Nutrient displacement associated with walnut supplementation in men. *J. Hum. Nutr. Diet.*, 27(Suppl. 2), S247–S254, 2014.
68. Pearson, K.R., Tey, S.L., Gray, A.R., Chisholm, A., and Brown, R.C., Energy compensation and nutrient displacement following regular consumption of hazelnuts and other energy-dense snack foods in non-obese individuals. *Eur. J. Nutr.*, 56, 1255–1267, 2017.
69. Sabaté, J., Cordero-Macintyre, Z., Siapco, G., Torabian, S., and Haddad, E., Does regular walnut consumption lead to weight gain? *Br. J. Nutr.*, 94, 859–864, 2005.

70. Zaveri, S., and Drummond, S., The effect of including a conventional snack (cereal bar) and a nonconventional snack (almonds) on hunger, eating frequency, dietary intake and body weight. *J. Hum. Nutr. Diet.*, 22, 461–468, 2009.
71. Li, Z., Song, R., Nguyen, C., Zerlin, A., Karp, H., Naowamondhol, K., Thames, G. et al., Pistachio nuts reduce triglycerides and body weight by comparison to refined carbohydrate snack in obese subjects on a 12-week weight loss program. *J. Am. Coll. Nutr.*, 29, 198–203, 2010.
72. Wang, X., Li, Z., Liu, Y., Lv, X., and Yang, W., Effects of pistachios on body weight in Chinese subjects with metabolic syndrome. *Nutr. J.*, 11, 20, 2012.
73. Salas-Salvadó, J., Fernández-Ballart, J., Ros, E., Martinez-González, M.A., Fitó, M., Estruch, R., Corella, D. et al., Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: One-year results of the predimed randomized trial. *Arch. Int. Med.*, 168, 2449–2458, 2008.
74. Sabaté, J., Nut consumption and body weight. *Am. J. Clin. Nutr.*, 78(Suppl. 3), 647S–650S, 2003.
75. Flores-Mateo, G., Rojas-Rueda, D., Basora, J., Ros, E., and Salas-Salvadó, J., Nut intake and adiposity: Meta-analysis of clinical trials. *Am. J. Clin. Nutr.*, 97, 1346–1355, 2013.
76. Dreher, M.L., Maher, C.V., and Kearney, P., The traditional and emerging role of nuts in healthful diets. *Nutr. Rev.*, 54, 241–245, 1996.
77. Mintel, Nuts, Seeds and Trail Mix US, June 2016. Published online at: http://academic.mintel.com/display/747802/# (accessed June 4, 2018).
78. Vreeland, C., Tracking ingredient trends. *Candy Industry*, 180, 44–48, 2015.
79. King, J.C., Blumberg, J., Ingwersen, L., Jenab, M., and Tucker, K.L., Tree nuts and peanuts as components of a healthy diet. *J. Nutr.*, 138(Suppl.), 1736S–1740S, 2008.
80. Nielsen, S.J., Kit, B.K., and Ogden, C.L., Nut consumption among US adults, 2009–2010. *NCHS Data Brief*, 176, 1–8, 2014.
81. Sterling, S.R., Bertrand, B., Judd, S., and Baskin, M.L., Nut intake among overweight and obese African-American women in the rural south. *Am. J. Health Behav.*, 40, 585–593, 2016.
82. Rehm, C.D., and Drewnowski, A., Replacing American snacks with tree nuts increases consumption of key nutrients among US children and adults: Results of an NHANES modeling study. *Nutr. J.*, 16, 17, 2017.
83. O'Neil, C.E., Keast, D.R., Fulgoni, V.L., and Nicklas, T.A., Tree nut consumption improves nutrient intake and diet quality in US adults: An analysis of National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Asia Pac. J. Clin. Nutr.*, 19, 142–150, 2010.
84. O'Neil, C.E., Nicklas, T.A., and Fulgoni V.L., Tree nut consumption is associated with better nutrient adequacy and diet quality in adults: National health and nutrition examination survey 2005–2010. *Nutrients*, 7, 595–607, 2015.
85. Ibarrola-Jurado, N., Bulló, M., Guasch-Ferré, M., Ros, E., Martinez-González, M.A., Corella, D., Fiol, M. et al., Cross-sectional assessment of nut consumption and obesity, metabolic syndrome and other cardiometabolic risk factors: The PREDIMED study. *PLoS One*, 8, e57367, 2013.
86. Casas-Agustench, P., Bulló, M., Ros, E., Basora, J., Salas-Salvadó, J., and on behalf of the Nureta-PREDIMED Investigators, Cross-sectional association of nut intake with adiposity in a Mediterranean population. *Nutr. Metab. Cardiovas. Dis.*, 21, 518–525, 2011.

87. Guenther, P.M., Kirkpatrick, S.I., Reedy, J., Krebs-Smith, S.M., Buckman, D.W., Dodd, K.W., Casavale, K.O. et al., The healthy eating index-2010 is a valid and reliable measure of diet quality according to the 2010 dietary guidelines for Americans. *J. Nutr.*, 144, 399–407, 2014.
88. Bes-Rastrollo, M., Wedick, N.M., Martinez-Gonzalez, M.A., Li, T.Y., Sampson, L., and Hu, F.B., Prospective study of nut consumption, long-term weight change, and obesity risk in women. *Am. J. Clin. Nutr.*, 89, 1913–1919, 2009.
89. Griel, A.E., Eissenstat, B., Juturu, V., Hsieh, G., and Kris-Etherton, P.M., Improved diet quality with peanut consumption. *J. Am. Coll. Nutr.*, 23, 660–668, 2004.
90. Jaceldo-Siegl, K., Haddad, E., Oda, K., Fraser, G.E., and Sabaté, J., Tree nuts are inversely associated with metabolic syndrome and obesity: The Adventist Health Study-2. *PLoS One*, 9, e85133, 2014.
91. Stelmach-Mardas, M., Rodacki, T., Dobrowolska-Iwanek, J., Brzozowska, A., Walkowiak, J., Wojtanowska-Krosniak, A., Zagrodzki, P. et al., Link between food energy density and body weight changes in obese adults. *Nutrients*, 8, UNSP229, 2016.
92. Albert, C.M., Gaziano, J.M., Willett, W.C., and Manson, J.E., Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. *Arch. Intern. Med.*, 162, 1382–1387, 2002.
93. Bes-Rastrollo, M., Sabaté, J., Gomez-Gracia, E., Alonso, A., Martinez, J.A., and Martinez-Gonzalez, M.A., Nut consumption and weight gain in a Mediterranean cohort: The SUN study. *Obesity (Silver Spring)*, 15, 107–116, 2007.
94. Jiang, R., Manson, J.E., Stampfer, M.J., Liu, S., Willett, W.C., and Hu, F.B., Nut and peanut butter consumption and risk of type 2 diabetes in women. *J. Am. Med. Assoc.*, 288, 2554–2560, 2002.
95. Zemaitis, J., and Sabaté, J., Effect of almond consumption on stool weight and stool fat. *FASEB J.*, 15, A602, 2001.
96. Iyer, S.S., Boateng, L.A., Sales, R.L., Coelho, S.B., Lokko, P., Monteiro, J.B., Costa, N.M. et al., Effects of peanut oil consumption on appetite and food choice. *Int. J. Obes.*, 30, 704–710, 2005.
97. Baer, D.J., and Novotny, J.A., Metabolizable energy from cashew nuts is less than that predicted by Atwater factors. *Nutrients*, 11, 33, 2019.
98. Garg, M.L., Blake, R.J., and Wills, R.B.H., Macadamia nut consumption lowers plasma total and LDL cholesterol levels in hypercholesterolemic men. *J. Nutr.*, 133, 1060–1063, 2003.
99. Jenkins, D.J., Kendall, C.W., Marchie, A., Parker, T.L., Connelly, P.W., Qian, W., Haight, J.S. et al., Dose response of almonds on coronary heart disease risk factors: Blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: A randomized, controlled, crossover trial. *Circulation*, 106, 1327–1332, 2002.
100. Johnston, C.S., and Buller, A.J., Vinegar and peanut products as complementary foods to reduce postprandial glycemia. *J. Am. Diet. Assoc.*, 105, 1939–1942, 2005.
101. Lovejoy, J.C., Most, M.M., Lefevre, M., Greenway, F.L., and Rood, J.C., Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. *Am. J. Clin. Nutr.*, 76, 1000–1006, 2002.
102. McKiernan, F., Lokko, P., Kuevi, A., Sales, R.L., Costa, N.M., Bressan, J., Alfenas, R.C. et al., Effects of peanut processing on body weight and fasting plasma lipids. *Br. J. Nutr.*, 104, 418–426, 2010.

103. Mercanligil, S.M., Arslan, P., Alasalvar, C., Okut, E., Akgul, E., Pinar, A., Geyik, P.O. et al., Effects of hazelnut-enriched diet on plasma cholesterol and lipoprotein profiles in hypercholesterolemic adult men. *Eur. J. Clin. Nutr.*, 61, 212–220, 2006.
104. Morgan, W.A., and Clayshulte, B.J., Pecans lower low density lipoprotein cholesterol in people with normal lipid levels. *J. Am. Diet. Assoc.*, 100, 312–318, 2000.
105. Wu, H., Pan, A., Yu, Z., Qi, Q., Lu, L., Zhang, G., Yu, D. et al., Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome. *J. Nutr.*, 140, 1937–1942, 2010.
106. Yücesan, F.B., Orem, A., Kural, B.V., Orem, C., and Turan, I., Hazelnut consumption decreases the susceptibility of LDL to oxidation, plasma oxidized LDL level and increases the ratio of large/small LDL in normolipidemic healthy subjects. *Anatol. J. Cardiol.*, 10, 28–35, 2010.
107. McArthur, B.M., Considine, R.V., and Mattes, R.D. Mastication of nuts under realistic eating conditions: Implications for energy balance. *Nutrients*, 10, 710, 2018.

Chapter 6

Nut Consumption and Cardiovascular Disease

Tasnim F. Imran and Luc Djoussé

6.1 Introduction 155
6.2 Nut Consumption and Risk of Clinical Cardiovascular Disease 156
6.2.1 Total Cardiovascular Disease 156
6.2.2 Coronary Heart Disease 157
6.2.3 Stroke or Transient Ischemic Attack 157
6.2.4 Atrial Fibrillation 163
6.2.5 Heart Failure 163
6.2.6 Peripheral Arterial Disease 163
6.2.7 Sudden Cardiac Death 163
6.3 Conclusion 164
References 164

6.1 Introduction

Tree nuts have been a regular component of the human diet from long before agricultural times [1]. They are defined as dry fruits that contain a seed within the ovary wall that becomes hard at maturity. These include almonds, Brazil nuts, walnuts, hazelnuts, chestnuts, cashews, pecans, macadamias, and pistachios [2]. Although peanuts are classified as legumes, they are often included in studies of nuts and are referred to as nuts due to their similar nutritional compositions and culinary uses. Nuts contain important nutrients such as polyunsaturated fats, vitamin E, dietary fiber, potassium, magnesium, and antioxidants, which may reduce the risk of cardiovascular disease (CVD) *via* improvement of lipid profiles, glucose regulation, and antioxidant effects [3–5]. In addition to these health benefits, it is also important to

consider the sustainability of nut consumption on a global scale. Nuts have a lower water footprint as compared to other types of food and thus may be more sustainable for the planet. For instance, the global average footprint for nuts (9,063 m^3/t) is much lower than that of meat such as beef (15,415 m^3/t) [6].

Because nuts are energy-dense foods with a high fat content, some consumers may have the misconception that nut consumption leads to weight gain. However, several epidemiologic and short-term clinical trials have found that nut intake not only did not induce weight gain, but also was inversely associated with body mass index (BMI) [7]. Other clinical trials have found that intervention with tree nuts either leads to a decrease in body weight [8–10] or has no effect on total body weight [11] (see Chapter 7 for details).

Large cohort studies have reported an inverse association between nut consumption and incident coronary heart disease (CHD), and short-term feeding trials have documented beneficial effects of nuts on lipid profiles and biomarkers of cardiovascular risk [8]. Thus, in 2003, the United States Food and Drug Administration issued a statement linking nut intake with a reduced risk of CVD [12]. Since then, nuts have been included in the American Heart Association's report on goals for health promotion and disease reduction for 2020 [13], in the recent American Heart Association's/American College of Cardiology guidelines on lifestyle factors to reduce CVD risk [14], and in the Canadian Cardiovascular Society guidelines [15]. Nuts are also an important component of the Mediterranean diet [16] and a part of the planet-based dietary patterns recommended for overall health [17]. In this chapter, we summarize the evidence supporting the beneficial effects of nut consumption on clinical CVD.

6.2 Nut Consumption and Risk of Clinical Cardiovascular Disease

6.2.1 Total Cardiovascular Disease

In a study including three cohorts – 76,364 women from the Nurses' Health Study (NHS) (1980 to 2012), 92,946 women from the NHS II (1991–2013), and 41,526 men from the Health Professionals Follow Up Study (HPFS) (1986–2012) – who did not have CVD at baseline, 14,136 cases of incident CVD were found over 5,063,439 person-years of follow-up. The multivariable model hazard ratio (HR) for those who consumed one serving of nuts (28 g) at least five times per week compared to those who never consumed nuts was 0.86 (95% CI: 0.79-0.93) [18]. Similarly, a meta-analysis including 12 studies found that higher nut intake was associated with a lower risk of CVD, with a HR of 0.79 (95% CI: 0.70–0.88, $I^2 = 60\%$) per 28 g/day increase in nut intake [19]. Another recent meta-analysis including 18 prospective cohort studies and 8,862 cases of incident CVD found a relative risk (RR) of 0.70 (95% CI: 0.60–0.81) for CVD for each incremental nut serving per day [20]. In the PREvención con DIeta MEDiterránea (PREDIMED) trial, a multicenter trial in Spain which assigned 7,447 participants to either a Mediterranean diet supplemental with extra virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advised to reduce fat), the primary end-point of a major cardiovascular event (myocardial infarction [MI], stroke, or death from cardiovascular causes), occurred in 288 participants over a median follow up of 4.8 years. The HR was 0.72 (95% CI 0.54–0.95) for the group with nuts compared to the control diet group [21].

Overall, these studies suggest an inverse association of nut consumption and risk of CVD with at least a modest effect or greater.

6.2.2 Coronary Heart Disease

In a meta-analysis of cohort studies including 315,397 participants (12,331 cases of CHD), one serving/day increase in nut intake was associated with a 29% lower risk of CHD (pooled RR: 0.71, 95% CI: 0.63–0.80, I^2 = 47%, n = 11 studies) and a 21% lower risk of CVD (RR: 0.79, 95% CI: 0.70–0.88, I^2 = 60%, n = 12 studies). A nonlinear association was observed, with only a slight reduction in risk above 15–20 g/day of nut consumption [19]. Similarly, in another meta-analysis of observational studies, nut consumption was associated with a 24% lower risk of fatal ischemic heart disease (HR: 0.76, 95% CI: 0.69–0.84, I^2 = 28%, n = 6 studies with 6749 events) and a 22% lower risk of nonfatal ischemic heart disease (HR: 0.78, 95% CI: 0.67–0.92, I^2 = 0%, n = 4 studies, 2101 events) per weekly 24.8 g servings taken over a month [22]. Another recent meta-analysis found that nut consumption was associated with a lower risk of CVD mortality (five studies, RR: 0.73, 95% CI: 0.68–0.78) and CHD (three studies, RR: 0.66, 95% CI: 0.48–0.91) [23]. In an analysis of 169,340 women from the NHS and 41,526 men from the HPFS, the multivariable adjusted HR for CVD and CHD for those who consumed one serving of nuts (28 g) five or more times per week compared with those who never consumed nuts were 0.86 (95% CI: 0.79–0.93) and 0.80 (95% CI: 0.72–0.89), respectively, after 5,063,439 person-years of follow-up [18]. In the PREDIMED study, the HR for the incidence of MI in the Mediterranean diet group with nuts was 0.76 (95% CI: 0.47–1.25) compared to the control diet group [21]. Although not statistically significant – likely due to a low number of events (31 cases of myocardial infarction) – there is an effect in the direction of lowered risk.

In summary, results from large-scale cohort studies are consistent with beneficial effects of tree nuts on CHD risk [18,19,22–24], whereas findings from randomized trials are mixed regarding the effects of tree nuts on cardiovascular biomarkers. Table 6.1 summarizes the key clinical studies on nut consumption and CVD. Figure 6.1 lists the postulated effects of nut consumption on subclinical factors.

6.2.3 Stroke or Transient Ischemic Attack

In a prospective cohort of 26,285 German participants from the European Prospective Investigation into the Cancer and Nutrition Potsdam study, people who never consumed nuts had a 56% higher risk of stroke (HR: 1.56, 95% confidence interval: 1.17–2.08) compared to individuals who consumed less than half portion per week after 8 years of follow-up; no dose–response relationship was noted in this study [25]. A dose-response meta-analysis of 396,768 participants (9272 total stroke cases) demonstrated a nonsignificant lower risk of stroke (RR: 0.93, 95% CI: 0.83–1.05, I^2 = 14%, P heterogeneity = 0.31) for one serving per day increase in nut consumption with evidence of a nonlinear association between nut consumption and stroke risk (J-shaped curve) [19].

In another meta-analysis that included 228,799 subjects and 5,669 incident cases of total stroke, the highest nut-consumption category was associated

Table 6.1 Summary of Evidence on Nut Consumption and Clinical Cardiovascular Disease

Study	*Sample Size*	*Outcome*	*Measure*	*References*
Total CVD				
Meta-analysis (*n* = 11 studies)	*n* = 315,397 12,331 cases	CVD	RR: 0.79 (95% CI: 0.70–0.88).	[19]
Prospective cohorts	*n* = 76,364 Nurses' Health Study I *n* = 92,946 Nurses' Health Study II *n* = 41,526 Health Professionals Follow Up Study 14,136 cases	CVD	HR for those who consumed one serving of nuts (28 g) at least five times/week compared to those who never consumed nuts:0.86 (95% CI: 0.79–0.93).	[18]
Meta-analysis (*n* = 18 studies)	8,862 cases	CVD	RR: 0.70 (95% CI: 0.60–0.81) for CVD for each incremental nut serving per day.	[20]
PREDIMED Randomized trial	*n* = 7,447 288 cases	Composite of MI and stroke of cardiovascular death	HR: 0.72 (95% CI 0.54–0.95) for Mediterranean diet with nuts compared to control diet group.	[21]
CHD				
Meta-analysis (*n* = 11 studies)	*n* = 315,397 12,331 cases	CHD	One serving/day increase in nuts RR: 0.71 (95% CI: 0.63–0.80).	[19]
Meta-analysis (*n* = 6 studies)	*n* = 501,791 6,749 cases	Fatal ischemic heart disease Nonfatal ischemic heart disease	Nut consumption. Fatal ischemic heart disease: RR: 0.76 (95% CI: 0.69–0.84). Nonfatal ischemic heart disease: RR: 0.78 (95% CI: 0.67–0.92). Per weekly, 24.8 g servings taken over a month.	[22]
PREDIMED trial	*n* =7,447 31 cases	MI	HR 0.76 (95% CI: 0.47–1.25) for Mediterranean diet with nuts compared to control group.	[21]

(*Continued*)

Table 6.1 (Continued) Summary of Evidence on Nut Consumption and Clinical Cardiovascular Disease

Study	*Sample Size*	*Outcome*	*Measure*	*References*
Stroke				
Prospective cohort	*n* = 26,285	Stroke	Those who never consumed nuts: RR: 1.56 (95% CI: 1.17–2.08).	[25]
Meta-analysis	*n* = 396,768 9,272 cases	Stroke	One serving/day increase in nuts: RR: 0.93 (95% CI: 0.83–1.05). J-shaped curve.	[19]
Meta-analysis	*n* = 228,799 5,669 cases	Stroke Ischemic Hemorrhagic	Highest category of nut consumption compared to lowest group: RR: 0.90 (95% CI: 0.81–0.99). Ischemic stroke: RR: 0.97 (95% CI: 0.84–1.10). Hemorrhagic stroke: RR: 1.17 (95% CI: 0.54–2.54).	[26]
Prospective cohort	*n* = 21,078 men	Stroke	Nuts < 1, 1, 2–4, 5–6, and ≥ 7 times/week: RR: 1.13 (95% CI: 0.78–1.62). RR: 1.05 (95% CI: 0.70–1.58). RR: 0.49 (95% CI: 0.27–0.89). RR: 1.50 (95% CI: 0.79–2.84). RR: 1.84 (95% CI: 0.95–3.57). (*P* for quadratic trend 0.12)	[27]
PREDIMED trial	*n* =7,447 32 cases	Stroke	HR: 0.54 (95% CI 0.35–0.82) for Mediterranean diet with nuts compared to control group.	[21]

(*Continued*)

Table 6.1 (Continued) Summary of Evidence on Nut Consumption and Clinical Cardiovascular Disease

Study	*Sample Size*	*Outcome*	*Measure*	*References*
Atrial Fibrillation				
Prospective cohort	*n* = 21,054 men	Atrial fibrillation	RRs: 1.00 (0.90–1.11), 1.09 (0.97–1.21), 1.07 (0.95–1.21), and 0.91 (0.70–1.17) across increasing categories of nut consumption (*P* for trend 0.26).	[28]
			Median follow-up of 24 years	
PREDIMED trial	*n* = 6,705 72 cases	Atrial fibrillation	HR: 0.89 (95% CI: 0.65–1.20) for Mediterranean diet with nuts compared to control group.	[29]
Heart Failure				
PREDIMED trial	*n* = 7,403 94 cases	Heart failure	Mediterranean diet supplemented with nuts compared to low fat diet: RR: 0.92 (95% CI: 0.56–1.49).	[30]
Prospective cohort	*n* = 20,796 men	Heart failure	RRs: 0.98 (95% CI: 0.83–1.15), 1.06 (95% CI: 0.89–1.27), and 1.01 (95% CI: 0.84–1.22) for nut consumption of < 1, 1, and ≥ 2 servings/week, respectively (*P* for linear trend: 0.64) in both lean and overweight men.	[31]

(*Continued*)

Table 6.1 (Continued) Summary of Evidence on Nut Consumption and Clinical Cardiovascular Disease

Study	*Sample Size*	*Outcome*	*Measure*	*References*
PAD				
Cross-sectional analysis	*n* = 3,312,403 219,527 cases	PAD	Daily nut consumption: 21% (95% CI: 20%–23%) lower odds of having PAD compared to nut intake of less than once per month.	[33]
Randomized controlled trial PREDIMED	*n* = 7,447 89 cases	PAD	HR for Mediterranean diet plus nuts compared to placebo (low fat diet): 0.50 (95% CI: 0.30–0.81) at 4.8 years follow-up.	[29]
Sudden Cardiac Death				
Prospective cohort	*n* = 21,454 men	Sudden cardiac death	Nut consumption 2+/week: RR: 0.53 (95% CI: 0.30–0.92).	[35]

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral arterial disease; PREDIMED, PREvención con DIeta MEDiterránea (Prevention with Mediterranean Diet); RR, relative risk.

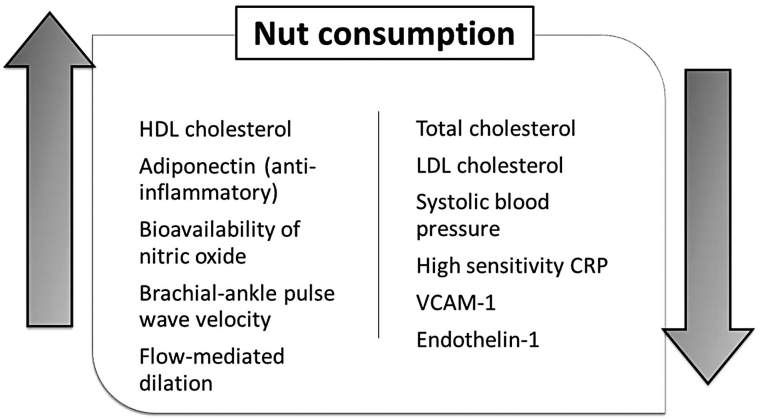


Figure 6.1 Postulated effects of nut consumption on subclinical disease. *Abbreviations*: CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VCAM-1, vascular cell adhesion molecule-1.

with a 10% lower risk of total stroke compared to the lowest category of nut consumption (pooled RR: 0.90, 95% CI: 0.81-0.99; *P* heterogeneity = 0.53, I^2 = 0, *n* = 8 studies). There was no benefit of nuts on ischemic stroke (RR: 0.97, 95% CI: 0.84–1.10; I^2 = 0) or hemorrhagic stroke (RR: 1.17, 95% CI: 0.54–2.54; I^2 = 77.3%) [26]. Additionally, this risk was modified by gender, in that high nut consumption was associated with a lower risk of stroke in women (RR: 0.85, 95% CI: 0.75–0.97) but not in men (RR: 0.95, 95% CI: 0.82–1.11) [26]. In a large cohort study of 21,078 men, nut consumption was not associated with total or ischemic stroke after 21 years of follow-up. However, there was a suggestive nonlinear relationship between nut consumption and risk of hemorrhagic stroke – multivariable adjusted HRs (95% CI) for hemorrhagic stroke for subjects consuming nuts < 1, 1, 2–4, 5–6, and ≥ 7 times/week were 1.13 (0.78–1.62), 1.05 (0.70–1.58), 0.49 (0.27–0.89), 1.50 (0.79–2.84), and 1.84 (0.95–3.57), respectively (*P* for quadratic trend 0.12) [27]. In a study including three cohorts – 169,340 women from the NHS I and II and 41,526 men from the HPFS – the risk estimate for stroke among participants who consumed tree nuts two or more times per week compared to those who never consumed nuts was 0.94 (95% CI: 0.88–1.05). Although the relative risk did not reach statistical significance, there was a trend in the direction of lower risk with higher nut consumption [18]. In the PREDIMED study, the HR for the incidence of stroke in the Mediterranean diet group with nuts was 0.54 (95% CI: 0.35–0.82) compared to the control diet group, indicating a sizable reduction in risk of stroke in participants who consumed nuts [21].

Overall, current evidence suggests that the relation between nut intake and stroke may be complex. Although not reaching statistical significance, all point estimates are in the direction of lower risk of stroke with nut consumption. Several studies have examined total stroke (which includes fatal and nonfatal, and ischemic and hemorrhagic strokes) as the outcome, while only a handful of studies have examined the subtypes of stroke separately. Although there is overlap with risk factors, ischemic and hemorrhagic strokes differ in their pathophysiologic mechanisms and may have different associations with nut intake. More studies are needed to further elucidate the relation of nut intake with stroke subtypes.

6.2.4 Atrial Fibrillation

Few studies have examined the relation of nut consumption with incidence of atrial fibrillation. In a cohort of 21,054 male subjects from the Physicians' Health Study, nut consumption was not associated with the risk of atrial fibrillation; HRs (95% CI) for incident atrial fibrillation were 1.0 (reference category), 1.00 (0.90–1.11), 1.09 (0.97–1.21), 1.07 (0.95–1.21), and 0.91 (0.70–1.17) across increasing categories of nut consumption (*P* for trend 0.26) after a median follow-up of 24 years. Results were not altered when stratified by BMI or age [28]. In the PREDIMED trial, the intervention with a Mediterranean diet supplemented with nuts did not affect the incidence of atrial fibrillation when compared to the control group [29]. More studies are needed to examine the association between nut intake and incidence of atrial fibrillation.

6.2.5 Heart Failure

In the PREDIMED trial, after a median follow-up of 4.8 years, a total of 94 heart-failure cases occurred. There was a nonsignificant 32% reduction in heart-failure risk when comparing the Mediterranean diet supplemented with extra virgin olive oil (HR: 0.68, 95% CI: 0.41–1.13) with the control group and no meaningful reduction in heart-failure risk when people receiving the Mediterranean diet supplemented with nuts were compared to the control group (HR: 0.92, 95% CI: 0.56–1.49) [30]. In a prospective cohort of 20,976 men from the Physicians' Health Study, nut consumption was not associated with incident heart failure after 19.6 years of follow-up with multivariable adjusted; HRs were 1.0 (reference category), 0.98 (95% CI: 0.83–1.15), 1.06 (95% CI: 0.89–1.27), and 1.01 (95% CI: 0.84–1.22) for nut consumption of < 1, 1, and ≥ 2 servings/week, respectively (*P* for linear trend: 0.64) in both lean and overweight men [31]. Since subtypes of heart failure were not examined in these studies, it is unclear whether tree nut consumption could influence the risk of heart failure with preserved or reduced ejection fraction. Further studies are needed to clarify this important question, given the growing burden of heart failure. Nut intake can modulate nitric oxide production and result in blood pressure reduction, which in turn modulate the development of heart failure [32].

6.2.6 Peripheral Arterial Disease

In a cross-sectional analysis of 3,312,403 individuals screened for peripheral arterial disease (PAD) (219,527 cases of prevalent PAD), daily consumption of tree nuts was associated with a 21% (95% CI: 20%–23%) lower odds of having PAD compared to a nut intake of less than once per month in a multivariable adjusted model [33]. In the PREDIMED trial, the HR for incident peripheral arterial disease for participants in the Mediterranean diet plus nuts was 0.50 (95% CI: 0.30–0.81) when compared to controls (low-fat diet group) [34].

6.2.7 Sudden Cardiac Death

In a prospective cohort of US male physicians, nut consumption was inversely associated with the risk of sudden cardiac death [35]. Among 21,454 participants, those

who consumed nuts 2+ times per week had a 47% lower risk of sudden cardiac death (RR: 0.53, 95% CI: 0.30–0.92) compared to people who rarely or never consumed nuts after 17 years of follow-up [35]. Other studies are needed to confirm these findings.

6.3 Conclusion

The review of currently available data (mostly from observational studies and the PREDIMED trial) suggests a modest but consistent inverse association between nut consumption and CVD and CHD risk. In addition, the association between nut consumption and stroke incidence remains equivocal. Further studies are needed to clarify the relation of nut intake with stroke subtypes (e.g., hemorrhagic and ischemic strokes) and other major cardiovascular endpoints. Given the current burden of CHD in the world, and the absence of weight gain with tree nut consumption, it is reasonable to advise nut consumption as part of an overall healthy diet for the prevention of CVD (in the absence of allergies to tree nuts and/or peanuts).

References

1. Eaton, S.B., and Konner, M., Paleolithic nutrition. A consideration of its nature and current implications. *N. Engl. J. Med.*, 312, 283–289, 1985.
2. Sabaté, J., Ros, E., and Salas-Salvadó, J., Nuts: Nutrition and health outcomes. Preface. *Br. J. Nutr.*, 96(Suppl. 2), 1S–2S, 2006.
3. Sabaté, J., Oda, K., and Ros, E., Nut consumption and blood lipid levels: A pooled analysis of 25 intervention trials. *Arch. Intern. Med.*, 170, 821–827, 2010.
4. Rajaram, S., and Sabaté, J., Nuts, body weight and insulin resistance. *Br. J. Nutr.*, 96(Suppl. 2), 79S–86S, 2006.
5. Jenkins, D.J., Kendall, C.W., Josse, A.R., Salvatore, S, Brighenti, F, Augustin, L.S., Ellis, P.R. et al., Almonds decrease postprandial glycemia, insulinemia, and oxidative damage in healthy individuals. *J. Nutr.*, 136, 2987–2992, 2006.
6. Downs, S.M., and Fanzo, J., Is a cardio-protective diet sustainable? A review of the synergies and tensions between foods that promote the health of the heart and the planet. *Curr. Nutr. Rep.*, 4, 313–322, 2015.
7. Vadivel, V., Kunyanga, C.N., and Biesalski, H.K., Health benefits of nut consumption with special reference to body weight control. *Nutrition*, 28, 1089–1097, 2012.
8. Salas-Salvadó, J., Fernandez-Ballart, J., Ros, E., Martinez-Gonzalez, M.A., Fito, M., Estruch, R., Corella, D. et al., Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: One-year results of the PREDIMED randomized trial. *Arch. Intern. Med.*, 168, 2449–2458, 2008.
9. Bes-Rastrollo, M., Sabaté, J., Gómez-Gracia, E., Alonso, A., Martínez, J.A., and Martínez-González, M.A., Nut consumption and weight gain in a Mediterranean cohort: The SUN Study. *Obesity (Silver Spring)*, 15, 107–116, 2007.
10. Mukuddem-Petersen, J., Stonehouse, W., Jerling, J.C., Hanekom, S.M., and White, Z., Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: A controlled feeding trial. *Br. J. Nutr.*, 97, 1144–1153, 2007.
11. Flores-Mateo, G., Rojas-Rueda, D., Basora, J., Ros, E., and Salas-Salvadó, J., Nut intake and adiposity: Meta-analysis of clinical trials. *Am. J. Clin. Nutr.*, 97, 1346–1355, 2013.

12. Food and Drug Administration (FDA), *Qualified Health Claims: Letter of Enforcement Discretion – Nuts and Coronary Heart Disease, Docket No 02P-0505*, Food and Drug Administration, Washington, DC, 2003.
13. Lloyd-Jones, D.M., Hong, Y., Labarthe, D., Mozaffarian, D., Appel, L.J., Van Horn, L., Greenlund, K. et al., American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*, 121, 586–613, 2010.
14. Eckel, R.H., Jakicic, J.M., Ard, J.D., de Jesus, J.M., Miller, N.H., Hubbard, V.S., Lee, I.M. et al., 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.*, 63(25 Part B), 2889–2934, 2014.
15. Anderson, T.J., Grégoire, J., Hegele, R.A., Couture, P., Mancini, G.B., McPherson, R., Francis, G.A. et al., 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can. J. Cardiol.*, 29, 151–167, 2013.
16. Bach-Faig, A., Berry, E.M., Lairon, D., Reguant, J., Trichopoulu, A., Dimini, S., Medina, F.X. et al., Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr.*, 14, 2274–2284, 2011.
17. U.S. Department of Health and Human Services and U.S. Department of Agriculture, *Dietary Guidelines for Americans*, 7th ed., U.S. Government Printing Office, Washington, DC, 2010.
18. Guasch-Ferré, M., Liu, X., Malik, V.S., Sun, Q., Willett, W.C., Manson, J.E., Rexrode, K.M. et al., Nut consumption and risk of cardiovascular disease. *J. Am. Coll. Cardiol.*, 70, 2519–2532, 2017.
19. Aune, D., Keum, N., Giovannuci, E., Fadnes, L.T., Bofetta, P., Greenwood, D.C., Tonstad, S. et al., Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review and dose response meta-analysis of prospective studies. *BMC Medicine*, 14, 207, 2016.
20. Luo, C., Zhang, Y., Ding, Y., Shan, Z.L., Chen, S.J., Yu, M., Hu, F.B. et al., Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: A systematic review and meta-analysis. *Am. J. Clin. Nutr.*, 100, 256–269, 2014.
21. Estruch, R., Ros, E., Salas-Salvadó, J, Covas, M.I., Corella, D., Arós, F., Gómez-Gracia, E. et al., Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra virgin olive oil or nuts. *N. Engl. J. Med.*, 378, e34, 2018.
22. Afshin, A., Micha, R., Khatibzadeh, S., and Mozaffarian, D., Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: A systematic review and meta-analysis. *Am. J. Clin Nutr.*, 100, 278–288, 2014.
23. Mayhew, A.J., de Souza, R.J., Meyre, D., Anand, S.S., and Mente, A., A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. *Br. J. Nutr.*, 115, 212–225, 2016.
24. Schwingshackl, L., Hoffmanni, G., Missbach, B., Stelmach-Mardas, M., and Boeing, H., An umbrella review of nuts intake and risk of cardiovascualr disease. *Curr. Pharm. Des.*, 23, 1016–1027, 2017.
25. Giuseppe, R., Fjeld, M.K., Dierkes, J., Theoflylaktopoulou, D., Arregiu, M., Boeing, H., and Weikert, C., The association between nut consumption and the risk of total and ischemic stroke in a German cohort study. *Eur. J. Clin. Nutr.*, 69, 431–435, 2015.

26. Shi, Z.Q., Tang, J.J., Wu, H., Xie, C.Y., and He, Z.Z., Consumption of nuts and legumes and risk of stroke: A meta-analysis of prospective cohort studies. *Nutr. Metab. Cardiovasc. Dis.*, 24, 1262–1271, 2014.
27. Djousse, L., Gaziano, J.M., Kase, C., and Kurth, T., Nut consumption and risk of stroke in US male physicians. *Clin. Nutr.*, 25, 605–609, 2010.
28. Khawaja, O., Gaziano, J.M., and Djousse, L., Nut consumption and risk of atrial fibrillation in the Physicians' Health Study. *Nutr. J.*, 11, 17, 2012.
29. Martínez-González, M.A., Toledo, E., Arós, F., Fiol, M., Corella, D., Salas-Salvadó, J., Ros, E. et al., Extra virgin olive oil consumption reduces risk of atrial fibrillation: The PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation*, 130, 18–26, 2014.
30. Papadaki, A., Martinez-González, M.A., Alonso-Gomez, A., Rekondo, J., Salas-Salvadó, J., Corella, D., Ros, E. et al., Medieterranean diet and risk of heart failure: Results from the PREDIMED randomized controlled trial. *Eur. J. Heart Fail.*, 19, 1179–1185, 2017.
31. Djousse, L., Rudich, T., and Gaziano, J.M., Nut consumption and risk of heart failure in the Physicians' Health study I. *Am. J. Clin. Nutr.*, 88, 930–933, 2008.
32. Storniolo, C.E., Casillas, R., Bullo, M., Castaner, O., Ros, E., Saez, G.T., Toledo, E. et al., A Mediterranean diet supplemented with extra virgin olive oil or nuts improves endothelial markers involved in blood pressure control in hypertensive women. *Eur. J. Nutr.*, 56, 89–97, 2017.
33. Heffron, S.P., Rockman, C.B., Gianos, E., Guo, Y., and Berger, J.S., Greater frequency of nut consumption is associated with lower prevalence of peripheral arterial disease. *Prev. Med.*, 72, 15–18, 2015.
34. Ruiz-Canela, M., Estruch, R., Corella, D., Salas-Salvadó, J., and Martínez-González, M.A., Association of Mediterranean diet with peripheral artery disease. The PREDIMED randomized trial. *JAMA*, 311, 415–417, 2014.
35. Albert, C.M., Gaziano, J.M., Willet, W.C., and Manson, J.E., Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. *Arch. Intern. Med.*, 162, 1382–1387, 2002.

Chapter 7

Nut Consumption and Adiposity

Maira Bes-Rastrollo and Miguel Ángel Martínez-González

7.1 Introduction 167
7.2 Epidemiological Evidence 168
7.2.1 Prospective Cohort Studies 169
7.2.2 Long-Term Randomized Clinical Trials 172
7.3 Systematic Reviews and Meta-Analyses 175
7.4 Biological Plausibility 176
7.5 Conclusion 177
References 178

7.1 Introduction

Nuts have been part of our food culture since time immemorial. Even the first hominids consumed nuts to feed themselves [1]. Nuts are nutrient-dense foods, rich in macronutrients, micronutrients, and bioactive phytochemicals. Their unique composition is thought to be responsible for their beneficial health effects [2]. Plausible biological mechanisms, magnitude of the associations, and consistency among populations support the observed associations with the incidence of cardiovascular disease (CVD) and all-cause mortality [3], and suggest a potential role for nuts in reducing cancer and cognitive impairment [4].

Almonds, hazelnuts, walnuts, pistachios, cashews, Brazil nuts, pecans, and pine nuts are dry fruits with one seed, of which the ovary wall becomes hard at ripeness. Peanuts are legumes from a botanical point of view, but they have similar nutrient profiles to tree nuts, which is why they are usually considered nuts from

a consumer's perspective [2]. Nuts are nutritious foods. They are good sources of antioxidants, plant sterols, unsaturated fatty acids, and vegetable protein [5,6]. As a consequence, nuts may be beneficial for preventing chronic diseases.

The high-energy, high-fat content of nuts (between 50% and 70% of their weight) is responsible for the popular but unfounded belief that their consumption may lead to weight gain [7]. Therefore, the general population tends to avoid the consumption of this food, and even in clinical practice settings, the healthfulness of nuts has been questioned because of the concern about their potential to contribute to weight gain. This chapter summarizes current knowledge on the topic of nut consumption and adiposity.

7.2 Epidemiological Evidence

The first study that reported a cross-sectional negative association between the frequency of nut consumption and body mass index (BMI) was published in 1992 in the context of the Adventist Health Study [8]. Later, several cross-sectional studies also found an inverse association between nut consumption and BMI [9,10]. A review including cross-sectional studies concluded that adding nuts to a calorie-restricted diet enhanced insulin sensitivity and was associated with improved rates of weight loss [11]. Nevertheless, it is known that nut consumers are more likely to have healthy lifestyle habits. Also, in these cross-sectional studies, the temporal sequence of the association between nut consumption and body weight cannot be determined, and it is always possible that participants with lower body weight may be systematically more prone to consume nuts; that is, reverse causality bias cannot be discarded in cross-sectional studies.

Longitudinal studies are better protected against reverse causality bias, but it is always possible that subjects less prone to future weight gain might have self-selected themselves for higher nut consumption. In this context, the best design is a randomized controlled trial (RCT), wherein nut consumption is not self-selected but randomly allocated. A recent meta-analysis of RCTs assessing the effects of walnut-enriched diets *versus* control diets on blood lipids and CVD risk factors concluded that walnut-enriched diets were not associated with greater weight after follow-up [12]. However, the maximum follow-up of the 26 RCTs included in this systematic review was only 1 year. It is possible that the effect of nut consumption on weight gain might be gradual, and a positive association on body weight or obesity can only be observed over a longer period of time. For this reason, it seems important to evaluate this association using long-term epidemiological studies, with good control of confounding and selection bias. The appropriate statistical control for a wide array of baseline characteristics, lifestyles, and dietary habits should be very strict in observational studies in order to reduce the distorting effects derived from the fact that participants with healthier lifestyles might be more likely to self-select themselves for higher nut consumption.

Evidence to date from long-term and well-controlled epidemiological studies is based on prospective cohorts and two RCTs conducted each one in Europe and the United States. After applying appropriate methods to control for confounding derived from self-selection, all of these studies concluded that nut consumption was not associated with higher weight gain or with higher risk of developing overweight or obesity.

7.2.1 Prospective Cohort Studies

Table 7.1 summarizes the published prospective cohort studies on long-term nut consumption and weight gain or risk of overweight, obesity, and abdominal obesity. The first long-term prospective epidemiological study that assessed the effect of nut consumption on weight change was the Spanish Seguimiento Universidad de Navarra (SUN) cohort in 2007 [13]. Among 8,865 adult men and women, and after adjusting for age, sex, baseline BMI, leisure time physical activity, smoking status, snacking between meals, TV watching, and total energy intake, participants consuming nuts at least twice per week did not exhibit higher risk of gaining 5 or more kg; in fact a lower risk was observed, with an odds ratio (OR) of 0.71 (95% confidence interval [CI], 0.54–0.93). Higher nut consumption was not associated with higher risk of developing overweight/obesity during follow-up. Even those in the highest category of nut consumption gained less weight than those who never or almost never consumed nuts, after adjusting for multiple baseline characteristics. These results were consistent with those updated several years later in this same cohort, with a dynamic design that allows for a progressive higher accrual of participants [14].

These first results found from the SUN cohort were replicated 2 years later by the Nurses' Health Study II (NHS-II), with 51,188 female participants assessed after an 8-year follow-up period [15]. Women who reported consuming nuts (tree nuts plus peanuts) at least twice per week experienced a slightly lower average weight gain (5.04; se: 0.12 kg) than did women who rarely ate nuts (5.55; se: 0.04 kg) after adjusting for a wide array of potentially confounding factors, including age, BMI, alcohol intake, physical activity, smoking, postmenopausal hormone use, oral contraceptive use, glycemic load, and intakes of total fiber, trans fat, alcohol, fruit, vegetables, red meat, processed meat, refined grain, whole grain, snacks, sugar-sweetened beverages, diet beverages, low-fat dairy products, and high-fat dairy products. Interestingly, in this study, estimates were also adjusted for changes in covariates and changes in soft-drink consumption during follow-up, which had previously been reported to be associated with weight gain in the NHS-II cohort and other cohorts. Also, additional analyses were conducted to adjust for changes in prudent and Western dietary patterns based on the results from principal component analysis of 39 predefined food groups. After controlling for all these factors, the findings were similar to those originally reported by the SUN cohort.

In 2011, Mozaffarian et al. [16] conducted large prospective analyses with 120,877 US women and men from the NHS-I and -II and health professionals follow-up cohorts. Their objective was to evaluate lifestyle, including repeated 4-year changes in food consumption as predictors of 4-year weight changes repeatedly assessed during a 20-year period. Increased consumptions of yogurt, fruits, whole grains, nuts, and vegetables were associated with concurrent weight losses during these 4-year periods. Specifically, each increase of one serving per day of nuts was associated with −0.26 kg (95% CI: −0.44 to −0.08) after adjusting for a wide set of potentially confounding variables, including sex, age, baseline BMI, sleep duration, changes in smoking status, physical activity, television watching, alcohol use, and all of the dietary factors assessed. Importantly, in this large study, many restrictions were applied to eliminate additional sources of potential confounding.

Table 7.1 Published Prospective Cohort Studies on Long-Term Nut Consumption and Weight Gain or Risk of Overweight, Obesity, or Abdominal Obesity

Country	*Study*	*Subject (n)*	*Follow-Up*	*Outcome*	*Exposure (Comparison)*	*Results*	*References*
Spain	SUN cohort	8,865	2.3 years	Average weight gain	> = 2 servings/week *versus* never or almost never (ref)	Weight gain difference between groups = –410 g (95% CI: 0.54–0.93)[a]	[13]
Spain	SUN cohort	8,865	2.3 years	OR for gaining > = 5 kg	> = 2 servings/week *versus* never or almost never (ref)	OR = 0.71 (95% CI: 0.54–0.93)[a]	[13]
Spain	SUN cohort	6,630	2.3 years	OR for overweight/ obesity	> = 2 servings/week *versus* never or almost never (ref)	OR = 0.73 (95% CI: 0.48–1.11)[a]	[13]
USA	Nurses' Health Study II	51,188	8 years	Average weight gain	> = 2 servings/week *versus* rare consumption	5.04 kg *versus* 5.55 kg ($P < 0.001$)[b]	[15]
USA	Nurses' Health Study II	408,664	8 years	HR for obesity	> = 2 servings/week *versus* rare consumption	HR = 0.62 (0.32–0.99)[b]	[15]
USA	Nurses´ Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study	120,877	4 years	Weight change (kg)	For each increase of a daily serving of nuts	–0.26 (95% CI: –0.44 to –0.08)[c]	[16]

(*Continued*)

Table 7.1 (Continued) Published Prospective Cohort Studies on Long-Term Nut Consumption and Weight Gain or Risk of Overweight, Obesity, or Abdominal Obesity

Country	*Study*	*Subject (n)*	*Follow-Up*	*Outcome*	*Exposure (Comparison)*	*Results*	*References*
Spain	SUN cohort	9,887	6 years	OR for abdominal obesity (waist > = 94 cm in men and > = 80 cm in women)	> = 2 serving/week *versus* never or almost never	Men: OR = 0.86 (95% CI: 0.68–1.09) Women: OR = 0.69 (95% CI: 0.66–0.84)[d]	[17]
Europe	EPIC-Panacea Study	373,293	5 years	Average weight gain (kg)	4th quartile (> 6 g/day) *versus* non-consumers	Weight gain differences between groups: –0.07 kg (95% CI: –0.12 to –0.02)[e]	[18]
Europe	EPIC-Panacea Study	373,293	5 years	RR for overweight/ obesity	4th quartile (> 6 g/day) *versus* non-consumers	RR = 0.95 (95% CI: 0.90–0.99)[e]	[18]

Abbreviations: BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; OR, odds ratio; ref, reference group; RR, risk ratio; SUN, Seguimiento Universidad de Navarra (University of Navarra Follow-up).

[a] Adjusted for age, baseline BMI, leisure-time physical activity, smoking status, snacking, television watching time, and total energy intake.

[b] Adjusted for age, baseline BMI, alcohol intake, physical activity, smoking, postmenopausal hormone use, oral contraceptive use, glycemic load, and intakes of total fiber, trans fat, fruit, vegetables, red meat, processed meat, refined grains, whole grains, snacks, sugar-sweetened beverages, diet beverages, low-fat dairy products, high-fat dairy products, and changes in confounders between time periods (except BMI).

[c] Adjusted for age, baseline BMI, sleep duration, changes in physical activity, alcohol use, television watching, smoking, fruits, vegetables, whole-fat dairy foods, low-fat dairy foods, potato chips, potatoes, whole grains, refined grains, sugar-sweetened beverages, 100% fruit juices, diet soda, sweets and desserts, processed meats, unprocessed red meats, trans fat, and fried foods.

[d] Adjusted for age, baseline BMI, smoking, physical activity, alcohol intake, and total energy intake.

[e] Adjusted for age, sex, baseline BMI, follow-up time, total energy intake, educational level, physical activity, smoking status at follow-up, plausibility of dietary energy reporting, and modified relative Mediterranean diet score (without fruit and nut component).

Fernandez-Montero et al. [17] studied the long-term effects of tree nuts on metabolic syndrome (MetS) in 9,887 participants of the SUN cohort. Results assessing the components of MetS showed an inverse association with incident abdominal obesity both in men and women who reported the consumption of at least two servings per week of nuts compared to those who never or almost never consumed nuts. Among women, the magnitude of the association was higher.

The largest long-term observational epidemiological study conducted so far in the field of nut consumption and weight gain is the study carried out with data from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Panacea cohort [18]. It comprised 373,293 men and women, 25–70 years old, from 10 European countries. The authors found that long-term weight gain was lower in subjects consuming higher amounts of nuts including peanuts. Similarly, those who consumed the highest amounts of nuts (fourth quartile) had a 5% lower risk of becoming overweight or obese over 5 years (relative risk: 0.95; 95% CI, 0.92–0.98).

7.2.2 Long-Term Randomized Clinical Trials

Table 7.2 summarizes the published RCTs on long-term nut consumption and weight gain or risk of overweight, obesity, and abdominal obesity. Simultaneous to the previous reported findings, a large RCT to assess the role of the Mediterranean diet (MedDiet) on cardiovascular prevention, the PREvención con DIeta MEDiterránea (PREDIMED) trial, was started in Spain (the recruitment lasted from 2003 to 2009). In the PREDIMED trial, one of the three randomized arms received advice to consume tree nuts (30 g/day) and a free allotment of mixed nuts to ensure this level of daily consumption (50% walnuts, 25% almonds, and 25% hazelnuts). In 2008, Salas-Salvadó et al. [19] published preliminary results of the PREDIMED trial, but included only a subgroup (n = 1224) of the initial participants assessed after a 1-year follow-up. Participants allocated to MedDiet supplemented with nuts were those with the highest reductions in prevalence of abdominal obesity from 64.5% to 59.6%. At the same time, they experienced the highest reversion rate of MetS (18.9%) compared to those allocated to the control group (11.7%).

Recently, PREDIMED investigators reported the effect of the high-fat MedDiets recommended in the trial on body weight and waist circumference (WC) after 5 years of follow-up [20]. The group randomly allocated to a MedDiet rich in nuts showed no evidence of weight gain associated with nut consumption. Conversely, the results showed a modest reduction in WC compared to the control group.

The results of a secondary analysis on weight changes of the 2-year randomized trial Walnuts and Healthy Aging (WAHA) study, primarily designed to examine the effects of walnuts on age-related cognitive impairment and macular degeneration, were recently published [21]. Authors specifically studied the effects of long-term walnut supplementation (approximately 15% of daily energy requirements) on body weight in free-living elders compared with control elders who followed their habitual diet and abstained from walnuts or excessive intake of other nuts (> 2 servings/week). The results showed that an average of nearly 300 kcal from walnuts on a daily basis for 2 years (even when advice on foods to be replaced when adding walnuts to the diet was not provided) neither led to weight gain nor caused any significant change in body composition when the results were compared with the control group (not eating nuts or only occasionally).

Table 7.2 Published Randomized Controlled Trials on Long-Term Nut Consumption and Weight Gain or Risk of Overweight, Obesity, or Abdominal Obesity

Country	*Study*	*Subject (n)*	*Follow-Up*	*Outcome*	*Exposure (Comparison)*	*Results*	*References*
Spain	PREDIMED trial	1,224	1 year	Prevalence (%) of abdominal obesity (1-year changes)	MedDiet + nuts *versus* control (low-fat diet)	64.5% (baseline) to 59.6% (1-year) *versus* 69.8% (baseline) to 67.1% (1-year).[a]	[19]
Spain	PREDIMED trial	3,985	5 years	Average weight change (kg)	MedDiet + nuts *versus* control (low-fat diet)	Weight changes differences between groups: –0.075 (95% CI: –0.500 to 0.350).[b]	[20]
Spain	PREDIMED trial	3,985	5 years	Average change in WC (cm)	MedDiet + nuts *versus* control (low-fat diet)	Weight changes differences between groups: –0.936 (95% CI: –1.600 to –0.271).[b]	[20]
USA	WAHA	307	2 years	Weight (kg) (95% CI)	Walnut intervention group (~15% DEN *versus* control group (habitual diet with no walnuts)	Baseline: 77.1 (74.5, 79.6), 1-year: 76.9 (74.4, 79.4), and 2-year: 76.7 (74.1, 79.2) *versus* baseline: 75.6 (73.0, 78.2), 1-year: 75.3 (72.7, 77.9), and 2-year: 75.0 (72.4, 77.6) (*P* - value group x time interaction effect = 0.671).	[21]
USA	WAHA	307	2 years	Body fat (kg)	Walnut intervention group (~15% DEN *versus* control group (habitual diet with no walnuts)	Baseline: 25.5 (24.4, 26.7), 1-year: 25.9 (24.9, 27.0), and 2-year: 26.4 (25.3, 27.4) *versus* baseline: 25.5 (24.3, 26.2), 1-year: 25.7 (24.6, 26.8), and 2-year: 26.0 (24.8, 27.1) (*P* - value group × time interaction effect = 0.528).	[21]

(*Continued*)

Table 7.2 (Continued) Published Randomized Controlled Trials on Long-Term Nut Consumption and Weight Gain or Risk of Overweight, Obesity, or Abdominal Obesity

Country	*Study*	*Subject (n)*	*Follow-Up*	*Outcome*	*Exposure (Comparison)*	*Results*	*References*
USA	WAHA	307	2 years	WC	Walnut intervention group (~15% DEN *versus* control group (habitual diet with no walnuts)	Baseline: 99.4 (97.3, 101.6), 1-year: 99.6 (97.5, 101.7), and 2-year: 99.7 (97.6, 101.8) *versus* baseline: 98.6 (96.4, 100.8), 1-year: 98.6 (96.5, 100.8), and 2-year: 98.6 (96.4, 100.8) (*P* - value group × time interaction effect = 0.651).	[21]

Abbreviations: CI, confidence interval; DEN, daily energy needs; PREDIMED, PREvención con DIeta MEDiterránea (Prevention with Mediterranean Diet); WAHA, Walnuts and Healthy Aging; WC, waist circumference.

[a] $P < 0.05$.

[b] Adjusted for age, sex, center, smoking status, diabetes, dyslipidemia, hypertension, educational level, leisure-time physical activity, baseline BMI, total energy intake, and alcohol intake.

7.3 Systematic Reviews and Meta-Analyses

A meta-analysis of prospective studies on different food groups and risk of overweight, obesity, and weight gain [22] concluded that nut consumption was associated with lower weight gain, defined as either more than 2 kg per year, or 5 kg or more in an average time period of 2.3 years. The summary risk ratio for weight gain was 0.76 (95% CI: 0.58–0.99). In the same meta-analysis, authors found no association between nut consumption and the risk of overweight or obesity.

A systematic review specifically on nut consumption and risk of overweight/obesity was published by Li et al. [23] in 2018 following the MOOSE guidelines. They included six cohort studies with results on overweight, obesity, or MetS in 420,890 subjects and 62 RCTs with information on changes in body weight parameters in 7184 participants. The results from this systematic review and meta-analysis allay any fear about the supposed weight-gain effects of consuming nuts in the context of a healthy diet. For each additional serving per week of nuts, the risk of overweight was reduced by 3% and, for obesity only, it was reduced by 5%. In addition, the pooled results of RCTs suggested that nut supplementation could lower body weight, BMI, and WC. Interestingly, the authors stratified the effects of nuts on different anthropometric variables and according to the type of nuts used in the feeding trials. Regarding body weight, studies conducted with almonds were those with higher influence in the random effects models and the only ones that presented a statistically significant inverse association. The confidence intervals of the results for nut types different from almonds comprised always the null value. Similarly, findings were presented for BMI and the results of nine studies conducted with walnuts found a statistically significant association for a modest increase. For WC, almonds were the nut type most represented, and they also showed a statistically significant inverse association. On the other hand, the results of three studies with pistachios suggested a statistically significant association with modestly increased values. This review attempted to elucidate the effect of different types of nuts on weight gain, but clearly further studies are needed to clarify the existence of a differential effect on anthropometrics depending on particular nuts. Based on the evidence from the long-term prospective studies and RCTs previously discussed, most of the studies that evaluated the effect of mixed nuts were based on the items included in the food frequency questionnaires. In the case of the PREDIMED trial, the MedDiet plus nuts arm of the trial comprised mixed nuts (walnuts, almonds, and hazelnuts). In the WAHA trial, obviously walnuts were supplemented. Results from the NHS, in general, did not differ between tree nuts and peanuts.

Regarding specifically walnuts, Guasch-Ferre et al. [12] in their updated meta-analysis and systematic review of RCTs on effects on blood lipids and other CVD risk factors found that, compared to control diets, walnut-enriched diets did not lead to significant differences in weight change, which contrasts with findings of the meta-analysis of Li et al. [23]. The key issue here is that supplementation with nuts or a higher consumption of nuts, despite contributing to an inherent additional increment in total energy intake, did not lead to weight gain in the available studies.

Similarly, when hazelnut consumption was specifically assessed in another systematic review and Bayesian meta-analysis, Perna et al. [24] found that BMI remained substantially unchanged.

In a systematic review of RCTs aimed at evaluating the effect of tree nuts on MetS criteria, authors concluded that there were no adverse effects on WC across different nut types [25]. However, they pointed out that their conclusions were limited by the short duration and poor quality of the majority of available RCTs, as well as by the existence of unexplained heterogeneity among studies. Therefore, there is plenty of room for improving scientific evidence, and larger, longer, and higher quality trials are needed.

In 2013, Flores-Mateo et al. [26] conducted the first meta-analysis of RCTs specifically examining changes in adiposity variables in relation to nut consumption. From the results of 33 RCTs included in the meta-analysis, authors concluded that nut-enriched diets did not increase adiposity measures. They identified the study focus (energy restriction compared with weight-loss maintenance) as a potential explanation for the heterogeneity between studies. As expected, those studies with nuts and energy restriction were more prone to observe weight loss than those without any energy restriction. Therefore, from a public health perspective, in the promotion of nut consumption among the general population, it is very important to highlight the idea of food substitution and moderation in serving size instead of food addition. Otherwise, if a person consumes the entire bag of nuts in addition to other snacks, for sure he/she will put on weight in the near future.

7.4 Biological Plausibility

There are several mechanisms that support the null effects or even an inverse association between nut consumption and weight gain (Figure 7.1).

- Nuts are rich in dietary fiber and protein, which are associated with satiety and satiation [27,28].
- The fiber content of nuts may additionally induce a delay in gastric emptying and subsequent nutrient absorption that potentially suppresses hunger [27,28].
- The protein, fiber, and unsaturated fat content of nuts may also increase resting energy expenditure and thermogenesis [27,28].
- The high unsaturated fat content of nuts is the cause of a suggested effect on higher fat oxidation rates [27,28].
- Because of their structure and composition, whole nuts are not completely chewed, and therefore, the total amounts of lipids liberated from the nuts are incompletely absorbed and are lost in the feces, leading to some degree of energy loss [27–31].
- Nuts tend to replace processed snacks rich in sugar, fat, and refined grains, foods with a high-risk profile for weight gain. Such replacement is likely to be a plausible explanation for the beneficial effects of nuts observed in the prevention of weight gain [28,32].
- It is suggested that nut components such as polyphenols and fiber have prebiotic properties that might improve the gut microbiome, and as a consequence prevent weight gain [33].

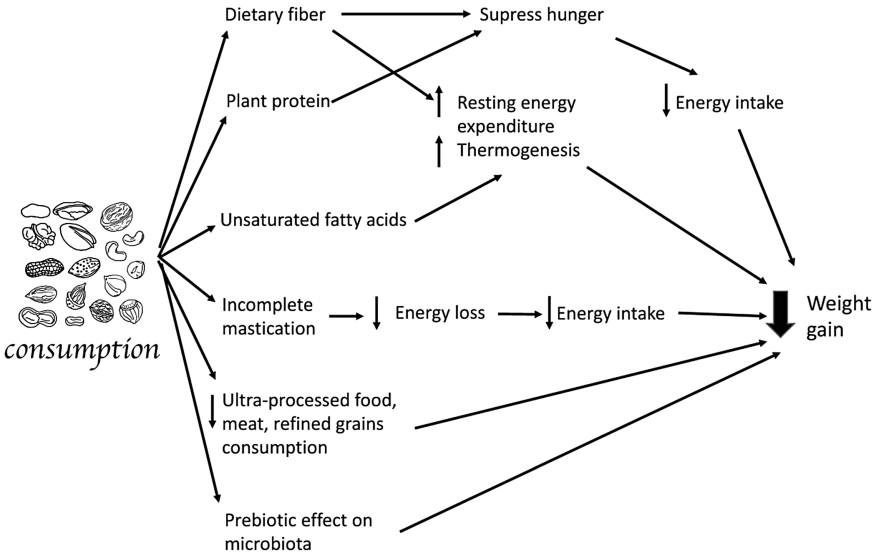


Figure 7.1 Potential plausible biological mechanisms supporting a null association between nut consumption and weight gain. (Adapted from Jackson, C.L. and Hu, F.B., *Am. J. Clin. Nutr.*, 100(Suppl.1), 408S, 2014 and Lamuela-Raventos, R.M. and Onge, M.S., *Crit. Rev. Food Sci. Nutr.*, *57*, 3154, 2017.)

7.5 Conclusion

Based on the available scientific evidence so far, consumption of nuts is not associated with weight gain or risk of overweight or obesity. Rather, the inclusion of nuts in restricted-calorie diets appears to be a good strategy to help people to lose weight or maintain a healthy body weight. Importantly, they should not be added, but should replace alternative unhealthy snacks.

Similarly to olive oil [34], nuts are a good example that not all energy-dense foods are associated with weight gain in a context of a healthy dietary pattern. Presumably, nuts are protective against weight gain despite their high energy density because most energy is made up of healthy fats in the forms of unsaturated fatty acids. Therefore, nut consumption is a good example of the need to focus nutritional recommendations on overall food and diet quality instead of focusing on single nutrients. However, in the context of the current obesity pandemic, there is a need for clear messages and practical resources for obesity prevention. Weight gain is gradual and difficult to detect and reverse. Prevention should be the priority. It seems critical to stress the importance of replacement. Using nuts to replace other less healthful foods may represent an evidence-based and very practical advice. The awareness of serving size and total calorie intake should be simultaneously highlighted in order to avoid positive energy balance. As exemplified by findings of the PREDIMED trial, consumption of moderate amounts of nuts (a handful, approximately 30 g per day) can be incorporated to a dietary pattern such as the MedDiet to prevent CVD, type 2-diabetes, and other non-communicable diseases. Otherwise, consumption of nuts as added foods to the diet, while sitting in front of the TV, might not be the best strategy to prevent weight gain.

References

1. Goren-Inbar, N., Sharon, G., Melamed, Y., and Kislev, M., Nuts, nut cracking, and pitted stones at Gesher Benot Ya'aqov, Israel. *Proc. Natl. Acad. Sci. USA*, 99, 2455–2460, 2002.
2. Sabate, J., Ros, E., and Salas-Salvado, J., Nuts: Nutrition and health outcomes. *Br. J. Nutr.*, 96(Suppl.2), 1S–2S, 2006.
3. Aune, D., Keum, N., Giovannucci, E., Fadnes, L.T., Boffetta, P., Greenwood, D.C., Tonstad, S. et al., Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review and dose-response meta-analysis of prospective studies. *BMC Med.*, 14, 207, 2016.
4. Grosso, G., and Estruch, R., Nut consumption and age-related disease. *Maturitas*, 85, 11–16, 2016.
5. Blomhoff, R., Carlsen, M.H., Andersen, L.F., and Jacobs, D.R.Jr., Health benefits of nuts: Potential role of antioxidants. *Br. J. Nutr.*, 96(Suppl. 2), 52S–60S, 2006.
6. Segura, R., Javierre, C., Lizarraga, M.A., and Ros, E., Other relevant components of nuts: Phytosterols, folate and minerals. *Br. J. Nutr.*, 96(Suppl. 2), 36S–44S, 2006.
7. Sabate, J., Nut consumption and body weight. *Am. J. Clin. Nutr.*, 78(Suppl. 3), 647S–650S, 2003.
8. Fraser, G.E., Sabaté, J., Beeson, W.L., and Strahan, T.M., A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch. Intern. Med.*, 152, 1416–1424, 1992.
9. O'Neil, C.E., Fulgoni III, V.L., and Nicklas, T.A., Tree nut consumption is associated with better adiposity measures and cardiovascular and metabolic syndrome health risk factors in U.S. adults: NHANES 2005–2010. *Nutr. J.*, 14, 64, 2015.
10. Jaceldo-Siegl, K., Haddad, E., Oda, K., Fraser, G.E., and Sabate, J., Tree nuts are inversely associated with metabolic syndrome and obesity: The Adventist Health Study-2. *PLoS One*, 9, e85133, 2014.
11. Rajaram, S., and Sabate, J., Nuts, body weight and insulin resistance. *Br. J. Nutr.*, 96(Suppl. 2), 79S–86S, 2006.
12. Guasch-Ferre, M., Li, J., Hu, F.B., Salas-Salvado, J., and Tobias, D.K., Effects of walnut consumption on blood lipids and other cardiovascular risk factors: An updated met-analysis and systematic review of controlled trials. *Am. J. Clin. Nutr.*, 108, 174–187, 2018.
13. Bes-Rastrollo, M., Sabaté, J., Gomez-Gracia, E., Alonso, A., Martinez, J.A., and Martinez-Gonzalez, M.A., Nut consumption and weight gain in a Mediterranean cohort: The SUN Study. *Obesity*, 15, 107–116, 2007.
14. Martinez-Gonzalez, M.A., and Bes-Rastrollo, M., Nut consumption, weight gain and obesity: Epidemiological evidence. *Nutr. Metab. Cardiovasc. Dis.*, 21(Suppl. 1), 40S–45S, 2011.
15. Bes-Rastrollo, M., Wedick, N.M., Martinez-Gonzalez, M.A., Li, T.Y., Sampson, L., and Hu, F.B., Prospective study of nut consumption, long-term weight change, and obesity risk in women. *Am. J. Clin. Nutr.*, 89, 1913–1919, 2009.
16. Mozaffarian, D., Hao, T., Rimm, E.B., Willett, W.C., and Hu, F.B., Changes in diet and lifestyle and long-term weight gain in women and men. *New Engl. J. Med.*, 364, 2392–2404, 2011.

17. Fernandez-Montero, A., Bes-Rastrollo, M., Beunza, J.J., Barrio-Lopez, M.T., de la Fuente-Arrillaga, C., Moreno-Galarraga, L., and Martínez-González, M.A., Nut consumption and incidence of metabolic syndrome after 6-year follow-up: The SUN (Seguimiento Universidad de Navarra, University of Navarra follow-up) Cohort. *Public Health Nutr.*, 16, 2064–2072, 2013.
18. Freisling, H., Noh, H., Slimani, N., Chajes, V., May, M.M., Peeters, P.H., Weiderpass, E. et al., Nut inatke and 5-year changes in body weight and obesity risk in adults: Results from the EPIC-PANACEA study. *Eur. J. Nutr.*, 57, 2399–2408, 2018.
19. Salas-Salvadó, J., Fernandez-Ballart, J., Ros, E., Martinez-Gonzalez, M.A., Fito, M., Estruch, R., Corella, D. et al., Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status. *Arch. Intern. Med.*, 168, 2449–2458, 2008.
20. Estruch, R., Martinez-Gonzalez, M.A., Corella, D., Salas-Salvado, J., Fito, M., Chiva-Blanch, G., Fiol, M. et al., Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A pre-specified secondary outcomes analysis of the PREDIMED randomised controlled trial. *Lancet Diabetes Endocrinol.*, 7, e6–e17, 2019.
21. Bitok, E., Rajaram, S., Jaceldo-Siegl, K., Oda, K., Sala-Vila, A., Serra-Mir, M., Ros, E. et al., Effects of long-term walnut supplementation on body weight in free-living elderly: Results of a randomized controlled trial. *Nutrients*, 10, E1317, 2018.
22. Schlesinger, S., Neuenschwander, M., Schwedhelm, C., Hoffmann, G., Bechthold, A., Boeing, H., and Schwingshackl, L., Food groups and risk of overweight, obesity, and weight gain: A systematic review and dose-response meta-analysis of prospective studies. *Adv. Nutr.*, 10, 205–218, 2019.
23. Li, H., Li, X., Yuan, S., Jin, Y., and Lu, J., Nut consumption and risk of metabolic syndrome and overweight/obesity: A meta-analysis of prospective cohort studies and randomized trials. *Nutr. Metab. (Lond)*, 15, 46, 2018.
24. Perna, S., Giacosa, A., Bonitta, G., Bologna, C., Isu, A., Guido, D., and Rondanelli, M., Effects of hazelnut consumption on blood lipids and body weight: A systematic review and Bayesian meta-analysis. *Nutrients*, 8, 747, 2016.
25. Blanco, M.S., Kendall, C.W.C., Viguiliouk, E., Augustin, L.S., Ha, V., Cozma, A.I., Mirrahimi, A. et al., Effect of tree nuts on metabolic syndrome criteria: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*, 4, e004660, 2014.
26. Flores-Mateo, G., Rojas-Rueda, D., Basora, J., Ros, E., and Salas-Salvado, J., Nut intake and adiposity: Meta-analysis of clinical trials. *Am. J. Clin. Nutr.*, 97, 1346–1355, 2013.
27. Tan, S.Y., Dhillon, J., and Mattes, R.D., A review of the effects of nuts on appetite, food intake, metabolism, and body weight. *Am. J. Clin. Nutr.*, 100(Suppl. 1), 412S–422S, 2014.
28. Jackson, C.L., and Hu, F.B., Long term associations of nut consumption with body weight and obesity. *Am. J. Clin. Nutr.*, 100(Suppl. 1), 408S–411S, 2014.
29. Novotny, J.A., Gebauer, S.K., and Baer, D.J., Discrepancy between the Atwater factor predicted and empirically measured energy values of almonds in human diets. *Am. J. Clin. Nutr.*, 96, 296–301, 2012.
30. Baer, D.J., Gebauer, S.K., and Novotny, J.A., Walnuts consumed by healthy adults provide less available energy than predicted by the Atwater factors. *J. Nutr.*, 146, 9–13, 2016.

31. Baer, D.J., and Novotny, J.A., Metabolizable energy from cashew nuts is less than that predicted by Atwater factors. *Nutrients*, 11, E33, 2018.
32. Bitok, E., Jaceldo-Siegl, K., Rajaram, S., Serra-Mir, M., Roth, I., Feitas-Simoes, T., Ros, E. et al., Favourable nutrient intake and displacement with long-term walnut supplementation among elderly: Results of a randomized trial. *Br. J. Nutr.*, 118, 201–201, 2017.
33. Lamuela-Raventos, R.M., and Onge, M.S., Prebiotic nut compounds and human microbiota. *Crit. Rev. Food Sci. Nutr.*, 57, 3154–3163, 2017.
34. Bes-Rastrollo, M., Sanchez-Villegas, A., de la Fuente, C., de Irala, J., Martinez, J.A., and Martinez-Gonzalez, M.A., Olive oil consumption and weight changes: The SUN prospective cohort study. *Lipids*, 41, 249–256, 2006.

Chapter 8

Nuts in the Prevention and Management of Diabetes

Stephanie K. Nishi, Effie Viguiliouk, Sonia Blanco Mejia, David J.A. Jenkins, John L. Sievenpiper, and Cyril W.C. Kendall

8.1 Introduction 182
8.2 Nuts in the Prevention and Management of Diabetes 182
8.2.1 Findings from Prospective Cohort Studies 182
8.2.1.1 Nuts and Metabolic Syndrome 183
8.2.1.2 Nuts and Diabetes Incidence 191
8.2.1.3 Nuts and Diabetes Mortality 193
8.2.1.4 Strengths, Limitations, and Conclusion 193
8.2.2 Findings from Randomized Controlled Trials 194
8.2.2.1 Nuts and Glycemic Control in Individuals with High Diabetes Risk 194
8.2.2.2 Nuts and Glycemic Control in Individuals with Diabetes 208
8.3 Potential Mechanisms and Barriers to Consumption 211
8.4 Conclusion 212
Funding 212
Conflicts of Interest 212
References 215

8.1 Introduction

Nuts are nutrient-dense foods, rich in unsaturated fatty acids, vegetable protein, fiber, and minerals (e.g., magnesium and potassium), as well as bioactive components such as polyphenols, tocopherols, phytosterols, and phenolics [1–4]. From a consumer perspective, the term *nuts* encompasses tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia, pecans, pine nuts, pistachios, and walnuts), defined as dry fruits with one seed in which the ovary wall becomes hard at maturity; and peanuts, which are technically a legume but share a similar nutritional profiles to tree nuts.

Publications on nuts and cardiovascular disease (CVD), specifically those relating to blood lipids, have led to a qualified health claim from the Food and Drug Administration (FDA) in 2003, stating that "*eating 1.5 ounces (~ 42.5 g) of most nuts as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease*" [5]. Nuts are a component of numerous dietary patterns, such as the Mediterranean, vegetarian, and Portfolio dietary patterns, associated with the prevention of non-communicable diseases including benefits for diabetes and glycemic control [6–8]. Some diabetes clinical practice guidelines recommendations currently acknowledge nuts (Table 8.1); however, recommendations are inconsistent, non-specific, and occasionally non-existent [9–12]. Moreover, despite the recognized health benefits associated with nut consumption, intake is relatively low and does not normally meet the level noted in the FDA health claim for heart disease risk reduction. In North America, only approximately 6.8% of Americans are tree nut consumers with a mean intake of 44.3 g/day, whereas per capita usual intake has been reported as 3.3 g/day [13]. Similarly, Canadian nut consumers composed less than 5% of the population on any given day with a mean intake of 18 g/day according to the 2004 Canadian Community Health Survey (CCHS) [14]. Worldwide, combined nut and seed intake ranged from 0.2 to 152.7 g/day, with a global daily mean of 8.9 g [15].

The chapter summarizes and discusses the highest quality evidence, namely systematic reviews and meta-analyses (SRMAs) of prospective cohort studies and randomized controlled trials (RCTs), as well as individual RCTs and prospective cohort studies evaluating the effect of nuts (in their whole and/or butter forms) on the prevention and management of diabetes.

8.2 Nuts in the Prevention and Management of Diabetes

8.2.1 Findings from Prospective Cohort Studies

Epidemiological studies have assessed the association of nut consumption with the prevention and management of diabetes. The association of nut consumption with metabolic syndrome (MetS), diabetes incidence, or diabetes mortality has been assessed in 15 prospective cohorts (Table 8.2). These prospective cohorts tended to assess a combination of nuts rather than a specific nut type, *via* use of food frequency questionnaires. All of the studies consisted of a follow-up duration of $\geq$ 5 years varying in the number of participants, from a couple thousand to a hundred thousand individuals, and country of conduct, including Australia (1 cohort), Iran (1 cohort), China (2 cohorts), Europe (4 cohorts, one each in Finland, Germany, the Netherlands, and Spain), and the US (7 cohorts). The findings from

Table 8.1 Recommendations on Nut Intake in Diabetes Guidelines

Guideline Association	*Recommendation*	*Grade Assessment*	*References*
American Diabetes Association	Eating foods rich in long-chain n-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA), is recommended to prevent or treat CVD.	Grade B	[9]
Diabetes Canada (formerly Canadian Diabetes Association)	Dietary patterns emphasizing nuts to improve glycemic control may be considered in people with T2DM.	Grade B, Level 2	[10]
Diabetes UK	Dietary patterns, specifically the Mediterranean and DASH-style diets, are recommended to reduce CVD risk factors and CVD events in people with diabetes. Key features of these diets include eating more whole grains, fruits, vegetables, fish, nuts, and legumes (pulses).	Grade 3	[11]
European Association for the Study of Diabetes	Consumption of two to three servings of – preferably oily – fish each week and plant sources of n-3 fatty acids (e.g., rapeseed oil, soybean oil, nuts, and some green leafy vegetables) are recommended to ensure an adequate intake of n-3 fatty acids.	Grade B	[12]

Abbreviations: ALA, α-linolenic acid; CVD, cardiovascular disease; DASH, Dietary Approach to Stop Hypertension; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; T2DM, type-2 diabetes mellitus.

these prospective cohorts in regards to risk of MetS, diabetes incidence, and diabetes mortality, are summarized and discussed in the following sections.

8.2.1.1 Nuts and Metabolic Syndrome

One prospective cohort study conducted in Spain assessed the association between nut consumption, specifically walnuts, almonds, hazelnuts, and peanuts, and risk of developing MetS [16]. MetS was defined according to the International Diabetes Federation (IDF) and American Heart Association (AHA)/National Heart, Lung, and Blood Institute harmonizing definition [17], where MetS was recognized if at least three of the following five components were present:

1. Elevated waist circumference according to the population- and country-specific definition.
2. Elevated triacylglycerols ($\geq$ 1.7 mmol/L) or the presence of drug treatment for elevated triacylglycerols.

Table 8.2 Prospective Cohort Studies Assessing the Association between Nut Intake and Metabolic Syndrome, Diabetes Incidence, and Mortality

References	*Study Characteristics*	*Participants (n, Sex, and Age)*	*Outcome of Interest*	*Cases (n)*	*Follow-Up (Years)*	*Dietary Assessment*	*Exposure Details*[a]	*Outcomes*	*Adjustments*
Metabolic Syndrome									
Fernandez-Montero et al. [16]	The SUN Cohort, Prospective Cohort (Spain)	9887, M+F, and age: 18-101 years	MetS	567	6	Validated FFQ 136 items	Walnuts, almonds, hazelnuts, and peanuts[b]: Never/almost never 1–3 serving/month 1 serving/week ≥ 2 servings/week	 1.00 0.72 (0.56–0.91) 0.79 (0.60–1.04) 0.73 (0.54–0.99)	Age, smoking, physical activity, alcohol consumption, total energy intake, and BMI.
Shang et al. [18]	MCCS: Prospective Cohort (Australia)	5324, M+F, and age: 35–70 years	MetS	459	11.2	Validated FFQ 121 items	Legumes and nuts: Q1[c] Q2 Q3 Q4	 1.00 1.17 (0.89–1.54) 0.88 (0.66–1.19) 0.74 (0.53–1.04)	Age, gender, follow-up period, ethnicity, socio-economic status, physical activity, smoking status, alcohol intake, BMI, waist circumference, blood pressure, plasma total cholesterol, plasma glucose, glycemic index, intake of energy, fiber, sodium, potassium, magnesium, vitamin C, vitamin E, saturated fat, monounsaturated fat, polyunsaturated fat, and trans fat.
Diabetes Incidence									
Asghari et al. [25]	TLGS: Prospective Cohort (Iran)	1984, M+F, and age: ≥20 years	T2DM incidence	150	6.2	Validated FFQ, NA	Nuts: < 1 serving/week 1–1.99 servings/week 2–3.99 servings/week ≥ 4 servings/week	 1.00 NA 0.51 (0.26–0.97) 0.47 (0.25–0.90)	Age, gender, BMI, serum cholesterol, triacylglycerols, smoking, and energy intake.

(*Continued*)

Table 8.2 (Continued) Prospective Cohort Studies Assessing the Association between Nut Intake and Metabolic Syndrome, Diabetes Incidence, and Mortality

References	*Study Characteristics*	*Participants (n, Sex, and Age)*	*Outcome of Interest*	*Cases (n)*	*Follow-Up (Years)*	*Dietary Assessment*	*Exposure Details*[a]	*Outcomes*	*Adjustments*
Kochar et al. [23]	PHS-1: Prospective Cohort (USA)	20,224, M, and age: 40.7–87.1 years	T2DM incidence	1828	19.2	Validated FFQ 19 items	Nuts: 0 serving/week < 1 serving/week 1 serving/week 2–4 servings/week 5–6 servings/week ≥ 7 servings/week	 1.0 1.06 (0.93–1.20) 1.10 (0.95–1.26) 0.97 (0.82–1.14) 0.99 (0.76–1.30) 0.87 (0.61–1.24)	Age, smoking, randomization arm, breakfast consumption, cereal, dairy, red meat, physical activity, BMI, and history of hypertension.
Montonen et al. [20]	FMCHES: Prospective Cohort (Finland)	4304, M+F, and age: 40–69 years	T2DM incidence	383	23	FFQ, NA	Peas and nuts: < 2 g/day 2–4 g/day 5–8 g/day > 8 g/day	 1.0 0.73 (0.55–0.95) 0.81 (0.61–1.07) 0.90 (0.67–1.20)	Age, sex, BMI, energy intake, smoking, family history of diabetes, and geographic area
Nettleton et al. [22]	MESA: Prospective Cohort (USA)	5011, M+F, and age: 45–84 years	T2DM incidence	413	~5	Validated FFQ 120 items	Nuts/seeds: Comparison per one unit increase (servings/day)	 1.00 0.94 (0.84–1.06)	Energy intake, study center, age, sex, race/ethnicity, education, active leisure-time physical activity, current smoking status, smoking pack-years, current weekly supplement use, intakes of whole grains, vegetables, low-fat dairy, coffee, soda, red meat, processed meat, high-fat dairy, and white potatoes.

(*Continued*)

Table 8.2 (Continued) Prospective Cohort Studies Assessing the Association between Nut Intake and Metabolic Syndrome, Diabetes Incidence, and Mortality

References	*Study Characteristics*	*Participants (n, Sex, and Age)*	*Outcome of Interest*	*Cases (n)*	*Follow-Up (Years)*	*Dietary Assessment*	*Exposure Details*[a]	*Outcomes*	*Adjustments*
Pan et al. [24]	NHS: Prospective Cohort (USA)	58,063, F, and age: 52–77 years	T2DM incidence	3166	22	Validated FFQ 130 items	Tree nuts and peanuts: Never/rarely < 1 serving/week 1 serving/week 2–4 servings/week ≥ 5 servings/week	 1.00 0.99 (0.92–1.05) 1.05 (0.96–1.15) 0.98 (0.87–1.11) 1.00 (0.87–1.14)	Age, smoking, family history of diabetes, physical activity, total energy intake, alcohol intake, BMI, diet, and magnesium.
							Tree nuts: Never/rarely < 1 serving/week 1 serving/week ≥ 2 servings/week	 1.00 1.03 (0.96–1.10) 1.07 (0.95–1.19) 1.00 (0.86–1.15)	
							Peanuts: Never/rarely < 1 serving/week 1 serving/week ≥ 2 servings/week	 1.00 1.03 (0.97–1.09) 1.06 (0.95–1.17) 1.05 (0.92–1.19)	
Pan et al. [24]	NHS II: Prospective Cohort (USA)	79,893, F, and age: 35–52 years	T2DM incidence	2764	18	Validated FFQ 130 items	Tree nuts and peanuts: Never/rarely < 1 serving/week 1 serving/week 2–4 servings/week ≥ 5 servings/week	 1.00 0.99 (0.92–1.06) 1.00 (0.89–1.12) 1.00 (0.86–1.17) 1.02 (0.85–1.23)	Age, smoking, family history of diabetes, physical activity, total energy intake, alcohol intake, BMI, diet, and magnesium.
							Tree nuts: Never/rarely <1 serving/week 1 serving/week ≥ 2 servings/week	 1.00 1.00 (0.93–1.08) 1.03 (0.89-1.19) 0.94 (0.75–1.17)	
							Peanuts: Never/rarely < 1 serving/week 1 serving/week ≥ 2 servings/week	 1.00 1.01 (0.94–1.08) 1.11 (0.97–1.27) 1.01 (0.81–1.25)	

(*Continued*)

Table 8.2 (Continued) Prospective Cohort Studies Assessing the Association between Nut Intake and Metabolic Syndrome, Diabetes Incidence, and Mortality

References	*Study Characteristics*	*Participants (n, Sex, and Age)*	*Outcome of Interest*	*Cases (n)*	*Follow-Up (Years)*	*Dietary Assessment*	*Exposure Details*[a]	*Outcomes*	*Adjustments*
Parker et al. [19]	IWHS: Prospective Cohort (USA)	35,988, postmenopausal women, F, and age: 55–69 years	T2DM incidence	1831	12	Validated FFQ 127 items	Nuts: 0 serving/week < 1 serving/week 1–4 servings/week ≥ 5 servings/week	 1.0 0.98 (0.87–1.10) 1.06 (0.93–1.22) 1.51 (1.13–2.04)	Age, BMI, waist/hip ratio, physical activity, smoking status, pack-years of smoking, alcohol consumption, total daily energy intake, educational attainment, estrogen use, and dietary factors (fiber, polyunsaturated fat, saturated fat, monounsaturated fat, trans fatty acids, servings per day of total fruit, total vegetables, whole grains, fish and seafood, and daily intake of magnesium).
Villegas et al. [21]	SWHS: Prospective Cohort (China)	64,191, F, and age: 40–70 years	T2DM incidence	1608	4.6	Validated FFQ 77 items	Peanuts: Q1 Q2 Q3 Q4 Q5	 1.0 0.80 (0.69–0.94) 0.95 (0.82–1.11) 0.79 (0.68–0.92) 0.80 (0.68–0.93)	Age, energy intake, BMI, waist-to-hip ratio, smoking, alcohol intake, vegetable intake, fiber intake, physical activity, income level, education level, occupation, and hypertension.
von Ruesten et al. [26]	EPIC-Potsdam: Prospective Cohort (Europe)	23,531, M+F, and age: 35–65 years	T2DM incidence	837	8	Validated FFQ 148 items	Nuts: Comparison per one unit increase (5 g/day)	 1.00 0.95 (0.90–1.00)	Age, sex, smoking status (never, former, and current), pack-years of smoking, alcohol consumption (g/day), leisure-time physical activity (walking, cycling, and sports in hours per week), BMI, waist-to-hip ratio, prevalent hypertension at baseline (yes/no), history of high blood lipid levels at baseline (yes/no), education (vocational training or lower degree *versus* trade school, technical school, or university), vitamin supplementation (yes/no), non-consumption of the respective good group (yes/no), and total energy intake.

(*Continued*)

Table 8.2 (Continued) Prospective Cohort Studies Assessing the Association between Nut Intake and Metabolic Syndrome, Diabetes Incidence, and Mortality

References	*Study Characteristics*	*Participants (n, Sex, and Age)*	*Outcome of Interest*	*Cases (n)*	*Follow-Up (Years)*	*Dietary Assessment*	*Exposure Details*[a]	*Outcomes*	*Adjustments*
Diabetes Mortality									
Bao et al. [34]	NHS: Prospective Cohort (USA)	76,464, F, and age: 34–59 years	T2DM mortality	220	30	Validated FFQ 61–116 items	Tree nuts and peanuts:		Age, race, BMI, level of physical activity, smoking status, multivitamin use, aspirin use, family history, myocardial infarction, cancer, diabetes status, hypertension, hypercholesterolemia, and intake of: total energy, alcohol, red or processed meat, fruits, and vegetables, menopausal status, and hormone use.
							Never	1.00	
							< 1 serving/week	0.86 (0.62–1.20)	
							1 serving/week	0.68 (0.42–1.10)	
							2–4 servings/week	0.70 (0.41–1.18)	
							≥ 5 servings/week	0.83 (0.35–1.96)	
							Tree nuts:		
							Never	1.00	
							< 1 serving/week	0.68 (0.46–1.00)	
							1 serving/week	0.98 (0.48–2.02)	
							≥ 2 servings/week	1.15 (0.54–2.48)	
							Peanuts:		
							Never	1.00	
							< 1 serving/week	0.76 (0.52–1.10)	
							1 serving/week	1.08 (0.58–2.00)	
							≥ 2 servings/week	0.98 (0.47–2.03)	
Bao et al. [34]	HPFS: Prospective Cohort (USA)	51,529, M, and age: 45–70 years	T2DM mortality	NA	24	Validated FFQ	Tree nuts and peanuts:		Age, race, BMI, level of physical activity, smoking status, multivitamin use, aspirin use, family history, myocardial infarction, cancer, diabetes status, hypertension, hypercholesterolemia, and intake of: total energy, alcohol, red or processed meat, fruits, and vegetables.
							Never	1.00	
							< 1 serving/week	1.32 (0.65–2.65)	
							1 serving/week	0.76 (0.34–1.68)	
							2–4 servings/week	1.02 (0.49–2.12)	
							≥ 5 servings/week	0.85 (0.35–2.11)	
							Tree nuts:		
							Never	1.00	
							< 1 serving/week	0.95 (0.54–1.66)	
							1 serving/week	1.12 (0.53–2.37)	
							≥ 2 servings/week	0.89 (0.42–1.89)	
							Peanuts:		
							Never	1.00	
							< 1 serving/week	0.84 (0.47–1.51)	
							1 serving/week	0.89 (0.43–1.84)	
							≥ 2 servings/week	0.63 (0.31–1.28)	

(*Continued*)

Table 8.2 (Continued) Prospective Cohort Studies Assessing the Association between Nut Intake and Metabolic Syndrome, Diabetes Incidence, and Mortality

References	*Study Characteristics*	*Participants (n, Sex, and Age)*	*Outcome of Interest*	*Cases (n)*	*Follow-Up (Years)*	*Dietary Assessment*	*Exposure Details*[a]	*Outcomes*	*Adjustments*
Luu et al. [35]	SCCS: Prospective Cohort (USA)	71,764, M+F, and age 40–79 years	T2DM mortality	338	5.4	FFQ 89 items	Tree nuts and peanuts, African Americans:		Age, sex, education, occupation, household income, marital status, smoking pack-years, alcohol consumption, BMI, physical activity, vitamin supplement use, Charlson Comorbidity Index, metabolic conditions (hypertension, heart disease, diabetes, obesity, and hypercholesterolemia), total energy intake, red meat intake, chicken intake, seafood intake, vegetable intake, and fruit intake.
							< 0.95 g/day	1.00	
							0.95–< 3.08 g/day	0.81 (0.56–1.19)	
							3.08–< 7.30 g/day	0.84 (0.56–1.26)	
							7.30–< 18.45 g/day	0.78 (0.52–1.17)	
							≥ 18.45 g/day	0.55 (0.35–0.88)	
							Tree nuts and peanuts, European descent:		
							< 0.95 g/day	1.00	
							0.95–< 3.08 g/day	1.00 (0.48–2.08)	
							3.08–< 7.30 g/day	0.65 (0.29–1.46)	
							7.30–< 18.45 g/day	1.35 (0.68–2.67)	
							≥ 18.45 g/day	0.76 (0.34–1.70)	
Luu et al. [35]	SMHS: Prospective Cohort (China)	61,123, M, and age 40–74 years	T2DM mortality	125	6.5	Validated FFQ 84 items	Peanuts:		Age, sex, education, occupation, household income, smoking status, alcohol consumption, BMI, physical activity, regular tea consumption, Charlson Comorbidity Index, metabolic conditions (hypertension, heart disease, diabetes, obesity, and unspecified dyslipidemia), total energy intake, red meat intake, chicken/duck intake, seafood intake, vegetable intake, and fruit intake.
							< 0.14 g/day	1.00	
							0.14–< 0.72 g/day	1.43 (0.74–2.74)	
							0.72–< 1.45 g/day	1.02 (0.56–1.85)	
							1.45–< 2.54 g/day	0.86 (0.50–1.47)	
							≥ 2.54 g/day	1.38 (0.83–2.30)	

(*Continued*)

Table 8.2 (Continued) Prospective Cohort Studies Assessing the Association between Nut Intake and Metabolic Syndrome, Diabetes Incidence, and Mortality

References	*Study Characteristics*	*Participants (n, Sex, and Age)*	*Outcome of Interest*	*Cases (n)*	*Follow-Up (Years)*	*Dietary Assessment*	*Exposure Details*[a]	*Outcomes*	*Adjustments*
Luu et al. [35]	SWHS: Prospective Cohort (China)	73,142, F, and age 40–70 years	T2DM mortality	314	12.2	Validated FFQ 87 items	Peanuts: < 0.14 g/day 0.14–< 0.72 g/day 0.72–< 1.45 g/day 1.45–< 2.54 g/day ≥ 2.54 g/day	 1.00 0.71 (0.51–1.00) 0.48 (0.33–0.70) 0.91 (0.67–1.25) 0.84 (0.59–1.20)	Age, sex, education, occupation, income per capita, smoking status, alcohol consumption, BMI, physical activity, regular tea consumption, Charlson Comorbidity Index, metabolic conditions (hypertension, heart disease, diabetes, obesity, and unspecified dyslipidemia), total energy intake, red meat intake, chicken/duck intake, seafood intake, vegetable intake, and fruit intake.
van den Brandt et al. [33]	NCS: Prospective Cohort (the Netherlands)	120,852, M+F, and age 55–69 years	T2DM mortality	158	10	Validated FFQ 150 items	Tree nuts & peanuts: Never 0.1–< 5 g/day 5–< 10 g/day > 10 g/day	 1.00 0.45 (0.24–0.83) 0.22 (0.08–0.63) 0.70 (0.32–1.51)	Age at baseline, sex, cigarette smoking, number of cigarettes smoked per day, years of smoking, history of physician-diagnosed hypertension and diabetes, body weight, BMI, non-occupational physical activity, highest level of education, intake of alcohol, vegetables and fruit, energy, use of nutritional supplements, and in women postmenopausal hormone replacement therapy.

Abbreviations: BMI, body mass index; F, females; FFQ, food frequency questionnaire; FMCHES, Finnish Mobile Clinic Health Examination Survey; HPFS, Health Professional Follow-Up Study; IWHS, Iowa Women's Health Study; M, males; MCCS, Melbourne Collaborative Cohort Study; MESA, Multi-Ethnic Study of Atherosclerosis; MetS, metabolic syndrome; NA, not available; NCS, Netherlands Cohort Study; NHS, Nurses' Health Study; PHS, Physicians' Health Study; SCCS, Southern Community Cohort Study; SMHS, Shanghai Men's Health Study; SUN, Seguimiento Universidad de Navarra; SWHS, Shanghai Women's Health Study; T2DM, type-2 diabetes mellitus; TLGS, Tehran Lipid and Glucose Study;

[a] Serving = 28 g unless otherwise noted.

[b] Serving equaled ~ 50 g.

[c] Q1 to Q # represent the quartiles/quintiles of intake where specific servings or amounts were not reported.

3. Reduced high-density lipoprotein (HDL)-cholesterol (< 1.03 mmol/L in males and < 1.3 mmol/L in females) or drug treatment for reduced HDL-cholesterol.
4. Elevated blood pressure (systolic ≥ 130 mm Hg and/or diastolic ≥ 85 mm Hg) or presence of antihypertensive drug treatment in a patient with history of hypertension.
5. Elevated fasting glucose ≥ 5.6 mmol/L or drug treatment for elevated glucose.

Participants (n = 9887) were followed for a minimum of 6 years as part of the Seguimiento Universidad de Navarra (SUN) Project prospective cohort study formed of Spanish University graduates free of MetS and/or diabetes at baseline. Participants who consumed at least 2 servings (one serving ≈50 g) of nuts per week exhibited a 34% lower risk of MetS than those who never/almost never consumed nuts after adjustment for age and sex (OR: 0.66, 95% CI: 0.49-0.89; P-trend = 0.042). However, in addition to being older, nut consumers tended to be more physically active, to consume more alcohol, and to be former rather than current smokers. When adjusted for these confounding factors along with total energy intake and body mass index, the association was no longer significant (OR: 0.73, 95% CI: 0.54, 0.99; P-trend = 0.23). When assessed by sex, no association was seen among men (OR: 0.97, 95% CI: 0.67–1.39; P-trend = 0.58), but the inverse linear trend was significant among women (OR: 0.31, 95% CI: 0.16–0.61; P-trend = 0.001) [16].

In the Melbourne Collaborative Cohort Study (MCCS), the relationship between protein intakes, including a category assessing nuts and legumes, with incidence of MetS and changes in its components were examined in 5,324 participants between the ages of 27 and 80 years. MetS was defined in a similar manner as in the SUN cohort. Protein from legume and nut intakes as a percentage of energy was found to be associated with decreased likelihood of incident MetS over the 11-year follow-up after adjustment for potential confounding factors [18].

Based on the findings from the SUN and MCCS cohort studies, there is some suggestion that nut intake may be associated with reduced risk of the development of MetS; however, these findings are limited in that they are specific to people from Spain and Australia/New Zealand, respectively. Moreover, the MCCS cohort assessed the relationship of legume and nut protein intakes and did not separate the analysis of protein from nut intake alone, nor did it consider the whole nut as opposed to just the protein component.

8.2.1.2 Nuts and Diabetes Incidence

Nine prospective cohorts have shown inconsistent findings regarding the association between nut consumption and incidence of type-2 diabetes mellitus (T2DM) [19–26] (Figure 8.1).

When prospective cohorts have been systematically reviewed and meta-analyzed, no associations between nut consumption and risk of T2DM have been observed [27–32]. It should be noted that not all nine of the prospective cohorts were included in each or any of the three systematic reviews and meta-analyses that have been conducted to date assessing nut intake and T2DM incidence. Potential reasons for why all nine cohorts may not have been included are publication date or not

Diabetes end point	References for SRMA	Number of studies	Number of participant	Pooled effect estimates RR (95% CI)	$I^{2,b}$ (%)
Diabetes incidence					
	Luo et al. [31]	5	356,893	1.00 (0.84, 1.19)	67.7
	Afshin et al. [30][a]	6	230,216	0.87 (0.81, 0.94)	21.8
	Guo et al. [28]	6	263,663	0.98 (0.84, 1.15)	67.7
	Zhou et al. [29]	6	342,213	0.92 (0.78, 1.09)	78.7
	Wu et al. [27]	5	263,406	0.98 (0.84, 1.14)	74.2
	Schwingshackl et al. [32]	8	313,847	0.95 (0.85, 1.05)	67
Diabetes mortality	Aune et al. [36]	4	202,751	0.68 (0.52, 0.90)	0.0

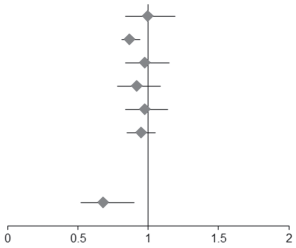


Figure 8.1 Summary of systematic reviews and meta-analyses of prospective cohorts looking at the association between nut consumption (highest *versus* lowest intake levels) and diabetes endpoints. *Abbreviations*: RR, relative risk; SRMA, systematic review and meta-analysis. [a] Data are from five prospective cohorts and one randomized controlled trial (PREDIMED). [b] I^2 refers to the degree of inter-study heterogeneity, where 0%–40% might not be important heterogeneity; 30%–60% may be moderate heterogeneity; 50%–90% may be substantial heterogeneity; and 75%–100% may be considerable heterogeneity.

meeting inclusion and exclusion criteria. Schwingshackl et al. [32] conducted the most recent of the six systematic reviews and meta-analyses, which included eight studies with 313,847 participants and 27,016 T2DM cases with no significant association for the highest *versus* lowest nut intake (RR: 0.95; 95% CI 0.85–1.05; I^2 = 67%). It should be noted that the meta-analysis included both RCTs and observational studies, in addition to studies that assessed nuts and seeds combined [32]. Wu et al. [27] conducted the next most recent of the three systematic reviews and meta-analyses, which involved five cohorts of 263,406 participants and 11,610 T2DM cases. There was no statistically significant association between consumption of nuts and risk of developing T2DM (RR: 0.98; 95% CI: 0.84–1.14; I^2 = 74.2%). The systematic reviews and meta-analyses by Afshin et al. [30], Guo et al. [28], and Zhou et al. [29], which were published the year prior to the meta-analysis of Wu et al. [27], each involved six studies, although the cohorts included differed between these meta-analyses. Afshin et al. [30] presented an inverse association with T2DM risk with 13,308 cases of 230,216 participants (RR: 0.87; 95% CI: 0.81–0.94). It should be noted that the meta-analysis included both RCTs and observational studies, in addition to studies that assessed nuts and seeds combined [30]. While Guo et al. [28] and Zhou et al. [29] showed similar findings of null associations between nut intake with risk of T2DM when comparing never/rare consumers with those consuming > 2 servings (about 28 g) per week (Figure 8.1), this lack of association was also observed in dose–response analyses.

As mentioned, inconsistencies have been observed in the cohorts assessing nut consumption and incidence of T2DM and this is evident from the I^2 statistic in each of six meta-analyses which are all, save one [30], above 60%, indicating substantial between-study heterogeneity (Figure 8.1). Wu et al. [27] and Zhou et al. [29] could not identify the source of heterogeneity. In a sensitivity analysis conducted by Guo et al. [28], it was found that results from the Iowa Women's Health Study

(IWHS) cohort substantially affected the pooled results of their meta-analysis, such that when this cohort was removed from the analyses, the model became more homogeneous (I^2 = 31.1%) with a RR of 0.90 (95% CI: 0.80, 1.00) compared to 0.98 (95% CI: 0.84, 1.15) and I^2 = 67.7%, P = 0.008 when all cohorts were included. Reasons why the IWHS might contribute to the observed heterogeneity may be due in part to the overall low mean intake of nuts in this cohort (reported mean nut intake was 0.75 servings/week). It has also been suggested that the older mean population age, the inclusion of only one dietary measure compared to multiple dietary measures, and the methods used for the diagnosis of T2DM possibly explain why findings from the IWHS differed from those of other cohorts [19].

8.2.1.3 Nuts and Diabetes Mortality

Four prospective cohorts have suggested nut intake to be associated with a mostly non-significant reduction in diabetes mortality (Table 8.2) [33–35]. These findings were supported by a systematic review and meta-analysis of prospective cohort studies indicating higher nut intake to be associated with reduced risk of mortality from diabetes when comparing both highest *versus* lowest intake of nuts (Figure 8.1) [36]. A similar finding was also observed in the dose–response analysis [36]. Specifically, a 39% reduction in the relative risk of diabetes mortality was shown with a one-serving-per-day increase in nut consumption, where one serving equals 28 g. Based on the findings of this meta-analysis and the assumption that the associations observed between nut consumption and diabetes mortality are causal, the authors estimated that for the regions assessed (e.g., North and South America, Europe, Southeast Asia, and Western Pacific), 139,000 deaths due to diabetes may be attributable to a nut intake below 20 g/day [36].

8.2.1.4 Strengths, Limitations, and Conclusion

The main strengths of these prospective cohorts are the long duration of follow-up (ranging up to 30 years) and large number of participants in the included studies, providing sufficient power to detect an association. However, several limitations need to be mentioned. In addition to the typical weaknesses demonstrated by prospective cohort studies, such as inability to determine causation, most included studies were limited by the questions asked in the food frequency questionnaires (FFQ) and, thus, most did not provide data on the types of nuts consumed or their preparation, such as whether they were salted, spiced, roasted, or raw. Tree nuts and peanuts are often grouped together in FFQs and are sometimes also combined within a question including seeds and/or other legumes. Thus, it was not possible to examine the influence of types of nuts or preparation methods on diabetes risk or mortality. As well, it is acknowledged that FFQs are prone to measurement error. Even though the majority of these FFQs are stated as being validated, it has been suggested that there may be poorer dietary assessment among men, thus leading to higher measurement error. For example, in a repeatability study of the FFQ used in the SUN cohort, the correlation coefficient for nut intake was 0.76 among women, but only 0.37 among men [37]. Despite the acknowledged weaknesses of FFQs, they remain the most practical and feasible approach for assessing dietary intake in large epidemiological studies. Additional limitations of the described studies are that the dose of nut intake remained relatively low even in the highest quartiles of the

analyses (with estimated median nut intakes ranging from 0 to 213 g/week) or were not sufficiently described, being presented as times or servings per day without an equivalent gram amount noted. Moreover, the majority of cohorts evaluated nut consumption at baseline as the dietary exposure. However, dietary habits may have changed during the study follow-up period. This could have potentially resulted in misclassification of exposure biasing results, thus possibly explaining the null association with T2DM.

The overall evidence from prospective cohort studies suggests non-significant to potential beneficial associations of nut consumption with the management and prevention of diabetes. Yet, future prospective cohort analyses and systematic reviews and meta-analyses of prospective cohorts specific to nut intake, their distinct types, and their preparation method with diabetes morbidity and mortality will help improve our understanding and inform trial design.

8.2.2 Findings from Randomized Controlled Trials

8.2.2.1 Nuts and Glycemic Control in Individuals with High Diabetes Risk

The effect of nut consumption on glycemic control in individuals at risk for diabetes (e.g., individuals with prediabetes, MetS, or one or more criteria of MetS) has been investigated in over 25 RCTs (Table 8.3). The effect of various types of nuts have been assessed, including almonds (6 trials), Brazil nuts (1 trial), cashews (1 trial), macadamias (1 trial), pecans (1 trial), peanuts (3 trials), pistachios (5 trials), walnuts (5 trials), and mixed nuts (4 trials), at intakes ranging from 20 to 85.5 g/day. More than half of these trials had a follow-up duration ≥ 12 weeks (58%) and a parallel design (73%), and varied in sample size (median: 63 individuals, range: 18–210 individuals) and country of conduct, including the US (11 trials); Spain (4 trials); Australia, Brazil, China, and Korea (2 trials each); and India, Iran, and South Africa (1 trial each). The findings from these RCTs in regards to biomarkers of glycemic control, including hemoglobin A1c (HbA_{1c}), fasting glucose, fasting insulin, and homeostatic model assessment for insulin resistance (HOMA-IR), as well as MetS risk, are summarized and discussed in the following sections.

HbA_{1c}. Seven RCTs have assessed the effect of nut consumption on HbA_{1c} levels in individuals at risk for diabetes (Table 8.3). The majority of these trials showed no significant impact on HbA_{1c}. One reason for this may be because individuals had well-controlled HbA_{1c} levels at baseline across all trials, with mean HbA_{1c} levels ranging from 5.67% to 5.92%. This suggests that the incorporation of nuts into the diet helps little with the management of HbA_{1c} levels in individuals at risk for developing diabetes who have good glycemic control. Of these trials, one showed a significant difference between the peanut intervention and the control (grain bar), where the control showed a significant lowering in HbA_{1c} compared to peanuts (–0.25% *versus* –0.18%, $P = 0.001$) [38]. In this trial, participants were asked to consume peanuts (28 g/day) or the grain bar control (40 g/day) as a preload 1 hour prior to their dinner meal for 8 weeks. Participants were encouraged to continue the feeding protocol after the end of the trial and return for follow-up testing at 12 and 16 weeks. At 16 weeks, however, there were no significant differences in HbA_{1c} levels between the control and peanuts (–0.07% *versus* –0.16%, $P = 0.159$), suggesting that there was either a deviation from following the original protocol or that there may be no effect

Table 8.3 Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
At Risk for Diabetes											
Estruch et al. [56][a]	210 high CVD risk (NR) 69 years	Spain	Parallel	12	Mixed nuts	Mixed nuts (30 g/day) + Mediterranean diet	Extra-VOO (~143 mL/day) + Mediterranean diet	NR	NR	NR	NR
							Low fat AHA diet	NR	↓	↓	↓
Schutte et al. [100]	62 MetS (28 M, 34 F) 45 years	South Africa	Parallel	8	Cashews	Cashews (~85.5 g/day)	Control diet	NR	↑	NR	NR
					Walnuts	Walnuts (~85.5 g/day)		NR	↔	NR	NR
Li et al. [42]	52 O (NR) 46 years	USA	Parallel	12	Pistachios	Pistachios (53 g/day) + weight reduction diet (500 kcal/day less)	Pretzels (56 g/day) + weight reduction diet (500 kcal/day less)	NR	↔[b]	↔	NR
Wien et al. [58]	65 PD (17 M, 48 F) 54 years	USA	Parallel	16	Almonds	Almonds (60 g/day) + ADA diet	ADA diet	↔	↔	↓	↓

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
Wu et al. [61]	189 MetS (105 M, 84 F) 48 years	China	Parallel	12	Walnuts	Walnuts (30 g/day in 100 g of bread) + AHA diet	Flaxseeds (30 g/day in 100 g of bread) + AHA diet	NR	↔[c]	NR	NR
							AHA diet	↔	↔	↔	NR
Casas-Agustench et al. [57]	50 MetS (28 M, 22 F) 52 years	Spain	Parallel	12	Mixed nuts	Mixed nuts (30 g/day) + prudent diet	Prudent diet	NR	↔	↓	↓
Maranhão et al. [49]	18 O (F only) 15 years	Brazil	Parallel	16	Brazil nuts	Brazil nuts (~20 g/day)	Lactose (1 capsule/day)	NR	↔	↔	↔
Katz et al. [101]	46 OW (18 M, 28 F) 57 years	USA	Crossover	8	Walnuts	Walnuts (56 g/day) + Ad libitum diet	Ad libitum diet	NR	↔	↔	↔
Wang et al. [43]	86 MetS (NR) 51 years	China	Parallel	12	Pistachios	Pistachios (70 g/day) + AHA step 1 diet	AHA step 1 diet	NR	↓[c]	NR	NR
						Pistachios (42 g/day) + AHA step 1 diet		NR		NR	NR

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
Anderson et al. [102]	22 OW (NR) 55 years	USA	Parallel	6	Pistachios	Pistachios (35.4 g/day)	NR	NR	↔	↔	NR
Johnston et al. [38]	44 OW/O (16 M, 28 F) 41 years	USA	Parallel	8	Peanuts	Low-fat diet with peanuts (28 g/day)	Low-fat diet with grain bar (40 g/day)	↑	↔	↔	NR
Somerset et al. [103]	64 OW (10 M, 54 F) 43 years	Australia	Parallel	10	Macadamias	Macadamias (~47 g/day) + regular diet	Regular diet	NR	↔	NR	NR
Tan and Mattes [104]	137 T2DM risk (48 M, 89 F) 30 years	USA	Parallel	4	Almonds	Almonds (43 g/day) + regular diet	Regular diet	NR	↔	↔	NR
Abazarfard et al. [46]	100 OW/O (F only) 43 years	Iran	Parallel	12	Almonds	Almonds (50 g/day) + restricted-energy diet	Restricted-energy diet	NR	↓	NR	NR

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
Domenech et al. [47][a]	157 high CVD risk (70 M, 87 F) 67 years	Spain	Parallel	52	Mixed nuts	Mixed nuts (30 g/day) + Mediterranean diet	Extra-VOO (~143 mL/day) + Mediterranean diet	NR	NR	NR	NR
							Low-fat AHA diet	NR	↔	NR	NR
Gulati et al. [41]	68 MetS (37 M, 31 F) 42 years	India	Parallel	24	Pistachios	Pistachios (~49 g/day) + standard diet for Asian Indians	Standard diet for Asian Indians	↔	↓	↔	NR
Hernandez-Alonso et al. [48]	54 PD (29 M, 25 F) 55 years	Spain	Crossover	16	Pistachios	Pistachios (57 g/day)	Control diet	↔	↓	↓	↓
Lee et al. [45]	60 MetS (NR) 35-65 years	Korea	Parallel	6	Mixed nuts	Mixed nuts (30 g/day) + prudent diet	Prudent diet	↔	↔	↔	↔

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
Moreira Alves et al. [52]	65 OW/O (M only) 27 years	Brazil	Parallel	4	Peanuts	Hypocaloric diet with conventional peanuts (56 g/day)	Hypocaloric and nut-free diet	NR	↔	↔	↔
						Hypocaloric diet with high oleic peanuts (56 g/day)					
Barbour et al. [51]	61 OW/O (29 M, 32 F) 65 years	Australia	Crossover	12	Peanuts	High oleic peanuts (15%–20% energy)	Habitual and nut free diet	NR	↔	↔	↔
Njike et al. [50]	56 T2DM risk (17 M, 39 F) 57 years	USA	Crossover	24	Walnuts	Walnuts (56 g/day) + regular diet	Regular diet	↔	↔	NR	NR
Njike et al. [50]	56 T2DM risk (14 M, 42 F) 53 years	USA	Crossover	24	Walnuts	Walnuts (56 g/day) + Ad libitum diet	Ad libitum diet	↔	↔	NR	NR

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
Dhillon et al. [44]	86 OW/O (21 M, 65 F) 31 years	USA	Parallel	12	Almonds	Almonds (15% energy) + energy-restricted diet (500 kcal/day less)	Energy-restricted and nut-free diet (500 kcal/day less)	NR	↔	↔	NR
Le et al. [105]	107 OW/O (F only) 50 years	USA	Parallel	24	Walnuts	Walnuts (42 g/day) + lower-CHO and higher-fat diet	Lower-CHO and higher-fat diet Lower-fat and higher-CHO diet	NR	NR	NR	NR
Le et al. [105]	106 OW/O + IR (F only)	USA	Parallel	24	Walnuts	Walnuts (42 g/day) + lower-CHO and higher-fat diet	Lower-CHO and higher-fat diet Lower-fat and higher-CHO diet	NR	NR	NR	NR
Jung et al. [53]	84 OW/O (11 M, 73 F) 52 years	Korea	Crossover	4	Almonds	Almonds (56 g/day) + typical Korean diet	Cookies (70 g/day) + typical Korean diet	NR	↔	NR	NR

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
Lee et al. [54]	31 OW/O (18 M, 13 F) 46 years	USA	Crossover	4	Almonds	Almonds (42.5 g/day) + average American diet	Average American diet	NR	↔	↔	↔
							Dark chocolate + cocoa powder (61 g/day) + average American diet	NR	↔	↓	↔
McKay et al. [55]	26 OW/O (21 M, 5 F) 60 years	USA	Crossover	4	Pecan	Pecans (~42.5 g/day) + typical American diet	Typical American diet	NR	↔	↓	↓
Diabetes											
Lovejoy et al. [64]	30 T2DM (13 M, 17 F) 53.8 years	USA	Crossover	4	Almonds	High-fat and high-almond diet (37% total fat and 10% from almonds)	High-fat control diet (37% total fat and 10% from olive or canola oil)	↔	↔	↔	NR
						Low-fat and high-almond diet (25% total fat and 10% from almonds)	Low-fat control diet (25% total fat and 10% olive or canola oil)				

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
Wien et al. [65]	65 T2DM/OW (28 M, 37 F) 27-79 years	USA	Parallel	24	Almonds	Low-calorie diet including 84 g of almonds per day	Low-calorie, self-selected complex carbohydrate diet + 2 teaspoons of safflower oil	NR	↔	↔	↔
Tapsell et al. [66]	58 T2DM (34 M, 24 F) 59.3 years	Australia	Parallel	24	Walnuts	Modified-low-fat diet including 30 g of walnuts per day	Low-fat diet Modified low-fat diet	↔	NR	NR	NR
Tapsell et al. [67]	35 T2DM (M/F NR) 54 years	Australia	Parallel	52	Walnuts	Low-fat diet including 30 g of walnuts per day	Low-fat diet	↔	↔	↓	NR
Ma et al. [68]	22 T2DM (10 M, 14 F)[d] 58.1 years	USA	Crossover	8	Walnuts	Walnut-enriched ad libitum diet (56 g of walnuts per day)	Ad libitum diet	↔	↔	↑	↔
Cohen and Johnston [69]	13 T2DM (7 M, 6 F) 66 years	USA	Parallel	12	Almonds	1 oz (~28 g) of almonds 5 days per week	2 cheese sticks 5 days per week	↓	↔	↔	NR

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	Participants (n, Health Status, Sex, and Age)	Country	Design	Follow-Up (Weeks)	Nut Type	Intervention(s)	Control(s)	Outcomes (Mean Differences)			
								HbA_{1c}	FG	FI	HOMA-IR
Jenkins et al. [70,81]	117 T2DM (78 M, 39 F) 62 years	Canada	Parallel	24	Mixed nuts	Full-nut dose (75 g of mixed nuts per day) Half-nut dose (half mixed nuts + half muffin per day)	NCEP step 2 diet including 1 muffin per day	↓	↔	NR	NR
Li et al. [71]	20 T2DM (9 M, 11 F) 58 years	Taiwan	Crossover	4	Almonds	NCEP step 2 diet with almonds replacing 20% of total energy intake	NCEP step 2 diet	NR	↓	↓	↓
Darvish Damavandi et al. [72]	43 T2DM (9 M, 34 F) 53.5 years	Iran	Parallel	8	Cashews	Regular diet including 30 g of cashews per day	Regular diet	NR	↔	↓	NR
Darvish Damavandi et al. [73]	48 T2DM (15 M, 33 F) 55.7 years	Iran	Parallel	8	Hazelnuts	Self-selected diet with hazelnuts replacing 10% of total energy intake	Self-selected diet	NR	↔	NR	NR
Parham et al. [74]	44 T2DM (11 M, 33 F) 51.5 years	Iran	Crossover	12	Pistachios	Previous diet with 50 g of pistachios per day	Previous diet without pistachios	↓	↔	NR	↔
Sweazea et al. [75]	20 T2DM (9 M, 12 F)[d] 56.3 years	USA	Parallel	12	Almonds	Regular diet with 43 g of almonds 5-7 times weekly	Regular diet	↔	↔	↔	↔

(*Continued*)

Table 8.3 (Continued) Randomized Controlled Trials Assessing the Effect of Nut Intake on Glycemic Control Outcomes in Individuals with and at Risk of Diabetes

References	*Participants (n, Health Status, Sex, and Age)*	*Country*	*Design*	*Follow-Up (Weeks)*	*Nut Type*	*Intervention(s)*	*Control(s)*	*Outcomes (Mean Differences)*			
								HbA_{1c}	*FG*	*FI*	*HOMA-IR*
Sauder et al. [76]	30 T2DM (15 M, 15 F) 56.1 years	USA	Crossover	4	Pistachios	AHA diet with pistachios providing 20% of total energy intake	AHA diet	↔	↔	↔	↔
Chen et al. [77]	33 T2DM (13 M, 20 F) 54.9 years	Taiwan	Crossover	12	Almonds	NCEP step II diet with whole almonds replacing 20% of daily calorie intake	NCEP step II diet	↔	↔	↔	↔
Mohan et al. [78]	269 T2DM (145 M, 124 F) 50.8 years	India	Parallel	12	Cashews	Standard diabetic diet with 30 g cashew nuts/ day	Standard diabetic diet	↔	↔	↔	↔

Abbreviations: ADA, American Diabetes Association; AHA, American Heart Association; CHO, carbohydrate; CVD, cardiovascular disease; F, females; FG, fasting glucose; FI, fasting insulin; HbA_{1c}, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; IR, insulin resistant; M, males; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; NR, not reported; O, obese; OW, overweight; PD, prediabetes; T2DM, type-2 diabetes mellitus; VOO, virgin olive oil

[a] Both of these trials are from the PREDIMED study.

[b] Paper did not report a significant lowering, but calculation of mean differences using meta-analytic techniques were found to be significant as reported in Blanco Mejia S. et al., *BMJ Open*, 4, e004660, 2014 (Figure 8.2).

[c] Paper did not test for differences, but calculation of mean differences using meta-analytic techniques were found to be significant as reported in Blanco Mejia S. et al., *BMJ Open*, 4, e004660, 2014 (Figure 8.2).

[d] Male and female numbers are based on the baseline number of participants and not the number of participants analyzed in the glycemic control outcomes noted in the total.

over the longer term. Given that HbA_{1c} levels reflect blood glucose levels in the preceding 3 months (~90 days or 12 weeks) [39], an 8-week follow-up duration may not have been a sufficient amount of time to assess the impact of peanut consumption on HbA_{1c}. Thus, more studies are needed to clarify this finding. Given the overall findings from available trials, the majority of which had a follow-up duration of ≥ 12 weeks (5/7 trials), it appears that nut consumption might help in the management of HbA_{1c} in individuals with well controlled levels. However, given the small number of trials in this area, more trials are needed to better understand the impact of nut consumption on HbA_{1c} in those at risk for developing diabetes, especially in individuals with HbA_{1c} levels that are within a higher risk range.

Fasting Glucose. One SRMA of RCTs has previously been published in this area assessing the effect of tree nut consumption on fasting glucose in individuals with one or more criteria of the MetS (11 trials, n = 841). Tree nut consumption was shown to non-significantly lower fasting glucose mean differences [MD] = −0.06 mmol/L, 95% CI: −0.17, 0.06 mmol/L) (Figure 8.2) [40]. There was evidence of substantial heterogeneity (I^2 = 56%, P = 0.01), which means that the effect differed across trials. In particular, all trials showing a significant lowering in fasting glucose levels prescribed pistachios [41–43], suggesting that they may be more beneficial than other nuts for lowering fasting glucose levels in this population; however, more studies are needed to confirm this. There are also several other RCTs that were not included in this meta-analysis due to their ineligibility (e.g., non-tree nuts, inappropriate control arm) or because they were published after the publication of this systematic review and meta-analysis (Table 8.3) [38,44–55]. Of these trials, some showed that nut consumption significantly lowered fasting glucose compared to their respective controls, with mean differences ranging from −0.2 to −0.66 mmol/L [46,48,56], whereas the remaining trials showed no significant impact on fasting glucose. There did not appear to be a particular nut type, amount, follow-up duration, or baseline fasting glucose range in trials that showed a benefit *versus* those

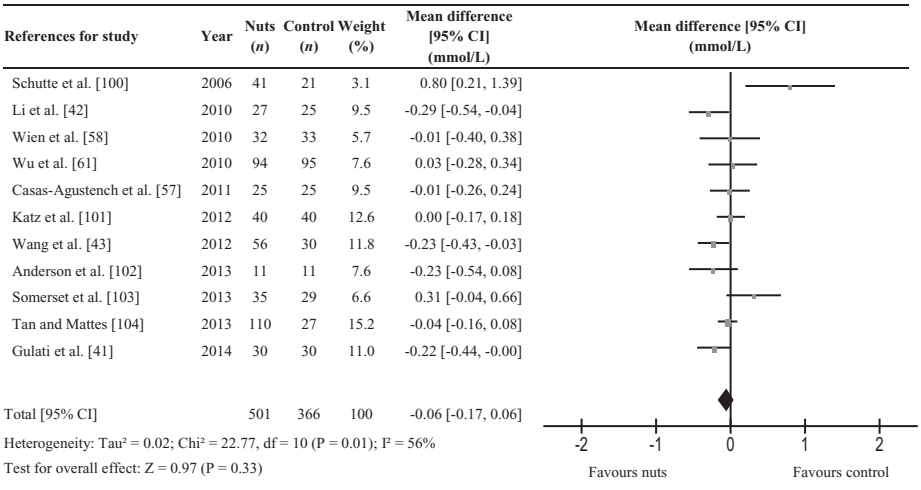


Figure 8.2 Modified forest plot of randomized trials adapted from Blanco Mejia S. et al., *BMJ Open*, 4, e004660, 2014, assessing the effect of tree nut consumption on fasting glucose in individuals with one or more criteria of the metabolic syndrome.

that did not. Therefore, the findings from available trials appear to be inconsistent. The inclusion of data from these trials and future trials will likely change the overall pooled effect estimate in future systematic reviews and meta-analyses and improve our understanding of the effect of nuts on fasting glucose in individuals at risk for diabetes.

Fasting Insulin and HOMA-IR. Eighteen RCTs have assessed the effect of nut consumption on fasting insulin in individuals at risk for diabetes (Table 8.3). Several of these trials showed that nut consumption significantly lowered fasting insulin compared to the respective controls, with mean differences ranging from –13.89 to –31.60 pmol/L [48,55–58], whereas the remaining trials showed no significant impact on fasting insulin. Similar findings were seen in trials assessing the effect of nut consumption on HOMA-IR. Of the 11 available trials (Table 8.3), approximately half showed that nut consumption significantly lowered HOMA-IR compared to their respective controls, with mean differences ranging from –0.51 to –1.66, whereas the remaining trials showed no significant impact on HOMA-IR. There did not appear to be a particular nut type, amount, follow-up duration, or baseline range that was present in trials that showed a benefit *versus* those that did not. Therefore, the effect of nut consumption on fasting insulin levels and HOMA-IR appears to be inconsistent. More trials are needed to improve our understanding of the effect of nuts on fasting insulin and HOMA-IR in individuals at risk for diabetes.

MetS Risk. The large multicenter Prevención con Dieta Mediterránea (PREDIMED) trial showed that consumption of mixed nuts in the context of a Mediterranean diet resulted in a greater reversion in the prevalence of MetS in comparison to advice on a low-fat diet over 1 year (13.7% *versus* 2.0%, $P = 0.01$), where the odds ratio for the reversion of MetS was 1.7 (95% CI: 1.1, 2.6) [59]. Following this 1-year analysis, the full and final PREDIMED cohort, after a median follow-up of 4.8 years, was assessed to determine the long-term effects of a Mediterranean diet plus nuts on MetS. Findings indicated that among the 5,801 participants, 3,707 with MetS at baseline, the risk of MetS incidence did not differ significantly between the intervention and control groups, whereas in those who had MetS at baseline, reversion occurred in 28.2% of participants, with the Mediterranean diet plus nuts being significantly more likely to revert MetS compared with the low-fat control diet (Figure 8.3) [60]. The reversion rate of MetS was also assessed in another RCT, which was conducted in 189 Chinese individuals with MetS over 12 weeks, comparing the effect of walnuts (30 g/day) in the context of an AHA diet to an AHA diet alone, and it showed no significant differences between the two groups (25.5% *versus* 21.1%) [61]. Given the small number of studies and inconsistent findings, more trials are needed to improve our understanding.

Diabetes Incidence. The PREDIMED multicenter trial assessed the efficacy of nut consumption in relation to T2DM incidence, first in participants at the Reus, Spain center [62], followed by a subgroup analysis of all PREDIMED participants who did not have diabetes at baseline and for whom the incidence of diabetes could be ascertained during follow-up [63]. Findings from PREDIMED-Reus indicated a reduction of diabetes incidence by 52% with consumption of a Mediterranean diet supplemented with mixed nuts compared to the control (HR: 0.48, 95% CI: 0.24, 0.96) [62]. When all PREDIMED participants free of diabetes at baseline were analyzed ($n = 3541$), the reduction observed with consumption of a Mediterranean diet supplemented with mixed nuts in the risk of T2DM incidence compared to the control remained marginal and was no longer significant (HR: 0.82; 95% CI: 0.61,

Outcome	NTC	NP	NC	Pooled effect estimates: Risk ratio [95% CI]	Pooled effect estimates: Risk ratio [95% CI]	Test for overall effect	Heterogeneity
Diabetes incidence	2	2387	193	0.75 [0.58, 0.99]		$P = 0.04$	$I^2 = 48\%$ ($P = 0.16$)
Metabolic syndrome incidence	1	3819[a]	NO[b]	0.92 [0.79, 1.08]		$P = 0.32$	NA
Metabolic syndrome reversion	1	2416[a]	NO[b]	0.78 [0.65, 0.93]		$P = 0.005$	NA

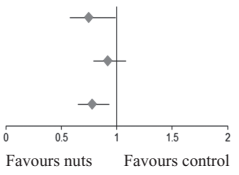


Figure 8.3 Summary of randomized controlled trials of clinical outcomes (metabolic syndrome incidence and reversion [Adapted from Babio, N. et al. *Can. M. Assoc. J.*, 186, E649, 2014] and diabetes incidence [Adapted from Salas-Salvado, J. et al., *Diabetes Care*, 34, 14, 2011 and *Ann. Intern. Med.*, 160, 1, 2014]). To allow the summary estimated for each endpoint to be displayed on the same axis, odds ratio and hazard ratios were transformed to risk ratios and 95% CIs. *Abbreviations*: NA, not applicable; NC, number of cases; NO, not obtainable; NP, number of participants; NTC, number of trial comparisons. [a] Values are based on baseline data; however, the authors noted that these numbers were reduced for the analyses due to missing data. [b] Values were not obtainable from the original manuscript nor from the authors.

1.10) [63]. However, when combined using fixed effects, the risk ratio indicated a significant reduction in diabetes incidence with consumption of a Mediterranean diet supplemented with mixed nuts compared with control 0.75 (95% CI: 0.58, 0.99) (Figure 8.3).

8.2.2.1.1 Strengths, Limitations, and Conclusion Overall, the existing body of evidence from RCTs shows inconsistent findings with regards to nut consumption and its effects on glycemic control outcomes in individuals at risk for diabetes. In particular, in the assessment of the effect of nuts on HbA_{1c}, the majority of trials showed that nut consumption did not significantly alter HbA_{1c} levels; however, this may be due to the participants having well-controlled levels at baseline, whereas analyses in those with elevated HbA_{1c} (e.g., individuals with diabetes) present with significant, yet moderate, HbA_{1c} benefits (described in Section 8.2.2.2). Furthermore, the majority of these trials were ≥ 12 weeks, which is considered to be a sufficient period of time to observe meaningful changes in HbA_{1c}. In order to improve our overall understanding in this area, more RCTs are needed, especially trials with longer follow-up duration, since just over half of the trials discussed herein were ≥ 12 weeks and were conducted in individuals with higher risk baseline ranges for the different glycemic control biomarkers. Furthermore, a SRMA of RCTs in this area would be useful to better understand the overall effect of nut consumption on glycemic control outcomes in individuals at risk for developing diabetes, as well as for understanding which factors have the most optimal impact on glycemic control. For example, it would be useful to understand which foods should be replaced with nuts in the diet for the most beneficial impact, as the current trials vary in this regard – some prescribe proportional reductions to all foods, others suggest replacing carbohydrate- or saturated fat–rich foods, whereas others provide no specific instructions on food replacement. Meta-analytic techniques would allow one to explore these

types of questions. Lastly, no trials to date have assessed the effect of hazelnuts or pine nuts in this area. Therefore, future trials and SRMAs of RCTs will help improve our understanding, inform clinical practice guidelines and dietary recommendations, and improve the health of individuals at risk for diabetes.

8.2.2.2 Nuts and Glycemic Control in Individuals with Diabetes

The effect of nut consumption on glycemic control outcomes (HbA_{1c}, fasting glucose, fasting insulin, and HOMA-IR) in individuals with T2DM has been investigated in 15 RCTs [64–78] (Table 8.3). Several nut types have been assessed at intakes ranging from 30 to 84 g/day, including almonds (6 trials), walnuts (3 trials), pistachios (2 trials), cashews (2 trials), hazelnuts (1 trial), and mixed nuts (1 trial). Most trials were longer term (60% ≥ 12 weeks) and had a parallel design (60%) but varied in sample size (median: 35 individuals, range: 13 to 269 individuals) and country of conduct, including the US (6 trials), Iran (3 trials), 2 trials each in Australia and Taiwan, and 1 trial each in Canada and India. To date, there have been no RCTs evaluating the effect of pecans, pine nuts, Brazil nuts, macadamias, or peanuts in this area. Viguiliouk et al. [79] conducted the only SRMA of RCTs assessing the effect of tree nuts on glycemic control in diabetes (12 trials, 450 participants). This SRMA included trials ≥ 3 weeks duration conducted in T2DM and compared the effect of diets containing tree nuts to isocaloric diets without tree nuts on HbA_{1c}, fasting glucose, fasting insulin, and/or HOMA-IR, the results of which are discussed in this section. There has also been another SRMA, conducted by Blanco Mejia et al. [40], which assessed the effect of tree nuts on MetS criteria, including fasting glucose, in individuals with and without diabetes. The results of this SRMA were stratified by health status, including T2DM, which are also discussed in this section.

HbA_{1c}. Eleven RCTs have assessed the effect of nut consumption on HbA_{1c} in individuals with diabetes (Table 8.3). Seven trials [64,66–70,76] have been meta-analyzed by Viguiliouk et al. [79], while 4 additional trials [74,77,78,80] and a reanalysis [81] of Jenkins et al. [70] have been published since this SRMA. Seven trials (8 comparisons) were included (n = 274) in the overall pooled effect estimate for the effect of tree nuts on HbA_{1c} in T2DM, which showed diets containing tree nuts led to a significant but modest lowering in HbA_{1c} compared to diets without tree nuts (MD= −0.07% [95% CI: −0.10, −0.03%]), with no significant inter-study heterogeneity (I^2 = 37%) (Figure 8.4). Sensitivity analyses, by either removal of a single study or using a different correlation coefficient (0.25 and 0.75), did not modify the significance of the pooled effect estimate. The authors were unable to detect any statistically significant subgroup effects by nut type or any other subgroup. The additional three trials [77,78,80] showed no significant effect between diets, while the other [74] showed a significant decrease in HbA_{1c} in the individuals randomized to the pistachio group. The reanalysis by Jenkins et al. [81] did not result in any changes in significance for the two comparison groups included in the SRMA. Nonetheless, the additional four trials and the reanalysis might impact the overall pooled effect estimate of the SRMA.

Fasting Glucose. Fourteen RCTs have assessed the effect of nut consumption on fasting glucose in individuals with diabetes (Table 8.3). Ten trials [64,65,67–72,76,82] have been meta-analyzed by Blanco Mejia et al. [40] and Viguiliouk et al. [79], while four additional trials [74,77,78,80] and a reanalysis [81] of Jenkins et al. [70] have been published since these SRMAs. Ten RCTs (11 comparisons) were included (n = 413) in the overall pooled effect estimate for the effect of tree nuts on

Comparison	Trials	NP	Pooled effect estimates MD (95% CIs)	SMD (95% CIs)	SMD (95% CIs)	I^2	*P-value*
HbA_{1c}	8	274	-0.07 [-0.10, -0.03]	-1.39 [-1.98, -0.59]		37%	< 0.001
Fasting glucose	11	413	-0.15 [-0.27, -0.02]	-0.71 [-1.28, -0.09]		35%	0.03
Fasting insulin	9	286	-3.42 [-10.06, 3.21]	-0.34 [-0.99, 0.32]		72%	0.31
HOMA-IR	3	107	-0.24 [-0.51, 0.04]	-0.99 [-2.10, 0.16]		87%	0.10

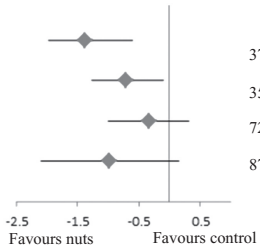


Figure 8.4 Summary of systematic reviews and meta-analysis of randomized controlled markers of glycemic control. The pooled effect estimates adapted from Viguiliouk, E. et al., PLoS ONE, 9, e103376, 2014 (open access journal), assessing the effect of diets containing nuts on markers of glycemic control. To allow the summary estimates for each end point to be displayed on the same axis, MDs were transformed to SMDs and pseudo-95% CIs, which were derived directly from the original mean difference and 95% CI. *Abbreviations*: HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; MD, mean differences; NP, number of participants; SMD, standardized mean differences.

fasting glucose in T2DM, which showed a discrepancy between the significance in the two SRMAs. Viguiliouk et al. [79] showed that diets containing tree nuts led to as significant but modest lowering in fasting glucose compared to diets without tree nuts (MD= −0.15 mmol/L [95% CI: −0.27, −0.02 mmol/L]), while Blanco Mejia et al. [40] showed no significance effect (MD= −0.16 mmol/L [95% CI: −0.37, 0.05 mmol/L]), with no significant inter-study heterogeneity (I^2 = 35%) (Figure 8.4). The discrepancy between the SRMAs results was in the value for the pooled correlation used for imputing missing standard deviations, as Blanco Mejia et al. [40] included additional RCTs (trials with other health status such as dyslipidemia, MetS criteria, and otherwise healthy) to calculate the correlation. Sensitivity analyses showed a change in the pooled effect estimate from significant to non-significant with the independent removal of three RCTs [70,71,73] and when using the 0.75 correlation coefficient in paired analyses of crossover trials. The authors were unable to detect any statistically significant subgroup effects by nut type or any other subgroup. From the additional trials, none of the four [74,77,78,80] showed any significant effect between diets. The reanalysis by Jenkins et al. [81] did not show any changes in significance for the two comparison groups included in the SRMAs. Nonetheless, the additional four RCTs and the reanalysis might impact the overall pooled effect estimate of the SRMAs.

Fasting Insulin. Eleven RCTs have assessed the effect of nut consumption on fasting insulin in individuals with diabetes (Table 8.3). Eight trials [64,65,67–69,71,72,76] have been meta-analyzed by Viguiliouk et al. [79], while three additional trials [77,78,80] have been published since this SRMA. Eight RCTs (9 comparisons) were included (n = 286) in the overall pooled effect estimate for the effect of tree nuts on fasting insulin in T2DM, which showed diets containing tree nuts had no significant effect on fasting insulin in comparison to diets without tree nuts (MD = −3.42 pmol/L [95% CI: −10.06, 3.21 pmol/L]), with substantial unexplained inter-study

heterogeneity (I^2 = 72%) (Figure 8.4). Sensitivity analyses, consisting of removal of a single study or use of a different correlation coefficient (0.25 and 0.75), did not modify the significance of the pooled effect estimate. The authors were unable to detect any statistically significant subgroup effects by nut type or any other subgroup. From the additional trials, all three [77,78,80] showed no significant effect between diets. It seems that the additional three trials might not impact the overall pooled effect estimate of the SRMAs.

HOMA-IR. Seven RCTs have assessed the effect of nut consumption on HOMA-IR in individuals with diabetes (Table 8.3). Three trials [65,68,71] have been meta-analyzed by Viguiliouk et al. [79], while four additional trials [74,77,78,80] have been published since this SRMA. Three RCTs (3 comparison) were included (n = 107) in the overall pooled effect estimate for the effect of tree nuts on HOMA-IR in T2DM, which showed that diets containing tree nuts had no significant effect on HOMA-IR in comparison to diets without tree nuts (MD = −0.24 [95% CI: −0.51, 0.04]), with considerable unexplained inter-study heterogeneity (I^2 = 87%) (Figure 8.4). Sensitivity analyses consisting of the removal of single trials showed that the removal of Ma et al. [68] changed the overall effect from non-significant to significant, but sensitivity analyses using different correlation coefficients (0.25 and 0.75) did not modify the significance of the pooled effect estimate. The authors were unable to detect any statistically significant subgroup effects by nut type or any other subgroup. From the additional RCTs, none of the four [74,77,78,80] showed any significant effect between diets. Even though the number of additional trials is higher than the number of those included in the SRMA, it seems that adding them might not impact the overall pooled effect estimate of the SRMA.

8.2.2.2.1 Strengths, Limitations, and Conclusion Strengths of the available evidence of nut consumption on glycemic control outcomes in individuals with T2DM include the fact that there have been two SRMAs evaluating the evidence up to 2014. Second, since 2014 there have been four additional RCTs evaluating the evidence on all markers of glycemic control (HbA_{1c}, fasting glucose, fasting insulin, and HOMA-IR). Lastly, even though one paper included in the SRMAs was retracted and re-evaluated, the re-evaluation did not result in any changes in the significance of the effects for the two comparisons included and might not have an impact in the two outcomes (HbA_{1c} and fasting glucose) reported. Despite these strengths, limitations are still present, including the fact that one of the studies [70] that provided data for HbA_{1c} and fasting glucose was retracted at the authors' request due to lack of adjustment for repeated measures in the same individual. Nonetheless, the reanalysis [81] of the data did not result in any changes in the significance of the effects for either outcome. Second, none of the included SRMAs performed a dose-response analysis or incorporated the Grading of Recommendations Assessment, Development, and Evaluation for the certainty in the overall evidence and strength. Lastly, there have been no RCTs evaluating the effect of pecans, pine nuts, Brazil nuts, macadamias, or peanuts in this area. However, since all nut types have similar nutrient profiles, the recommendation can be extended to include all type of nuts.

The overall evidence suggests that the inclusion of nuts in the diets of individuals with T2DM seems to have a modest positive effect in long and short-term blood glucose control as seen for HbA_{1c} and fasting glucose respectively, while having a neutral effect on insulin resistance (fasting insulin and HOMA-IR). However, there is a need for larger and longer RCTs that evaluate the markers of glycemic control,

including other types of nuts, as primary endpoints in order to support the current evidence. It is also necessary to re-evaluate the markers of glycemic control with the new published trials, including a dose-response analysis and an evaluation of the overall evidence strength.

8.3 Potential Mechanisms and Barriers to Consumption

There are several biological mechanisms which may explain the proposed recommendations of nut consumption for the management and prevention of diabetes, including, but not limited to, nutrient displacement, antioxidant effect, magnesium content, monounsaturated fatty acid (MUFA) profiles, and synergistic effect between polyunsaturated fatty acids (PUFA), MUFA, polyphenols, and carotenoids for micro ribonucleic acid modulation. The ability of nuts to improve glycemic control may relate to a carbohydrate displacement mechanism by which nuts reduce the glycemic load of the diet by displacing high glycemic index carbohydrates [79]. However, more trials investigating the effect of displacing ≥ 5% energy from carbohydrates with tree nuts are needed to strengthen the results determining if a clinically meaningful change in HbA_{1c} is achievable [79]. Bioactive compounds, such as polyphenols and phytosterols, found in nuts have been implicated in antioxidant activities. Individuals consuming nuts compared to those with little consumption have shown a significant reduction of DNA damage and protein thiol concentrations, a marker of protein oxidative damage [83,84]. Other proposed factors relate to the micro- and macronutrient composition of nuts. From a micronutrient standpoint, magnesium plays an important role in carbohydrate metabolism, yet low blood levels of magnesium are commonly seen in individuals with T2DM [85]. Nuts are rich in magnesium, with a content ranging from 121 to 376 mg/100 g [86]. SRMAs of prospective cohorts and RCTs in individuals with T2DM indicate reduced diabetes risk as well as glycemic control benefits with magnesium intake [87–89]. Similarly, benefits have been observed with MUFA intake and glycemic control as evaluated by SRMAs, wherein nuts are a source of MUFAs with amounts ranging from 9 to 59 g/100 g [86]. This is of interest, since fatty acids have been shown to influence glucose metabolism by altering cell membrane function, enzyme activity, insulin signaling, and gene expression [90]. In particular, a SRMA of RCTs in individuals with abnormal glucose tolerance showed that high MUFA diets were effective as reducing HbA_{1c} [91]. MUFAs in combination with PUFAs, polyphenols, and carotenoids act synergistically to modulate miRNAs, where miRNAs have been recognized as being biomarkers and regulators for various metabolic pathways, including insulin secretion, glucose homeostasis, and carbohydrate and lipid metabolism [92]. This has been shown with consumption of 50–57 g/day of pistachios for a period of 1–4 months resulting in positive effects on glucose control modulating specific miRNAs, improving insulin sensitivity through the P13K-AKT signaling pathway [93].

In spite of the proposed mechanisms of action and the epidemiological studies as well as RCTs showing the health benefits of eating nuts, individuals and health professionals have had the unfounded belief that because nuts have a high fat content, they should be consumed sparingly for fear of gaining weight [94]. Scientific findings about the benefits of nut consumption and the appropriate translation of information to inform individuals' knowledge and perception of eating nuts indicate that there is inadequate knowledge regarding the protective aspect of nuts on

diabetes [94]. Particularly, nut consumption by low-income adults has been shown to not meet recommended amounts, with the suggestion that the affordability of nuts may be a limiting factor in their intake [95]. Also, older adults have frequently reported avoidance of nut consumption due to dental issues [96]. These barriers to nut consumption are of concern, since older, lower-income adults tend to be those at higher risk of diabetes and CVD.

Allergies are another important consideration in regards to nut consumption. Prevalence of tree nut and peanut allergies range from 0.05 to almost 5%, albeit prevalence of individual tree nut allergies has been shown to vary significantly by region. For example, hazelnut allergy was the most common tree nut allergy in Europe, with walnuts and cashews being the most prevalent tree nut allergies in the US [97,98]. Nut consumption is not recommended for individuals with such a contraindication, despite the potential benefits for diabetes prevention and management.

8.4 Conclusion

Findings from the available SRMAs of prospective cohorts and RCTs, as well as subsequent individual prospective cohorts and RCTs, support the consumption of nuts, showing a lack of negative effect with the potential to help maintain glucose control *via* HbA_{1c} levels in individuals with prediabetes and improve glycemic control in those with T2DM. Despite their purported nutritional value and noted health benefits, worldwide nut-consumption levels remain low [15,99]. Future research is needed to assess the effects of specific nut types, in addition to conducting larger and longer RCTs evaluating markers of glycemic control as primary endpoints in order to support the current evidence, as well as further assessing the barriers and facilitators of nut intake. Overall, the existing data supports the inclusion of nuts as part of a healthy plant-based diet for the prevention and management of diabetes.

Funding

DJAJ was funded by the Government of Canada through the Canada Research Chair Endowment, and JLS was funded by a Diabetes Canada Clinician Scientist Award.

Conflicts of Interest

EV serves as a scientific advisor for New Era Nutrition. DJAJ has received research grants from Saskatchewan & Alberta Pulse Growers Associations, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd., Unilever Canada and Netherlands, Barilla, the Almond Board of California, Agriculture and Agri-food Canada, Pulse Canada, Kellogg's Company, Canada, Quaker Oats, Canada, Procter & Gamble Technical Centre Ltd., Bayer Consumer Care, Springfield, NJ, Pepsi/Quaker, International Nut & Dried Fruit (INC), Soy Foods Association of North America, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company,

Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Soy Nutrition Institute (SNI), the Canola and Flax Councils of Canada, the Calorie Control Council, the Canadian Institutes of Health Research (CIHR), the Canada Foundation for Innovation (CFI)and the Ontario Research Fund (ORF). He has received in-kind supplies for trials as a research support from the Almond board of California, Walnut Council of California, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, WhiteWave Foods. He has been on the speaker's panel, served on the scientific advisory board and/or received travel support and/or honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the development of the NuVal scoring system), the Coca-Cola Company, EPICURE, Danone, Diet Quality Photo Navigation (DQPN), Better Therapeutics (FareWell), Verywell, True Health Initiative (THI), Institute of Food Technologists (IFT), Soy Nutrition Institute (SNI), Herbalife Nutrition Institute (HNI), Saskatchewan & Alberta Pulse Growers Associations, Sanitarium Company, Orafti, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamentals for Health (NFH), Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, Abbott Laboratories, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the United States Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association (CDA). He is a member of the International Carbohydrate Quality Consortium (ICQC). His wife, Alexandra L Jenkins, is a director and partner of Glycemic Index Laboratories, Inc., and his sister, Caroline Brydson, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. JLS has received research support from the Canadian Foundation for Innovation, Ontario Research Fund, Province of Ontario Ministry of Research and Innovation and Science, Canadian Institutes of health Research (CIHR), Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), American Society for Nutrition (ASN), INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, The Tate and Lyle Nutritional Research Fund at the University of Toronto, The Glycemic Control

and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers), and the Nutrition Trialists Fund at the University of Toronto (a fund established by an inaugural donation from the Calorie Control Council). He has received in-kind food donations to support a randomized controlled trial from the Almond Board of California, California Walnut Commission, American Peanut Council, Barilla, Unilever, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, and WhiteWave Foods. He has received travel support, speaker fees and/or honoraria from Diabetes Canada, Mott's LLP, Dairy Farmers of Canada, FoodMinds LLC, International Sweeteners Association, Nestlé, Pulse Canada, Canadian Society for Endocrinology and Metabolism (CSEM), GI Foundation, Abbott, Biofortis, ASN, Northern Ontario School of Medicine, INC Nutrition Research & Education Foundation, European Food Safety Authority (EFSA), Comité Européen des Fabricants de Sucre (CEFS), and Physicians Committee for Responsible Medicine. He has or has had ad hoc consulting arrangements with Perkins Coie LLP, Tate & Lyle, and Wirtschaftliche Vereinigung Zucker e.V. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Obesity Canada. He serves or has served as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of theInternational Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Sobeys Inc. CWCK has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada (AAFC), Almond Board of California, American Peanut Council, Barilla, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, International Nut and Dried Fruit Council,International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd, Pulse Canada and Unilever. He has received in-kind research support from the Almond Board of California, American Peanut Council, Barilla, California Walnut Commission, Kellogg Canada, Loblaw Companies, Quaker (Pepsico), Primo, Unico, Unilever, WhiteWave Foods/Danone. He has received travel support and/or honoraria from the American Peanut Council, Barilla, California Walnut Commission, Canola Council of Canada, General Mills, International Nut and Dried Fruit Council, International Pasta Organization, Loblaw Brands Ltd, Nutrition Foundation of Italy, Oldways Preservation Trust, Paramount Farms, Peanut Institute, Pulse Canada, Sun-Maid, Tate & Lyle, Unilever and White Wave Foods. He has served on the scientific advisory board for the International Tree Nut Council, International Pasta Organization, McCormick Science Institute and Oldways Preservation Trust. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD and is a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. SKN and SBM report no known related conflicts of interest.

References

1. U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed September 28, 2018).
2. Health Canada, Canadian Nutrient File. Published online at http://webprod3.hc-sc.gc.ca/cnf-fce/index-eng.jsp (accessed September 28, 2018).
3. King, J.C., Blumberg, J., Ingwersen, L., Jenab, M., and Tucker, K.L., Tree nuts and peanuts as components of a healthy diet. *J. Nutr.*, 138, 1736S–1740S, 2008.
4. Bolling, B.W., McKay, D.L., and Blumberg, J.B., The phytochemical composition and antioxidant actions of tree nuts. *Asia Pac. J. Clin. Nutr.*, 19, 117–123, 2010.
5. U.S. Food and Drug Administration (USDA), Guidance for Industry: A Food Labeling Guide (12. Appendix D: Qualified Health Claims). Published online at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064923.htm (accessed September 28, 2018).
6. Chiavaroli, L., Nishi, S.K., Khan, T.A., Braunstein, C.R., Glenn, A.J., Mejia, S.B., Rahelic, D. et al., Portfolio dietary pattern and cardiovascular disease: A systematic review and meta-analysis of controlled trials. *Prog. Cardiovasc. Dis.*, 61, 43–53, 2018.
7. Yokoyama, Y., Barnard, N.D., Levin, S.M., and Watanabe, M., Vegetarian diets and glycemic control in diabetes: A systematic review and meta-analysis. *Cardiovasc. Diagn. Ther.*, 4, 373–382, 2014.
8. Schwingshackl, L., Missbach, B., Konig, J., and Hoffmann, G., Adherence to a Mediterranean diet and risk of diabetes: A systematic review and meta-analysis. *Public Health Nutr.*, 18, 1292–1299, 2015.
9. The American Diabetic Association (ADA), Lifestyle management: Standards of medical care in diabetes-2018. *Diabetes Care*, 41, 38S–50S, 2018.
10. Sievenpiper, J.L., Chan, C.B., Dworatzek, P.D., Freeze, C., and Williams, S.L., Nutrition therapy. *Can. J. Diabetes*, 42(Suppl. 1), 64S–79S, 2018.
11. Dyson, P.A., Twenefour, D., Breen, C., Duncan, A., Elvin, E., Goff, L., Hill, A. et al., Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. *Diabet Med.*, 35, 541–547, 2018.
12. Mann, J.I., De Leeuw, I., Hermansen, K., Karamanos, B., Karlstrom, B., Katsilambros, N., Riccardi, G. et al., Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. *Nutr. Metab. Cardiovasc. Dis.*, 14, 373–394, 2004.
13. O'Neil, C.E., Fulgoni, V.L., and Nicklas, T.A., Tree nut consumption is associated with better adiposity measures and cardiovascular and metabolic syndrome health risk factors in U.S. Adults: NHANES 2005–2010. *Nutr. J.*, 14, 64, 2015.
14. Public Health Agency of Canada, National Single Day Food Consumption Report: Analysis of the 24-hour Dietary Recall Data from the Canadian Community Health Survey (CCHS), Cycle 2.2, Nutrition (2004), and Assessment for Food Consumption Frequency among Canadians. Published online at http://www.phac-aspc.gc.ca (accessed September 28, 2018).
15. Micha, R., Khatibzadeh, S., Shi, P., Andrews, K.G., Engell, R.E., and Mozaffarian, D., Global, regional and national consumption of major food groups in 1990 and 2010: A systematic analysis including 266 country-specific nutrition surveys worldwide. *BMJ Open*, 5, e008705, 2015.

16. Fernandez-Montero, A., Bes-Rastrollo, M., Beunza, J.J., Barrio-Lopez, M.T., de la Fuente-Arrillaga, C., Moreno-Galarraga, L., and Martinez-Gonzalez, M.A., Nut consumption and incidence of metabolic syndrome after 6-year follow-up: The SUN (Seguimiento Universidad de Navarra, University of Navarra Follow-up) Cohort. *Public Health Nutr.*, 16, 2064–2072, 2013.
17. Alberti, K.G., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J. C. et al., Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*, 120, 1640–1645, 2009.
18. Shang, X., Scott, D., Hodge, A., English, D.R., Giles, G.G., Ebeling, P.R., and Sanders, K.M., Dietary protein from different food sources, incident metabolic syndrome and changes in its components: An 11-year longitudinal study in healthy community-dwelling adults. *Clin. Nutr.*, 36, 1540–1548, 2017.
19. Parker, E.D., Harnack, L.J., and Folsom, A.R., Nut consumption and risk of type 2 diabetes. *JAMA*, 290, 38–39, author reply 39–40, 2003.
20. Montonen, J., Jarvinen, R., Heliovaara, M., Reunanen, A., Aromaa, A., and Knekt, P., Food consumption and the incidence of type II diabetes mellitus. *Eur. J. Clin. Nutr.*, 59, 441–448, 2005.
21. Villegas, R., Gao, Y.T., Yang, G., Li, H.L., Elasy, T.A., Zheng, W., and Shu, X.O., Legume and soy food intake and the incidence of type 2 diabetes in the Shanghai Women's Health Study. *Am. J. Clin. Nutr.*, 87, 162–167, 2008.
22. Nettleton, J.A., Steffen, L.M., Ni, H., Liu, K., and Jacobs, D.R., Jr., Dietary patterns and risk of incident type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care*, 31, 1777–1782, 2008.
23. Kochar, J., Gaziano, J.M., and Djousse, L., Nut consumption and risk of type II diabetes in the Physicians' Health Study. *Eur. J. Clin. Nutr.*, 64, 75–79, 2010.
24. Pan, A., Sun, Q., Manson, J.E., Willett, W.C., and Hu, F.B., Walnut consumption is associated with lower risk of type 2 diabetes in women. *J. Nutr.*, 143, 512–518, 2013.
25. Asghari, G., Ghorbani, Z., Mirmiran, P., and Azizi, F., Nut consumption is associated with lower incidence of type 2 diabetes: The Tehran Lipid and Glucose Study. *Diabetes Metab.*, 43, 18–24, 2017.
26. von Ruesten, A., Feller, S., Bergmann, M.M., and Boeing, H., Diet and risk of chronic diseases: Results from the first 8 years of follow-up in the EPIC-Potsdam study. *Eur. J. Clin. Nutr.*, 67, 412–419, 2013.
27. Wu, L., Wang, Z., Zhu, J., Murad, A.L., Prokop, L.J., and Murad, M.H., Nut consumption and risk of cancer and type 2 diabetes: A systematic review and meta-analysis. *Nutr. Rev.*, 73, 409–425, 2015.
28. Guo, K., Zhou, Z., Jiang, Y., Li, W., and Li, Y., Meta-analysis of prospective studies on the effects of nut consumption on hypertension and type 2 diabetes mellitus. *J. Diabetes*, 7, 202–212, 2015.
29. Zhou, D., Yu, H., He, F., Reilly, K.H., Zhang, J., Li, S., Zhang, T. et al., Nut consumption in relation to cardiovascular disease risk and type 2 diabetes: A systematic review and meta-analysis of prospective studies. *Am. J. Clin. Nutr.*, 100, 270–277, 2014.
30. Afshin, A., Micha, R., Khatibzadeh, S., and Mozaffarian, D., Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: A systematic review and meta-analysis. *Am. J. Clin. Nutr.*, 100, 278–288, 2014.

31. Luo, C., Zhang, Y., Ding, Y., Shan, Z., Chen, S., Yu, M., Hu, F.B. et al., Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: A systematic review and meta-analysis. *Am. J. Clin. Nutr.*, 100, 256–269, 2014.
32. Schwingshackl, L., Hoffmann, G., Lampousi, A.M., Knuppel, S., Iqbal, K., Schwedhelm, C., Bechthold, A. et al., Food groups and risk of type 2 diabetes mellitus: A systematic review and meta-analysis of prospective studies. *Eur. J. Epidemiol.*, 32, 363–375, 2017.
33. van den Brandt, P.A., and Schouten, L.J., Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: A cohort study and meta-analysis. *Int. J. Epidemiol.*, 44, 1038–1049, 2015.
34. Bao, Y., Han, J., Hu, F.B., Giovannucci, E.L., Stampfer, M.J., Willett, W.C., and Fuchs, C.S., Association of nut consumption with total and cause-specific mortality. *N. Engl. J. Med.*, 369, 2001–2011, 2013.
35. Luu, H.N., Blot, W.J., Xiang, Y.B., Cai, H., Hargreaves, M.K., Li, H., Yang, G. et al., Prospective evaluation of the association of nut/peanut consumption with total and cause-specific mortality. *JAMA Intern. Med.*, 175, 755–766, 2015.
36. Aune, D., Keum, N., Giovannucci, E., Fadnes, L.T., Boffetta, P., Greenwood, D.C., Tonstad, S. et al., Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review anddose-response meta-analysis of prospective studies. *BMC Med.*, 14, 207, 2016.
37. de la Fuente-Arrillaga, C., Ruiz, Z.V., Bes-Rastrollo, M., Sampson, L., and Martinez-Gonzalez, M.A., Reproducibility of an FFQ validated in Spain. *Public Health Nutr.*, 13, 1364–1372, 2010.
38. Johnston, C.S., Trier, C.M., and Fleming, K.R., The effect of peanut and grain bar preloads on postmeal satiety, glycemia, and weight loss in healthy individuals: An acute and a chronic randomized intervention trial. *Nutr. J.*, 12, 35, 2013.
39. Saudek, C.D., Kalyani, R.R., and Derr, R.L., Assessment of glycemia in diabetes mellitus: Hemoglobin A1c. *J. Assoc. Physicians India*, 53, 299–305, 2005.
40. Blanco Mejia, S., Kendall, C.W., Viguiliouk, E., Augustin, L.S., Ha, V., Cozma, A.I., Mirrahimi, A. et al., Effect of tree nuts on metabolic syndrome criteria: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*, 4, e004660, 2014.
41. Gulati, S., Misra, A., Pandey, R.M., Bhatt, S.P., and Saluja, S., Effects of pistachio nuts on body composition, metabolic, inflammatory and oxidative stress parameters in Asian Indians with metabolic syndrome: A 24-wk, randomized control trial. *Nutrition*, 30, 192–197, 2014.
42. Li, Z., Song, R., Nguyen, C., Zerlin, A., Karp, H., Naowamondhol, K., Thames, G. et al., Pistachio nuts reduce triglycerides and body weight by comparison to refined carbohydrate snack in obese subjects on a 12-week weight loss program. *J. Am. Coll. Nutr.*, 29, 198–203, 2010.
43. Wang, X., Li, Z., Liu, Y., Lv, X., and Yang, W., Effects of pistachios on body weight in Chinese subjects with metabolic syndrome. *Nutr. J.*, 11, 20, 2012.
44. Dhillon, J., Tan, S.Y., and Mattes, R.D., Almond consumption during energy restriction lowers truncal fat and blood pressure in compliant overweight or obese adults. *J. Nutr.*, 146, 2513–2519, 2016.
45. Lee, Y.J., Nam, G.E., Seo, J.A., Yoon, T., Seo, I., Lee, J.H., Im, D. et al., Nut consumption has favorable effects on lipid profiles of Korean women with metabolic syndrome. *Nutr. Res.*, 34, 814–820, 2014.

46. Abazarfard, Z., Salehi, M., and Keshavarzi, S., The effect of almonds on anthropometric measurements and lipid profile in overweight and obese females in a weight reduction program: A randomized controlled clinical trial. *J. Res. Med. Sci.*, 19, 457–464, 2014.
47. Domenech, M., Roman, P., Lapetra, J., Garcia de la Corte, F.J., Sala-Vila, A., de la Torre, R., Corella, D. et al., Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: One-year randomized, clinical trial. *Hypertension*, 64, 69–76, 2014.
48. Hernandez-Alonso, P., Salas-Salvado, J., Baldrich-Mora, M., Juanola-Falgarona, M., and Bullo, M., Beneficial effect of pistachio consumption on glucose metabolism, insulin resistance, inflammation, and related metabolic risk markers: A randomized clinical trial. *Diabetes Care*, 37, 3098–3105, 2014.
49. Maranhao, P.A., Kraemer-Aguiar, L.G., de Oliveira, C.L., Kuschnir, M.C., Vieira, Y.R., Souza, M.G., Koury, J.C. et al., Brazil nuts intake improves lipid profile, oxidative stress and microvascular function in obese adolescents: A randomized controlled trial. *Nutr. Metab.*, 8, 32, 2011.
50. Njike, V.Y., Ayettey, R., Petraro, P., Treu, J.A., and Katz, D.L., Walnut ingestion in adults at risk for diabetes: Effects on body composition, diet quality, and cardiac risk measures. *BMJ Open Diabetes Res. Care*, 3, e000115, 2015.
51. Barbour, J.A., Howe, P.R., Buckley, J.D., Bryan, J., and Coates, A.M., Effect of 12 weeks high oleic peanut consumption on cardio-metabolic risk factors and body composition. *Nutrients*, 7, 7381–7398, 2015.
52. Moreira Alves, R.D., Boroni Moreira, A.P., Macedo, V.S., Bressan, J., de Cassia Goncalves Alfenas, R., Mattes, R., and Brunoro Costa, N.M., High-oleic peanuts: New perspective to attenuate glucose homeostasis disruption and inflammation related obesity. *Obesity (Silver Spring)*, 22, 1981–1988, 2014.
53. Jung, H., Chen, C.O., Blumberg, J.B., and Kwak, H.K., The effect of almonds on vitamin E status and cardiovascular risk factors in Korean adults: A randomized clinical trial. *Eur. J. Nutr.*, 57, 2069–2079, 2018.
54. Lee, Y., Berryman, C.E., West, S.G., Chen, C.O., Blumberg, J.B., Lapsley, K.G., Preston, A.G. et al., Effects of dark chocolate and almonds on cardiovascular risk factors in overweight and obese individuals: A randomized controlled-feeding trial. *J. Am. Heart Assoc.*, 6, e005162, 2017.
55. McKay, D.L., Eliasziw, M., Chen, C.Y.O., and Blumberg, J.B., A pecan-rich diet improves cardiometabolic risk factors in overweight and obese adults: A randomized controlled trial. *Nutrients*, 10, 339, 2018.
56. Estruch, R., Martinez-Gonzalez, M.A., Corella, D., Salas-Salvado, J., Ruiz-Gutierrez, V., Covas, M.I., Fiol, M. et al., Effects of a Mediterranean-style diet on cardiovascular risk factors: A randomized trial. *Ann. Intern. Med.*, 145, 1–11, 2006.
57. Casas-Agustench, P., Lopez-Uriarte, P., Bullo, M., Ros, E., Cabre-Vila, J.J., and Salas-Salvado, J., Effects of one serving of mixed nuts on serum lipids, insulin resistance and inflammatory markers in patients with the metabolic syndrome. *Nutr. Metab. Cardiovasc. Dis.*, 21, 126–135, 2011.
58. Wien, M., Bleich, D., Raghuwanshi, M., Gould-Forgerite, S., Gomes, J., Monahan-Couch, L., and Oda, K., Almond consumption and cardiovascular risk factors in adults with prediabetes. *J. Am. Coll. Nutr.*, 29, 189–197, 2010.
59. Salas-Salvado, J., Fernandez-Ballart, J., Ros, E., Martinez-Gonzalez, M.A., Fito, M., Estruch, R., Corella, D. et al., Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: One-year results of the PREDIMED randomized trial. *Arch. Intern. Med.*, 168, 2449–2458, 2008.

60. Babio, N., Toledo, E., Estruch, R., Ros, E., Martinez-Gonzalez, M.A., Castaner, O., Bullo, M. et al., Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. *Can. M. Assoc. J.*, 186, E649–E657, 2014.
61. Wu, H., Pan, A., Yu, Z., Qi, Q., Lu, L., Zhang, G., Yu, D. et al., Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome. *J. Nutr.*, 140, 1937–1942, 2010.
62. Salas-Salvado, J., Bullo, M., Babio, N., Martinez-Gonzalez, M.A., Ibarrola-Jurado, N., Basora, J., Estruch, R. et al., Reduction in the incidence of type 2 diabetes with the Mediterranean diet: Results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care*, 34, 14–19, 2011.
63. Salas-Salvado, J., Bullo, M., Estruch, R., Ros, E., Covas, M.I., Ibarrola-Jurado, N., Corella, D. et al., Prevention of diabetes with Mediterranean diets: A subgroup analysis of a randomized trial. *Ann. Intern. Med.*, 160, 1–10, 2014.
64. Lovejoy, J.C., Most, M.M., Lefevre, M., Greenway, F.L., and Rood, J.C., Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. *Am. J. Clin. Nutr.*, 76, 1000–1006, 2002.
65. Wien, M.A., Sabate, J.M., Ikle, D.N., Cole, S.E., and Kandeel, F.R., Almonds vs complex carbohydrates in a weight reduction program. *Int. J. Obes.*, 27, 1365–1372, 2003. Erratum appears in *Int. J. Obes.*, 28, 459, 2004.
66. Tapsell, L.C., Gillen, L.J., Patch, C.S., Batterham, M., Owen, A., Bare, M., and Kennedy, M., Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with type 2 diabetes. *Diabetes Care*, 27, 2777–2783, 2004.
67. Tapsell, L.C., Batterham, M.J., Teuss, G., Tan, S.Y., Dalton, S., Quick, C.J., Gillen, L.J. et al., Long-term effects of increased dietary polyunsaturated fat from walnuts on metabolic parameters in type II diabetes. *Eur. J. Clin. Nutr.*, 63, 1008–1015, 2009.
68. Ma, Y., Njike, V.Y., Millet, J., Dutta, S., Doughty, K., Treu, J.A., and Katz, D.L., Effects of walnut consumption on endothelial function in type 2 diabetic subjects: A randomized controlled crossover trial. *Diabetes Care*, 33, 227–232, 2010.
69. Cohen, A.E., and Johnston, C.S., Almond ingestion at mealtime reduces postprandial glycemia and chronic ingestion reduces hemoglobin A(1c) in individuals with well-controlled type 2 diabetes mellitus. *Metabolism*, 60, 1312–1317, 2011.
70. Jenkins, D.J., Kendall, C.W., Banach, M.S., Srichaikul, K., Vidgen, E., Mitchell, S., Parker, T. et al., Nuts as a replacement for carbohydrates in the diabetic diet. *Diabetes Care*, 34, 1706–1711, 2011. Retraction in *Diabetes Care*, 39, 319, 2016.
71. Li, S.C., Liu, Y.H., Liu, J.F., Chang, W.H., Chen, C.M., and Chen, C.Y., Almond consumption improved glycemic control and lipid profiles in patients with type 2 diabetes mellitus. *Metabolism*, 60, 474–479, 2011.
72. Darvish Damavandi, R., Shidfar, F., Rajab, A., Mohammadi, V., and Hoseini, S., The effects of cashew consumption on serum glucose, insulin and lipoprotein in type 2 diabetic patients. *Iranian J. Endocrinol. Metab.*, 14, 325–334, 2012.
73. Darvish Damavandi, R., Eghtesadi, S., Shidfar, F., Heydari, I., and Foroushani, A.R., Effects of hazelnuts consumption on fasting blood sugar and lipoproteins in patients with type 2 diabetes. *J. Res. Med. Sci.*, 18, 314–321, 2013.
74. Parham, M., Heidari, S., Khorramirad, A., Hozoori, M., Hosseinzadeh, F., Bakhtyari, L., and Vafaeimanesh, J., Effects of pistachio nut supplementation on blood glucose in patients with type 2 diabetes: A randomized crossover trial. *Rev. Diabetic Stud.*, 11, 190–196, 2014.

75. Sweazea, K.L., Johnston, C.S., Ricklefs, K.D., and Petersen, K.N., Almond supplementation in the absence of dietary advice significantly reduces C-reactive protein in subjects with type 2 diabetes. *J. Funct. Foods*, 10, 252–259, 2014.
76. Sauder, K.A., McCrea, C.E., Ulbrecht, J.S., Kris-Etherton, P.M., and West, S.G., Effects of pistachios on the lipid/lipoprotein profile, glycemic control, inflammation, and endothelial function in type 2 diabetes: A randomized trial. *Metabolism*, 64, 1521–1529, 2015.
77. Chen, C.M., Liu, J.F., Li, S.C., Huang, C.L., Hsirh, A.T., Weng, S.F., Chang, M.L. et al., Almonds ameliorate glycemic control in Chinese patients with better controlled type 2 diabetes: A randomized, crossover, controlled feeding trial. *Nutr. Metab.*, 14, 51, 2017.
78. Mohan, V., Gayathri, R., Jaacks, L.M., Lakshmipriya, N., Anjana, R.M., Spiegelman, D., Jeevan, R.G. et al., Cashew nut consumption increases HDL cholesterol and reduces systolic blood pressure in Asian Indians with type 2 diabetes: A 12-week randomized controlled trial. *J. Nutr.*, 148, 63–69, 2018.
79. Viguiliouk, E., Kendall, C.W., Blanco Mejia, S., Cozma, A.I., Ha, V., Mirrahimi, A., Jayalath, V.H. et al., Effect of tree nuts on glycemic control in diabetes: A systematic review and meta-analysis of randomized controlled dietary trials. *PLoS One*, 9, e103376, 2014.
80. Sweazea, K.L., Johnston, C.S., Ricklefs, K.D., and Petersen, K.N, Almond supplementation in the absence of dietary advice significantly reduces C-reactive protein in subjects with type 2 diabetes. *J. Funct. Foods*, 10, 252–259, 2014.
81. Jenkins, D.J.A., Kendall, C.W.C., Lamarche, B., Banach, M.S., Srichaikul, K., Vidgen, E., Mitchell, S. et al., Nuts as a replacement for carbohydrates in the diabetic diet: A reanalysis of a randomised controlled trial. *Diabetologia*, 61, 1734–1747, 2018.
82. Damavandi, R.D., Eghtesadi, S., Shidfar, F., Heydari, I., and Foroushani, A.R., Effects of hazelnuts consumption on fasting blood sugar and lipoproteins in patients with type 2 diabetes. *J. Res. Med. Sci.*, 18, 314–321, 2013.
83. Jenkins, D.J., Kendall, C.W., Josse, A.R., Salvatore, S., Brighenti, F., Augustin, L.S., Ellis, P.R. et al., Almonds decrease postprandial glycemia, insulinemia, and oxidative damage in healthy individuals. *J. Nutr.*, 136, 2987–2992, 2006.
84. Lopez-Uriarte, P., Nogues, R., Saez, G., Bullo, M., Romeu, M., Masana, L., Tormos, C. et al., Effect of nut consumption on oxidative stress and the endothelial function in metabolic syndrome. *Clin. Nutr.*, 29, 373–380, 2010.
85. Chaudhary, D.P., Sharma, R., and Bansal, D.D., Implications of magnesium deficiency in type 2 diabetes: A review. *Biol. Trace Elem. Res.*, 134, 119–129, 2010.
86. Ros, E., Health benefits of nut consumption. *Nutrients*, 2, 652–682, 2010.
87. Dong, J.Y., Xun, P., He, K., and Qin, L.Q., Magnesium intake and risk of type 2 diabetes: Meta-analysis of prospective cohort studies. *Diabetes Care*, 34, 2116–2122, 2011.
88. Larsson, S.C., and Wolk, A., Magnesium intake and risk of type 2 diabetes: A meta-analysis. *J. Intern. Med.*, 262, 208–214, 2007.
89. Song, Y., He, K., Levitan, E.B., Manson, J.E., and Liu, S., Effects of oral magnesium supplementation on glycaemic control in type 2 diabetes: A meta-analysis of randomized double-blind controlled trials. *Diabet Med.*, 23, 1050–1056, 2006.
90. Riserus, U., Willett, W.C., and Hu, F.B., Dietary fats and prevention of type 2 diabetes. *Prog. Lipid Res.*, 48, 44–51, 2009.

91. Schwingshackl, L., Strasser, B., and Hoffmann, G., Effects of monounsaturated fatty acids on glycaemic control in patients with abnormal glucose metabolism: A systematic review and meta-analysis. *Ann. Nutr. Metab.*, 58, 290–296, 2011.
92. Honardoost, M., Sarookhani, M.R., Arefian, E., and Soleimani, M., Insulin resistance associated genes and miRNAs. *Appl. Biochem. Biotechnol.*, 174, 63–80, 2014.
93. Ribeiro, P.V.M., Silva, A., Almeida, A.P., Hermsdorff, H.H., and Alfenas, R.C., Effect of chronic consumption of pistachios (*Pistacia vera* L.) on glucose metabolism in pre-diabetics and type 2 diabetics: A systematic review. *Crit. Rev. Food Sci. Nutr.*, 59, 1115–1123, 2019.
94. Pawlak, R., Colby, S., and Herring, J., Beliefs, benefits, barriers, attitude, intake and knowledge about peanuts and tree nuts among WIC participants in eastern North Carolina. *Nutr. Res. Pract.*, 3, 220–225, 2009.
95. Leung, C.W., Ding, E.L., Catalano, P.J., Villamor, E., Rimm, E.B., and Willett, W.C., Dietary intake and dietary quality of low-income adults in the Supplemental Nutrition Assistance Program. *Am. J. Clin. Nutr.*, 96, 977–988, 2012.
96. Yong, L.C., Gray, A.R., Chisholm, A., Leong, S.L., Tey, S.L., and Brown, R.C., Barriers to and facilitators and perceptions of nut consumption among the general population in New Zealand. *Public Health Nutr.*, 20, 3166–3182, 2017.
97. McWilliam, V., Koplin, J., Lodge, C., Tang, M., Dharmage, S., and Allen, K., The prevalence of tree nut allergy: A systematic review. *Curr. Allergy Asthma Rep.*, 15, 54, 2015.
98. Sicherer, S.H., Munoz-Furlong, A., Godbold, J.H., and Sampson, H.A., US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J. Allergy Clin. Immunol.*, 125, 1322–1326, 2010.
99. International Nut and Dried Fruit Council (INC), *Nuts and Dried Fruits, Statistical Yearbook 2017/2018 and Nutfruit Magazine July 2018*, INC, Reus, Spain, 2018.
100. Schutte, A.E., Van Rooyen, J.M., Huisman, H.W., Mukuddem-Petersen, J., Oosthuizen, W., Hanekom, S.M., and Jerling, J.C., Modulation of baroreflex sensitivity by walnuts *versus* cashew nuts in subjects with metabolic syndrome. *Am. J. Hypertens.*, 19, 629–636, 2006.
101. Katz, D.L., Davidhi, A., Ma, Y., Kavak, Y., Bifulco, L., and Njike, V.Y., Effects of walnuts on endothelial function in overweight adults with visceral obesity: A randomized, controlled, crossover trial. *J. Am. Coll. Nutr.*, 31, 415–423, 2012.
102. Anderson, A.D., Anderson, M.M., Jacobson, J.L., Popko, M.R., Young, J.R., Limburg, P.J., and Wilson, T., Metabolic effects of bedtime pistachio consumption for 6 weeks in overweight persons. *FASEB J.*, 27, 1072.20, 2013.
103. Somerset, S.M., Graham, L., and Markwell, K., Isoenergetic replacement of dietary saturated with monounsaturated fat *via* macadamia nuts enhances endothelial function in overweight subjects. *e-SPEN J.*, 8, e113–e119, 2013.
104. Tan, S.Y., and Mattes, R.D., Appetitive, dietary and health effects of almonds consumed with meals or as snacks: A randomized, controlled trial. *Eur. J. Clin. Nutr.*, 67, 1205–1214, 2013.
105. Le, T., Flatt, S.W., Natarajan, L., Pakiz, B., Quintana, E.L., Heath, D.D., Rana, B.K. et al., Effects of diet composition and insulin resistance status on plasma lipid levels in a weight loss intervention in women. *J. Am. Heart Assoc.*, 5, e002771, 2016.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 9

Nut Consumption and Cancer

Heinz Freisling and Hwayoung Noh

9.1 Introduction 224
9.2 Cancer Chemoprevention by Nuts 224
9.2.1 Epidemiological Studies 225
9.2.1.1 Breast Cancer 225
9.2.1.2 Colorectal Cancer 225
9.2.1.3 Esophageal and Gastric Cancer 228
9.2.1.4 Lung Cancer 228
9.2.1.5 Ovarian Cancer 229
9.2.1.6 Lymphomas 229
9.2.1.7 Leukemia 229
9.2.1.8 Pancreatic Cancer 229
9.2.1.9 Prostate Cancer 229
9.2.2 *In Vitro* and *In Vivo* Animal Studies 229
9.2.2.1 Breast Cancer 231
9.2.2.2 Colorectal Cancer 231
9.2.2.3 Prostate Cancer 234
9.2.3 Human Intervention Studies Including Meta-Analyses 234
9.2.3.1 Intervention Studies 234
9.2.3.2 Meta-Analyses 235
9.3 Cancer Death 236
9.4 Conclusion 236
Acknowledgment 242
References 242

9.1 Introduction

In 2016, there were 17.2 million cancer cases and 8.9 million cancer deaths globally, and cancer incidence increased by 28% between 2006 and 2016 [1]. Cancer incidence is also increasing in adults younger than 50 years as exemplified in cancers of the colorectum or breast [2,3]. This increasing cancer burden is thought to be due to population aging and environmental changes such as smoking, obesity, and unhealthy dietary habits [1,4]. Conversely, factors such as a healthy diet, being physically active, and maintaining ideal body weight can have a strong influence on cancer prevention [5]. It has been estimated that up to 50% of cancer cases can be prevented [6]. Therefore, there is considerable interest in studying the impact of lifestyle changes, in particular diet, on cancer development and progression [7]. There is compelling evidence that nutrition has substantial effects on the incidence and progression of cancer [8].

Both observational and intervention studies have shown that a high intake of nuts is associated with a reduced risk of coronary heart disease (CHD) and possibly other health outcomes such as diabetes, obesity, cancer, and all-cause mortality [9,10]. Higher nut consumption may also play a role in reducing risk of individual cancer types [10]; however, epidemiological data on nuts and cancer risk are less extensive than for cardiovascular disease (CVD). Further, a better understanding of underlying mechanisms for potential risk reduction associated with a higher intake of nuts is also needed.

This chapter provides a review of the literature on epidemiological and mechanistic evidence of associations between higher intake of different types of nuts and cancer risk, and assesses coherence of the respective results between the studies *in vitro/in vivo* and in humans.

9.2 Cancer Chemoprevention by Nuts

The large international variation in cancer rates that are minimally explained by genetic factors points towards the importance of modifiable risk factors, such as diet, in cancer etiology [11,12]. A more holistic view of the evidence shows that most diets that are protective against cancer are rich in foods of plant origin [7]. Relatively unprocessed foods of plant origin are rich in nutrients and dietary fiber. Higher consumption of these foods, instead of processed foods and sugars, could protect against weight gain, overweight, and obesity as well as obesity-related cancers [5]. A reasonably high consumption of nuts (> 1 serving of nuts per week compared to no consumption) has been associated with a 10% lower body weight gain in adults in the European Prospective Investigation into Cancer and Nutrition (EPIC)-PANACEA cohort, a subcohort of the EPIC study, which included 373,293 men and women aged 25–70 years at baseline from 10 European countries, with a median follow-up time of 5 years [13]. In the same study population, the EPIC-PANACEA cohort, adult weight gain was positively associated with colorectal cancer risk [14]. Nuts contain high amounts of nutrients such as unsaturated fats, protein, vitamins (alpha-tocopherol, folate, and niacin), minerals (magnesium, calcium, and potassium), and phytochemicals – all of which may offer anti-carcinogenic, anti-inflammatory, and antioxidant properties (see Chapter 2 for details). Nuts have also been shown to modulate the gut microbiota, and new mechanistic hypotheses on diet–cancer relationships include

interactions between host and environmental factors in selecting microbiota that in turn influence carcinogenesis [15].

9.2.1 Epidemiological Studies

Current scientific evidence regarding the association between human nutrition and cancer has been derived mostly from prospective studies and a few randomized controlled trials with cancer endpoints [12]. Here, we discuss epidemiological studies from around the world on nut consumption and risk of cancer at different anatomical sites. The focus is on prospective observational studies, but a few large population-based case-control studies are also considered. Epidemiological studies on different cancers are reviewed in the following sections.

9.2.1.1 Breast Cancer

A total of five prospective cohort studies and one large population-based case-control study on nut consumption and breast cancer risk were published before December 2017 (Table 9.1). A prospective cohort study in 15,773 Swedish women aged 46–75 years at baseline with a mean follow-up time of 10.3 years reported null associations between higher nut intake (median 6 g/day) and risk of breast cancer compared to non-consumers [16]. Similarly, in the Nurses' Health Study (NHS) II, wherein 88,803 women aged 24–43 years at baseline were recruited and 2,830 cases occurred during 20-year follow-up, no association between the frequency of nut consumption and risk of pre- or postmenopausal breast cancer risk was detected [17]. In addition, in the same cohort, replacing one serving/day of red meat with one serving of nuts was not associated with a reduced risk of breast cancer, although a suggestive inverse association was observed [18]. Furthermore, in the Netherlands Cohort Study that included more than 60,000 women aged 55–69 years and followed up for more than 20 years, no significant association between nut intake and total breast cancer risk was observed. However, a statistically significant inverse association between higher nut intake and risk of estrogen receptor-negative postmenopausal breast cancer was reported [19]. For proliferative benign breast disease, a study from the NHS II cohort reported that two or more servings of nuts per week during adolescence were associated with a 36% lower risk compared with an intake of less than one serving per month [20]. Similarly, in a cohort of pre-adolescent and adolescent girls, compared to non-consumers, one or more servings of nuts and peanut butter three times/week was associated with a significantly lower risk of developing benign breast disease during follow-up [21]. Finally, a large population-based case–control study in the United States showed a significant inverse association between higher nut intake in adolescence and risk of breast cancer in adulthood, with a stronger association for postmenopausal than premenopausal tumors [22].

9.2.1.2 Colorectal Cancer

Four prospective cohort studies and one large case-control study investigated associations between nut consumption and colorectal cancer risk (Table 9.2). One of the earliest studies investigating associations between nut consumption and

Table 9.1 Studies on Nut Consumption and Risk of Breast Cancer

Country	*Study Name*	*Cases (n)*	*Years of Follow-Up*	*Sex*	*RR*	*95% CI*	*Contrast*	*References*
Sweden	Malmo Diet and Cancer Cohort	330	10.3	F	0.98	0.75 – 1.27	6 g/day *versus* none	[16]
USA	Nurses' Health Study II	2830	20.0	F	0.98	0.88 – 1.10	Per 1 serving/day	[17]
The Netherlands	Netherlands Cohort Study	2321	20.3	F	1.02	0.94 – 1.11	Per 10 g/day	[19]
USA	Nurses' Health Study II	682	–	F	0.64[a]	0.48 – 0.85	≥ 2 servings/week *versus* < 1 serving / month	[20]
USA	Growing Up Today Study	112	3.0	F	0.56[a]	0.35 – 0.87	1 + servings/3 days *versus* none	[21]
USA	Ontario Cancer Registry	2865	Case-control	F	0.76[b]	0.61 – 0.95	1 serving/day *versus* < 1 serving/month	[22]

Abbreviation: F, female.
[a] Benign breast disease was the outcome.
[b] Odds ratio from case-control design.

Table 9.2 Studies on Nut Consumption and Risk of Colorectal Cancer

Country	*Study Name*	*Cases (n)*	*Years of Follow-Up*	*Sex*	*RR*	*95% CI*	*Contrast*	*References*
USA	Adventist Health Study	157	6.0	F, M	0.68	0.45 – 1.04	> 4 times/week *versus* < 1 time/week	[23]
10 European Countries	EPIC	1329	4.8	F, M	0.91	0.75 – 1.11	Highest quintile *versus* lowest quintile	[24]
Taiwan	Cancer Screening Cohort	107	10.0	F, M	F: 0.42 M: 0.73	0.21 – 0.84 0.44 – 1.21	> 2 times/week *versus* < 1 time/week	[25]
USA	Nurses' Health Study	1503	30.0	F	0.87	0.72 – 1.05	> 2 times/week *versus* < 1 time/week	[26]
Korea	National Cancer Center Korea	923	Case-control	F, M	F: 0.30[a] M: 0.28[a]	0.15 – 0.60 0.17 – 0.47	≥ 3 times/week *versus* none	[27]

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; M, male.
[a] Odds ratio from case-control design.

incident colon cancer reported a 32% reduced risk (95% Confidence Interval [CI]: –4% to 55%) in 32,051 white men and women of the Seventh-Day Adventist Health Study (AHS), wherein 157 cases occurred during a 6-year follow-up, comparing > 4 times/week consumption with less than once/week [23]. Subsequently, Jenab et al. [24] reported a statistically significant 21% reduced risk for colorectal cancer in women but a null association in men, comparing highest with the lowest intake categories across 10 European countries in the EPIC. In a prospective cohort study in 12,026 men and 11,917 women aged 30–65 years at baseline from Taiwan with 10-year follow-up, higher peanut consumption of more than 2 times/week was associated with a statistically significant reduced risk of developing colorectal cancer in women and with a non-significant reduction in men, compared to lower consumption with less than once/week [25]. In addition, women participating in the NHS who consumed nuts 2 or more times per week had a statistically significant 13% lower risk of colorectal cancer compared with those who rarely consumed nuts, but the association was not statistically significant. In the same study, no association was observed for peanut-butter consumption [26]. Finally, a large population-based case-control study in Korea, where nut consumption frequency and patterns may differ compared with other countries, found a statistically significant inverse association between higher nut consumption and risk of colorectal cancer, and associations persisted for all subsites of the colon and rectum among both men and women, with the exception of proximal colon cancer for women [27].

9.2.1.3 Esophageal and Gastric Cancer

Among older American adults aged 50–71 years at baseline in the National Institutes of Health (NIH), American Association of Retired Persons (AARP) Diet and Health Study with a median follow-up time of 15.5 years, higher nut consumption was inversely associated with risk of developing non-cardia gastric adenocarcinoma (Hazard Ratio, HR: 0.73 [95% CI: 0.57, 0.94]); a similar inverse association was reported for peanut-butter consumption [28]. In the same study, no significant associations between the highest and lowest intakes of nuts or peanut butter and the risk of gastric cardia adenocarcinoma, esophageal adenocarcinoma, or esophageal squamous cell carcinoma were observed [28]. In a regional case-control study from China (Yanting County), highest *versus* lowest frequency of peanut consumption was inversely associated with esophageal squamous cell carcinoma risk (Odds Ratio, OR 0.31, 95% CI 0.16–0.59) [29].

9.2.1.4 Lung Cancer

In the Environment and Genetics in Lung Cancer Etiology (EAGLE) study, a population-based case-control study, and in the prospective cohort of the NIH-AARP study, a higher frequency of nut consumption was inversely associated with overall lung cancer risk (highest *versus* lowest quintile, OR_{EAGLE} = 0.74; 95% CI, 0.57–0.95; HR_{AARP} = 0.86; 95% CI, 0.81–0.91), regardless of smoking status. Results from the prospective cohort showed similar associations across histologic subtypes and more pronounced benefits from nut consumption for those who smoked 1–20 cigarettes/day (OR_{EAGLE} = 0.61; 95% CI, 0.39–0.95; HR_{AARP} = 0.83; 95% CI, 0.74–0.94) [30].

9.2.1.5 Ovarian Cancer

In a prospective population-based cohort study among 47,140 Swedish women aged 30–49 years at baseline with a median follow-up time of 16 years, no statistically significant association between intake of specific food items rich in phytoestrogens, including nuts, and ovarian cancer risk was found [31].

9.2.1.6 Lymphomas

In a prospective cohort of 35,159 Iowa women aged 55–69 years at baseline with a 20-year follow-up, no associations between intakes of specific antioxidant-rich foods, including nuts, and lymphoma risk was observed [32].

9.2.1.7 Leukemia

In the EPIC study, associations between dietary intakes and risk of total leukemia and leukemia subtypes were investigated, and no associations were detected for nut consumption [33].

9.2.1.8 Pancreatic Cancer

After adjusting for main known risk factors, women who consumed a 28 g serving size of nuts > 2 times/week experienced a significantly lower risk of pancreatic cancer (Risk Ratio [RR], 0.65; 95% CI, 0.47–0.92; P for trend < 0.007) when compared with those who largely abstained from nuts in the large prospective NHS, which included 75,680 women aged 30–55 years at enrollment and ascertained 466 incident cases during a 30-year follow-up [34].

9.2.1.9 Prostate Cancer

One of the first prospective analyses of selected food groups related to the risk of prostate cancer in men of the AHS and found a statistically non-significant inverse association with higher nut consumption (Table 9.3) [35]. More than 25 years later, the role of nuts in prostate cancer development and survival after prostate cancer diagnosis was investigated in the Health Professionals Follow-up Study [36]. Among about 47,000 men followed over 26 years, 6,810 individuals developed prostate cancer, and associations between eating nuts frequently and incidence of all prostate cancers were largely null, including advanced and fatal cancers [36]. There is some evidence that higher levels of plasma alpha-tocopherol or plasma selenium concentrations might be inversely associated with prostate cancer risk [5]. Both nutrients are found in high concentrations in certain nuts, such as selenium in Brazil nuts and alpha-tocopherol in almonds and hazelnuts [37].

9.2.2 In Vitro *and* In Vivo *Animal Studies*

In vitro and *in vivo* experimental studies to determine whether nuts can help combat cancer are instrumental to understand potential mechanisms and whether results are coherent with studies in humans. Potential anti-cancer properties of nuts or

Table 9.3 Studies on Nut Consumption and Risk of Prostate Cancer

Country	*Study Name*	*Cases (n)*	*Years of Follow-Up*	*Sex*	*RR*	*95% CI*	*Contrast*	*References*
USA	Adventist Health Study	180	6.0	M	0.79	0.41 – 1.22	≥ 5 times/week *versus* < 1 times/week	[35]
USA	Health Professional Follow-Up Study	6810	26.0	M	0.98	0.89 – 1.09	≥ 5 times/week *versus* < 1 times/months	[36]

Abbreviation: M, male.

phytochemicals present in them relate to several cellular processes involved in tumor development and progression, including cell survival, cell proliferation, cell invasion, and angiogenesis [38,39]. The principal findings from *in vivo* and some *in vitro* studies, mostly conducted with walnuts, are discussed next and summarized in Table 9.4.

9.2.2.1 Breast Cancer

In a pilot study by Hardman and Ion [40], consumption of 18% of energy from walnuts significantly decreased the growth rate of implanted human breast cancer tumors in nude mice. As a likely mechanism for the lower growth, the authors suspected the suppression of proliferation of cells that might transform into cancer cells or suppression of the growth of metastatic sites in the tumor by the walnut omega-3 fatty acid and alpha-linolenic acid. Subsequently, the same investigators [41] showed that exposure to small amounts of walnuts in the diet of C(3)1 TAg transgenic mice, a well-characterized breast cancer model, slowed the development and reduced the multiplicity of mammary gland cancers. Walnuts in the diet were associated with alterations in cell signaling pathways involved in proliferation, cell differentiation, and apoptosis.

In addition, Garcia et al. [39] investigated the effects of polyunsaturated fatty acids (PUFA) plus phytomelatonin from walnuts in the development of implanted mammary gland adenocarcinoma. BALB/c mice were fed a semisynthetic diet supplemented with either 6% walnut oil and 8% walnut flour containing phytomelatonin (walnut diet, WD) or 6% corn oil plus commercial melatonin (melatonin diet, MD), or the control diet (CD) containing only 6% of corn oil. Plasma melatonin, apoptosis, tumor infiltration, and survival time were significantly lower in CD mice than in MD and WD mice ($P < 0.05$). The authors concluded that melatonin along with PUFA from a walnut diet exerts a selective inhibition of some cyclooxygenase and lipoxygenase activities and has a synergistic anti-tumor effect on a mammary gland adenocarcinoma model [39]. Finally, Chen et al. [42] reported that ellagic acid, a polyphenol that abounds in walnuts, inhibited the growth of breast cancer cells, and the TGF-β/Smads signaling pathway was proposed as the potential molecular mechanism for regulating cell cycle arrest and inhibiting proliferation *in vitro*.

In summary, *in vivo* and *in vitro* studies demonstrated a reduced growth and multiplicity of breast cancer tumors in association with walnuts or their main characteristic compounds, and these findings are coherent with data from observational studies in humans, in whom inverse associations between higher nut consumption and risk of breast cancer were reported. Of the investigated mechanistic aspects, suppression of proliferation, alterations in cell signaling pathways involved in cell differentiation and apoptosis, and selective inhibition of cyclooxygenase and lipoxygenase activities have been put forward.

9.2.2.2 Colorectal Cancer

Nagel et al. [43] examined the effects of dietary walnut and flaxseed oil supplementation on colorectal cancer growth and possible underlying mechanisms *in vivo* in female nude mice. They found that isocaloric amounts of walnuts and flaxseed oil, compared with corn oil, inhibited colorectal cancer growth rate by 30%–45%, and that tumor weight was decreased. Their data suggest that consumption of walnuts

Table 9.4 Potential Anticancer Properties of Nuts Based on *In Vitro* and *In Vivo* Experimental Studies

Cancer Model	*Putative Mechanism of Nuts' Dietary Factor*	*Dietary Factor*	*References*
Human breast cancer tumors in nude mice.	Suppression of cell proliferation or suppression of metastasis.	18% of dietary energy from walnuts.	[40]
C(3)1 TAg transgenic mice, breast cancer.	Alterations in cell signaling related to proliferation, differentiation, and apoptosis.	Walnuts in the diet.	[41]
Implanted mammary gland adenocarcinoma in BALB/c mouse model.	Inhibition of cyclooxygenase and lipoxygenase.	6% walnut oil or 8% walnut flour containing phytomelatonin.	[39]
Breast cancer cells.	Growth inhibition of breast cancer cells through cell cycle arrest and inhibition of proliferation.	Ellagic acid, abundant in walnuts.	[42]
HT-29 human colon cancer cells in nude mice.	Inhibition of tumor growth rate through suppression of angiogenesis.	Walnut and flaxseed oil.	[43]
Mice treated with organotropic colon carcinogen.	Tumor suppression associated with alterations in gut bacteria.	Dietary walnut of up to 15% of total caloric intake.	[44]
ACF in rats treated with azoxymethane.	ACF and cell turnover reduced.	Diet containing whole almonds, almond meal, or almond oil.	[49]
TRAMP	Reduced TRAMP mouse prostate cancer growth and size and declined in plasma IGF-1, resistin, and LDL.	Whole almonds as part of a high-fat diet.	[50]
TRAMP	Reduced TRAMP mouse prostate cancer growth and size and improved insulin sensitivity and effects on cellular energy status and tumor suppression.	Whole walnuts and walnut oil.	[51]
Implanted tumor model in nude mice.	Reduced number and growth of LNCaP human prostate cancer cells and decreased oxidative stress.	Standard mouse diet supplemented with walnuts.	[52]

Abbreviations: ACF, aberrant crypt foci; IGF-1, plasma insulin-like growth factor-1; LDL, low-density lipoprotein; TRAMP, transgenic adenocarcinoma of the mouse prostate.

might be beneficial against the progression of colorectal cancer by suppressing angiogenesis [43]. Dietary walnut consumption at concentrations of ~7% and ~9% by weight, equivalent to 10%–15% of total energy intake, showed protection against colon cancer after a potent carcinogen insult in a well-established mouse cancer model [44]. The described cancer protection was associated with significant alterations in gut bacteria, which appeared to be associated with tumor suppression [44]. In another mouse model after colon cancer–cell injection, expression of miRNAs 1903, 467c, and 3068 significantly decreased, and expression of miRNA 297a significantly increased in the walnut-treated group as compared to the control diet [45]. These results indicate that changes in the miRNA expression profiles likely affect target gene transcripts involved in pathways of anti-inflammation, anti-vascularization, anti-proliferation, and apoptosis [45].

Guan et al. [46] examined the effect of walnuts on intestinal homeostasis and intestinal tumorigenesis and growth in wild-type mice, two *Adenomatous polyposis coli (Apc)* models ($Apc^{1638N/+}$ and $Apc^{\Delta 14}$) mice, and in MC38 colon cancer cells *in vivo*, respectively. They found that walnuts significantly reduced circulating C-C Motif chemokine ligand 5 (CCL5) and preserved intestinal stem cell (ISC) function during a high-fat diet (HFD) with 7.6% walnuts (HFD+W) mice, compared with HFD control mice. Also, tumor multiplicity was reduced in $Apc^{1638N/+}$ HFD+W mice, and tumor growth was inhibited in $Apc^{\Delta 14}$ HFD+W mice compared to HFD controls. These results indicate that walnut intake could prevent obesity-induced colon cancer.

Koh et al. [47] examined the effect of walnut phenolic extract (WPE) on intestinal inflammation and colitis-associated colon cancer using human colonic epithelial cell line, COLO205, both acute and chronic mice models, and a murine model of colitis-associated colon cancer (CAC). They found that WPE significantly inhibited proinflammatory cytokine (e.g., interleukin-8 [IL-8] and Interleukin-1α [IL-1α]) mRNA expression by inhibiting nuclear factor-kB (NF-κB) signaling in COLO205 cells. Also, WPE reduced the severity of colitis in association with attenuation of NF-kB signaling in the colons of both colitis models and reduced tumor development in the CAC model. Another study by Choi et al. [48] assessed the effect of WPE on mitochondria in a colon cancer stem-cell model (CSCs). The WPE treatment promoted the transcription of genes associated with mitochondrial functions and metabolic pathways and enhanced glycolysis and oxidative pathways in colon CSCs. These results suggest that walnuts potentially prevent intestinal inflammation, thereby exhibiting chemopreventive effects on bowel tumorigenesis.

Davis and Iwahashi [49] assessed the effect of almonds on colon cancer. The effects of diets containing whole almonds, almond meal, or almond oil on aberrant crypt foci (ACF) and cell turnover in azoxymethane-treated F344 male rats were investigated. Whole almond ACF and cell turnover were both significantly lower than in wheat bran and cellulose diet groups (–30% and –40%, respectively), while almond meal and almond oil ACF and almond meal cell turnover declines were only significant *versus* cellulose ($P < 0.05$). The authors suggest that almond consumption might reduce colon cancer risk *via* at least one almond lipid-associated component [49].

In summary, *in vivo* studies suggest that consumption of nuts (walnuts, much studied in this regard, and almonds) inhibits growth of colorectal cancers and, more specifically, colon cancer. Among the investigated pathways, suppression of angiogenesis, proliferation, and inflammation, as well as increased apoptosis and favorable alterations to gut bacteria, have been put forward as potential mechanisms.

9.2.2.3 Prostate Cancer

A diet containing walnuts has been shown to reduce prostate cancer growth and tumor size in two models: a transgenic model [50,51] and an implanted tumor model [52]. Davis et al. [50] evaluated the effects of whole walnuts fed as part of a high-fat diet on tumor growth in the transgenic adenocarcinoma of the mouse prostate (TRAMP) cancer model. They found that whole walnuts fed as part of a high-fat diet reduced TRAMP mouse prostate cancer growth and tumor size. The walnut diet–consuming animals also showed declines in plasma insulin-like growth factor-1 (IGF-1), resistin, and low-density lipoprotein (LDL)-cholesterol, elevations of which have all been linked to tumor growth. The authors further suggested that the walnut effects are not due to their specific fatty acid or tocopherol content [50]. These findings were confirmed in the study by Kim et al. [51], wherein prostate cancer growth was reduced by walnut-containing diets in the TRAMP animal cancer model (comparing whole walnuts, walnut oil, and other oils). They could also show that walnut-containing diets improved insulin sensitivity and decreased IGF-1. Further, walnut diets increased microseminprotein-beta (MSMB) mRNA, a tumor suppressor, and decreased cyclooxygenase-2 (COX-2) mRNA, both reported to inhibit prostate tumor growth [51].

Reiter et al. [52] used an implanted tumor model to investigate whether a standard mouse diet supplemented with walnuts reduced the establishment and growth of LNCaP human prostate cancer cells in nude (nu/nu) mice. The walnut-enriched diet reduced the number and the growth of tumors; only 3 of 16 (18.7%) of the walnut-fed mice developed tumors, while 14 of 32 control diet–fed mice (44.0%) developed tumors [52]. Furthermore, it was found that walnut-fed mice had less than one-half the hepatic F2-isoprostane concentrations of control mice. The authors suggested that decreased concentrations of F2-isoprostanes following dietary exposure to walnuts would indicate decreased oxidative stress, likely due to the richness of antioxidants in these nuts [52].

In summary, *in vivo* models suggest that diets containing walnuts reduce the risk of prostate cancer. Mechanistically, declines in plasma levels of IGF-1, resistin, LDL-cholesterol together with reduced oxidative stress and inflammation, and increased expression of tumor suppressors have been suggested as potential cancer protective pathways.

9.2.3 Human Intervention Studies Including Meta-Analyses

A well conducted human intervention study in the form of a randomized controlled trial is the best study design for determining a causal relation between an intervention and its putative outcomes, but it is rare in public health concerning nutrition and clinical events. Intervention studies with intermediate outcomes that are risk factors for a disease are more feasible and may provide mechanistic insight. Meta-analyses provide summary evidence evaluating and combining results of relevant studies.

9.2.3.1 Intervention Studies

In a secondary analysis of the Prevención con Dieta Mediterránea (PREDIMED) trial [53], a non-significant risk reduction of first invasive breast cancer (n = 35

cases) with a hazard ratio: 0.59 (95% CI: 0.26–1.35) was observed in 4,152 postmenopausal women with the Mediterranean diet supplemented with mixed nuts (30 g/day: 15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds) [54]. This association was not significant, probably due to the small number of incident cases (n = 35) during the relatively short follow-up period of 4.8 years.

Hu et al. [55] tested the potential effects of supplementation of Brazil nuts and green tea extract alone or in combination on genetic and epigenetic biomarkers related to colorectal cancer development in a randomized clinical trial involving 32 human volunteers (> 50 years of age). They found that a 6-week intervention with Brazil nuts or green tea extract alone affected gene expressions associated with selenoproteins, wingless/integrated (WNT) signaling, inflammation, and DNA methylation [55]. Higher levels of circulating selenium and selenoproteins have been shown to be inversely associated with colorectal cancer in the prospective EPIC study [56].

Simon et al. [57] examined whether short-term consumption of walnuts, a food rich in alpha-linolenic acid, affects levels of serum prostate-specific antigen (PSA), a marker of prostate enlargement, inflammation, and cancer. In a 12-month randomized crossover study in 40 middle-aged men, no significant difference between mean PSA level after a 6-month walnut-supplemented diet (1.05 mu g/L, 95% CI [0.81, 1.37]) and after a 6-month control diet (1.06 mu g/L, 95% CI [0.81, 1.38]) (P = 0.86) was observed.

Focusing on tocopherols, Spaccarotella et al. [58] also assessed the effect of walnuts, rich in gamma-tocopherol, on markers of prostate and vascular health in men at risk for prostate cancer. They conducted an 8-week walnut supplementation study to examine effects on serum tocopherols and PSA in 21 men. Based on the observed findings of a significant decrease in the alpha-tocopherol : gamma-tocopherol ratio with an increase in serum gamma-tocopherol and a trend towards an increase in the ratio of free PSA : total PSA, the authors suggested that walnuts might improve biomarkers of prostate and vascular status.

A pilot study by Jia et al. [59] investigated the effects of almond consumption on DNA damage and oxidative stress among 30 regular cigarette smokers randomly divided into three groups. After 4 weeks, lower levels of urinary 8-OH-dG and single-strand DNA breaks in the two almond-treated groups as compared with the control group were observed. Furthermore, the malondialdehyde level, a surrogate marker of oxidative stress, was lower in the almond-treated groups than in the controls. The authors concluded from the results of this pilot study that almond consumption has preventive effects on oxidative stress and DNA damage caused by smoking [59].

9.2.3.2 Meta-Analyses

A systematic review and meta-analysis of 11 cohort studies and 20 case-control studies found that nut consumption was inversely associated with risk of all cancers combined (RR 0.85, 95% CI 0.76–0.95) for the highest *versus* lowest nut consumption category [10]. Regarding specific cancer sites, inverse associations between nut intake and cancers of the colorectum, endometrium, and pancreas were found [10]. There were no significant associations with upper-aerodigestive tract cancer, breast cancer, gastric cancer, glioma, hepatocellular carcinoma, leukemia (including acute myeloid leukemia), lymphoma, ovarian cancer, prostate cancer, or stomach cancer, among others [10].

Wu et al. [60] also reviewed and meta-analyzed the literature with regard to dietary protein sources and incidence of breast cancer. After combining data from three cohort studies, including 4,506 cases among 148,807 participants, it was concluded that nut consumption was not associated with risk of breast cancer; the summary RR per serving/day was 0.96 (95% CI 0.84–1.09) [60].

Schwingshackl et al. [61] reviewed prospective studies investigating associations between 12 food groups, including nuts, and risk of colorectal cancer. Six studies with 7,283 cases were included in the high *versus* low consumption analysis (range: 0–22 g/day of nuts) and no association was observed (RR: 0.96; 95% CI 0.90, 1.02) for the highest *versus* lowest nut consumption category [61]. In a subgroup analysis, an inverse association for nut consumption and colon cancer but not rectal cancer was reported [61].

9.3 Cancer Death

In a systematic review and meta-analysis of prospective studies, nut consumption was inversely associated with risk of cancer death when highest *versus* lowest categories of consumption were compared (RR: 0.86; 95% CI: 0.75, 0.98) [62]. In a subsequent meta-analysis of prospective studies investigating nut consumption and risk of CVD, total cancer, and all-cause and cause-specific mortality in adult populations, the summary RRs per 28 g/day increase in nut intake was 0.85 (95% CI: 0.76–0.94) for total cancer [9]. Including three additional prospective studies, Chen et al. [63] estimated a summary RRs for high compared with low nut consumption of 0.87 (95% CI: 0.80–0.93) for cancer mortality (11 studies with 21,353 deaths).

In a study using PREDIMED data, Guasch-Ferre et al. [64] conducted a cohort analysis with baseline consumption of nuts as the exposure and mortality outcomes. Subjects in the upper category of total nut consumption had a significant 40% (95% CI –37% to –98%) reduction of cancer deaths (n = 130).

As described, in the Health Professionals Follow-up study, associations between frequent nut intake (five or more times per week) and prostate-cancer-specific mortality were null [36]. However, those diagnosed with prostate cancer who consumed nuts five or more times per week had a lower risk of dying from other causes (than cancer) by more than 30% compared to men who ate nuts once or less per month. Of the 4,346 men diagnosed with non-metastatic prostate cancer during the 26 years of follow-up, only about 10% died from prostate cancer. Roughly, one third of the cancer patients died from CVD and the rest from other causes. Although not specifically reported, survival benefits related to frequent nut consumption might have been particularly linked to a reduced CVD incidence and mortality among prostate cancer patients [36].

9.4 Conclusion

Evidence from multiple lines of research, encompassing cell line studies, animal models, prospective and retrospective observational studies, meta-analyses, and interventional studies, is suggestive that higher consumption of nuts is inversely associated with the risk of certain cancers and of dying from cancer (Table 9.5).

Table 9.5 Summary of Evidence for Associations between Nut Consumption and Cancer

Cancer Type	*Summary of Evidence*	*References*
Breast	Three prospective cohort studies found no association of nut intake with overall breast cancer risk.	[16,17,19]
	These null findings were confirmed in a meta-analysis that combined the results of these three cohorts with a total of 4,506 cases.	[60]
	A population-based case-control study reported a statistically significant inverse association with breast cancer risk.	[22]
	A statistically non-significant risk reduction of breast cancer (n = 35) was found in a secondary analysis of the PREDIMED randomized trial.	[53]
	A systematic review and meta-analysis that included case-control studies found no association with breast cancer risk.	[10]
	Two prospective cohort studies found a significant inverse association with benign breast disease as outcome.	[20,21]
	There is some indication that associations may differ by menopausal status and ER/PR subtypes with a statistically significant inverse association with ER/PR negative postmenopausal breast cancer risk reported in one large prospective cohort study.	[19]
	Mechanistic evidence from animal models supports a potential breast cancer protective role of higher nut intake.	[39–42]
	There is insufficient evidence that higher nut consumption decreases overall breast cancer risk, but further studies are warranted with attention to population subgroups as defined by menopausal status and breast cancer subtypes.	

(*Continued*)

Table 9.5 (Continued) Summary of Evidence for Associations between Nut Consumption and Cancer

Cancer Type	*Summary of Evidence*	*References*
Colorectum	Four prospective cohort studies reported a non-significant inverse association between nut intake and colorectal cancer risk.	[23–26]
	A meta-analysis that combined results of these four and two additional case-control studies ,with a total of 7,283 cases, reported a weak statistically non-significant inverse association with colorectal cancer risk; in a subgroup analysis, a statistically significant inverse association was observed for colon cancer risk, but not for rectal cancer risk; these findings are in line with an earlier systematic review and meta-analysis.	[61]
	A population-based case-control study reported a statistically significant inverse association with colorectal cancer risk.	[27]
	There is indication that associations may differ by colorectal cancer subsite and are confined to colon cancer.	[61]
	Mechanistic evidence from animal models supports a potential colon cancer protective role of higher nut intake.	[43–49]
	There is limited suggestive evidence that higher nut consumption decreases risk of colon cancer, but further studies are warranted with specific attention to anatomical subsites of colorectal cancer.	
Esophagus	One prospective cohort study reported a non-significant inverse association of nut intake with esophageal adenocarcinoma risk.	[28]
	A small regional case-control study reported a statistically significant inverse association between peanut consumption and esophageal squamous cell carcinoma risk.	[29]
	There is insufficient evidence that higher nut intake decreases esophageal cancer risk, and further studies are warranted with specific attention to cancer subtypes.	
Endometrium	A meta-analysis of two case-control studies found a statistically significant inverse association between nut intake and endometrial cancer risk.	[10]
	There is insufficient evidence that higher nut intake decreases endometrial cancer risk, and further studies with a prospective design are warranted.	

(*Continued*)

Table 9.5 (Continued) Summary of Evidence for Associations between Nut Consumption and Cancer

Cancer Type	*Summary of Evidence*	*References*
Lung	One prospective cohort study and one population-based case-control study found a statistically significant inverse association between nut intake and lung cancer risk. *There is insufficient evidence that higher nut intake decreases lung cancer risk, and further studies are warranted.*	[30]
Lymphomas	One prospective cohort study reported a null association between nut intake and leukemia risk. *There is insufficient evidence that higher nut intake decreases lymphoma risk, and further studies are warranted.*	[32]
Leukemia	One prospective cohort study reported a null association between nut intake and lymphoma risk. *There is insufficient evidence that higher nut intake decreases leukemia risk, and further studies are warranted.*	[33]
Ovaries	One prospective cohort study reported a statistically non-significant inverse association between nut intake and ovarian cancer risk.	[31]
	A meta-analysis that included this cohort study and two case-control study reported a statistically non-significant inverse association. *There is insufficient evidence that higher nut intake decreases ovarian cancer risk, and further studies are warranted.*	[10]
Pancreas	One prospective cohort study found a statistically significant inverse association between nut intake and pancreatic cancer risk. *There is insufficient evidence that higher nut intake decreases pancreatic cancer risk, and further studies are warranted.*	[34]

(*Continued*)

Table 9.5 (Continued) Summary of Evidence for Associations between Nut Consumption and Cancer

Cancer Type	*Summary of Evidence*	*References*
Prostate	Two prospective cohort studies reported a statistically non-significant inverse association between nut intake and prostate cancer risk.	[35,36]
	A meta-analysis of four case-control studies reported a statistically non-significant inverse association.	[10]
	Mechanistic evidence from animal models supports a potential prostate cancer protective role of higher nut intake.	[50–52]
	There is limited suggestive evidence that higher nut consumption decreases risk of prostate cancer, but further prospective studies are warranted with specific attention to subtypes of aggressive prostate cancer.	
Stomach	One prospective cohort study reported a statistically significant inverse association between nut intake and gastric non-cardia adenocarcinoma risk.	[28]
	In the same study reported a statistically non-significant inverse association with gastric cardia adenocarcinoma.	[28]
	A meta-analysis of two case-control studies reported null effect results.	[10]
	There is insufficient evidence that higher nut intake decreases stomach cancer risk, and further studies are warranted.	
Cancer-specific death	Three independent meta-analyses of mostly prospective cohort studies reported a statistically significant inverse association between higher nut intake and total cancer mortality.	[9,62,63]
	In a cohort analysis of the PREDIMED trial, higher nut intake was inversely associated with cancer death.	[64]
	A prospective cohort study reported a null association between higher nut intake and prostate cancer–specific mortality. However, higher nut intake was significantly inversely associated with mortality from other causes (than cancer) in those diagnosed with prostate cancer.	[36,58]
	There is probable strong evidence that higher nut consumption is associated with reduced total cancer mortality.	

Abbreviations: ER/PR, oestrogen/progesterone receptor; PREDIMED, Prevención con Dieta Mediterránea.

Among the 11 cancer sites investigated in the literature, inverse associations were most consistent across studies for colorectal cancer and more specifically with colon cancer. This is also in line with strong evidence accrued by the World Cancer Research Fund/American Institute for Cancer Research that foods containing dietary fiber are probably inversely associated with colorectal cancer [7]. Potential mechanisms include suppression of angiogenesis, proliferation, and inflammation, as well as increased apoptosis and favorable induced changes in gut bacteria. Indirectly, a higher consumption of nuts may be linked to a reduced risk of colorectal cancer through reduced weight gain during adult life.

Despite the many studies conducted investigating nut intake and breast cancer, the available evidence is insufficient. *In vivo* studies are coherent with epidemiological studies and with the results of a secondary analysis of a randomized controlled trial. However, associations for these studies, including a meta-analysis of epidemiological studies, did not reach formal statistical significance, and the strengths of the associations were modest, with a ~4% lower risk per serving (~30 g)/day. In contrast, an intake of one serving/day in the large PREDIMED randomized controlled trial was associated with a non-significant 41% lower risk. There is a suggestion that associations may differ by menopausal status and estrogen/progesterone receptor subtypes, with more apparent inverse associations for postmenopausal cancer and for estrogen receptor-negative subtypes. Assuming a true association between nut consumption and breast cancer risk, likely mechanistic pathways are suppression of proliferation, alterations in cell signaling pathways involved in cell differentiation and apoptosis, and a selective inhibition of some cyclooxygenase and lipoxygenase activities. Reduced weight gain in adulthood could indirectly translate into an inverse association between higher nut intake and breast cancer risk.

There is also suggestive, but still limited, evidence for an inverse association between higher nut consumption and prostate cancer incidence. *In vivo* and *in vitro* studies concur with the epidemiological evidence. Mechanistically, declines in plasma levels of IGF-1, resistin, LDL-cholesterol, reduced oxidative stress, and inflammation and increased expression of tumor suppressors have been put forward as potential cancer protective pathways. This is supported by suggestive evidence that higher levels of plasma alpha-tocopherol or plasma selenium concentrations might be inversely associated with prostate cancer risk [7]. Both nutrients are found in high concentrations in some nuts [37].

There is also insufficient evidence for an inverse association between higher nut consumption and risk for cancers of the esophagus, endometrium, lung, ovaries, pancreas, and stomach. Observed associations for these cancer sites were inverse but not significant and, due to the limited number of cases, no conclusions could be drawn. This evidence comes from few epidemiological studies, and further prospective studies, clinical trials, and mechanistic studies are necessary.

In summary, frequent nut consumption may reduce inflammation and oxidative stress, increase apoptosis, and favorably modify gut bacteria, as well as support weight maintenance during adult life. These factors have all been implicated in the development of cancer. Nuts in the diet may also have a role in the tertiary prevention in cancer survivors. More research with improved exposure assessment for specific types of nuts and possibly better biomarkers of nut consumption is warranted to give further support to the promising observations of a putative chemopreventive effect of nuts.

Acknowledgment

The authors are staff members of the International Agency for Research on Cancer/World Health Organization. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice, C., Akinyemiju, T.F., Al Lami, F.H., Alam, T., Alizadeh-Navaei, R., Allen, C., Alsharif, U. et al., Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.*, 4, 1553–1568, 2018.
2. Deen, K.I, Silva, H., Deen, R., and Chandrasinghe, P.C., Colorectal cancer in the young, many questions, few answers. *World J. Gastrointest. Oncol.*, 8, 481–488, 2016.
3. Johnson, R.H., Chien, F.L., and Bleyer, A., Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. *JAMA*, 309, 800–805, 2013.
4. Torre, L.A., Bray, F., Siegel, R.L., Ferlay, J., Lortet-Tieulent, J., and Jemal, A., Global cancer statistics, 2012. *CA Cancer J. Clin.*, 65, 87–108, 2015.
5. WCRF/AICR, *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective, A Summary of the Third Expert Report*, World Cancer Research Fund/American Institute for Cancer Research, Washington, DC, 2018.
6. Colditz, G.A., Wolin, K.Y., and Gehlert, S., Applying what we know to accelerate cancer prevention. *Sci. Transl. Med.*, 4,127rv124, 2012.
7. WCRF/AICR, *Diet*, *Nutrition*, *Physical Activity and Cancer*: *A Global Perspective*, *A Summary of the Third Expert Report*, *Continuous Update Project Expert Report 2018*, *Recommendations and Public Health and Policy Implications*, World Cancer Research Fund/American Institute for Cancer Research, Washington, DC, 2018.
8. Zitvogel, L., Pietrocola, F., and Kroemer, G., Nutrition, inflammation and cancer. *Nat. Immunol.*, 18, 843–850, 2017.
9. Aune, D., Keum, N., Giovannucci, E., Fadnes, L.T., Boffetta, P., Greenwood, D.C., Tonstad, S. et al., Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review and dose-response meta-analysis of prospective studies. *BMC Med.*, 14, 207, 2016.
10. Wu, L., Wang, Z., Zhu, J.J., Murad, A.L., Prokop, L.J., and Murad, M.H., Nut consumption and risk of cancer and type 2 diabetes: A systematic review and meta-analysis. *Nutr. Rev.*, 73, 409–425, 2015.
11. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., and Jemal, A., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.*, 68 394–424, 2018.
12. Mahabir, S., Willett, W.C., Friedenreich, C.M., Lai, G.Y., Boushey, C.J., Matthews, C.E., Sinha, R. et al., Research strategies for nutritional and physical activity epidemiology and cancer prevention. *Cancer Epidemiol. Biomark. Prev.*, 27, 233–244, 2018.

13. Freisling, H., Noh, H., Slimani, N., Chajes, V., May, A.M., Peeters, P.H., Weiderpass, E. et al., Nut intake and 5-year changes in body weight and obesity risk in adults: Results from the EPIC-PANACEA study. *Eur. J. Nutr.*, 57, 2399–2408, 2018.
14. Aleksandrova, K., Pischon, T., Buijsse, B., May, A.M., Peeters, P.H., Bueno-de-Mesquita, H.B., Jenab, M. et al., Adult weight change and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Eur. J. Cancer*, 49, 3526–3536, 2013.
15. Schulz, M.D., Atay, C., Heringer, J., Romrig, F.K., Schwitalla, S., Aydin, B., Ziegler, P.K. et al., High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature*, 514, 508–512, 2014.
16. Sonestedt, E., Borgquist, S., Ericson, U., Gullberg, B., Landberg, G., Olsson, H., and Wirfalt, E., Plant foods and oestrogen receptor alpha- and beta-defined breast cancer: Observations from the Malmo Diet and Cancer cohort. *Carcinogenesis*, 29, 2203–2209, 2008.
17. Farvid, M.S., Cho, E., Chen, W.Y., Eliassen, A.H., and Willett, W.C., Dietary protein sources in early adulthood and breast cancer incidence: Prospective cohort study. *BMJ*, 348, g3437, 2014.
18. Farvid, M.S., Cho, E., Chen, W.Y., Eliassen, A.H., and Willett, W.C., Adolescent meat intake and breast cancer risk. *Int. J. Cancer*, 136, 1909–1920, 2015.
19. van den Brandt, P.A., and Nieuwenhuis, L., Tree nut, peanut, and peanut butter intake and risk of postmenopausal breast cancer: The Netherlands Cohort Study. *Cancer Causes Control*., 29, 63–75, 2018.
20. Su, X.F., Tamimi, R.M., Collins, L.C., Baer, H.J., Cho, E.Y., Sampson, L., Willett, W.C. et al., Intake of fiber and nuts during adolescence and incidence of proliferative benign breast disease. *Cancer Causes Control*, 21, 1033–1046, 2010.
21. Berkey, C.S., Willett, W.C., Tamimi, R.M., Rosner, B., Frazier, A.L., and Colditz, G.A., Vegetable protein and vegetable fat intakes in pre-adolescent and adolescent girls, and risk for benign breast disease in young women. *Breast Cancer Res. Treat.*, 141, 299–306, 2013.
22. Liu, Y., Colditz, G.A., Cotterchio, M., Boucher, B.A., and Kreiger, N., Adolescent dietary fiber, vegetable fat, vegetable protein, and nut intakes and breast cancer risk. *Breast Cancer Res. Treat.*, 145, 461–470, 2014.
23. Singh, P.N., and Fraser, G.E., Dietary risk factors for colon cancer in a low-risk population. *Am. J. Epidemiol.*, 148, 761–774, 1998.
24. Jenab, M., Ferrari, P., Slimani, N., Norat, T., Casagrande, C., Overad, K., Olsen, A. et al., Association of nut and seed intake with colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol. Biomark. Prev.*, 13,1595–1603, 2004.
25. Yeh, C.C., You, S.L., Chen, C.J., and Sung, F.C., Peanut consumption and reduced risk of colorectal cancer in women: A prospective study in Taiwan. *World J. Gastroentero.*, 12, 222–227, 2016.
26. Yang, M., Hu, F.B., Giovannucci, E.L., Stampfer, M.J., Willett, W.C., Fuchs, C.S., Wu, K. et al., Nut consumption and risk of colorectal cancer in women. *Eur. J. Clin. Nutr.*, 70, 333–337, 2016.
27. Lee, J., Shin, A., Oh, J.H., and Kim, J., The relationship between nut intake and risk of colorectal cancer: A case control study. *Nutr. J.*, 17, 37, 2018.
28. Hashemian, M., Murphy, G., Etemadi, A., Dawsey, S.M., Liao, L.M., and Abnet, C.C., Nut and peanut butter consumption and the risk of esophageal and gastric cancer subtypes. *Am. J. Clin. Nutr.*, 106, 858–864, 2017.
29. Zhao, Y., Zhao, L., Hu, Z., Wu, J., Li, J., Qu, C., He, Y. et al., Peanut consumption associated with a reduced risk of esophageal squamous cell carcinoma: A case-control study in a high-risk area in China. *Thoracic Cancer*, 9, 30–36, 2018.

30. Lee, J.T., Lai, G.Y., Liao, L.M., Subar, A.F., Bertazzi, P.A., Pesatori, A.C., Freedman, N.D. et al., Nut consumption and lung cancer risk: Results from two large observational studies. *Cancer Epidemiol. Biomark. Prev.*, 26, 826–836, 2017.
31. Hedelin, M., Lof, M., Andersson, T.M., Adlercreutz, H., and Weiderpass, E., Dietary phytoestrogens and the risk of ovarian cancer in the women's lifestyle and health cohort study. *Cancer Epidemiol. Biomark. Prev.*, 20, 308–317, 2011.
32. Thompson, C.A., Habermann, T.M., Wang, A.H., Vierkant, R.A., Folsom, A.R., Ross, J.A., and Cerhan, J.R., Antioxidant intake from fruits, vegetables and other sources and risk of non-Hodgkin's lymphoma: The Iowa Women's Health Study. *Int. J. Cancer*, 126, 992–1003, 2010.
33. Saberi Hosnijeh, F., Peeters, P., Romieu, I., Kelly, R., Riboli, E., Olsen, A., Tjonneland, A. et al., Dietary intakes and risk of lymphoid and myeloid leukemia in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Nutr. Cancer*, 66, 14–28, 2014.
34. Bao, Y., Hu, F.B., Giovannucci, E.L., Wolpin, B.M., Stampfer, M.J., Willett, W.C., and Fuchs, C.S., Nut consumption and risk of pancreatic cancer in women. *Br. J. Cancer*, 109, 2911–2916, 2013.
35. Mills, P.K., Beeson, W.L., Phillips, R.L., and Fraser, G.E., Cohort study of diet, lifestyle, and prostate cancer in Adventist men. *Cancer*, 64, 598–604, 1989.
36. Wang, W.K., Yang, M., Kenfield, S.A., Hu, F.B., Stampfer, M.J., Willett, W.C., Fuchs, C.S. et al., Nut consumption and prostate cancer risk and mortality. *Br. J. Cancer*, 115, 371–374, 2016.
37. Falasca, M., Casari, I., and Maffucci, T., Cancer chemoprevention with nuts. *J. Natl. Cancer Inst.*, 106, dju238, 2014
38. Gupta, S.C., Kim, J.H., Prasad, S., and Aggarwal, B.B., Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. *Cancer Metastasis Rev.*, 29, 405–434, 2010.
39. Garcia, C.P., Lamarque, A.L., Comba, A., Berra, M.A., Silva, R.A., Labuckas, D.O., Das, U.N. et al., Synergistic anti-tumor effects of melatonin and PUFAs from walnuts in a murine mammary adenocarcinoma model. *Nutrition*, 31, 570–577, 2015.
40. Hardman, W.E., and Ion, G., Suppression of implanted MDA-MB 231 human breast cancer growth in nude mice by dietary walnut. *Nutr. Cancer*, 60, 666–674, 2008.
41. Hardman, W.E., Ion, G., Akinsete, J.A., and Witte, T.R., Dietary walnut suppressed mammary gland tumorigenesis in the C(3)1 TAg mouse. *Nutr. Cancer*, 63, 960–970, 2011.
42. Chen, H.S., Bai, M.H., Zhang, T., Li, G.D., and Liu, M., Ellagic acid induces cell cycle arrest and apoptosis through TGF-beta/Smad3 signaling pathway in human breast cancer MCF-7 cells. *Int. J. Oncol.*, 46, 1730–1738, 2015.
43. Nagel, J.M., Brinkoetter, M., Magkos, F., Liu, X., Chamberland, J.P., Shah, S., Zhou, J.R. et al., Dietary walnuts inhibit colorectal cancer growth in mice by suppressing angiogenesis. *Nutrition*, 28, 67–75, 2012.
44. Nakanishi, M., Chen, Y.F., Qendro, V., Miyamoto, S., Weinstock, E., Weinstock, G.M., and Rosenberg, D.W., Effects of walnut consumption on colon carcinogenesis and microbial community structure. *Cancer Prev. Res.*, 9, 692–703, 2016.
45. Tsoukas, M.A., Ko, B.J., Witte, T.R., Dincer, F., Hardman, W.E., and Mantzoros, C.S., Dietary walnut suppression of colorectal cancer in mice: Mediation by miRNA patterns and fatty acid incorporation. *J. Nutr. Biochem.*, 26, 776–783, 2015.

46. Guan, F., Tabrizian, T., Novaj, A., Nakanishi, M., Rosenberg, D.W., and Huffman, D.M., Dietary walnuts protect against obesity-driven intestinal stem cell decline and tumorigenesis. *Front. Nutr.*, 5, 37, 2018.
47. Koh, S.J., Choi, Y.I., Kim, Y., Kim, Y.S., Choi, S.W., Kim, J.W., Kim, B.G. et al., Walnut phenolic extract inhibits nuclear factor kappaB signaling in intestinal epithelial cells, and ameliorates experimental colitis and colitis-associated colon cancer in mice. *Eur. J. Nutr.*, 58, 1603–1613, 2019.
48. Choi, J., Shin, P.K., Kim, Y., Hong, C.P., and Choi, S.W., Metabolic influence of walnut phenolic extract on mitochondria in a colon cancer stem cell model. *Eur. J. Nutr.*, 58, 1635–1645, 2019.
49. Davis, P.A., and Iwahashi, C.K., Whole almonds and almond fractions reduce aberrant crypt foci in a rat model of colon carcinogenesis. *Cancer Letters*, 165, 27–33, 2001.
50. Davis, P.A., Vasu, V.T., Gohil, K., Kim, H., Khan, I.H., Cross, C.E., and Yokoyama, W., A high-fat diet containing whole walnuts (*Juglans regia*) reduces tumour size and growth along with plasma insulin-like growth factor 1 in the transgenic adenocarcinoma of the mouse prostate model. *Br. J. Nutr.*, 108, 1764–1772, 2012.
51. Kim, H., Yokoyama, W., and Davis, P.A., TRAMP prostate tumor growth is slowed by walnut diets through altered IGF-1 levels, energy pathways, and cholesterol metabolism. *J. Med. Food.*, 17, 1281–1286, 2014.
52. Reiter, R.J., Tan, D.X., Manchester, L.C., Korkmaz, A., Fuentes-Broto, L., Hardman, W.E., Rosales-Corral, S.A. et al., A walnut-enriched diet reduces the growth of LNCaP human prostate cancer xenografts in nude mice. *Cancer Invest.*, 31, 365–373, 2013.
53. Estruch, R., Ros, E., Salas-Salvado, J., Covas, M.I., Corella, D., Aros, F., Gomez-Gracia, E. et al., Primary prevention of cardiovascular disease with a Mediterranean diet. *N. Engl. J. Med.*, 368, 1279–1290, 2013.
54. Toledo, E., Salas-Salvado, J., Donat-Vargas, C., Buil-Cosiales, P., Estruch, R., Ros, E., Corella, D. et al., Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: A Randomized Clinical Trial. *JAMA Intern. Med.*, 175, 1752–1760, 2015.
55. Hu, Y., McIntosh, G.H., Le Leu, R.K., Somashekar, R., Meng, X.Q., Gopalsamy, G., Bambaca, L. et al., Supplementation with Brazil nuts and green tea extract regulates targeted biomarkers related to colorectal cancer risk in humans. *Br. J. Nutr.*, 116, 1901–1911, 2016.
56. Hughes, D.J., Fedirko, V., Jenab, M., Schomburg, L., Meplan, C., Freisling, H., Bueno-de-Mesquita, H.B. et al., Selenium status is associated with colorectal cancer risk in the European prospective investigation of cancer and nutrition cohort. *Int. J. Cancer*, 136, 1149–1161, 2015.
57. Simon, J.A., Tanzman, J.S., and Sabate, J., Lack of effect of walnuts on serum levels of prostate specific antigen: A brief report. *J. Am. Coll. Nutr.*, 26, 317–320, 2007.
58. Spaccarotella, K.J., Kris-Etherton, P.M., Stone, W.L., Bagshaw, D.M., Fishell, V.K., West, S.G., Lawrence, F.R. et al., The effect of walnut intake on factors related to prostate and vascular health in older men. *Nutr. J.*, 7, 13, 2008.
59. Jia, X.D., Li, N., Zhang, W.Z., Zhang, X.P., Lapsley, K., Huang, G.W., Blumberg, J. et al., A pilot study on the effects of almond consumption on DNA damage and oxidative stress in smokers. *Nutr. Cancer*, 54, 179–183, 2006.
60. Wu, J., Zeng, R., Huang, J., Li, X., Zhang, J., Ho, J.C., and Zheng, Y., Dietary protein sources and incidence of breast cancer: A Dose-Response Meta-Analysis of Prospective Studies. *Nutrients*, 8, 730, 2016.

61. Schwingshackl, L., Schwedhelm, C., Hoffmann, G., Knuppel, S., Laure Preterre, A., Iqbal, K., Bechthold, A. et al., Food groups and risk of colorectal cancer. *Int. J. Cancer*, 142, 1748–1758, 2018.
62. Grosso, G., Yang, J., Marventano, S., Micek, A., Galvano, F., and Kales, S.N., Nut consumption on all-cause, cardiovascular, and cancer mortality risk: A systematic review and meta-analysis of epidemiologic studies. *Am. J. Clin. Nutr.*, 101, 783–793, 2015.
63. Chen, G.C., Zhang, R., Martinez-Gonzalez, M.A., Zhang, Z.L., Bonaccio, M., van Dam, R.M., and Qin, L.Q., Nut consumption in relation to all-cause and cause-specific mortality: A meta-analysis 18 prospective studies. *Food Funct.*, 8, 3893–3905, 2017.
64. Guasch-Ferre, M., Bullo, M., Martinez-Gonzalez, M.A., Ros, E., Corella, D., Estruch, R., Fito, M. et al., Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. *BMC Med.*, 11, 164, 2013.

Chapter 10

Nut Consumption and All-Cause and Cause-Specific Mortality and Longevity

A Review of the Evidence

Dagfinn Aune

10.1 Introduction 248
10.2 Nut Consumption and All-Cause Mortality and Longevity 248
10.3 Nut Consumption and Cause-Specific Mortality 252
10.3.1 CVD Mortality 252
10.3.1.1 CHD Mortality 252
10.3.1.2 Stroke Mortality 253
10.3.1.3 Potential Mechanisms for a Reduced CVD Mortality with Nuts 253
10.3.2 Cancer Mortality 254
10.3.3 Mortality from Other Causes (Neurodegenerative, Respiratory, Infections, Diabetes, and Kidney Disease) 254
10.3.4 Mortality in Patient Populations (Type-2 Diabetes, Heart Failure, and Cancer) 255
10.4 Conclusion 256
Acknowledgment 257
References 257

10.1 Introduction

Tree nuts are botanically defined as a dry fruit containing one seed within the ovary wall that becomes hard at maturity, and they include walnuts, almonds, hazelnuts, cashews, pistachios, and pecans [1]. Brazil nuts are botanically classified as seeds, while peanuts are botanically classified as legumes; however, all of these are referred to as nuts because of a similar nutrient content and culinary use. Nuts have a high content of protein, mono- and poly-unsaturated fatty acids (MUFA, PUFA), fiber, and several vitamins (vitamin E, riboflavin, and niacin) and minerals (magnesium, potassium, and copper) [2]. Nuts also have a high content of antioxidants, with walnuts, pecans, and pistachios being particularly rich [3]. The beneficial nutrient profile of nuts may reduce blood concentrations of low-density lipoprotein (LDL)-cholesterol and triacylglycerols (TAG) and, therefore, contribute to reduce the risk of coronary heart disease (CHD), a finding that has been frequently observed in epidemiological studies [4]. Detailed information about nut constituents, bioactives, and antioxidant activity are presented in Chapter 2 of this book. Other bioactive compounds found in nuts are the phenolic compounds, including ellagic acid, anacardic acid, genistein, resveratrol, and inositol phosphates, all of which have antioxidant properties and may contribute to reducing cancer risk by inducing cell cycle arrest and apoptosis, and inhibiting cell proliferation, migration, invasion, and angiogenesis [5]. However, to date, the epidemiological evidence regarding nut consumption and cancer risk has been limited.

Although intake of nuts, in general, is quite low compared to other food groups, there is considerable variation in the intake of nuts between countries and regions worldwide, and there has been a trend of increasing consumption globally from a mean intake of 6.6 g/day in 1990 to 8.9 g/day in 2010 [6]. Nut intake ranged from 0.3 g/day in southern sub-Saharan Africa in 2010 to 16.3 g/day in west sub-Saharan Africa and 32.6 g/day in Southeast Asia, and from 3–3.5 g/day in Central and Western Europe to 11.2 g/day in Eastern Europe and 5.2 g/day in Northern America [6]. There is also some variation in nut intake within regions; for example, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a European multi-center cohort study including 23 centers across 10 countries, the mean intake of nuts was 4 g/day across countries ranging from 2.04 g/day in Sweden and the United Kingdom to 8.42 g/day in the Netherlands [7].

This chapter summarizes the evidence relating nut consumption to risk of all-cause and cause-specific mortality and to longevity, with a focus on data from individual prospective cohort studies as well as large-scale systematic reviews and meta-analyses. In addition, further studies which have been published since these meta-analyses were published are reviewed.

10.2 Nut Consumption and All-Cause Mortality and Longevity

The association between nut consumption and all-cause mortality has been investigated in a large number of studies, and findings have been consistent regarding the direction of the association. All 15 studies (16 risk estimates) on nut consumption and all-cause mortality [8–22] reported relative risks (RRs) below one with higher nut consumption, and 11 of these risk estimates were statistically significant

[10–14,16–18,20,22]. In a meta-analysis of these studies including 85,870 deaths and 819,448 participants, the summary RR was 0.78 (95% confidence interval [CI]: 0.72–0.84, I^2 = 66%, n = 16) per 28 g/day (Figure 10.1a) [23]. There was evidence of a nonlinear association, $P_{\text{nonlinearity}} < 0.0001$, with no further reductions in mortality with an intake above 15–20 g/day (Figure 10.1b) [23]. The summary RRs from the nonlinear dose–response analysis were 0.89 (95% CI: 0.87–0.91), 0.84 (95% CI: 0.81–0.87), 0.82 (95% CI: 0.79–0.85), 0.82 (95% CI: 0.80–0.84), 0.84 (95% CI: 0.82–0.85), and 0.85 (95% CI: 0.83–0.86) for an intake of 5, 10, 15, 20, 25, and 28 g/day respectively, compared to nonconsumers (Table 10.1) [23]. Both consumption of tree nuts and peanuts were associated with reduced all-cause mortality, with summary RRs = 0.82 (95% CI: 0.75–0.90, I^2 = 70%, n = 4) and 0.77 (95% CI: 0.69–0.86, I^2 = 64%, n = 5) per 10 g/day, respectively. However, there was no association between peanut butter and mortality, with summary RR = 0.94 (95% CI: 0.86-1.02, I^2 = 0%, n = 2) [23]. The inverse association between total nut consumption and mortality was observed in men and women, in European and North American studies, in studies with large and small numbers of deaths, in studies of high and medium study quality, and when stratified by whether the studies adjusted or not for a wide range of potential confounders, including age, education, family history of CHD, body mass index (BMI), smoking, alcohol, physical activity, hypertension, hypercholesterolemia, intake of red and/or processed meat, fish, fruits and vegetables, dairy, and energy intake, among others [23]. The association was slightly stronger among studies with a short follow-up compared to studies with a long follow-up, and this might be explained by regression dilution bias, as few studies had repeated measurements of nut consumption.

In contrast to these results are the findings from the Prevención con Dieta Mediterránea (PREDIMED) trial, a parallel-group, multicenter, randomized trial of a Mediterranean diet supplemented either with extra-virgin olive oil or with nuts, as compared with a control group who were advised to eat a low-fat diet [24]. Although the study did find a 28%–31% reduction in risk of the primary endpoint (a composite of myocardial infarction, stroke, and death from cardiovascular causes) in both intervention groups, the hazard ratio (HR) was 1.12 (95% CI: 0.86–1.47) for all-cause mortality in the Mediterranean diet with nuts group compared to the control group and 0.90 (95% CI: 0.69–1.18) in the Mediterranean diet plus olive oil group compared to the control group [24]. The reasons(s) for these inconsistencies are unclear but might include differences in the exposure definition – the PREDIMED study investigated a Mediterranean diet supplemented with nuts or olive oil, while the observational studies have analyzed only nut consumption; differences in the length of follow-up – for example, many of the observational studies had a follow-up duration of between 10 and 30 years [23], while the PREDIMED study only had a median follow-up of 4.8 years; limited statistical power (the sample size of PREDIMED was calculated for the primary endpoint but not for other secondary endpoints), with 87 cardiovascular disease (CVD) deaths and 348 all-cause deaths compared to 18,655 CVD cases and 85,870 deaths in the meta-analysis [23]; or simply chance variation.

Few studies have investigated differences in longevity in relation to nut consumption. Fraser and Shavlik [25] found that among participants with covariates at medium risk eating nuts ≥ 5 times/week *versus* < once/week was associated with a 2.74 (95% CI: 1.60–3.88) year longer life expectancy among men, and a 1.87 (95% CI: 0.72–3.02) year longer life expectancy among women. Among participants with covariates at high risk, the respective results showed a 2.87 (95% CI: 1.64–4.11) year longer life expectancy among men and a 1.18 (95% CI: 0.06–2.29) year longer life

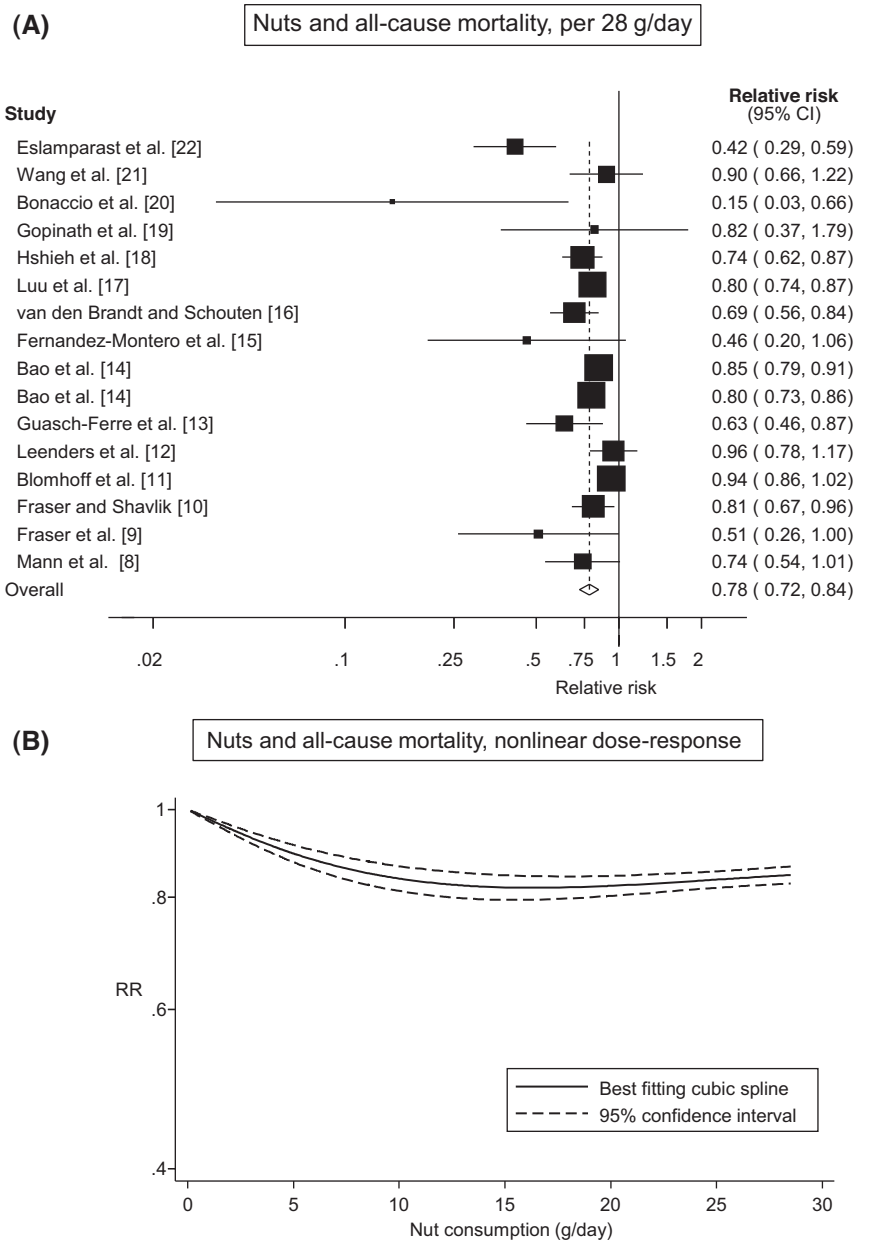


Figure 10.1 Nut consumption and all-cause mortality, linear (A) and nonlinear (B) dose–response analyses. (Adapted from Aune, D. et al., *BMC Med.*, 14, 207, 2016, Open access journal.)

Table 10.1 Relative Risks and 95% Confidence Intervals from Nonlinear Dose–Response Analyses of Nut Consumption and Various Disease Mortalities

	Amount (g/day)								
Outcomes	*0*	*5*	*10*	*15*	*20*	*25*	*28*	$P_{nonlinearity}$	*References*
All-cause mortality	1.00	0.89 (0.87–0.91)	0.84 (0.81–0.87)	0.82 (0.79–0.85)	0.82 (0.80–0.84)	0.84 (0.82–0.85)	0.85 (0.83–0.86)	< 0.0001	[8–20,22]
CVD mortality	1.00	0.88 (0.87–0.89)	0.82 (0.80–0.84)	0.80 (0.79–0.82)	0.81 (0.80–0.83)	0.84 (0.82–0.86)	0.85 (0.83–0.88)	< 0.0001	[11,13,14,16–19,22]
CHD mortality	1.00	0.88 (0.86–0.90)	0.80 (0.78–0.83)	0.77 (0.74–0.79)	0.75 (0.73–0.78)	0.74 (0.71–0.77)	0.74 (0.71–0.78)	< 0.0001	[8,11,14,16–19,26]
Stroke mortality	1.00	0.91 (0.85–0.96)	0.87 (0.80–0.95)	0.88 (0.81–0.95)	0.91 (0.85–0.98)	0.95 (0.88–1.03)	–	0.006	[14,16–19,29]
Total cancer mortality	1.00	0.93 (0.91–0.96)	0.90 (0.86–0.94)	0.88 (0.85–0.92)	0.88 (0.85–0.91)	0.89 (0.85–0.92)	–	0.003	[13,14,16–18,22]
Respiratory disease mortality	1.00	0.78 (0.69–0.90)	0.72 (0.63–0.82)	0.67 (0.56–0.80)	0.63 (0.49–0.81)	–	–	0.10	[14,16]
Diabetes mortality	1.00	0.80 (0.69–0.93)	0.72 (0.60–0.86)	0.71 (0.62–0.82)	0.74 (0.63–0.86)	0.76 (0.60–0.97)	–	0.07	[14,16,17]
NDD mortality	1.00	0.99 (0.93–1.06)	0.82 (0.75–0.90)	0.67 (0.55–0.80)	0.55 (0.42–0.73)	–	–	0.009	[14,16]

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; NDD, neurodegenerative disease.

expectancy among women [25]. The combination of different health factors including a vegetarian diet, high exercise, high nut consumption, medium tertile of BMI, never smoking, and ever use of hormone replacement therapy (among women only), compared with a nonvegetarian diet, low-exercise, low nut consumption, highest tertile of BMI, past smoking, and never use of hormone replacement therapy, was associated with a difference in life expectancy of 10 years among men and women [25].

10.3 Nut Consumption and Cause-Specific Mortality

10.3.1 CVD Mortality

All the cohort studies that have assessed the association between nut intake and overall CVD mortality have shown inverse associations [11,13,14,16–19,21,22]. These findings are most likely driven to a large degree by the inverse association with CHD mortality, given the less clear association between nut consumption and risk of stroke mortality. In a meta-analysis of nine cohort studies on nut consumption and CVD mortality, the summary RR for high *versus* low nut intake was 0.76 (95% CI: 0.67–0.86, I^2=65%, $P_{\text{heterogeneity}}$ = 0.004) per 28 g/day [23]. Some evidence of nonlinearity was observed with no further reduction in risk with intakes above 15 g/day (Table 10.1) [23]. In the PREDIMED study, there was no association between the consumption of a Mediterranean diet combined with nut consumption and CVD mortality (HR = 1.02, 95% CI: 0.63–1.67), although a suggestive inverse association was observed for the Mediterranean diet and olive oil group (HR = 0.62, 95% CI: 0.36–1.06) [24]. The potential reasons for these inconsistencies have been discussed under the section on all-cause mortality.

10.3.1.1 CHD Mortality

The Adventist Health Study (AHS) first reported on the association between nut consumption and the risk of CHD mortality in 1992 [26]. The HR for ≥ 5 servings/week of nuts *versus* < 1 serving/week was 0.52 (95% CI: 0.36–0.76) for fatal myocardial infarction, and 0.59 (95 %CI: 0.45–0.78) for coronary deaths [26]. Further studies followed up on these findings in subsequent years, including the Oxford Vegetarian Study (OVS) [8], the Nurses' Health Study (NHS) [27], and the Physicians' Health Study (PHS) [28]. The OVS found no association between more frequent nut intake and ischemic heart disease deaths, reporting a HR of 0.87 (95% CI: 0.45–1.68) for ≥ 5 servings of nuts per week *versus* < 1 serving/week, whereas the NHS observed a nonsignificant inverse association with fatal CHD (HR = 0.60, 95% CI: 0.33–1.10) [27]. In the PHS, an inverse association was observed between regular nut intake and risk of CHD death (HR = 0.70, 95% CI: 0.50–0.98 for ≥ 2 servings/week *versus* < 1 serving/month), and a particularly strong inverse association was observed for sudden cardiac death (HR = 0.53, 95% CI: 0.30–0.92) but not for nonsudden CHD death (HR = 0.84, 95% CI: 0.55-1.28) [28]. Most studies that subsequently have been published showed inverse associations between higher nut intake and CHD mortality [11,14,16,17,19–21], although in one study the association was not statistically significant [18]. Several meta-analyses have also been published in relation to the association between nut consumption and CHD mortality. The most recent meta-analysis found a summary RR of CHD mortality of 0.69 (95% CI: 0.63–0.75, I^2 = 0%,

n = 9) per 28 g/day of total nut intake in the linear dose–response analysis [23]. Notably, there was a nonlinear inverse association between nut intake and CHD mortality, with little benefit beyond an intake of 20–25 g/day (Table 10.1) [23]; however, the high-end of nut intake across studies was 28 g/day (one serving per day), and thus it is difficult to say whether the risk is further reduced with intakes of 2–3 servings per day based on current data.

10.3.1.2 Stroke Mortality

Data regarding nut consumption and the risk of stroke mortality has rather consistently shown no significant association [16,17,19–21,29,30]. In a meta-analysis of seven cohort studies on nut intake and stroke mortality, there was no association in the linear dose–response analysis (summary RR = 0.95 [95% CI: 0.79–1.15, I^2 = 0%, $P_{\text{heterogeneity}}$ = 0.64]) per 28 g/day. However, in the nonlinear dose–response analysis, a slight U-shaped association was observed with a reduced risk at 10–15 g/day but no association at an intake of 25 g/day (Table 10.1) [23].

10.3.1.3 Potential Mechanisms for a Reduced CVD Mortality with Nuts

With regard to the mechanisms that may explain a beneficial effect of nut consumption on risk of CHD mortality, it has been shown in randomized trials that a high nut intake reduces total cholesterol, LDL-cholesterol, and LDL to high-density lipoprotein (HDL) cholesterol ratio, as well as TAG in a dose–response manner [4]. Another more recent meta-analysis of randomized trials also found that nut consumption reduced total cholesterol, LDL- cholesterol, apolipoprotein B (apo B), and TAG [31]; however, the dose–response analysis suggested that there was little or no reduction in total and LDL-cholesterol with nut intakes up to 20–30 g/day, and the lipid-lowering effects were more apparent with very high intakes of 60–100 g/day [31], which is slightly in contrast to the findings of a meta-analysis that found no or little further benefit in reducing risk of mortality from CVD and all-causes with an intake beyond 15–20 g/day [23]. However, the top range of intake across studies was 28 g/day (one serving per day) in this meta-analysis and, with the current epidemiological data, it is not possible to say whether intakes beyond one serving per day can provide further reductions in risk. Given the limited number of those who consume very high amounts of nuts in most populations, very large studies would probably be needed to clarify this question. While some nuts (such as Brazil nuts, heart nuts, pine nuts, and walnuts) have a high content of PUFAs, which are known to have beneficial effects on serum cholesterol, the rest are rich in MUFA (such as almonds, cashews, hazelnuts, macadamias, pecans, pistachios, and peanuts), which have been shown to have a neutral or mild hypocholesterolemic effect [32]. One meta-analysis also found that diets high in MUFA reduced body-fat mass and had a blood pressure lowering effect [33]. However, it has been shown that the reductions in serum cholesterol observed when people eat more nuts are approximately 25% larger than what can be predicted based on the fatty-acid composition of nuts [34], suggesting that other components of nuts are also likely to contribute to their beneficial effects on CHD mortality. Nuts are also high in fiber, vegetable protein, folate, niacin, vitamin E, potassium, magnesium, and phytochemicals, which may contribute to the reduction in CVD mortality (see Chapter 2 for details). In addition, a recent meta-analysis showed a beneficial effect of nut consumption on endothelial

function [35]. The observation that a high nut intake may reduce the risk of sudden cardiac death [28] suggests that nuts have antiarrhythmic properties and can reduce ventricular arrhythmias. This could be due to the alpha-linolenic acid content of walnuts, which can be elongated and desaturated to longer-chain PUFAs with established antiarrhythmic effects in some experimental models [36,37]. However, further studies are needed to clarify this question.

10.3.2 Cancer Mortality

Most of the studies that have assessed the association between nut consumption and total cancer risk [13,14,16–18,20,22,38] have focused on total cancer mortality [13,14,16–18,20,22], while one study reported on total cancer incidence [38]. Five [13,14,16,17,20] of the eight studies (seven publications) [13,14,16–18,20,22] evaluating nut consumption and total cancer mortality reported significant inverse associations, while the remaining studies reported nonsignificant associations [14,18,22]. In a meta-analysis of eight cohort studies, the summary RR was 0.85 (95% CI: 0.76–0.94, I^2 = 41.8%, n = 8) per 28 g/day of nuts [23] and, although the test for nonlinearity was not significant, there was no further reduction in risk with intakes above 15 g/day (Table 10.1). A significant inverse association was also observed between the intake of tree nuts and total cancer mortality with a summary RR = 0.80 (95% CI: 0.72–0.89, I^2 = 0%, n = 3) per 10 g/day, but not for peanuts, summary RR = 0.92 (95% CI: 0.82–1.03, I^2 = 30%, n = 5) [23]. Nuts contain several constituents including ellagic acid (walnuts), anacardic acid (cashews), genistein (hazelnuts and peanuts), resveratrol (peanuts), inositol (cashews and peanuts), and fiber (all nuts) that could reduce risk and mortality from cancer by inducing cell cycle arrest and apoptosis and inhibiting cell proliferation, migration, invasion, angiogenesis, and metastasis [39–43].

10.3.3 Mortality from Other Causes (Neurodegenerative, Respiratory, Infections, Diabetes, and Kidney Disease)

When nut consumption was analyzed in relation to specific causes of death other than CVD and cancer, there was evidence of inverse associations between nut intake and mortality from respiratory disease, summary RR = 0.48 (95% CI: 0.26–0.89, I^2 = 61%, n = 3), diabetes, summary RR = 0.61 (95% CI: 0.43–0.88, I^2 = 0%, n = 4), and infectious diseases, summary RR = 0.25 (95% CI: 0.07–0.85, I^2 = 54%, n = 2) per 28 g/day, but the associations with mortality from neurodegenerative disease (NDD), summary RR = 0.65 (95% CI: 0.40–1.08, I^2 = 5.9%, n = 3) and kidney disease, 0.27 (95% CI: 0.04–1.91, I^2 = 61%, n = 2) were not significant (Table 10.1) [23]. The summary RR per 10 g/day was 0.79 (95% CI: 0.62–1.01, I^2 = 0%, n = 3) and 0.69 (95% CI: 0.53–0.91, I^2 = 49.8%, n = 3) for the association between tree nuts and peanuts and respiratory disease mortality, respectively, and 0.42 (95% CI: 0.24–0.73, I^2 = 0%, n = 2) for the association between peanut consumption and kidney disease mortality [23]. None of the other associations between specific types of nuts and these mortality outcomes were significant. Although mechanisms are less clear with regard to other causes of death than CVD and cancer, a recent study in mice suggested that dietary fiber feeds the bacteria in the colon, while a lack of dietary fiber would induce bacteria to

break down the mucosa of the intestine as a source of nutrients; this can make the mice more prone to infections [44]. This mechanism might perhaps explain part of the inverse association between nut consumption and infectious disease mortality [23]; however, further epidemiologic studies are needed before the evidence can be considered conclusive in relation to these mortality outcomes, and further mechanistic studies are needed to clarify the underlying mechanisms.

Under the assumption of a causal relationship between nut consumption and reduced mortality, we estimated that approximately 4.4 million premature deaths might have been attributable to a nut intake below 20 g/day in 2013 globally (with the exception of Africa and the Middle East, areas for which we did not have data on nut intake) [23]. This included 1.2 million CHD deaths, 470,000 cancer deaths, 1.1 million respiratory disease deaths, and 140,000 diabetes deaths.

10.3.4 Mortality in Patient Populations (Type-2 Diabetes, Heart Failure, and Cancer)

In the EPIC study, there was an inverse association between consumption of nuts and seeds and all-cause mortality among 6,384 patients with diabetes mellitus; the HR was 0.94 (95% CI: 0.90–0.97) per 1 g/day among diabetes patients and 0.99 (95% CI: 0.98–1.00) among participants without diabetes [45]. In the NHS and the Health Professionals Follow-up Study (HPFS), the HR for patients with diabetes consuming nuts ≥ 5 times per week compared to < 1 serving per month was 0.66 (95% CI: 0.52–0.84) for CVD mortality and 0.69 (95% CI: 0.61–0.77) for all-cause mortality, but there was no association for cancer mortality (HR = 0.84, 95% CI: 0.67–1.06) [46]. When specific types of nuts were examined, the associations were stronger for tree nuts across all outcomes, with HRs of 0.61 (95% CI: 0.49–0.76), 0.73 (95% CI: 0.60–0.90), and 0.67 (95% CI: 0.60–0.74) for CVD, cancer, and all-cause mortality for an intake of ≥ 2 servings per week *versus* < 1 time per month, while the HRs for the same comparisons for peanuts were 0.86 (95% CI: 0.70–1.05), 0.87 (95% CI: 0.70–1.07), and 0.80 (95% CI: 0.72–0.90), respectively [46]. In the Women's Health Initiative, higher nut consumption was associated with lower mortality after diagnosis of heart failure [47] and the HR for the highest *versus* the lowest quartile of nut consumption was 0.86 (95% CI: 0.74–0.96). A recent analysis also suggested that high nut consumption might improve survival among colon cancer patients [48]. The study included 826 stage three colon cancer patients and, during a 6.5 year follow-up, 177 patients died and 199 patients experienced cancer recurrence or developed new primary tumors. Higher nut consumption was associated with improved disease-free survival and overall survival with HRs of 0.58 (95% CI: 0.37–0.92) and 0.43 (95% CI: 0.25–0.74) comparing nut consumption of ≥ 2 times per week *versus* never after adjustment for age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, BMI, physical activity, aspirin use, and glycemic load [48]. The association for recurrence-free survival was not significant: HR = 0.70 (95% CI: 0.42–1.16) for an intake of ≥ 2 times per week *versus* never. There was little evidence of modification of the association by other risk factors including sex, treatment, performance status, number of positive lymph nodes, BMI, physical activity, glycemic load, aspirin use, microsatellite status, and mutations in the KRAS, BRAF, PIK3CA genes, or by cyclooxygenase-2 expression. When stratified by type of nuts, inverse associations were observed for

tree nuts for all three outcomes with HRs of 0.54 (95% CI: 0.34–0.85) for ≥ 1 time per week *versus* never for disease-free survival, 0.56 (95% CI: 0.33–0.94) for recurrence free survival, and 0.47 (95% CI: 0.27–0.82) for overall survival, but the corresponding HRs for peanuts were 0.81 (95% CI: 0.53–1.23), 0.97 (95% CI: 0.61–1.53), and 0.60 (95% CI: 0.37–0.98), respectively [48]. In a secondary analysis using the cumulative average of pre-diagnosis and post-diagnosis nut consumption, the respective HRs for nut intake of ≥ 2 times per week *versus* never were 0.45 (95% CI: 0.33–0.62), 0.46 (95% CI: 0.32–0.64), and 0.43 (95% CI: 0.30–0.61) [48], suggesting a higher reliability of using repeated dietary assessments compared to using a single one. Although an analysis of the HPFS cohort found no association between nut consumption and prostate cancer incidence and mortality, follow-up of the prostate cancer patients after diagnosis showed that there was an inverse association between nut consumption and all-cause mortality and fatal prostate cancer. Comparing an intake of ≥ 5 times/week *versus* < 1 time/month, HRs were 0.66 (95% CI: 0.52–0.83) for all-cause mortality and 0.62 (95% CI: 0.36–1.07) for fatal prostate cancer, suggesting improved overall survival among those prostate cancer patients eating more nuts [49]. Although the current data are very limited with regard to nut consumption and survival among specific cancer groups, they are consistent with the overall evidence on nut consumption and mortality. However, further studies are needed before firm conclusions can be made.

10.4 Conclusion

There is strong evidence showing that high consumption of nuts is associated with reduced risk of mortality from all causes, total CVD, CHD, and total cancer. In addition, there is suggestive evidence that a high consumption of nuts may reduce mortality from respiratory disease, diabetes, and infections. Evidence does not support a clear association between nut consumption and stroke mortality, although a nonlinear U-shaped association cannot be excluded. Limited data is available on nut consumption and risk of mortality from CVD other than CHD and stroke, as well as risk of specific cancers and less common causes of death, and further studies are warranted to clarify these associations. To date, no studies have reported separate results for raw unsalted nuts and fried or roasted and salted nuts, and it would be important to clarify whether there are differences in the health effects of nuts depending on whether they are processed or not. None of the studies published on nut consumption and CVD, cancer, or mortality to date have made any attempts to correct for measurement error, so this is another point for improvement that might be important to consider in future studies. In addition, the high end of the range of nut intake in the current observational studies is one serving per day, a reason why any further studies might want to clarify what the shape of the dose–response relationship is between nut consumption, all-cause, and cause-specific mortality at higher levels of consumption, given that randomized trials suggested improvements in cardiovascular risk factors at higher levels of intake (60–100 g/day) [31]. Recently, metabolomic biomarkers have been identified for several foods, including nuts [50,51], and future studies might provide more definitive answers by incorporating such analyses. Current evidence supports recommendations to increase nut consumption among people without nut allergy and suggests that higher nut consumption reduces the risk of mortality from all causes, total CVD, CHD, and total cancer. If the observed associations between

nut consumption and reduced mortality are causal, increasing nut intake to 15–20 g/day globally in 2013 could have prevented 4.4 million premature deaths [23], signifying a substantial public health impact. This prediction concurs with the recent findings from a comprehensive assessment of mortality due to CVD, obesity, or diabetes attributable to 10 dietary factors in 2012 in the United States, which reported that the second cause of the largest numbers of estimated diet-related cardiometabolic deaths (8.5% of 702,308 deaths) was low nut/seed consumption (the first cause was high dietary sodium) [52].

Acknowledgment

This work was funded by the School of Public Health, Imperial College London and the South-East Regional Health Authority of Norway.

References

1. Sabate, J., Ros, E., and Salas-Salvado, J., Nuts: Nutrition and health outcomes. Preface. *Br. J. Nutr.*, 96(Suppl. 2), S1–S2, 2006.
2. Dreher, M.L., Maher, C.V., and Kearney, P., The traditional and emerging role of nuts in healthful diets. *Nutr. Rev.*, 54, 241–245, 1996.
3. Carlsen, M.H., Halvorsen, B.L., Holte, K., Bohn, S.K., Dragland, S., Sampson, L., Willey, C. et al., The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr. J.*, 9, 3, 2010.
4. Sabate, J., Oda, K., and Ros, E., Nut consumption and blood lipid levels: A pooled analysis of 25 intervention trials. *Arch. Intern. Med.*, 170, 821–827, 2010.
5. Falasca, M., Casari, I., and Maffucci, T., Cancer chemoprevention with nuts. *J. Natl. Cancer Inst.*, 106, dju238, 2014.
6. Micha, R., Khatibzadeh, S., Shi, P., Andrews, K.G., Engell, R.E., and Mozaffarian, D., Global, regional and national consumption of major food groups in 1990 and 2010: A systematic analysis including 266 country-specific nutrition surveys worldwide. *BMJ Open*, 5, e008705, 2015.
7. Jenab, M., Sabate, J., Slimani, N., Ferrari, P., Mazuir, M., Casagrande, C., Deharveng, G. et al., Consumption and portion sizes of tree nuts, peanuts and seeds in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts from 10 European countries. *Br. J. Nutr.*, 96(Suppl. 2), S12–S23, 2006.
8. Mann, J.I., Appleby, P.N., Key, T.J., and Thorogood, M., Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart*, 78, 450–455, 1997.
9. Fraser, G.E., Sumbureru, D., Pribis, P., Neil, R.L., and Frankson, M.A., Association among health habits, risk factors, and all-cause mortality in a black California population. *Epidemiology*, 8, 168–174, 1997.
10. Fraser, G.E., and Shavlik, D.J., Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study. *Arch. Intern. Med.*, 157, 2249–2258, 1997.
11. Blomhoff, R., Carlsen, M.H., Andersen, L.F., and Jacobs, D.R., Jr., Health benefits of nuts: Potential role of antioxidants. *Br. J. Nutr.*, 96(Suppl. 2), S52–S60, 2006.

12. Leenders, M., Sluijs, I., Ros, M.M., Boshuizen, H.C., Siersema, P.D., Ferrari, P., Weikert, C. et al., Fruit and vegetable consumption and mortality: European Prospective Investigation into Cancer and Nutrition. *Am. J. Epidemiol.*, 178, 590–602, 2013.
13. Guasch-Ferre, M., Bullo, M., Martinez-Gonzalez, M.A., Ros, E., Corella, D., Estruch, R., Fito, M. et al., Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. *BMC Med.*, 11, 164, 2013.
14. Bao, Y., Han, J., Hu, F.B., Giovannucci, E.L., Stampfer, M.J., Willett, W.C., and Fuchs, C.S., Association of nut consumption with total and cause-specific mortality. *N. Engl. J. Med.*, 369, 2001–2011, 2013.
15. Fernandez-Montero, A., Bes-Rastrollo, M., Barrio-Lopez, M.T., Fuente-Arrillaga, C.L., Salas-Salvado, J., Moreno-Galarraga, L., and Martinez-Gonzalez, M.A., Nut consumption and 5-y all-cause mortality in a Mediterranean cohort: The SUN project. *Nutrition*, 30, 1022–1027, 2014.
16. van den Brandt, P.A., and Schouten, L.J., Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: A cohort study and meta-analysis. *Int. J. Epidemiol.*, 44, 1038–1049, 2015.
17. Luu, H.N., Blot, W.J., Xiang, Y.B., Cai, H., Hargreaves, M.K., Li, H., Yang, G. et al., Prospective evaluation of the association of nut/peanut consumption with total and cause-specific mortality. *JAMA Intern. Med.*, 175, 755–766, 2015.
18. Hshieh, T.T., Petrone, A.B., Gaziano, J.M., and Djousse L., Nut consumption and risk of mortality in the Physicians' Health Study. *Am. J. Clin. Nutr.*, 101, 407–412, 2015.
19. Gopinath, B., Flood, V.M., Burlutksy, G., and Mitchell, P., Consumption of nuts and risk of total and cause-specific mortality over 15 years. *Nutr. Metab. Cardiovasc. Dis.*, 25, 1125–1131, 2015.
20. Bonaccio, M., Di Castelnuovo, A., De Curtis, A., Costanzo, S., Bracone, F., Persichillo, M., Donati, M.B. et al., Nut consumption is inversely associated with both cancer and total mortality in a Mediterranean population: Prospective results from the Moli-sani study. *Br. J. Nutr.*, 114, 804–811, 2015.
21. Wang, J.B., Fan, J.H., Dawsey, S.M., Sinha, R., Freedman, N.D., Taylor, P.R., Qiao, Y.L. et al., Dietary components and risk of total, cancer and cardiovascular disease mortality in the Linxian Nutrition Intervention Trials cohort in China. *Sci. Rep.*, 6, 22619, 2016.
22. Eslamparast, T., Sharafkhah, M., Poustchi, H., Hashemian, M., Dawsey, S.M., Freedman, N.D., Boffetta, P. et al., Nut consumption and total and cause-specific mortality: Results from the Golestan Cohort Study. *Int. J. Epidemiol.*, 46, 75–85, 2017.
23. Aune, D., Keum, N., Giovannucci, E., Fadnes, L.T., Boffetta, P., Greenwood, D.C., Tonstad, S. et al., Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review and dose-response meta-analysis of prospective studies. *BMC Med.*, 14, 207, 2016.
24. Estruch, R., Ros, E., Salas-Salvado, J., Covas, M.I., Corella, D., Aros, F., Gomez-Gracia, E. et al., Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N. Engl. J. Med.*, 378, e34, 2018.
25. Fraser, G.E., and Shavlik, D.J., Ten years of life: Is it a matter of choice? *Arch. Intern. Med.*, 161, 1645–1652, 2001.
26. Fraser, G.E., Sabate, J., Beeson, W.L., and Strahan, T.M., A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch. Intern. Med.*, 152, 1416–1424, 1992.

27. Hu, F.B., Stampfer, M.J., Manson, J.E., Rimm, E.B., Colditz, G.A., Rosner, B.A., Speizer, F.E. et al., Frequent nut consumption and risk of coronary heart disease in women: Prospective cohort study. *BMJ*, 317, 1341–1345, 1998.
28. Albert, C.M., Gaziano, J.M., Willett, W.C., and Manson, J.E., Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. *Arch. Intern. Med.*, 162, 1382–1387, 2002.
29. Yochum, L.A., Folsom, A.R., and Kushi, L.H., Intake of antioxidant vitamins and risk of death from stroke in postmenopausal women. *Am. J. Clin. Nutr.*, 72, 476–483, 2000.
30. di Giuseppe, R., Fjeld, M.K., Dierkes, J., Theoflylaktopoulou, D., Arregui, M., Boeing, H., Weikert, C. et al., The association between nut consumption and the risk of total and ischemic stroke in a German cohort study. *Eur. J. Clin. Nutr.*, 69, 431–435, 2015.
31. Del Gobbo, L.C., Falk, M.C., Feldman, R., Lewis, K., and Mozaffarian, D., Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: Systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am. J. Clin. Nutr.*, 102, 1347–1356, 2015.
32. Clarke, R., Frost, C., Collins, R., Appleby, P., and Peto, R., Dietary lipids and blood cholesterol: Quantitative meta-analysis of metabolic ward studies. *BMJ*, 314, 112–117, 1997.
33. Schwingshackl, L., Strasser, B., and Hoffmann, G., Effects of monounsaturated fatty acids on cardiovascular risk factors: A systematic review and meta-analysis. *Ann. Nutr. Metab.*, 59, 176–186, 2011.
34. Kris-Etherton, P.M., Yu-Poth, S., Sabate, J., Ratcliffe, H.E., Zhao, G., and Etherton, T.D., Nuts and their bioactive constituents: Effects on serum lipids and other factors that affect disease risk. *Am. J. Clin. Nutr.*, 70(Suppl.), 504S–511S, 1999.
35. Neale, E.P., Tapsell, L.C., Guan, V., and Batterham, M.J., The effect of nut consumption on markers of inflammation and endothelial function: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*, 7, e016863, 2017.
36. Ander, B.P., Hurtado, C., Raposo, C.S., Maddaford, T.G., Deniset, J.F., Hryshko, L.V., Pierce, G.N. et al., Differential sensitivities of the NCX1.1 and NCX1.3 isoforms of the Na+-Ca2+ exchanger to alpha-linolenic acid. *Cardiovasc. Res.*, 73, 395–403, 2007.
37. Billman, G.E., Kang, J.X., and Leaf, A., Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. *Circulation*, 99, 2452–2457, 1999.
38. von Ruesten, A., Feller, S., Bergmann, M.M., and Boeing, H., Diet and risk of chronic diseases: Results from the first 8 years of follow-up in the EPIC-Potsdam study. *Eur. J. Clin. Nutr.*, 67, 412–419, 2013.
39. Comba, A., Maestri, D.M., Berra, M.A., Garcia, C.P., Das, U.N., Eynard, A.R., and Pasqualini, M.E., Effect of omega-3 and omega-9 fatty acid rich oils on lipoxygenases and cyclooxygenases enzymes and on the growth of a mammary adenocarcinoma model. *Lipids Health Dis.*, 9, 112, 2010.
40. Labrecque, L., Lamy, S., Chapus, A., Mihoubi, S., Durocher, Y., Cass, B., Bojanowski, M.W. et al., Combined inhibition of PDGF and VEGF receptors by ellagic acid, a dietary-derived phenolic compound. *Carcinogenesis*, 26, 821–826, 2005.
41. Sung, B., Pandey, M.K., Ahn, K.S., Yi, T., Chaturvedi, M.M., Liu, M., and Aggarwal, B.B., Anacardic acid (6-nonadecyl salicylic acid), an inhibitor of

histone acetyltransferase, suppresses expression of nuclear factor-kappaB-regulated gene products involved in cell survival, proliferation, invasion, and inflammation through inhibition of the inhibitory subunit of nuclear factor-kappaBalpha kinase, leading to potentiation of apoptosis. *Blood*, 111, 4880–4891, 2008.

42. Carvalho, A.L., Annoni, R., Torres, L.H., Durao, A.C., Shimada, A.L., Almeida, F.M., Hebeda, C.B. et al., Anacardic acids from cashew nuts ameliorate lung damage induced by exposure to diesel exhaust particles in mice. *Evid. Based Complement. Alternat. Med.*, 2013, 549879, 2013.
43. Tsoukas, M.A., Ko, B.J., Witte, T.R., Dincer, F., Hardman, W.E., and Mantzoros, C.S., Dietary walnut suppression of colorectal cancer in mice: Mediation by miRNA patterns and fatty acid incorporation. *J. Nutr. Biochem.*, 26, 776–783, 2015.
44. Desai, M.S., Seekatz, A.M., Koropatkin, N.M., Kamada, N., Hickey, C.A., Wolter, M., Pudlo, N.A. et al., A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell*, 167, 1339–1353, 2016.
45. Sluik, D., Boeing, H., Li, K., Kaaks, R., Johnsen, N.F., Tjonneland, A., Arriola, L. et al., Lifestyle factors and mortality risk in individuals with diabetes mellitus: Are the associations different from those in individuals without diabetes? *Diabetologia*, 57, 63–72, 2014.
46. Liu, G., Guasch-Ferre, M., Hu, Y., Li, Y., Hu, F.B., Rimm, E.B., Manson, J.E. et al., Nut consumption in relation to cardiovascular disease incidence and mortality among patients with diabetes mellitus. *Circ. Res.*, 124, 920–929, 2019.
47. Levitan, E.B., Lewis, C.E., Tinker, L.F., Eaton, C.B., Ahmed, A., Manson, J.E., Snetselaar, L.G. et al., Mediterranean and DASH diet scores and mortality in women with heart failure: The Women's Health Initiative. *Circ. Heart Fail.*, 6, 1116–1123, 2013.
48. Fadelu, T., Zhang, S., Niedzwiecki, D., Ye, X., Saltz, L.B., Mayer, R.J., Mowat, R.B. et al., Nut consumption and survival in patients with stage III colon cancer: Results from CALGB 89803 (Alliance). *J. Clin. Oncol.*, JCO2017755413, 2018.
49. Wang, W., Yang, M., Kenfield, S.A., Hu, F.B., Stampfer, M.J., Willett, W.C., Fuchs, C.S. et al., Nut consumption and prostate cancer risk and mortality. *Br. J. Cancer*, 115, 371–374, 2016.
50. Guertin, K.A., Moore, S.C., Sampson, J.N., Huang, W.Y., Xiao, Q., Stolzenberg-Solomon, R.Z., Sinha, R. et al., Metabolomics in nutritional epidemiology: Identifying metabolites associated with diet and quantifying their potential to uncover diet-disease relations in populations. *Am. J. Clin. Nutr.*, 100, 208–217, 2014.
51. Playdon, M.C., Sampson, J.N., Cross, A.J., Sinha, R., Guertin, K.A., Moy, K.A., Rothman, N. et al., Comparing metabolite profiles of habitual diet in serum and urine. *Am. J. Clin. Nutr.*, 104, 776–789, 2016.
52. Micha, R., Peñalvo, J.L., Cudhea, F., Imamura, F., Rehm, C.D., and Mozaffarian, D., Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA*, 317, 912–924, 2017.

Chapter 11

Nuts and Brain Health

Cognition, Depression, and Neurodegenerative Diseases

Emilio Ros and Aleix Sala-Vila

11.1 Introduction 262
11.2 Epidemiological Studies 263
11.2.1 Nut Consumption and Cognition 263
11.2.2 Nut Consumption and Depression 265
11.2.3 Nut Consumption and Neurodegenerative Disease Mortality 266
11.3 Clinical Trials 267
11.3.1 Trials of Nut Consumption with Outcomes on Cognition 267
11.3.2 Trials of Nut Consumption with Outcome on Depression 270
11.4 Experimental Studies Relating Nuts to Brain Function 271
11.4.1 Experimental Studies with Walnuts 271
11.4.2 Experimental Studies with Other Nuts 272
11.5 Neuroprotective Properties of Nut Constituents 273
11.5.1 α-Linolenic Acid (ALA) 273
11.5.2 Polyphenols 275
11.5.3 Other Nut Components 276
11.6 Conclusion 278
References 280

11.1 Introduction

An unwanted consequence of increased lifespan and ensuing population aging in recent decades is a growing number of elderly individuals at risk of neurodegenerative disorders, particularly Alzheimer disease (AD), the most common type of dementia [1]. Brain pathology in AD consists of amyloid deposits, neurofibrillary tangles, and amyloid-rich neuritic plaques, together with neuron loss and gliosis [2]. However, a substantial proportion of patients with dementia in general or AD in particular also have evidence of vascular brain injury, including small artery arteriosclerosis, lacunar infarcts, microinfarcts, and hemorrhages [3]. AD and vascular brain injury share a heterogeneous and multifactorial physiopathology and a slow progression over decades before becoming clinically evident. Given the current lack of effective pharmacological treatments for AD and estimates that prevalence will triple by 2050, medical and public health efforts should focus on primary prevention [4]. Indeed, there is an increasing interest in preventive strategies for cognitive decline, a common harbinger of dementia [5].

Analysis of population-based data suggests that one-third of AD cases worldwide might be attributed to potentially modifiable risk factors [6]. Diet is a typical modifiable environmental factor that has been related to many non-communicable diseases with a link to AD, such as hypertension, cardiovascular disease (CVD), and diabetes [7]. There is increasing scientific evidence that, *via* a direct effect on the brain or by influencing risk factors shared by CVD and neurodegenerative disorders, nutrition may profoundly influence cognition and the risk of dementia and related disorders, including depression [8–10]. On the other hand, oxidative stress and inflammation are believed to play a pivotal role in the initiation and progression of AD and other neurodegenerative diseases [11,12]. It follows that, among nutritional strategies to fight cognitive decline and AD, foods and dietary patterns rich in antioxidants might be best suited. Indeed, there is accumulating evidence from epidemiologic studies that long-term adherence to plant-based dietary patterns, rich in antioxidant foods such as fruits, vegetables, whole grains, legumes, and nuts and often in seafood, is associated with better cognitive outcomes among older adults from diverse populations, as summarized in a recent systematic review of 32 cohort studies and six randomized controlled trials (RCTs) [13]. Of the studies included in that review, the Mediterranean diet (MeDiet) was by far the most investigated, with consistent evidence in support of protection against cognitive decline. Although more limited, research on other healthy plant-based diets such as the Dietary Approach to Stop Hypertension (DASH) diet, the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diet, and the so-called anti-inflammatory diets also showed promising results [13–15]. Neuroimaging studies have also suggested that increased adherence to the MeDiet is associated with greater brain volumes and lesser changes due to brain atrophy [14].

Nuts are an integral part of all plant-based diets; they have an optimal nutrient profile, particularly abundant monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) and polyphenols (see Chapter 2 for details); and their frequent consumption is associated with improved endothelial function and anti-inflammatory effects (see Chapter 4 for details), a consistent reduction in the risk of CVD (see Chapter 6 for details), and a possible beneficial effect on diabetes risk (see Chapter 8 for details). PUFAs and polyphenols are recognized nutrients with

a positive effect on brain metabolism and cognition, in part *via* their anti-inflammatory properties [16]. In addition, given that cardiovascular risk factors and CVD are established links of neurodegeneration, it can be predicted that nut consumption, already well known to benefit vascular function, would also favor cognition and overall brain health [17]. There have been few epidemiological studies and even fewer RCTs examining the effects of nut consumption on cognition [18], while no study has evaluated whether diets rich in nuts influence hard clinical outcomes (e.g., dementia or AD). On the other hand, some large prospective studies have reported data on nut consumption and mortality from neurodegenerative diseases and few have assessed the effect of nuts on depression, an established association of neurodegenerative disorders. In contrast, there have been a somewhat larger number of studies using nuts, particularly walnuts, in experimental models of brain aging and neurodegeneration. The findings of these studies are comprehensively reviewed here.

11.2 Epidemiological Studies

11.2.1 Nut Consumption and Cognition

Only five epidemiological studies have assessed consumption of nuts, exclusive of other food groups, for outcomes on cognitive function [19–23] (Table 11.1). While most studies showed a positive association, the quality of the evidence is low because three of them were cross-sectional and only two were prospective.

In a prospective study of middle-aged adults from the general Dutch population (Doetinchem Cohort Study), investigators assessed cognitive performance at baseline and after follow-up for 5 years in relation to quintiles of consumption of plant foods [19]. Results showed that highest nut intake was associated with better cognitive function at baseline and with lesser cognitive decline at follow-up in models adjusted for age; sex; level of education; total energy intake; intake of other fruits, vegetables, legumes, and juices; and baseline cognitive function. However, the follow-up association with delayed cognitive decline weakened when data were further adjusted for cardiovascular risk factors, suggesting that nut consumption may partly benefit cognition *via* reducing the cardiovascular risk profile.

A cross-sectional study nested within a sub-cohort of the PREvención con DIeta MEDiterránea (PREDIMED), a randomized nutrition intervention trial using supplemented MeDiets for the primary prevention of CVD, assessed the relation of consumption of various foods with cognitive function in 447 older individuals at high cardiovascular risk [20]. Of all the foods considered, only olive oil, coffee, wine, and walnuts (mean consumption 1.10 g/day, range 0–30 g/day), but not total nuts (mean consumption 5.13 g/day, range 0–60 g/day), related to better cognitive function independently of known risk factors for cognitive decline, consumption of other foods, and energy intake. Of note, total urinary polyphenol excretion, an objective biomarker of consumption of polyphenol-rich foods, was directly associated with working memory function. The overall findings of this study suggest that walnuts and other polyphenol-rich foods could counteract age-related cognitive decline.

A prospective study of a sub-cohort of 15,467 older women from the Nurses' Health Study (NHS) specifically assessed total nut intake in relation to cognitive

Table 11.1 Epidemiologic Studies Reporting Associations between Nut Consumption and Cognitive Function

Study Design (Source)	*No. of Study Subjects*	*Age (Years)*	*Subjects' Characteristics*	*Neuro-psychological Tests*	*Nut Dose/Day (Range)*	*Follow-Up, Years*	*Outcome*	*References*
Prospective (Doetinchem cohort)	2613	4–70	Men and women, general population	Tests of memory, information processing, cognitive flexibility – sum of test scores (global cognition)	Quintiles of consumption	5	Higher nut consumption associated with cognitive flexibility and global cognition at baseline and a trend to delayed cognitive decline at follow-up.	[19]
Cross-sectional (PREDIMED study)	447	55–80	Men and women at high cardiovascular risk	Comprehensive battery	Total nuts (0–60) Walnuts (0–30)	na	Walnuts, but not total nuts, associated with better working memory.	[20]
Prospective (Nurses' Health Study)	15467	Mean 74	Women from a selected cohort of nurses	TICS	From never / < 1 / month to ≥ 5 servings/ week	6	Higher long-term total nut intake associated with better average cognitive status for all cognitive outcomes.	[21]
Cross-sectional (NHANES)	5562 and 2975	2 groups: 20–59 ≥ 60	Men and women from the general population	Various cognitive tests	Walnuts with high certainty Walnuts with other nuts	na	Walnut consumption positively associated with cognitive function in the two groups.	[22]
Cross-sectional	894	50–> 80	Men and women from a population cohort	MoCa test	Tertiles of consumption	na	Higher nut consumption associated with delayed memory. Cognitively healthy adults consumed more nuts than those with MCI.	[23]

Abbreviations: MCI, mild cognitive impairment; MoCa, Montreal cognitive assessment (short-term memory recall ability, visuospatial abilities, executive functions, phonemic fluency ability, verbal abstraction ability, attention, concentration and working memory, language, and orientation); na, not applicable; NHANES, National Health and Nutrition Examination Survey; PREDIMED, PREvención con DIeta MEDiterránea; TICS, telephone interview of cognitive status.

function after adjustment for possible confounders [21]. A validated telephone interview for cognitive status evaluating mainly global cognition and verbal memory was administered every 2 years. Total nut intake was divided into five categories of frequency of servings (28 g per serving): never or < 1/month (46.6% of the cohort), 1–3/month (23.2%), 1/week (23.7%), 2–4/week (4.8%), and ≥ 5/week (1.7%). In spite of the low numbers of women consuming relatively high amounts, the results showed that higher long-term total nut consumption was associated with better average status for all cognitive outcomes analyzed. Noticeably, the difference in the global composite score between women consuming at least 5 servings of nuts/week and non-consumers of nuts was equivalent to the mean difference observed between women 2 years apart in age.

In the National Health and Nutrition Examination Survey (NHANES), a representative weighted sample of US adults is periodically assessed. In a round of 5,662 participants 20–90 years of age and in two rounds of those 60 years and older with 5,054 and 2,975 participants, respectively, cognitive tests were administered to random samples and related to consumption of walnuts, exclusive of other nuts, with a cross-sectional design [22]. While only approximately 8% of participants were reported to consume walnuts with high certainty, walnut consumption was associated with cognitive function in all groups. These results, however, must be taken with caution, because only one 24-hour diet recall is administered in NHANES and this can miss many individuals who do not consume nuts on a daily basis. Indeed, the numbers of persons consuming walnuts on the given day of the 24-hour diet recall was quite small, ranging from < 4% to 13% of participants evaluated in the three study groups.

Finally, a cross-sectional study of 894 Chinese adults aged 50 years and older assessed the association of consumption of various foods with cognitive status after adjustment for known risk factors of cognitive deterioration [23]. Concerning nuts, daily consumption was divided into three groups: ≤ 15 g, 15–30 g, and > 30 g, but numbers or percentages per group were not specified. The results showed that higher fruit, vegetable, and nut consumption were associated with delayed memory by covariance analysis. In this study, dietary factors were also compared between 248 participants with mild cognitive impairment (MCI) and 646 labeled as cognitively healthy, and data showed that normal individuals consumed more nuts than those with MCI (10.71 *versus* 7.14 g/day, $P < 0.05$).

Two additional epidemiological investigations evaluated consumption of plant foods including nuts in relation to cognitive outcomes. In a cross-sectional study of an elderly Norwegian cohort from the general population (n = 2031, ages 70–74 years), nuts were non-significantly associated with better cognitive performance, but only 16% of the participants were nut consumers [24]. A prospective investigation from the Seguimiento Universidad de Navarra cohort of university graduates in Spain assessed consumption of Mediterranean foods in relation to cognition at baseline and after 6–8 years of follow-up in 823 older participants, and it reported no association of the food group “fruits plus nuts” with changes in cognitive test scores [25].

11.2.2 Nut Consumption and Depression

Late-life depression is a common psychiatric disorder that much compromises older people’s quality of life. Depression is considered a risk factor for cognitive decline,

but the evidence for dementia is less clear [26]. However, given that major depression is commonly associated with attention problems, memory deficit, and impaired executive function, there is the question of whether depression may increase an individual's risk or just be an early marker of brain changes associated with cognitive decline [27]. Anyhow, nutrition has the capacity to influence depression risk to a similar extent that it does other non-communicable disorders, and a salutary role of healthy diets and a detrimental role of Western dietary patterns on depression risk has been suggested by a meta-analyses of cohort studies [28]. As with other health outcomes, prospective studies point to an anti-inflammatory dietary pattern such as the MeDiet as having a strong beneficial association with the risk of incident depression [29,30], which is not unexpected given the contribution of chronic inflammation to the pathophysiology of depression [31]. For a similar reason, depression is also a risk factor for coronary heart disease, although the association is bidirectional [32]. Nuts, a paradigmatic component of the MeDiet with anti-inflammatory properties, can also be postulated to have a salutary effect on depression, but the epidemiologic evidence is scanty and of suboptimal quality.

Nut consumption was reported to have a beneficial effect on depressive symptoms in a large cross-sectional study of Chinese adults [33]. In another cross-sectional report from NHANES conducted with data collected in the last decade, nut consumers, and particularly walnut consumers, disclosed lower depression scores than non-nut consumers, and this beneficial effect was more pronounced in women [34]. Again, food consumption was assessed only *via* 24-hour diet recalls, which can provide strong evidence for frequently consumed foods but, unless repeated, are much weaker for sporadically consumed foods such as nuts. In the Invecchiare in Chianti study, an Italian prospective investigation of 1,058 adults followed for up to 9 years with repeated measurements of diet and of depression scores, no association between consumption of nuts and depressive symptoms was observed [35].

11.2.3 Nut Consumption and Neurodegenerative Disease Mortality

While there is consistent epidemiologic evidence that nut consumption relates to lower all-cause and CVD mortality (see Chapter 10 for details), there is much less information on neurodegenerative disease mortality. Indeed, only two prospective studies collected data on this outcome [36,37]. The study by Bao et al. [36], a report of the seminal prospective cohorts of the NHS and the Health Professionals Follow-up Study, is the largest and more reliable, providing mortality data (1,969 deaths from neurodegenerative disease) on 76,464 women and 42,498 men during more than 3 million person-years of follow-up. The summary relative risks for neurodegenerative disease mortality comparing extreme quintiles of nut consumption were 0.61 (95% confidence interval [CI], 0.30–1.22) for women and 1.04 (95% CI, 0.44–2.45) for men, and neither of these two estimates was significant. The Netherlands Cohort Study followed 1,743 men and 1,950 women aged 55–69 years from the general population for 10 years and reported on total and cause-specific mortality in relation to total nut consumption [37]. Concerning neurodegenerative disease, only 80 deaths occurred, and there was a non-linear association with nut consumption, with a hazard ratio (HR) comparing extreme quartiles of 0.53 (95% CI, 0.25–1.14). In this study, the authors excluded peanut butter from the category "nuts" because of the customarily

high presence of salt and/or simple sugars in the former, which could override the presumed benefits associated with nut consumption. However, the results for the outcome here considered were similar. Thus, nut consumption does not appear to be related to deaths from neurodegenerative disorders, and clearly, more studies are warranted given the favorable tendency for women in the NHS and for both sexes in the Netherlands Cohort Study.

11.3 Clinical Trials

11.3.1 Trials of Nut Consumption with Outcomes on Cognition

Few RCTs have examined the effects of nuts on cognitive outcomes [38–42], and even fewer have sustained the intervention for more than 12 weeks (Table 11.2); hence, the level of evidence is still fragmentary. The largest RCTs with longest follow-up were two sub-studies of the landmark PREDIMED trial. PREDIMED was a successful nutrition intervention trial of primary CVD prevention using a MeDiet supplemented with either extra-virgin olive oil or mixed nuts (30 g/day: 15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts) *versus* a control diet (advice to follow a low-fat diet) in older individuals at high cardiovascular risk but no CVD at enrollment [43]. In a PREDIMED sub-study conducted in the Navarra recruiting center, two neuropsychological tests assessing general cognition were administered, but only at the end of the study after intervention for a median of 6.5 years; thus, changes over time were not assessed [39]. The results indicated that both MeDiets were associated with better cognitive outcomes compared to the control diet. In another PREDIMED sub-study carried out in the Barcelona recruiting center, a comprehensive cognitive battery was administered both at baseline and at trial's end after a median follow-up of 4.1 years [40]. Results showed that composites of memory performance, executive function, and global cognition improved above baseline with the two MeDiets, while values for all cognitive domains declined in participants assigned to the control diet. However, the improvement in executive function and global cognition with the nut-supplemented diet did not reach statistical significance compared to the control diet. Hence, the findings of this trial demonstrate that a MeDiet supplemented with mixed nuts can delay the age-related decline of memory function.

Three additional small, short-term RCTs tested walnuts [38], peanuts [41], or almonds [42] for cognitive outcomes. Surprisingly, given that intervention only lasted 8–12 weeks in these trials, the diets enriched with walnuts and peanuts were associated with significant improvements in the results of specific cognitive tests in comparison with the control diets without nuts (Table 11.2). In the study by Barbour et al. [41], short-term memory and verbal fluency improved with a high-oleic acid peanut diet compared to the control diet. In this trial, a transcranial Doppler was used to non-invasively measure blood flow velocity in the middle cerebral artery, and results showed that the peanut diet induced a small but significant increase in cerebrovascular reactivity, which can be equated to improved endothelial function of brain arteries [41]. On the other hand, in the study by Dhillon et al. [42], almond consumption for 12 weeks had no effect on cognitive performance compared to the control diet. In this trial, additional acute experiments were conducted to examine

Table 11.2 Randomized Controlled Trials of Nuts with Outcomes on Cognition

Study Design (Source)	*No. of Study Subjects*	*Age (Years)*	*Subjects' Characteristics*	*Neuro-psychological Tests*	*Nut Dose/Day (Range)*	*Comparator Diet*	*Follow-Up*	*Outcome*	*References*
Crossover, double-blind, placebo-controlled	64	18–25	College students	Verbal and non-verbal reasoning, memory, and mood.	Walnuts, raw, with skin, 60 g, administered in banana bread.	Placebo: banana bread of similar taste and texture without walnuts.	8 weeks	Inferential verbal reasoning improved with the walnut diet.	[38]
Parallel (Sub-sample of PREDIMED study)	522	55-80	Men and women, at high cardiovascular risk	MMSE and Clock Drawing Test (administered once, at the end of the study).	Total nuts 30 g (15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts), raw, with skin, supplementing a MeDiet.	Control diet based on advice to reduce all dietary fat.	6.5 years	MeDiets supplemented with nuts associated with better global cognition compared to control diet.	[39]
Parallel (Sub-sample of PREDIMED study)	334	55–80	Men and women at high cardiovascular risk	Comprehensive battery tapping on memory, executive function, and global cognitive domains (administered at baseline and end of study).	Total nuts, 30 g (15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts), raw, with skin, supplementing a MeDiet.	Control diet based on advice to reduce all dietary fat.	4.1 years	MeDiet supplemented with nuts associated with significantly better memory function and non-significant improvements in executive function and global cognition compared to control diet.	[40]

(*Continued*)

Table 11.2 (Continued) Randomized Controlled Trials of Nuts with Outcomes on Cognition

Study Design (Source)	*No. of Study Subjects*	*Age (Years)*	*Subjects' Characteristics*	*Neuro-psychological Tests*	*Nut Dose/Day (Range)*	*Comparator Diet*	*Follow-Up*	*Outcome*	*References*
Crossover	61	Mean 65	Overweight and obese men and women	Tests of memory (immediate and delayed recall and recognition), executive function (verbal fluency, inhibition), and processing speed.	High-oleic acid peanuts, unsalted, with skin, 56–84 g.	Habitual diet without nuts.	12 weeks	Short-term memory and verbal fluency improved with the peanut diet compared to control diet.	[41]
Parallel	86	Mean 31	Overweight and obese men and women	Tests of immediate and delayed memory and attention performance	Almonds, dry-roasted, lightly salted, providing 15% of energy in the context of an energy-restricted diet.	Energy-restricted control diet without nuts.	12 weeks	Immediate and delayed memory and attention performance improved to a similar extent with the almond and control diet.	[42]

Abbreviations: MeDiet, Mediterranean diet; MMSE, mini-mental state examination; PREDIMED, PREvención con Dieta MEDiterránea.

whether a high-fat lunch rich in almonds would influence the well-established post-lunch dip in alertness, memory, and vigilance. The findings revealed that, compared with a high-carbohydrate meal, almond consumption at lunch ameliorated the post-meal decline in memory but not in attention performance [42].

A small PREDIMED sub-study assessed plasma levels of brain-derived neurotrophic factor (BDNF), a positive biomarker of brain function, in 243 study subjects after 3 years of intervention [44]. Results showed increased BDNF concentrations in participants assigned the MeDiet supplemented with nuts in comparison with the control diet, particularly among those with prevalent depression (n = 37). Small numbers, however, dictate caution in the interpretation of these results, which have not been replicated.

Thus, the findings of the few RCTs examining the effects of nut consumption on cognitive outcomes after intervention with a MeDiet supplemented with nuts point towards a beneficial effect, but this might not be entirely attributable to nuts, as other components of the MeDiet also changed in these studies, and clearly, larger and longer-term studies are warranted. A large RCT lasting 2 years (Walnuts and Healthy Aging [WAHA]) examined the effects of a diet enriched with walnuts at 15% of energy *versus* a similar diet without nuts on cognitive outcomes in 700 healthy elders [45], and the results are expected soon. In any case, to maximize the opportunity of uncovering the beneficial effects of any experimental diet, individuals at high risk of cognitive impairment or already having memory complaints should perhaps be studied rather than those who are cognitively intact [46].

11.3.2 Trials of Nut Consumption with Outcome on Depression

A single RCT tested the hypothesis that nut consumption could help improve depression. In the PREDIMED trial, the MeDiet-plus-nuts arm disclosed a lower incidence of incident depression, with a multivariate HR of 0.78 (95% CI, 0.55–1.10) in comparison with participants assigned to the control group, although this was not significant. However, when the analysis was restricted to participants with type-2 diabetes (close to 50% of the cohort), the magnitude of the effect of the intervention with the MeDiet supplemented with nuts reached statistical significance, with a multivariate HR of 0.59 (95% CI, 0.36–0.98) [47].

Another RCT examined the role of walnuts in improving mood, a multi-pronged component of cognition that includes depression. In this study, 64 young students underwent a crossover, 8-week double-blind trial [48]. Walnuts were delivered in banana bread, consisting of two servings of finely ground walnuts (60 g/day), while the control diet had similar-looking and tasting banana bread without walnuts. The Profile of Mood States (POMS) questionnaire, an accepted scale used in studies of cognition, served to estimate the intensity of mood disturbance in the participants. The POMS covers six mood domains: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. No significant changes in mood were observed in the analyses of the whole study subjects, but there was a significant medium-effect size improvement in the total mood disturbance score in young men, which was not detected in young women. There was no reasonable explanation for the observed sex differences.

11.4 Experimental Studies Relating Nuts to Brain Function

11.4.1 Experimental Studies with Walnuts

The nutrient composition of walnuts differs from that of all other nuts in three important ways: a) they contain ~10% of energy as α-linolenic acid (ALA), the main vegetable n-3 (omega-3) PUFA; b) they are a rich source of phytomelatonin; and c) they possess more polyphenols than any other nut type [49,50]. Given that both n-3 PUFA and antioxidant polyphenols are considered critical brain foods [8,9], it is not surprising that most *in vitro* and *in vivo* experimental studies investigating the effects of nuts on brain function have been conducted with walnuts [51].

The first experimental animal studies with walnuts concerning brain health were conducted in the lab of the late Jim Joseph at the Human Nutrition Research Center on Aging at Tufts University in Boston, USA. Willis et al. [52] fed aged rats a control diet or 2%, 6%, or 9% walnut diets – equivalent to 0.4, 1.0, or 1.5 servings (28 g), respectively, of walnuts per day in humans – for 8 weeks before motor and cognitive testing. Results showed that the 2% and 6% walnut diets improved psychomotor performance and all the walnut diets improved working memory, although the 9% diet showed impaired reference memory. Thus, moderate rather than large amounts of walnuts improved cognition and motor performance in aged rats. Subsequently, the same investigators demonstrated in an *in vitro* model that walnut-extract exposure inhibited lipopolysaccharide (LPS)-induced activation of rat BV-2 microglia cells in culture through phospholipase D_2–mediated internalization of Toll-like receptor 4 [53]. This is a salutary effect because a pro-inflammatory phenotype of microglia can result in the production of cytotoxic intermediates and is associated with age-related neurodegeneration. Subsequent work from this lab using the same model of activated microglial cells indicated that serum metabolites from aged rats fed walnuts attenuated LPS-induced nitrite release and reduced pro-inflammatory tumor necrosis factor-alpha, cyclooxygenase-2, and inducible nitric oxide synthase production, suggesting antioxidant and anti-inflammatory protection or enhancement of membrane-associated functions in brain cells by walnut serum metabolites [54]. A recent study, again performed using the same *in vitro* model, indicated that bioactive compounds in walnuts were capable of modulating microglial activation through regulation of intracellular calcium and calmodulin expression [55].

An increase in the aggregation of misfolded or damaged polyubiquitinated proteins has been the hallmark of many age-related neurodegenerative diseases. Additional work from the Tufts University lab showed that a 6% or 9% walnut diet given to aged rats significantly reduced the aggregation of polyubiquitinated proteins and activated autophagy, a neuronal housekeeping function, in the *corpus striatum* and particularly the hippocampus [56], a critical brain area involved in memory function. The effectiveness of walnuts in activating autophagy in the brain provides evidence of a neuroprotective effect beyond antioxidant and anti-inflammatory actions. In another *in vitro* study from this research group, the cellular mechanisms by which walnuts and PUFAs influence neuronal health and functioning in aging was investigated in a model of rat hippocampal neurons, wherein cell death and calcium dysregulation was promoted with dopamine and LPS stimulation. Results showed that walnut extract, ALA, and docosahexaenoic acid (DHA, the main fish-derived omega-3 PUFA) significantly protected against cell death and calcium

dysregulation, providing further insight into the capacity of walnuts and their main components to protect against age-related cellular dysfunction [57].

Another group active in experimental walnut research in relation to neurodegeneration is that of Abha Chauhan at the New York State Institute for Basic Research in Developmental Disabilities. Fibrillar amyloid beta-protein (Aβ) is a major histo-pathologic feature in the brain of AD patients and a potent pro-oxidant promoting neuronal cell death. Early *in vitro* work from this lab indicated that walnut extract dose-dependently inhibited Aβ formation and was able to defibrillize preformed Aβ fibrils, thus keeping them in a soluble form, and additional experiments suggested that polyphenols were the anti-amyloidogenic component of walnuts [58]. Subsequent *in vitro* experiments in PC12 pheochromocytoma cells showed that walnut extract counteracted Aβ-induced oxidative stress and associated cell death [59]. Using Tg2576 transgenic mice, a long-used model of AD, these investigators also showed that feeding these mice diets containing 6% or 9% walnuts – equivalent to 1 or 1.5 servings of 28 g per day in humans – for 9–10 months resulted in a significant improvement in memory, learning skills, and motor development compared to the same mice on a control diet without walnuts [60]. Further work from this lab using the same mouse model, which aimed at uncovering the underlying mechanisms of neuroprotection by walnuts, showed that long-term (10 or 15 months) dietary supplementation with 6% or 9% walnuts was effective in reducing oxidative stress, as evidenced by decreased levels of reactive oxygen species, lipid peroxidation, and protein oxidation, as well as by enhanced activities of antioxidant enzymes [61]. Thus, if translated to humans, the results of these studies [58–61] overall suggest that dietary supplementation with walnuts might have a beneficial effect in reducing the risk, delaying the onset, or slowing the pathophysiological progression of AD.

A recent study in rats treated with D-galactose, a model of accelerated aging, assessed the effects of 6% and 9% walnut diets given for 8 weeks on cognitive behavior and hippocampal neurogenesis [62]. Behavioral tests showed that walnut diets significantly reversed spatial memory loss, locomotor activity deficiency, and reduced recognition behavior. Increased hippocampal neurogenesis by walnut diets was also demonstrated by increased expression of hippocampal-activated cyclic adenosine monophosphate (AMP) response element-binding protein and BDNF, two crucial molecules involved in hippocampal neurogenesis and the formation of memories. Additional experimental research from Iran [63] and Pakistan [64] using a rat model of amnesia induced by scopolamine, an agent that interrupts cholinergic transmission, shows that walnut feeding restores cholinergic function, which is impaired in AD, and prevents memory loss.

In summary, all published experimental studies with walnuts and their constituents suggest a beneficial effect on brain health.

11.4.2 Experimental Studies with Other Nuts

A few experimental investigations on nuts other than walnuts for effects on brain health have been published, three studying almonds [65–67] and one each hazelnuts [68] and pistachios [69]. In a study from India, Kulkarni et al. [65] investigated the effect of almond paste on cognitive function and brain cholinesterase activity in the rat model of scopolamine-induced amnesia. At daily doses of almonds equivalent to approximately 6 g in humans, administered orally for 1 or 2 weeks, the learning

skills and memory function of scopolamine-treated rats improved and brain cholinesterase activity decreased, hence implying augmentation of cholinergic transmission. Using a slightly different approach, researchers from Pakistan pre-treated rats with an oral almond suspension (400 mg/kg/day – a dose similar than used in the study from India) for 4 weeks prior to scopolamine injection, and documented improvements in memory retention and cholinergic function, as assessed by the increased acetylcholine content and reduced acetylcholinesterase activity in the hippocampus and frontal cortex of treated rats compared to control animals [66]. Subsequent work from this Pakistani group, using the same model and a similar research protocol, again showed improved memory function in addition to reduced brain oxidative stress in almond-treated rats compared to controls [67].

In another *in vivo* study using rats with neuroinflammation induced by intrahippocampal Aβ injection, researchers from Iran showed that feeding hazelnuts (800 mg/kg/day) for circa 16 days improved memory and ameliorated anxiety-related behavior while reducing inflammatory molecules and apoptosis in the hippocampus [68]. Recently, Indian investigators reported improved memory performance and reduced lipid peroxidation and glutathione levels in mice with scopolamine-induced amnesia pre-treated with oral ethanolic extracts of pistachios at doses of 200 and 400 mg/kg [69].

Therefore, although the level of experimental evidence is scarce on the effects of nuts other than walnuts on brain health, almonds, hazelnuts, and pistachios seem to share the beneficial effects of walnuts on cognition and neuroinflammation in a few rodent models of neurodegeneration. Interestingly, three of the types of nuts discussed here (almonds, hazelnuts, and walnuts) or oils derived from them are used in traditional Persian medicine in the treatment of memory loss and as food for the elderly [70].

11.5 Neuroprotective Properties of Nut Constituents

Nuts are nutritionally dense foods consisting of a unique matrix of macronutrients, micronutrients, and bioactive phytochemicals (see Chapter 2 for details). On the basis of prior experimental evidence and, to a lesser extent, findings from epidemiological studies relating nutrition to brain health, some of these nut constituents can be predicted to be neuroprotective. Among them, the best suited to be considered "brain nutrients" are PUFAs, particularly ALA, and polyphenols, although other nut components such as phytomelatonin, phytosterols, antioxidant tocopherols, and folic acid may also support neurological health and cognitive wellness. The possible contribution of these nut bioactives to the clinical and experimental effects of nuts on brain function discussed above will be briefly reviewed here.

11.5.1 α-Linolenic Acid (ALA)

Under physiological conditions, the bioavailability of ALA, an essential fatty acid, is nearly complete because it is readily absorbed in the intestinal tract. Once absorbed, ALA is converted to a small extent into its longer-chain counterpart eicosapentaenoic acid (EPA) and marginally into DHA, which is an important component of the phospholipids of neuronal membranes [71]. Of note, in clinical studies, ALA intake

has been shown to have anti-inflammatory effects *via* reduction of serum cytokine concentrations and of cytokine production by cultured peripheral blood mononuclear cells [72]. Although clinical data are inconclusive, experimental studies have also shown an antiarrhythmic effect of ALA, akin to that of DHA [71].

ALA has been much less studied than EPA and DHA in relation to health outcomes, so epidemiological studies are limited and have yielded conflicting results [71]. A meta-analysis of studies published up to May 2015 investigating fish consumption, n-3 PUFA intake, and the n-3 PUFA content of plasma fractions in relation to cognitive impairment, dementia, and Parkinson's disease concluded that seafood consumption and total n-3 PUFA intake, but not ALA intake (nine studies), related to better outcomes [73]. In the cited prospective Doetinchem Cohort Study [19], which was not included in this meta-analysis, ALA intake was associated with less global cognitive decline and memory impairment. Additional studies on this topic have since been published. In a recent longitudinal study of aging and dementia, the association between consumption of seafood and long-chain n-3 PUFAs with cognitive changes was assessed in 915 older individuals after follow-up for 5 years [74]. Findings indicated that higher ALA intake was associated with slower global cognitive decline, but only in *APOE* ε4 carriers. In a cross-sectional study of 672 cognitively normal participants with mean age of 80 years, higher ALA intake was associated with larger cortical thickness [75]. The findings of two brain pathological studies in brain donors also deserve to be mentioned. In an aging project involving 282 brain donors, the authors found decreased odds of cerebral macroinfarcts and microinfarcts in those who self-reported higher dietary ALA intake, first measured by a food frequency questionnaire at a mean of 4.5 years before death [76]. In a pathological study measuring fatty acids in various brain regions, unsaturated fatty acid metabolism, including ALA, was found to be dysregulated in the brains of patients with varying degrees of AD pathology [77]. Thus, the results of epidemiological studies are generally inconclusive regarding ALA and brain health.

A single RCT, the Alpha Omega Trial, designed primarily as a cardiovascular prevention study, tested the effects of ALA on cognitive impairment as a secondary endpoint. In this trial, 2,911 stable coronary patients from 60 to 80 years old were randomized to receive 400 mg/day EPA+DHA, 2 g/day ALA, 400 mg/day EPA+DHA plus 2 g/day ALA, or a placebo for a median of 3.3 years, and results showed no significant differences in cognitive decline for the active treatment groups *versus* the placebo [78]. However, ALA supplementation was associated with somewhat better results than EPA+DHA, as it significantly reduced cognitive decline in patients aged < 70 years and in those with fish intake > 20 g/day and reduced the risk of severe cognitive decline by approximately 10%, although without reaching statistical significance. However, the Mini Mental State Examination, a rough global measure of cognitive function, was the only neuropsychological test administered, which dictates caution in the interpretation of these findings.

Experimental studies have been more successful in uncovering the benefits of ALA in the brain akin to those observed for EPA and DHA, including neuroprotection, enhanced production of BDNF, vasodilation of brain arteries, and neuroplasticity [79]. *In vivo* experiments of natural aging in rats have demonstrated that long-term ALA supplementation prevents age-related memory deficits and brain neurodegeneration [80,81]. In line with the findings of Fisher et al. [54] in activated microglial cells treated with serum from walnut-fed rats, Lee et al. [82] found that addition of ALA to the culture medium of C6 glial cells treated with a neurotoxin

disclosed antioxidant and anti-inflammatory effects, translating into increased cell viability. Also, in a rat model of mild controlled cortical impact, the subcutaneous administration of ALA resulted in a significant reduction in brain bruise volume and protected against anxiety-like behavior [83]. Interestingly, in a study carried out in *Caenorhabditis elegans*, a worm with long-lived mutant forms widely used in aging research, treatment with ALA dose-dependently increased lifespan [84]. Thus, based on animal studies, supplementation with ALA appears to have cognitive benefits, showing neuroprotection through antioxidant, anti-inflammatory, and antiamyloid effects. The fact that walnuts are the only nuts containing significant amounts of ALA could favor their beneficial effects on brain health above those of other nut types.

11.5.2 Polyphenols

Polyphenols are a large family of heat-labile, water-soluble phytochemicals, and secondary metabolites of plants characterized by a chemical structure of hydroxyl groups on aromatic rings. They are capable of quenching oxygen-derived free radicals, with thousands of species grouped into five large classes (flavonoids, phenolic acids, stilbenes, lignans, and other polyphenols) [85]. Given the prevailing hypothesis that oxidative stress is a major driver of cognitive dysfunction and plays an important role in activating cell signaling pathways that contribute to lesion formation and promote the development of AD [11,12], exogenous antioxidants, particularly dietary polyphenols, are likely to benefit brain health.

Nuts are exceptionally rich in polyphenols (see Chapter 2 for details). Noticeably, compared to other tree nuts, walnuts have the highest level of bioactive polyphenols [86]. In nuts, polyphenols reside mostly in the skin (outer peel), where they help to perpetuate the species by protecting the plant's DNA from oxidative stress due to thermal or radiation injury, as well as protecting the seed from pathogenic microorganisms and insects due to their strong odor and taste. Thus, peeling or roasting of nuts results in sizeable polyphenol losses, as do boiling, frying, or microwave heating. In clinical studies, polyphenols from nuts are absorbed following acute ingestion, with attendant increases in plasma concentrations, enhancement of plasma antioxidant capacity, and reduced plasma lipid peroxidation [87,88]. There is also experimental evidence that polyphenols and their metabolites are able to cross the blood–brain barrier and attain brain tissues [89–91].

There is a vast literature suggesting neuroprotection by dietary polyphenols and foods rich in these compounds [8–10,92]. The few epidemiological studies that have investigated polyphenol intake in relation to cognitive aging or dementia have generally, but not always, reported a beneficial association, which might depend on specific polyphenol subtypes [93]. In a recent study from a French cohort of 1,329 older non-demented adults, Lefèvre-Arbogast et al. [94] assessed cumulative intake of various polyphenol subclasses and followed participants for 12 years for dementia outcomes. The polyphenol pattern studied combined several flavonoids, stilbenes (including resveratrol), lignans, and other subclasses from specific polyphenol-rich plant foods, including nuts. Compared with participants in the lower quintile of the polyphenol score, those in the higher quintile had a 50% lower risk of dementia (95% CI, 20% to 68%) in multivariate models, which suggests a robust neuroprotective power of these particular polyphenol subtypes. RCTs have been conducted

with specific polyphenols for outcomes on cognitive function, with mixed results according to systematic reviews [95,96]. Intake of resveratrol, a stilbene found in red grapes, red wine, blueberries, and peanuts, had no significant impact on factors related to memory and cognitive performance in five trials, although it appeared to enhance mood [96]. Finally, many experimental studies have examined the effects of polyphenols on brain health, with generally positive results concerning brain perfusion, synaptic plasticity, neuroinflammation, oxidative stress signaling, and autophagy, as reviewed [97].

11.5.3 Other Nut Components

Apart from ALA and polyphenols, other nut constituents, such as melatonin, phytosterols, antioxidant tocopherols, folic acid, and non-sodium minerals (potassium, magnesium, and calcium) have the capacity to beneficially impact brain health. There is ample experimental evidence that melatonin, a hormone synthetized by the mammalian pineal gland at night that is best known for its sleep-regulatory role, has pleiotropic effects, such as antioxidant, anti-inflammatory, and neuroprotective activities [98]. A role of melatonin in neurodegeneration has been suggested by the evidence that in preclinical stages of AD, when patients still manifest normal cognition, cerebrospinal fluid melatonin levels are reduced, which may be an early trigger and marker for the disease [99,100]. Experimental melatonin deficiency is also linked to degeneration of cholinergic neurons and Aβ accumulation in the brain of mice, reversible upon dietary supplementation [101]. Many plants contain sizable amounts of bioavailable melatonin [102], walnuts being one of its main food sources, with an average content of 350 ng/100 g. Melatonin from walnuts is absorbed, as shown by a roughly four-fold rise in serum levels in parallel with increased serum antioxidant activity in experiments with walnut-fed rats [103]. Thus, although direct proof is lacking, it is conceivable that melatonin might contribute to the beneficial effects of nuts, particularly walnuts, on brain health.

Phytosterols, a constituent of nuts that contributes to their cholesterol-lowering effects [104], are minimally absorbed from the intestinal tract but are able to cross the blood–brain barrier and accumulate in the membranes of central nervous system cells [105]. An experimental study in mice showed that one plant sterol, stigmasterol, reduced Aβ generation by modifying cleavages of the amyloid precursor protein when incorporated into neuronal membranes, suggesting that dietary intake of stigmasterol might be beneficial in preventing AD [106]. Experimental studies also support anti-inflammatory effects of phytosterols, albeit clinical studies have not yielded consistent results, as reviewed [107]. Theoretically, the richness of nuts in phytosterols might benefit neurological health and cognitive aging following long-term consumption.

The term vitamin *E* refers to four tocopherols (α- β- γ-, and δ-tocopherol), but only RRR-α-tocopherol is a true vitamin. Dietary tocopherols are bioavailable because, being small fatty molecules, their intestinal absorption takes place by similar mechanisms to dietary fat and enter the circulation *via* chylomicron particles [108]. Tocopherols are an integral component of all nuts, usually in the form of α-tocopherol, while walnuts are an excellent source of γ-tocopherol, a highly active free-radical scavenger and anti-inflammatory molecule [109]. The role of vitamin E in the prevention of AD is a matter of debate. In prospective studies, higher

consumption of foods rich in vitamin E (vegetable oils, nuts, and whole grains) appears to modestly reduce the long-term risk of dementia and AD [110], and plasma vitamin E levels are associated with lower prevalent AD in case-control studies [111]. However, RCTs of vitamin E supplementation in patients with cognitive impairment have failed to demonstrate improved cognition or delayed progression to dementia [9,112]. It must be noted that the α-tocopherol form of vitamin E, not γ-tocopherol, was always used in these RCTs. In this sense, it is interesting that, in autopsy studies of individuals deceased during an ongoing clinical-neuropathological cohort study in the US, brain γ-tocopherol concentrations, but not those of α-tocopherol, were associated with lower AD neuropathology, suggesting that γ-tocopherol is the neuroprotective form of vitamin E [113]. Again, these findings point to walnuts as potentially more active than other nuts in promoting brain health. Still, in experimental studies conducted in rodent models of aging or AD, vitamin E in its α-tocopherol form has been shown to reduce oxidative stress, attenuate the toxic effects of Aβ, and improve cognitive performance [114].

Folate is an essential water-soluble B vitamin required by most body tissues, including the brain, for one-carbon transfer reactions, which are essential for methylation processes involved in methionine regeneration and epigenetic changes, the synthesis of DNA and RNA nucleotides, and amino acid metabolism [115]. Cerebral folate sufficiency appears to be necessary to forestall age-related neuropathology and its consequences [116], and population-based studies have demonstrated that a low folate status is associated with mild cognitive impairment, dementia (particularly AD), and depression in older individuals [117]. However, as with supplemental vitamin E, there is little evidence that folic acid supplementation improves cognitive function or delays cognitive decline [9]. Elevated plasma homocysteine, a hallmark of folate deficiency, is also associated with cognitive impairment and dementia, but reducing plasma levels with folate supplementation has also proven ineffective to improve cognition [118]. Nuts are good sources of folate, with concentrations ranging from 11 to 240 μg per 100 g, peanuts being the richest, followed by hazelnuts and walnuts. As the dietary reference intake for adults (excluding pregnant and lactating women) of naturally occurring folate is 400 μg daily, long-term consumption of nuts contributes to some extent to an adequate folate status. Nevertheless, the role of folate in isolation in the possible neuroprotective effects of nuts is still unproven.

Nuts are also a good source of arginine, an essential amino acid for human development. It is a precursor of nitric oxide, the endogenous vasodilator, and as such contributes to blood pressure regulation and vasomotor tone [119], critical for vascular health, including appropriate cerebral blood flow.

Finally, non-sodium minerals (potassium, magnesium, and calcium) are also abundant in nuts [104] and may play a significant role in neuroprotection, although the evidence is still fragmentary. Some prospective studies have suggested an association of non-sodium mineral intake with improved cognition or a lower risk of dementia [120–122]. Thus, in 1081 community-dwelling Japanese individuals without dementia aged 60 years and older with a 17-year follow-up, higher dietary intakes of potassium, calcium, and magnesium were associated with a reduced risk of all-cause dementia, especially vascular dementia [120]. Cherbuin et al. [121] prospectively assessed 1,406 cognitively healthy individuals with a mean age of 62.5 years, who were followed for 8 years, and reported that higher intake of magnesium was associated with a decreased risk of MCI, albeit only in men, but no effect of calcium and an opposite effect of potassium were found. In a prospective study of 1,194

community-dwelling older adults followed for 2 years, higher potassium intake was associated neither with cognitive decline in the full cohort nor with micro- and macrostructural brain MRI indices assessed in a subset of participants [122]. Moreover, individuals suffering from AD have been shown to have lower plasma magnesium levels [123]. Hence, the most consistent beneficial association of dietary minerals with cognitive outcomes is for magnesium. In other studies, consistent inverse associations with stroke risk were found for intakes of potassium and magnesium but not calcium [124]. Current evidence from epidemiological studies suggests that higher magnesium intake, either dietary or *via* supplementation, is associated with a reduced potency of cardiovascular risk factors, including hypertension, metabolic syndrome, insulin resistance, and type-2 diabetes, besides being inversely related to the risk of total CVD and, particularly, stroke [125]. These effects of magnesium and, to a lesser extent, potassium are likely to contribute to the salutary effect of nuts on brain health.

An important aspect of nuts as possible neuroprotective agents is their capacity to beneficially impact vascular risk factors, such as blood pressure, glucoregulation, endothelial function, and inflammation, which are all linked to brain health [17]. The established association of nut consumption with reduced CVD outcomes (see Chapter 6 for details) and its putative beneficial effect on diabetes risk (see Chapter 8 for details) is also highly relevant to brain health.

11.6 Conclusion

Cognitive decline and dementia are major societal issues worldwide because of the aging population and the absence of effective treatment. Indeed, RCTs testing various interventions in patients with severe cognitive impairment or established AD have failed to show any benefit, probably because at this stage neuropathology is far advanced and irreversible. While there is still an urgent need to develop effective treatments for age-related neurodegenerative diseases, prevention strategies in preclinical stages represent an approach that needs to be tested, although presently it is still in its infancy. Because neurodegeneration and related clinical events, primarily dementia in general and AD in particular, are believed to be intimately linked to age-related increases in oxidative stress and inflammation, primary prevention could be achieved earlier in life by consuming a healthy diet, rich in antioxidant and anti-inflammatory phytochemicals. Data from epidemiological studies indeed suggest that long-term adherence to healthy, plant-based dietary patterns such as the MeDiet is associated with better cognition and a reduced incidence of dementia and AD. This could have been predicted based on the accumulated evidence from epidemiological studies and RCTs like PREDIMED concerning the beneficial effects of plant-based diets on other highly prevalent non-communicable diseases, such as total CVD, ischemic heart disease, and stroke and their risk factors, which are shared by neurodegenerative diseases. In fact, as reviewed here, evidence is beginning to accumulate that nuts, well known to positively impact risk factors for CVD and CVD itself, also support neurological health and cognitive wellness through a variety of mechanisms.

Limited epidemiological evidence suggests that regular nut consumption relates to better cognition and a lower incidence of depression, a prevalent clinical condition frequently associated with cognitive dysfunction, while data are not

available on dementia outcomes. Very few prospective studies have reported neurodegenerative disease mortality in relation to adherence to nuts, with neutral results. Few RCTs using nuts in isolation or supplemented to the MeDiet point towards a beneficial effect on cognition. Published experimental studies, mostly conducted with walnuts, endorse the beneficial effects of nuts on brain health. Nuts have a rich matrix of beneficial macronutrients such as PUFAs and arginine; micronutrients like tocopherols, folate, and non-sodium minerals; and bioactive phytochemicals, particularly polyphenols, phytosterols, and melatonin. According to the paradigm that food, not nutrients, is the fundamental unit in nutrition [126], all these nut constituents are likely to play a role in neuroprotection, working in concert to positively influence metabolic and vascular physiology pathways while counteracting oxidation and inflammation (Figure 11.1). As summarized in Figure 11.1, nut consumption improves cardiometabolic and brain health due to nuts' unique composition in bioactive nutrients and phytochemicals and a complex synergy among them with effects on diverse metabolic pathways. Unsaturated fatty acids and the main micronutrients and phytochemicals are represented together with their principal biological targets (long arrow connections). The net effects demonstrated in experimental and/or clinical studies on outcome variables related to cardiometabolic and neurological health for each relevant nut nutrient and for consumption of whole nuts are shown. For simplicity, not all nut constituents with an impact on metabolic pathways or synergies between them can be shown. For instance, dietary fiber

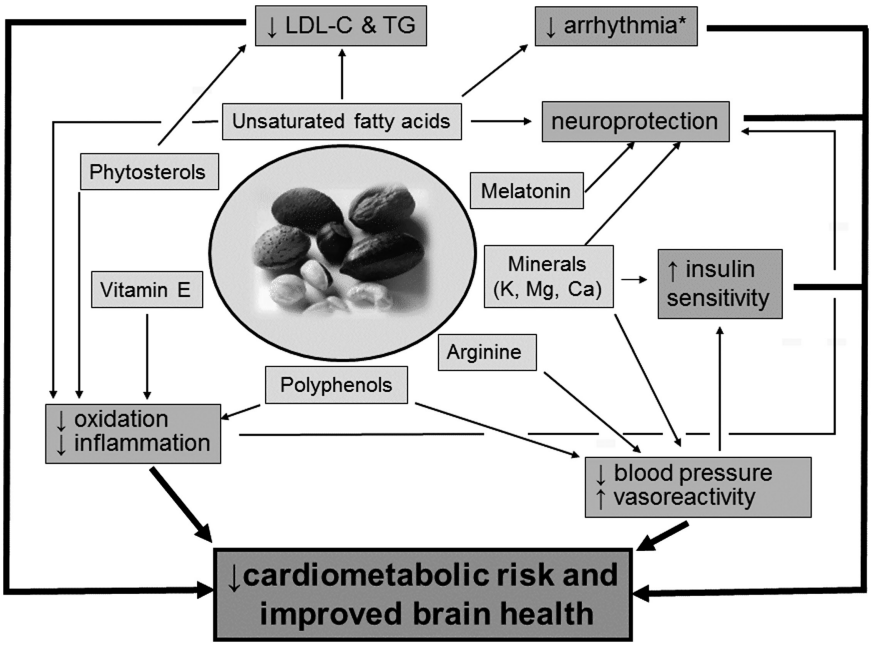


Figure 11.1 **(See color insert.)** Summary of mechanisms whereby nut consumption benefits cardiometabolic risk and brain health. *Note*: *Only α-linolenic acid may have an antiarrhythmic effect. *Abbreviations*: LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerols; K, potassium; Mg, magnesium; Ca, calcium.

(not shown), an integral component of nuts, will contribute to reducing low-density lipoprotein cholesterol and improving insulin sensitivity, while phytosterols and vitamin E may be neuroprotective directly besides effects ascribable to reducing oxidation and inflammation. Folate (not shown) is another putative neuroprotective nut component. The overall result of interactions among nut components ensuing consumption of whole nuts would be reduced incidence of and/or mortality from chronic non-communicable diseases such as CVD, diabetes, and neurodegenerative disorders.

In summary, there is incipient evidence that nut diets might be a useful tool to prevent or at least delay the cognitive decline that frequently affects older persons in the aging population. The recommendation to consume nuts frequently is an easy-to-implement lifestyle modification, known to help prevent chronic non-communicable disorders such as CVD, a benefit that is likely to extend to age-related neurodegenerative disorders such as cognitive impairment and dementia. While suggestive, the clinical evidence on the benefit of nut consumption on brain health is still preliminary. This underlines the need to perform larger and well-designed prospective studies in the general population and to conduct RCTs with as long a follow-up as possible in older individuals at risk of cognitive impairment.

References

1. Matthews, K.A., Xu, W., Gaglioti, A.H., Holt, J.B., Croft, J.B., Mack, D., and McGuire, L.C., Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. *Alzheimer's Dement.*, 15, 17–24, 2019.
2. Hyman, B.T., Phelps, C.H., Beach, T.G., Bigio, E.H., Cairns, N.J., Carrillo, M.C., Dickson, D.W. et al., National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's Dement.*, 8, 1–13, 2012.
3. Boyle, P.A., Wilson, R.S., Yu, L., Barr, A.M., Honer, W.G., Schneider, J.A., and Bennett, D.A., Much of late life cognitive decline is not due to common neurodegenerative pathologies. *Ann. Neurol.*, 74, 478–489, 2013.
4. Alzheimer's Association, 2018 Alzheimer's disease facts and figures. *Alzheimer's Dement.*, 14, 367–429, 2018.
5. Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., Cedazo-Minguez, A. et al., Defeating Alzheimer's disease and other dementias: A priority for European Science and Society. *Lancet Neurol.*, 15, 455–532, 2016.
6. Norton, S., Matthews, F.E., Barnes, D.E., Yaffe, K., and Brayne, C., Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurol.*, 13, 788–794, 2014.
7. Santos, C.Y., Snyder, P.J., Wu, W.C., Zhang, M., Echeverria, A., and Alber, J., Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. *Alzheimer's Dement.*, 7, 69–87, 2017.
8. Solfrizzi, V., Custodero, C., Lozupone, M., Imbimbo, B.P., Valiani, V., Agosti, P., Schilardi, A. et al., Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life cognitive disorders: A systematic review. *J. Alzheimers Dis.*, 59, 815–849, 2017.

9. Scarmeas, N., Anastasiou, C.A., and Yannakoulia, M., Nutrition and prevention of cognitive impairment. *Lancet Neurol.*, 17, 1006–1015, 2018.
10. Solfrizzi, V., Agosti, P., Lozupone, M., Custodero, C., Schilardi, A., Valiani, V., Sardone, R. et al., Nutritional intervention as a preventive approach for cognitive-related outcomes in cognitively healthy older adults: A systematic review. *J. Alzheimers Dis.*, 64(Suppl. 1), S229–S254, 2018.
11. Heneka, M.T., Carson, M.J., El Khoury, J., Landreth, G.E., Brosseron, F., Feinstein, D.L., Jacobs, A.H. et al., Neuroinflammation in Alzheimer's disease. *Lancet Neurol.*, 14, 388–405, 2015.
12. Mecocci, P., Boccardi, V., Cecchetti, R., Bastiani, P., Scamosci, M., Ruggiero, C., Baroni, M., A long journey into aging, brain aging, and Alzheimer's disease following the oxidative stress tracks. *J. Alzheimers Dis.*, 62, 1319–1335, 2018.
13. Chen, X., Maguire, B., Brodaty, H., and O'Leary, F., Dietary patterns and cognitive health in older adults: A systematic review. *J. Alzheimers Dis.*, 67, 583–619, 2019.
14. Gardener, S.L., and Rainey-Smith, S.R., The role of nutrition in cognitive function and brain ageing in the elderly. *Curr. Nutr. Rep.*, 7, 139–149, 2018.
15. Radd-Vagenas, S., Duffy, S.L., Naismith, S.L., Brew, B.J., Flood, V.M., and Fiatarone Singh, M.A., Effect of the Mediterranean diet on cognition and brain morphology and function: A systematic review of randomized controlled trials. *Am. J. Clin. Nutr.*, 107, 389–404, 2018.
16. Poulose, S.M., Miller, M.G., Scott, T., and Shukitt-Hale, B., Nutritional factors affecting adult neurogenesis and cognitive function. *Adv. Nutr.*, 8, 804–811, 2017.
17. Barbour, J.A., Howe, P.R., Buckley, J.D., Bryan, J., and Coates, A.M., Nut consumption for vascular health and cognitive function. *Nutr. Res. Rev.*, 27, 131–158, 2014.
18. Klimova, B., Kuca, K., Valis, M., and Hort, J., Role of nut consumption in the management of cognitive decline – A mini-review. *Curr. Alzheimer Res.*, 15, 877–882, 2018.
19. Nooyens, A.C., Bueno-de-Mesquita, H.B., van Boxtel, M.P., van Gelder, B.M., Verhagen, H., and Verschuren, W.M., Fruit and vegetable intake and cognitive decline in middle-aged men and women: The Doetinchem Cohort Study. *Br. J. Nutr.*, 106, 752–761, 2011.
20. Valls-Pedret, C., Lamuela-Raventós, R.M., Medina-Remón, A., Quintana, M., Corella, D., Pintó, X., Martínez-González, M.A. et al., Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. *J. Alzheimer Dis.*, 29, 773–782, 2012.
21. O'Brien, J., Okereke, O., Devore, E., Rosner, B., Breteler, M., and Grodstein, F., Longterm intake of nuts in relation to cognitive function in older women. *J. Nutr. Health Aging*, 18, 496–502, 2014.
22. Arab, L., and Ang, A., A cross sectional study of the association between walnut consumption and cognitive function among adult us populations represented in NHANES. *J. Nutr. Health Aging*, 19, 284–290, 2015.
23. Dong, L., Xiao, R., Cai, C., Xu, Z., Wang, S., Pan, L., and Yuan, L., Diet, lifestyle and cognitive function in old Chinese adults. *Arch. Gerontol. Geriatr.*, 63, 36–42, 2016.
24. Nurk, E., Refsum, H., Drevon, C.A., Tell, G.S., Nygaard, H.A., Engedal, K., and Smith, A.D., Cognitive performance among the elderly in relation to the intake of plant foods. The Hordaland Health Study. *Br. J. Nutr.*, 104, 1190–1201, 2010.

25. Galbete, C., Toledo, E., Toledo, J.B., Bes-Rastrollo, M., Buil-Cosiales, P., Marti, A., Gullén-Grima, F. et al., Mediterranean diet and cognitive function: The Sun Project. *J. Nutr. Health Aging*, 19, 305–312, 2015.
26. Baumgart, M., Snyder, H.M., Carrillo, M.C., Fazio, S., Kim, H., and Johns, H., Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's Dement.*, 11, 718–726, 2015.
27. Knight, M.J., and Baune, B.T., Cognitive dysfunction in major depressive disorder. *Curr. Opin. Psychiatry*., 31, 26–31, 2018.
28. Lai, J.S., Hiles, S., Bisquera, A., Hure, A.J., McEvoy, M., and Attia, J., A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *Am. J. Clin. Nutr.*, 99, 181–197, 2014.
29. Sanchez-Villegas, A., Delgado-Rodriguez, M., Alonso, A., Schlatter, J., Lahortiga, F., Serra, M.L., and Martinez-Gonzalez, M.A., Association of the Mediterranean dietary pattern with the incidence of depression: The Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. *Arch. Gen. Psychiatry*, 66, 1090–1098, 2009.
30. Adjibade, M., Assmann, K.E., Andreeva, V.A., Lemogne, C., Hercberg, S., Galan, P., and Kesse-Guyot, E., Prospective association between adherence to the Mediterranean diet and risk of depressive symptoms in the French SU.VI. MAX cohort. *Eur. J. Nutr.*, 57, 1225–1235, 2018.
31. Leonard, B.E., Inflammation and depression: A causal or coincidental link to the pathophysiology? *Acta Neuropsychiatr.*, 30, 1–16, 2018.
32. Vaccarino, V., Badimon, L., Bremner, J.D., Cenko, E., Cubedo, J., Dorobantu, M., Duncker, D.J. et al., Depression and coronary heart disease: 2018 ESC position paper of the working group of coronary pathophysiology and microcirculation developed under the auspices of the ESC Committee for Practice Guidelines. *Eur. Heart J.*, 2019, Jan 28. doi: 10.1093/eurheartj/ehy913 [Epub ahead of print].
33. Su, Q., Yu, B., He, H., Zhang, Q., Meng, G., Wu, H., Du, H. et al., Nut consumption is associated with depressive symptoms among Chinese adults. *Depress. Anxiety*, 33, 1065–1072, 2016.
34. Arab, L., Guo, R., and Elashoff, D., Lower depression scores among walnut consumers in NHANES. *Nutrients*, 11, E275, 2019.
35. Elstgeest, L.E.M., Visser, M., Penninx, B.W.J.H., Colpo, M., Bandinelli, S., and Brouwer, I.A., Bidirectional associations between food groups and depressive symptoms: Longitudinal findings from the Invecchiare in Chianti (InCHIANTI) study. *Br. J. Nutr.*, 121, 439–450, 2019.
36. Bao, Y., Han, J., Hu, F.B., Giovanucci, E.L., Stampfer, M.J., Willett, W.C., and Fuchs, C.S., Association of nut consumption with total and cause-specific mortality. *N. Engl. J. Med.*, 369, 2001–2011, 2013.
37. van den Brandt, P.A., and Schouten, L.J., Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: A cohort study and meta-analysis. *Int. J. Epidemiol.*, 44, 1038–1049, 2015.
38. Pribis, P., Bailey, R.N., Russell, A.A., Kilsby, M.A., Hernandez, M., Craig, W.J., Grajales, T. et al., Effects of walnut consumption on cognitive performance in young adults. *Br. J. Nutr.*, 107, 1393–1401, 2012.
39. Martínez-Lapiscina, E.H., Clavero, P., Toledo, E., Estruch, R., Salas-Salvadó, J., San Julián, B., Sanchez-Tainta, A. et al., Mediterranean diet improves cognition: The PREDIMED-NAVARRA randomized trial. *J. Neurol. Neurosurg. Psychiatry*, 84, 1318–1325, 2013.

40. Valls-Pedret, C., Sala-Vila, A., Serra-Mir, M., Corella, D., de la Torre, R., Martínez-González, M.Á., Martínez-Lapiscina, E.H. et al., Mediterranean diet and age-related cognitive decline: A randomized clinical trial. *JAMA Intern. Med.*, 175, 1094–1103, 2015.
41. Barbour, J.A., Howe, P.R.C., Buckley, J.D., Bryan, J., and Coates, A.M., Cerebrovascular and cognitive benefits of high-oleic peanut consumption in healthy overweight middle-aged adults. *Nutr. Neurosci.*, 20, 555–562, 2017.
42. Dhillon, J., Tan, S.Y., and Mattes, R.D., Effects of almond consumption on the post-lunch dip and long-term cognitive function in energy-restricted overweight and obese adults. *Br. J. Nutr.*, 117, 395–402, 2017.
43. Estruch, R., Ros, E., Salas-Salvadó, J., Covas, M.I., Corella, D., Arós, F., Gómez-Gracia, E. et al., Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N. Engl. J. Med.*, 378, e34, 2018.
44. Sánchez-Villegas, A., Galbete, C., Martinez-González, M.Á., Martinez, J.A., Razquin, C., Salas-Salvadó, J., Estruch, R. et al., The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: The PREDIMED-NAVARRA randomized trial. *Nutr. Neurosci.*, 14, 195–201, 2011.
45. Rajaram, S., Valls-Pedret, C., Cofán, M., Sabaté, J., Serra-Mir, M., Pérez-Heras, A.M., Arechiga, A. et al., The Walnuts and Healthy Aging study (WAHA): Protocol for a nutritional intervention trial with walnuts on brain aging. *Front. Aging Neurosci.*, 8, 333, 2017.
46. Moll van Charante, E.P., Richard, E., Eurelings, L.S., van Dalen, J.W., Ligthart, S.A., van Bussel, E.F., Hoevenaar-Blom, M.P. et al., Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): A cluster-randomised controlled trial. *Lancet*, 388, 797–805, 2016.
47. Sánchez-Villegas, A., Martínez-González, M.A., Estruch, R., Salas-Salvadó, J., Corella, D., Covas, M.I., Arós, F. et al., Mediterranean dietary pattern and depression: The PREDIMED randomized trial. *BMC Med.*, 11, 208–219, 2013.
48. Pribis, P., Effects of walnut consumption on mood in young adults—A randomized controlled trial. *Nutrients*, 8, E668, 2016.
49. Ros, E., and Mataix, J., Fatty acid composition of nuts—Implications for cardiovascular health. *Br. J. Nutr.*, 96(Suppl. 2), S29–S35, 2006.
50. Hayes, D., Angove, M.J., Tucci, J., and Dennis, C., Walnuts (*Juglans regia*) chemical composition and research in human health. *Crit. Rev. Food Sci. Nutr.*, 56, 1231–1241, 2016.
51. Poulose, S.M., Miller, M.G., and Shukitt-Hale, B., Role of walnuts in maintaining brain health with age. *J. Nutr.*, 144(Suppl. 4), 561S–566S, 2014.
52. Willis, L., Shukitt-Hale, B., Cheng, V., and Joseph, J.A., Dose-dependent effects of walnuts on motor and cognitive function in aged rats. *Br. J. Nutr.*, 101, 1140–1164, 2009.
53. Willis, L.M., Bielinski, D.F., Fisher, D.R., Matthan, N.R., and Joseph, J.A., Walnut extract inhibits LPS-induced activation of BV-2 microglia *via* internalization of TLR4: Possible involvement of phospholipase D2. *Inflammation*, 33, 325–333, 2010.
54. Fisher, D.R., Poulose, S.M., Bielinski, D.F., and Shukitt-Hale, B., Serum metabolites from walnut-fed aged rats attenuate stress-induced neurotoxicity in BV-2 microglial cells. *Nutr. Neurosci.*, 20, 103–109, 2017.
55. Thangthaeng, N., Poulose, S.M., Fisher, D.R., and Shukitt-Hale, B., Walnut extract modulates activation of microglia through alteration in intracellular calcium concentration. *Nutr Res.*, 49, 88–95, 2018.

56. Poulose, S.M., Bielinski, D.F., and Shukitt-Hale, B., Walnut diet reduces accumulation of polyubiquitinated proteins and inflammation in the brain of aged rats. *J. Nutr. Biochem.*, 24, 912–919, 2013.
57. Carey, A.N., Fisher, D.R., Joseph, J.A., and Shukitt-Hale, B., The ability of walnut extract and fatty acids to protect against the deleterious effects of oxidative stress and inflammation in hippocampal cells. *Nutr. Neurosci.*, 16, 13–20, 2013.
58. Chauhan, N., Wang, K.C., Wegiel, J., and Malik, M.N., Walnut extract inhibits the fibrillization of amyloid beta-protein, and also defibrillizes its preformed fibrils. *Curr. Alzheimer Res.*, 1, 183–188, 2004.
59. Muthaiyah, B., Essa, M.M., Chauhan, V., and Chauhan, A., Protective effects of walnut extract against amyloid beta peptide-induced cell death and oxidative stress in PC12 cells. *Neurochem Res.*, 36, 2096–2103, 2011.
60. Muthaiyah, B., Essa, M.M., Lee, M., Chauhan, V., Kaur, K., and Chauhan, A., Dietary supplementation of walnuts improves memory deficits and learning skills in transgenic mouse model of Alzheimer's Disease. *J. Alzheimers Dis.,* 42, 1397–1405, 2014.
61. Pandareesh, M.D., Chauhan, V., and Chauhan, A., Walnut supplementation in the diet reduces oxidative damage and improves antioxidant status in transgenic mouse model of Alzheimer's disease. *J. Alzheimers Dis.*, 64, 1295–1305, 2018.
62. An, L., Sun, Y., Zhang, W., Huang, X., Xue, R., Zhang, Y., and Wang, Y., Walnut diets up-regulate the decreased hippocampal neurogenesis and age-related cognitive dysfunction in d-galactose induced aged rats. *Food Funct.*, 9, 4755–4762, 2018.
63. Harandi, S., Golchin, L., Ansari, M., Moradi, A., Shabani, M., and Sheibani, V., Antiamnesic effects of walnuts consumption on scopolamine-induced memory impairments in rats. *Basic Clin. Neurosci.*, 6, 91–99, 2015.
64. Haider, S., Batool, Z., Ahmad, R.A., Siddiqui, R.A., and Haleem, D.J., Walnut supplementation reverses the scopolamine-induced memory impairment by restoration of cholinergic function *via* mitigating oxidative stress in rats: A potential therapeutic intervention for age related neurodegenerative disorders. *Metab. Brain Dis.*, 33, 39–51, 2018.
65. Kulkarni, K.S., Kasture, S.B., and Mengi, S.A., Efficacy study of *Prunus amygdalus* (almond) nuts in scopolamine-induced amnesia in rats. *Indian J. Pharmacol.*, 42, 168–173, 2010.
66. Batool, Z., Sadir, S., Liaquat, L., Tabassum, S., Madiha, S., Rafiq, S., Tariq, S. et al., Repeated administration of almonds increases brain acetylcholine levels and enhances memory function in healthy rats while attenuates memory deficits in animal model of amnesia. *Brain Res. Bull.*, 120, 63–74, 2016.
67. Batool, Z., Tabassum, S., Siddiqui, R.A., and Haider, S., Dietary supplementation of almond prevents oxidative stress by advocating antioxidants and attenuates impaired aversive memory in male rats. *Plant Foods Hum. Nutr.*, 73, 7–12, 2018.
68. Bahaeddin, Z., Yans, A., Khodagholi, F., Hajimehdipoor, H., and Sahranavard, S., Hazelnut and neuroprotection: Improved memory and hindered anxiety in response to intra-hippocampal Aβ injection. *Nutr. Neurosci.*, 20, 317–326, 2017.
69. Singh, S., Dharamveer, P., and Kulshreshtha, M., Pharmacological approach of *Pistacia vera* fruit to assess learning and memory potential in chemically-induced memory impairment in mice. *Cent. Nerv. Syst. Agents Med. Chem.*, 19, 125–132, 2019.

70. Gorji, N., Moeini, R., and Memariani, Z., Almond, hazelnut and walnut, three nuts for neuroprotection in Alzheimer's disease: A neuropharmacological review of their bioactive constituents. *Pharmacol Res.*, 129, 115–127, 2018.
71. Baker, E.J., Miles, E.A., Burdge, G.C., Yaqoob, P., and Calder, P.C., Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. *Prog. Lipid Res.*, 64, 30–56, 2016.
72. Zhao, G., Etherton, T.D., Martin, K.R., Gillies, P.J., West, S.G., and Kris-Etherton, P.M., Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. *Am. J. Clin. Nutr.*, 85, 385–391, 2007.
73. Zhang, Y., Chen, J., Qiu, J., Li, Y., Wang, J., and Jiao, J., Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: A dose-response meta-analysis of 21 cohort studies. *Am. J. Clin. Nutr.*, 103, 330–340, 2016.
74. van de Rest, O., Wang, Y., Barnes, L.L., Tangney, C., Bennett, D.A., and Morris, M.C., APOE epsilon4 and the associations of seafood and long-chain omega-3 fatty acids with cognitive decline. *Neurology*, 86, 2063–2070, 2016.
75. Staubo, S.C., Aakre, J.A., Vemuri, P., Syrjanen, J.A., Mielke, M.M., Geda, Y.E., Kremers, W.K. et al., Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. *Alzheimer's Dement.*, 13, 168–177, 2017.
76. Morris, M.C., Brockman, J., Schneider, J.A., Wang, Y., Bennett, D.A., Tangney, C.C., and van de Rest, O., Association of seafood consumption, brain mercury level, and APOE ε4 status with brain neuropathology in older adults. *JAMA*, 315, 489–497, 2016.
77. Snowden, S.G., Ebshiana, A.A., Hye, A., An, Y., Pletnikova, O., O'Brien, R., Troncoso, J. et al., Association between fatty acid metabolism in the brain and Alzheimer disease neuropathology and cognitive performance: A nontargeted metabolomic study. *PLoS Med.*, 14, e1002266, 2017.
78. Geleijnse, J.M., Giltay, E.J., and Kromhout, D., Effects of n-3 fatty acids on cognitive decline: A randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. *Alzheimer's Dement.*, 8, 278–287, 2012.
79. Blondeau, N., Lipsky, R.H., Bourourou, M., Duncan, M.W., Gorelick, P.B., and Marini, A.M., Alpha-linolenic acid: An omega-3 fatty acid with neuroprotective properties-ready for use in the stroke clinic? *Biomed. Res. Int.*, 2015, 519830, 2015.
80. Gao, H., Yan, P., Zhang, S., Nie, S., Huang, F., Han, H., Deng, Q. et al., Chronic alpha-linolenic acid treatment alleviates age-associated neuropathology: Roles of PERK/eIF2alpha signaling pathway. *Brain Behav. Immun.*, 57, 314–325, 2016.
81. Gao, H., Yan, P., Zhang, S., Huang, H., Huang, F., Sun, T., Deng, Q. et al., Long-term dietary alpha-linolenic acid supplement alleviates cognitive impairment correlate with activating hippocampal CREB signaling in natural aging rats. *Mol. Neurobiol.*, 53, 4772–4786, 2016.
82. Lee, A.Y., Lee, M.H., Lee, S., and Cho, E.J., Neuroprotective effect of alpha-linolenic acid against Aβ-mediated inflammatory responses in C6 glial cell. *J. Agric. Food Chem.*, 66, 4853–4861, 2018.
83. Figueiredo, T.H., Harbert, C.L., Pidoplichko, V., Almeida-Suhett, C.P., Pan, H., Rossetti, K., Braga, M.F.M. et al., Alpha-linolenic acid treatment reduces the contusion and prevents the development of anxiety-like behavior induced by a mild traumatic brain injury in rats. *Mol. Neurobiol.*, 55, 187–200, 2018.

84. Qi, W., Gutierrez, G.E., Gao, X., Dixon, H., McDonough, J.A., Marini, A.M., and Fisher, A.L., The ω-3 fatty acid α-linolenic acid extends *Caenorhabditis elegans* lifespan *via* NHR-49/PPARα and oxidation to oxylipins. *Aging Cell*., 16, 1125–1135, 2017.
85. Del Rio, D., Rodriguez-Mateos, A., Spencer, J.P., Tognolini, M., Borges, G., and Crozier, A., Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid. Redox Signal.*, 18, 1818–1892, 2013.
86. Sánchez-González, C., Ciudad, C.J., Noé, V., and Izquierdo-Pulido, M., Health benefits of walnut polyphenols: An exploration beyond their lipid profile. *Crit. Rev. Food Sci. Nutr.*, 57, 3373–3383, 2017.
87. Torabian, S., Haddad, E., Rajaram, S., Banta, J., and Sabaté, J., Acute effect of nut consumption on plasma total polyphenols, antioxidant capacity and lipid peroxidation. *J. Hum. Nutr. Diet.*, 22, 64–71, 2009.
88. Haddad, E.H., Gaban-Chong, N., Oda, K., and Sabaté, J., Effect of a walnut meal on postprandial oxidative stress and antioxidants in healthy individuals. *Nutr. J.*, 13, 4, 2014.
89. Gasperotti, M., Passamonti, S., Tramer, F., Masuero, D., Guella, G., Mattivi, F., and Vrhovsek, U., Fate of microbial metabolites of dietary polyphenols in rats: Is the brain their target destination? *ACS Chem. Neurosci.*, 6, 1341–1352, 2015.
90. Chen, T.Y., Kritchevsky, J., Hargett, K., Feller, K., Klobusnik, R., Song, B.J., Cooper, B. et al., Plasma bioavailability and regional brain distribution of polyphenols from apple/grape seed and bilberry extracts in a young swine model. *Mol. Nutr. Food. Res.*, 59, 2432–2447, 2015.
91. Figueira, I., Garcia, G., Pimpao, R.C., Terrasso, A.P., Costa, I., Almeida, A.F., Tavares, L. et al., Polyphenols journey through blood–brain barrier towards neuronal protection. *Sci. Rep.*, 7, 11456, 2017.
92. Sarubbo, F., Moranta, D., and Pani, G., Dietary polyphenols and neurogenesis: Molecular interactions and implication for brain ageing and cognition. *Neurosci. Biobehav. Rev.*, 90, 456–470, 2018.
93. Kesse-Guyot, E., Fezeu, L., Andreeva, V.A., Touvier, M., Scalbert, A., Hercberg, S., and Galan, P., Total and specific polyphenol intakes in midlife are associated with cognitive function measured 13 years later. *J. Nutr.*, 111, 1–8, 2012.
94. Lefèvre-Arbogast, S., Gaudout, D., Bensalem, J., Letenneur, L., Dartigues, J.F., Hejblum, B.P., Féart, C. et al., Pattern of polyphenol intake and the long-term risk of dementia in older persons. *Neurology*, 90, e1979–e1988, 2018.
95. Macready, A.L., Kennedy, O.B., Ellis, J.A., Williams, C.M., Spencer, J.P., and Butler, L.T., Flavonoids and cognitive function: A review of human randomized controlled trial studies and recommendations for future studies. *Genes Nutr.*, 4, 227–242, 2009.
96. Farzaei, M.H., Rahimi, R., Nikfar, S., and Abdollahi, M., Effect of resveratrol on cognitive and memory performance and mood: A meta-analysis of 225 patients. *Pharmacol Res.*, 128, 338–344, 2018.
97. Castelli, V., Grassi, D., Bocale, R., d'Angelo, M., Antonosante, A., Cimini, A., Ferri, C. et al., Diet and brain health: Which role for polyphenols? *Curr. Pharm. Des.*, 24, 227–238, 2018.
98. Tordjman, S., Chokron, S., Delorme, R., Charrier, A., Bellissant, E., Jaafari, N., and Fougerou, C., Melatonin: Pharmacology, functions and therapeutic benefits. *Curr. Neuropharmacol.*, 15, 434–443, 2017.
99. Wu, Y.H., Feenstra, M.G., Zhou, J.N., Liu, R.Y., Toranõ, J.S., Van Kan, H.J., Fischer, D.F. et al., Molecular changes underlying reduced pineal melatonin

levels in Alzheimer disease: Alterations in preclinical and clinical stages. *J. Clin. Endocrinol. Metab.*, 88, 5898–5906, 2003.
100. Zhou, J.N., Liu, R.Y., Kamphorst, W., Hofman, M.A., and Swaab, D.F., Early neuropathological Alzheimer's changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels. *J. Pineal. Res.*, 35, 125–130, 2003.
101. Lahiri, D.K., Chen, D.M., Lahiri, P., Bondy, S., and Greig, N.H., Amyloid, cholinesterase, melatonin, and metals and their roles in aging and neurodegenerative diseases. *Ann. N.Y. Acad. Sci.*, 1056, 430–449, 2005.
102. Meng, X., Li, Y., Li, S., Zhou, Y., Gan, R.Y., Xu, D.P., and Li, H.B., Dietary sources and bioactivities of melatonin. *Nutrients*, 9, E367, 2017.
103. Reiter, R.J., Manchester, L.C., and Tan, D.X., Melatonin in walnuts: Influence in levels of melatonin and total antioxidant capacity of blood. *Nutrition*, 21, 920–924, 2005.
104. Segura, R., Javierre, C., Lizarraga, M.A., and Ros, E., Other relevant components of nuts: Phytosterols, folates and minerals. *Br. J. Nutr.*, 96(Suppl. 2), S36–S44, 2006.
105. Vanmierlo, T., Bogie, J.F., Mailleux, J., Vanmol, J., Lütjohann, D., Mulder, M., and Hendriks, J.J., Plant sterols: Friend or foe in CNS disorders? *Prog. Lipid Res.*, 58, 26–39, 2015.
106. Burg, V.K., Grimm, H.S., Rothhaar, T.L., Grösgen, S., Hundsdörfer, B., Haupenthal, V.J., Zimmer, V.C. et al., Plant sterols the better cholesterol in Alzheimer's disease? A mechanistical study. *J. Neurosci.*, 33, 16072–16087, 2013.
107. Vilahur, G., Ben-Aicha, S., Diaz, E., Badimon, L., and Padro, T., Phytosterols and inflammation. *Curr. Med. Chem.*, 2018, June 22. doi: 10.2174/0929867325666180622151438 [Epub ahead of print].
108. Mathur, P., Ding, Z., Saldeen, T., and Mehta, J.L., Tocopherols in the prevention and treatment of atherosclerosis and related cardiovascular disease. *Clin. Cardiol.*, 38, 570–576, 2015.
109. Abdallah, I.B., Tlili, N., Martinez-Force, E., Rubio, A.G., Perez-Camino, M.C., Albouchi, A., and Boukhchina, S., Content of carotenoids, tocopherols, sterols, triterpenic and aliphatic alcohols, and volatile compounds in six walnuts (*Juglans regia* L.) varieties. *Food Chem.*, 173, 972–978, 2015.
110. Devore, E.E., Grodstein, F., van Rooij, F.J., Hofman, A., Stampfer, M.J., Witteman, J.C., and Breteler, M.M., Dietary antioxidants and long-term risk of dementia. *Arch. Neurol.*, 67, 819–825, 2010.
111. Mullan, K., Cardwell, C.R., McGuinness, B., Woodside, J.V., and McKay, G.J., Plasma antioxidant status in patients with Alzheimer's disease and cognitively intact elderly: A meta-analysis of case-control studies. *J. Alzheimers Dis.*, 62, 305–317, 2018.
112. Farina, N., Llewellyn, D., Isaac, M.G., and Tabet, N., Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database Syst. Rev.*, 1, CD002854, 2017.
113. Morris, M.C., Schneider, J.A., Li, H., Tangney, C.C., Nag, S., Bennett, D.A., Honer, W.G., and Barnes, L.L., Brain tocopherols related to Alzheimer's disease neuropathology in humans. *Alzheimer's Dement.*, 11, 32–39, 2015.
114. Gugliandolo, A., Bramanti, P., and Mazzon, E., Role of vitamin E in the treatment of Alzheimer's disease: Evidence from animal models. *Int. J. Mol. Sci.*, 18, E2504, 2017.
115. Zheng, Y., and Cantley, L.C., Toward a better understanding of folate metabolism in health and disease. *J. Exp. Med.*, 216, 253–266, 2019.

116. Enderami, A., Zarghami, M., and Darvishi-Khezri, H., The effects and potential mechanisms of folic acid on cognitive function: A comprehensive review. *Neurol. Sci.*, 39, 1667–1675, 2018.
117. Araújo, J.R., Martel, F., Borges, N., Araújo, J.M., and Keating, E., Folates and aging: Role in mild cognitive impairment, dementia and depression. *Ageing Res. Rev.*, 22, 9–19, 2015.
118. Smith, A.D., and Refsum, H., Homocysteine, B vitamins, and cognitive impairment. *Annu. Rev. Nutr.*, 36, 211–239, 2016.
119. Tong, B.C., and Barbul, A., Cellular and physiological effects of arginine. *Mini Rev. Med. Chem.*, 4, 823–832, 2004.
120. Ozawa, M., Ninomiya, T., Ohara, T., Hirakawa, Y., Doi, Y., Hata, J., Uchida, K. et al., Self-reported dietary intake of potassium, calcium, and magnesium and risk of dementia in the Japanese: The Hisayama Study. *J. Am. Geriatr. Soc.*, 60, 1515–1520, 2012.
121. Cherbuin, N., Kumar, R., Sachdev, P.S., and Anstey, K.J., Dietary mineral intake and risk of mild cognitive impairment: The PATH through life project. *Front. Aging Neurosci.*, 6, 1–8, 2014.
122. Nowak, K.L., Fried, L., Jovanovich, A., Ix, J., Yaffe, K., You, Z., and Chonchol, M., Dietary sodium/potassium intake does not affect cognitive function or brain imaging indices. *Am. J. Nephrol.*, 47, 57–65, 2018.
123. Barbagallo, M., Belvedere, M., Di Bella, G., and Dominguez, L.J., Altered ionized magnesium levels in mild-to-moderate Alzheimer's disease. *Magnes. Res.*, 24, S115–S121, 2011.
124. Adebamowo, S.N., Spiegelman, D., Willett, W.C., and Rexrode, K.M., Association between intakes of magnesium, potassium, and calcium and risk of stroke: 2 cohorts of US women and updated meta-analyses. *Am. J. Clin. Nutr.*, 10, 269–1277, 2015.
125. Rosique-Esteban, N., Guasch-Ferré, M., Hernández-Alonso, P., and Salas-Salvadó, J., Dietary magnesium and cardiovascular disease: A review with emphasis in epidemiological studies. *Nutrients*, 10, E168, 2018.
126. Jacobs, D.R. Jr., and Tapsell, L.C., Food, not nutrients, is the fundamental unit in nutrition. *Nutr. Rev.*, 65, 439–450, 2007.

Chapter 12

Nuts in Healthy Dietary Patterns and Dietary Guidelines

Elizabeth P. Neale and Linda C. Tapsell

12.1 Introduction 290
12.2 Nuts as Components of Healthy Dietary Patterns 290
12.2.1 Mediterranean Dietary Patterns 290
12.2.2 Vegetarian and Vegan Dietary Patterns 291
12.2.3 Dietary Approaches to Stop Hypertension 292
12.2.4 Impact of Nut Consumption on Healthy Dietary Patterns 292
12.3 The Inclusion of Nuts in Dietary Guidelines 293
12.3.1 Dietary Guidelines Established in the United States, Canada/Australia, New Zealand/the United Kingdom, and Ireland 295
12.3.2 Dietary Guidelines in the Mediterranean Region 302
12.3.3 Dietary Guidelines in Northern European Regions 303
12.3.4 Dietary Guidelines in South Asia and Asia 303
12.3.5 Dietary Guidelines in South American, Caribbean, and African Regions 304
12.4 Descriptive Consumption of Nuts 305
12.5 Conclusion 306
References 307

12.1 Introduction

Habitual consumption of nuts has been associated with a range of health benefits, particularly reduced risk of cardiovascular diseases (CVD) and coronary heart disease (CHD) [1,2]. Nut intake has also been shown to result in favorable changes in biomarkers of disease development and progression, including lipid levels [3], chronic inflammation [4,5], and endothelial function [4], among others.

The health benefits associated with nut consumption are thought to be linked to the unique nutritional profile of nuts. For example, nuts, particularly walnuts, are rich sources of polyunsaturated fatty acids (PUFA) such as α-linolenic acid [5]. Nuts also contain fiber, phytosterols, and antioxidants such as vitamin E, selenium, and polyphenols [5]. Unique features of nut composition, such as the encapsulation of their fatty acids within cell walls, leading to incomplete digestion and fat malabsorption, may also play a role in the negligible effects on body weight seen with regular nut consumption despite their energy density [6,7].

It should be noted, however, that we do not consume individual nutrients or foods in isolation, but rather whole diets comprising multiple foods [8]. Thus, while it is possible to identify their nutritional contribution, the overall health benefit from consuming nuts tends to be observed within the context of a whole diet. In part, dietary guidelines reflect this position by referring to a range of foods recommended for consumption, but they do not necessarily place foods in the context of meals and cuisines. In different regions of the world, nuts are consumed in varying amounts. This may reflect culinary patterns and cultural uses of food, but it can also highlight challenges for the implementation of dietary guidelines. This chapter discusses the significance of nuts in healthy dietary patterns and summarizes the position of nuts in a selection of dietary guidelines throughout the world. To view discordance between recommendations and consumption patterns, self-reported nut consumption is also considered from national surveys.

12.2 Nuts as Components of Healthy Dietary Patterns

Nuts have traditionally appeared in studies of dietary patterns associated with a range of health benefits, including reduced risk of disease and improved weight management [3]. These patterns can also be cuisine-based, such as seen in the Mediterranean diet and vegetarian diets, or specifically designed for disease management, as was the case with the Dietary Approaches to Stop Hypertension (DASH) diet.

12.2.1 Mediterranean Dietary Patterns

The Mediterranean diet describes the traditional dietary pattern of areas in the Mediterranean region, including Spain, Southern Italy and Turkey, Greece, and Crete [9]. Whilst there are variations between regions, the Mediterranean diet is typically characterized by a high intake of olive oil, fruits, vegetables, whole grains, and legumes, with limited intake of red meats and processed foods [9]. Nuts, including walnuts, almonds, hazelnuts, and pine nuts, also feature as key components of the Mediterranean diet [10].

The recent landmark study conducted throughout Spain, the Prevención con Dieta Mediterránea (PREDIMED) trial, tested the effects of a Mediterranean diet supplemented with either mixed nuts or extra virgin olive (EVOO) compared to a low-fat control diet [10]. The study arm supplemented with nuts received 30 g of mixed nuts (15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts) per day. Participants were also provided with shopping lists, meal plans, and recipes. Nut consumption also featured in a 14-item assessment tool designed to determine compliance to the Mediterranean diet, with consumption of three or more 30 g servings of nuts per week being allocated one point towards the total dietary score [11].

The PREDIMED study produced good compliance with nut consumption, and after a median follow-up of 4.8 years, a 28% reduction in the primary composite end point (myocardial infarction, stroke, or death from a cardiovascular cause) was reported compared to the low fat diet group [10]. Secondary analyses of the PREDIMED study have indicated that consumption of nuts (or EVOO) in the context of a Mediterranean diet also resulted in favorable health outcomes such as reduced blood pressure [12], reduced incidence of type-2 diabetes (T2D) [13], and peripheral artery disease [14], as well as reductions in levels of inflammatory biomarkers [15].

The role of the supplemented foods (mixed nuts and EVOO) was debated in the literature, given that differences between diet groups in individual food group consumption were mainly observed with the supplemented foods [16]. However, analyses of compliance to the overall Mediterranean dietary pattern found significant differences between groups, with the Mediterranean diet groups scoring higher than the controls on Mediterranean diet scores [17]. This meant that while the mixed nuts and EVOO may have driven shifts in dietary patterns, the overall dietary pattern was different between groups, and adherence to the Mediterranean diet, the main dietary variable of concern, was achieved. Nevertheless, the specific inclusion of nuts within the Mediterranean diet confirmed that they contributed to the improvements in health outcomes.

12.2.2 Vegetarian and Vegan Dietary Patterns

In contrast to the Mediterranean diet, vegetarian and vegan dietary patterns are characterized by the foods they exclude, ranging from red meat, chicken, and fish to eggs and dairy for individuals following a vegan diet. Consumption of a vegetarian or vegan dietary pattern has been associated with a range of health benefits, including reductions in blood pressure [18] and reductions in mortality from heart disease and cancer, but not of total cardiovascular and cerebrovascular diseases or all-cause mortality [19].

Given that many of the foods excluded in a vegetarian or vegan diet are high in protein, nuts provide an important source of protein in these dietary patterns. Emerging evidence suggests that substitution of plant protein, such as that provided by nuts, in place of protein from animal sources is associated with reduced risk of all-cause mortality [20] and improved glycemic control [21]. Although the evidence base in this area is complex due to variations between foods sources of protein [22], nuts appear particularly important in contributing to the health benefits derived from vegetarian dietary patterns.

12.2.3 Dietary Approaches to Stop Hypertension

Unlike the Mediterranean and vegetarian/vegan dietary patterns, which are informed by traditional cultural habits or ethical beliefs, the DASH diet was specifically designed to investigate the effect of a whole dietary pattern comprising favorable foods and nutrients on the management of hypertension [23,24]. The initial randomized controlled trial exploring the effects of a DASH diet featured a dietary pattern rich in fruits, vegetables, and low-fat dairy foods, with reduced intakes of snacks and sweets compared to the control diet, which was designed to provide nutrients in similar quantities to the typical American diet [23]. The DASH diet also contained a higher quantity of nuts than the control diet, with the 2,100 kcal DASH diet containing 0.7 servings of nuts, seeds, and legumes per day (compared to 0 servings in the control diet). Consumption of the DASH diet for 8 weeks resulted in significantly greater reductions in systolic and diastolic blood pressure than seen in the control group.

Following the success of the initial study using the DASH diet, DASH-sodium was developed, a multicenter randomized controlled trial exploring the effects of the DASH diet at high, intermediate, and low sodium levels [25]. The DASH-sodium diet continued to feature nuts, including 0.5 servings of nuts and seeds per day, in a 2,100 kcal diet [26]. While even the higher sodium DASH diet was found to significantly reduce blood pressure in comparison to the control diet, the combined effect of the DASH diet and reduced sodium intake resulted in the largest blood pressure reduction [27]. Thus, both the dietary pattern and the reduction in sodium content worked together to produce lower blood pressure.

In addition to its favorable effects on blood pressure, consumption of the DASH diet has been found to result in improvements in a range of other health outcomes. Consumption of the DASH diet has been reported to result in improvements in blood glucose control as well as reductions in the inflammatory biomarker C-reactive protein in diabetic individuals [28]. Evidence from a recent meta-analysis of observational studies confirms the anti-hypertensive effect of the DASH-style diets together with reduction of total and low-density lipoprotein cholesterol levels, and a greater beneficial effect in improving cardiovascular risk factors was apparent in subjects with an increased cardiometabolic risk [29]. A meta-analysis of observational studies exploring DASH-style dietary patterns among other healthy diets found reductions in the risk of CVD, cancer, T2D, neurodegenerative disease, and all-cause mortality [30]. The strong evidence base surrounding the DASH diet has underpinned much of the understanding of foods that make up healthy dietary patterns, with nuts continuing to appear as a key component.

12.2.4 Impact of Nut Consumption on Healthy Dietary Patterns

In addition to contributing to physiological effects, emerging evidence suggests that consumption of nuts may play a role in mediating the quality of the overall dietary pattern. In observational research, nut consumers also report higher intakes of other healthy foods, such as fruits, dark-green vegetables, and fish, compared to subjects reporting no or lower nut consumption [31–33]. Results from recent clinical trials indicate that diet quality improves in participants supplemented with walnuts

[34,35], resulting from increased consumption of healthy foods such as seafood and sources of plant protein [36]. These results suggest that consumption of nuts drives changes in dietary patterns by facilitating increased intake of other healthy foods, meaning that in addition to forming a key component of healthy dietary patterns, nuts may also be central to developing and maintaining healthy dietary indices.

As nutrition research shifts from a focus on individual nutrients to whole foods and diets [37], the evidence base continues to demonstrate the range of health benefits associated with healthy dietary patterns such as those described here. Recent meta-analyses have demonstrated the favorable effects of consuming healthy dietary patterns (which typically include nuts), including reductions in risk of T2D [38], reductions in blood pressure [29,39], and improvements in markers of chronic inflammation [40–42] and endothelial function [42]. Evidence for the relationship between dietary factors and chronic disease risk is evaluated in the development of dietary guidelines [37]. Whether nuts are considered in this evidence review depends on the determination of the associated research questions. Cultural eating patterns and local culinary habits may also be taken into account. The next section of this review considers the range of representations of nuts in dietary guidelines and how they compare with usual consumption patterns in the population.

12.3 The Inclusion of Nuts in Dietary Guidelines

Dietary guidelines are tools for translating the evidence base on nutrients, foods, and dietary patterns to consumers, for the dual purposes of ensuring adequate nutrient intake and decreasing the risk of chronic disease [37]. As highlighted above, there is substantial evidence for the positive relationships between consumption of nuts and dietary patterns featuring nuts and improvements in risk of chronic disease. This evidence base has been translated to consumer recommendations in food-based dietary guidelines globally [43], many of which promote nut consumption (Table 12.1). The positioning of nuts within dietary guidelines is often reflective of the food supply in a region; therefore, a selection of food-based dietary guidelines exemplifying guidelines surrounding nut consumption is discussed below. Selected guidelines are also limited to those published in the English language. Specific recommendations for nut consumption from these dietary guidelines, including recommended and serving sizes, are summarized in Table 12.2.

Given the large number of foods available for consumption, dietary guidance systems tend to group foods according to their primary nutrient composition. When this nutrient is protein, nuts can be found classified with other protein-rich foods such as meat, eggs, and fish [44–46]. As nuts also contain a large proportion of lipid, they have also been categorized with oils. Recommendations for nut consumption vary between dietary guidelines established for specific countries, ranging from advice presented at the food group level without specific reference to nuts, for example in the United Kingdom [47], to advice to consume a given amount of nuts, for example the minimum of 15 g/day listed in the Dutch Dietary Guidelines [48]. Serving sizes also varied, although 15–30 g appeared to be the most common portion size used (Table 12.2).

Table 12.1 Food-Based Dietary Guidelines Referring to Nut Consumption

Country	*Publication Year*	*Guidelines Found in English*
Albania	2008	√
Antigua and Barbuda	2013	√
Australia	2013	√
Austria	2010	No
Belgium[a]	2005	No
Belize	2012	√
Benin	2015	No
Brazil	2014	√
Canada	2007	√
Colombia	2014	No
Croatia	2002	No
Fiji	2009	√
Greece	1999	√
Grenada	2006	√
Guatemala	2012	No
Guyana	2004	√
India	2011	√
Iran	2006	No
Ireland	2011	√
Jamaica	2015	√
Latvia	2008	No
Lebanon	2013	√
Malaysia	2010	√
Malta	2016	√
Namibia	2000	√
Netherlands	2015	√
New Zealand	2015	√
Nigeria	2001	√
Oman	2009	√
Philippines	2012	√
Qatar	2015	√
Saint Kitts and Nevis	2010	√
Saint Lucia	2007	√
Saint Vincent and the Grenadines	2006	√
Sierra Leone	2016	√
South Africa	2012	√
Spain	2008	No
Sri Lanka	2011	√
Sweden	2015	√

(*Continued*)

Table 12.1 (Continued) Food-Based Dietary Guidelines Referring to Nut Consumption

Country	*Publication Year*	*Guidelines Found in English*
Switzerland	2011	No
Turkey	2006	√
United Kingdom	2016	√
United States of America	2015	√

Source: Adapted from Food and Agriculture Organisation of the United Nations, Food-based Dietary Guidelines. Published online at: http://www.fao.org/nutrition/education/food-dietary-guidelines/home/en/ (accessed July 28, 2018).

[a] Guidelines refer to "nut oil."

12.3.1 Dietary Guidelines Established in the United States, Canada/Australia, New Zealand/ the United Kingdom, and Ireland

Nuts are presented in a similar fashion in the dietary guidelines of these largely English-speaking countries. Nuts are seen as part of a healthy diet and are aligned with certain other foods based on elements of their nutritional composition, with emphasis on macronutrients, lipid, and protein. The approach to the development of the guidelines is also similar.

The Dietary Guidelines for Americans (DGA) were updated in 2015 following a review of the 2010 edition by the DGA Advisory Committee [49,50]. The update involved a highly comprehensive review incorporating four approaches: (1) conducting original systematic reviews of the literature; (2) utilizing existing systematic reviews, meta-analyses, and scientific reports from Federal bodies or scientific organizations; (3) analyzing national data on disease prevalence and food and nutrient intakes; and (4) food pattern modeling [49].

The 2015–2020 DGA emphasize the importance of consuming a healthy dietary pattern, which evidence reviews characterized as being plant-based and containing high amounts of fruits and vegetables, whole grains, seafood, nuts, and legumes, whilst containing moderate amounts of low- or no-fat dairy foods, lower quantities of red and processed meat, and low amounts of sugar-sweetened foods and drinks as well as refined grains [50]. The DGA provides quantitative recommendations for food consumption within three different variations of healthy dietary patterns, in order to translate the guidelines into practical advice for consumers. The Healthy U.S.-Style Eating Pattern was designed to be an example of a healthy style of eating based on reported food consumption in the United States. Within this dietary pattern, it is recommended that individuals consume 5 oz-equivalents (~71 g) of nuts, seeds, and soy products per week in the context of a 2,000 kcal/day diet, with varying amounts recommended for lower and higher energy diets. Other healthy dietary patterns designed to allow for other styles of eating also incorporate nuts: the Healthy Mediterranean-Style Eating Pattern includes 5 oz-equivalents (~71 g) of nuts, seeds, and soy products per week in the context of a 2,000 kcal/day diet, whereas the Healthy Vegetarian Eating Pattern includes 14 oz-equivalents (~199 g)/ week. Within the eating patterns, one oz-equivalent (~28.4 g) is considered to be ½ oz (~14.2 g) of nuts/seeds, to account for their energy-dense nature.

Table 12.2 Summary of Nut Consumption Recommendations in Selected Food-Based Dietary Guidelines Globally

Country and Publication Year	*Food Group Used to Classify Nuts*	*Qualitative Guideline Relating to Nuts*	*Quantitative Guideline Relating to Nuts*	*Serving Size*	*References*
Australia, 2013	Lean meats, poultry, fish, eggs, tofu, nuts, seeds, and legumes/beans.	"Enjoy a wide variety of nutritious foods from these five groups every day …."	For total food group: • Males aged 19–50 years: 3 serves per day. • Females aged 19–50 years: 2 ½ serves/day[b].	30 g[a]	[53]
Brazil, 2014	Natural or minimally processed foods.	"Make natural or minimally processed foods the basis of your diet." "Variety means foods of all types – cereals, legumes, roots, tubers, vegetables, fruits, nuts, milk, eggs, and meat."	-	-	[69]
Canada, 2007	Meat and alternatives.	-	For total food group: • Males aged 19–50 years: 3 serves per day. • Females aged 19–50 years: 2 serves per day[c].	60 mL	[51]
Greece, 1999	Olives, pulses, and nuts.	-	"Eat three or four servings of olives, pulses, and nuts per week."	One serve = half the portion size served in restaurants	[64]

(*Continued*)

Table 12.2 (Continued) Summary of Nut Consumption Recommendations in Selected Food-Based Dietary Guidelines Globally

Country and Publication Year	*Food Group Used to Classify Nuts*	*Qualitative Guideline Relating to Nuts*	*Quantitative Guideline Relating to Nuts*	*Serving Size*	*References*
India, 2011	Oils, fats, nuts, and oilseeds.	"Eat a variety of foods to ensure a balanced diet." "Oils and nuts are calorie-rich foods, and are useful for increasing the energy density and quality of food."	-	-	[44]
Ireland, 2011	Meat, poultry, fish, and/or alternatives.	"Choose lean meat and poultry; include fish (oily is the best) and remember peas, beans, and lentils are good alternatives."[d]	For total food group: • Males aged 19–50 years: 1 "main meal" serve and 1–2 "light meal" serves per day. • Females aged 19–50 years: 1 "main meal" serve and 1 "light meal" serve per day[c].	One handful ("light meal'' serve)	[63]
Lebanon, 2013	Protein-rich foods.	"Consume legume-based dishes regularly and enjoy some unsalted nuts and seeds."	For total food group: • Consume 5–6 ½ servings per day[e].	15 g	[66]
Malaysia, 2010	Fish, meat, poultry, eggs, legumes, and nuts.	"Consume moderate amounts of fish, meat, poultry, eggs, legumes, and nuts." "Include nuts and seeds in weekly diet."	For total food group: • 2–3 servings per day.	-	[68]
Malta, 2016	Meat and alternative products.	"Select a wide variety of nutritious foods from each of the six food groups every day …."	Consume 80–90 g nuts per week (20 g 4–5 times per week).	20 g	[65]

(*Continued*)

Table 12.2 (Continued) Summary of Nut Consumption Recommendations in Selected Food-Based Dietary Guidelines Globally

Country and Publication Year	*Food Group Used to Classify Nuts*	*Qualitative Guideline Relating to Nuts*	*Quantitative Guideline Relating to Nuts*	*Serving Size*	*References*
The Netherlands, 2015	Nuts.	-	"Eat at least 15 g of unsalted nuts daily."	15 g	[48]
New Zealand, 2015	Legumes, nuts, seeds, fish and other seafood, eggs, poultry, and/or red meat with the fat removed.	"Enjoy a variety of nutritious foods every day including some legumes, nuts, seeds, fish and other seafood, eggs, poultry, and/or red meat with the fat removed."	Two or more servings of legumes, nuts, or seeds per day[f].	30 g	[55]
Nordic Nutrition Recommendations, 2012[g]	Nuts and seeds.	"Decrease energy density, increase micronutrient density, and improve carbohydrate quality." "Improve dietary fat quality by balancing the fatty acid proportions" (with nuts listed as a food to increase).	-	-	[59]
Sierra Leone, 2016	Oil, nuts, and seeds.	"Use oil in moderation and eat nuts and seeds."	-	½ cup[h]	[45]
Sri Lanka, 2011	Nuts and oil seed.	"Consume moderate amount of fats."	Nuts and oil seed: • 2–4 servings per day.	15 g	[46]
The United Kingdom, 2016	Beans, pulses, fish, eggs, meat, and other proteins.	"Eat some beans, pulses, fish, eggs, meat and other proteins (including 2 portions of fish every week, one of which should be oily)."[d]	-	-	[47]

(*Continued*)

Table 12.2 (Continued) Summary of Nut Consumption Recommendations in Selected Food-Based Dietary Guidelines Globally

Country and Publication Year	*Food Group Used to Classify Nuts*	*Qualitative Guideline Relating to Nuts*	*Quantitative Guideline Relating to Nuts*	*Serving Size*	*References*
The United States, 2015	Protein foods.	"Consume a healthy eating pattern that accounts for all foods and beverages within an appropriate calorie level." "A healthy eating pattern is considered to include: a variety of vegetables and legumes, fruits, grains, fat-free or low-fat dairy, a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products, and oils."	Nuts, seeds, and soy products: • 5 oz-equivalents (~71 g) per week[i].	1 oz-equivalent (~28.4 g) = ½ oz (~14.2 g)	[50]

[a] Serve size used for the "lean meats, poultry, fish, eggs, tofu, nuts, seeds, and legumes/beans" group. When considered part of the "unsaturated spreads and oils group," a serve of nuts is 10 g.
[b] Guidelines given for Foundation Diet for adults aged 19–50 years. Younger or older individuals or those who are taller or more active have different requirements.
[c] Guidelines given for adults aged 19–50 years. Younger or older individuals have different requirements.
[d] Nuts not specifically mentioned in qualitative guidelines.
[e] In 2,000 kcal/day eating pattern. Recommended intakes vary at different energy levels.
[f] Or one serving of foods rich in animal protein per day.
[g] Used as the basis for the dietary guidelines of Denmark, Estonia, Finland, Iceland, Norway, and Sweden.
[h] Shelled groundnuts.
[i] In 2,000 kcal/day Healthy U.S.-Style Eating Pattern. Intakes vary in other recommended eating patterns and at different energy levels.

As with the United States DGA, Health Canada developed Canada's Food Guide [51] to promote healthy eating patterns for the national population. The guidelines were also developed based on evidence reviews evaluating the effect of food intake patterns on health outcomes. In addition, the guidelines were designed to align with current nutrient intake recommendations. Nuts were treated as part of the "meat and alternatives" group. Significantly, the accompanying resource document designed for educators and communicators notes that nuts are an energy-dense food, despite containing monounsaturated fatty acids (MUFA) and PUFA that are beneficial for cardiovascular health [52], implying the need to consider overall energy intakes in consequent dietary patterns. Nevertheless, there are culinary considerations; for example, the educator document contains suggestions for incorporating nuts into the diet, such as "add nuts to your vegetable stir-fry."

Unlike the United States DGA, Canada's Food Guide does not provide a specific recommendation for the amount of nuts to incorporate into a healthy dietary pattern. Instead, recommendations are made for the higher order "meat and alternatives" group, with guidance ranging from one serving per day (children aged 2–3 years) to three servings per day (males aged 18 years and older). One serving of shelled nuts is considered to be 60 mL (1/4 cup). Like the Australian Dietary Guidelines, highly active individuals are encouraged to consume additional foods from the core food group to meet their energy needs.

The Australian Dietary Guidelines [53] were updated in 2013 following a comprehensive series of evidence reviews. Systematic reviews of the evidence were conducted to explore the effect of nut and seed consumption on a range of outcomes, including risk of obesity and CVD. An umbrella review examining the effect of the Mediterranean diet on health or disease outcomes was also conducted. The Australian Dietary Guidelines recommend that Australians consume a variety of foods from the five food groups. Nuts are categorized with other protein-rich foods such as lean meat, poultry, fish, eggs, tofu, seeds, and legumes, with a serving of nuts considered to be 30 g. Like the DGA, the development of the Australian Dietary Guidelines utilized dietary modeling to translate nutrient requirements into recommended intakes of food groups [54]. Recommendations for the number of total servings of protein-rich foods varies between individuals based on age and gender, from one serving per day for children aged 2–3 years, to 3 ½ servings for pregnant women. In addition, nuts and seeds may also form part of an allowance for unsaturated-fat spreads and oils, with recommended intakes ranging from ½ serving (children aged 2–3 years), to 4 servings (men aged less than 70 years). In this case, a serving of unsaturated-fat spreads and oils is considered to be approximately 10 g of nuts. In addition to the recommended number of servings listed above, individuals who are taller or more active will also require additional doses of the five food groups and/or unsaturated-fat spreads and oils, as well as scope for including discretionary choices. These approaches demonstrate how advice on consumption of nuts is also framed around total dietary considerations, including dietary protein, fat, and total energy intake.

The New Zealand Ministry of Health released the Eating and Activity Guidelines for New Zealand Adults in 2015 [55], replacing the Food and Nutrition Guidelines for Adults [56] and incorporating physical activity guidelines (previously provided separately in Movement = Health [57]). The New Zealand Eating and Activity Guidelines were developed based on evidence reviews conducted for other dietary guidelines, including the Australian Dietary Guidelines [58], the

Nordic Nutrition Recommendations [59], and the DGA [49], in addition to systematic reviews conducted by global authorities such as the World Health Organization [60] and the World Cancer Research Fund [61]. With the release of the New Zealand Eating and Activity Guidelines, recommendations surrounding protein-rich foods were updated to align with the growing body of evidence for the beneficial effects of protein from plant and seafood sources [20,21]. As such, the protein-rich food group is now defined as "legumes, nuts, seeds, fish and other seafood, eggs, poultry (e.g., chicken), or red meat with the fat removed." Adults are recommended to consume either two or more servings of legumes, nuts, or seeds per day (with a serving of nuts defined as 30 g or a small handful), or one serving of foods rich in animal protein per day (such as fish or seafood, eggs, poultry, or red meat). The guidelines also include recommendations on how to include nuts in the diet, such as substituting nuts for less healthy foods. Thus, further shifts in considerations can be seen from this approach, moving to the protein source (plant or animal) and the need to make food choices at the expense of other foods in establishing healthy dietary patterns.

In the United Kingdom, the Eatwell Guide was released in 2016 by Public Health England [47], replacing the previous food guide, the Eatwell Plate. The revision was underpinned by food modeling based on the National Diet and Nutrition Survey as well as recommendations for nutrient consumption (the Dietary Reference Values) [62]. Nuts are categorized in the "beans, pulses, fish, eggs, meat, and other proteins" group in the Eatwell Guide. Unlike food guides from a number of other countries, nuts are not specifically mentioned in the food group name or listed in the recommendations for the group, which recommends consumers "eat more beans and pulses, two portions of sustainably sourced fish per week, one of which is oily." However, as has been the case in many guidelines to date, nuts are depicted pictorially in the guide and listed as an included component of the food group, but no additional details on types of nuts, serving sizes, or strategies for including nuts in the diet are provided.

Ireland's Healthy Eating Guidelines were revised in 2011 [63], prompted by the need to update the previous food guide to address a rising chronic disease burden. Revision of the existing food guide involved a process of evaluating the energy and nutrients content of diets aligning with the previous recommendations, and comparing these to requirements for various age and gender groups. The practicality of interpreting advice in the previous guide and the positioning of different food groups was also considered in the revision. As with the Eatwell Guide from the United Kingdom [47], nuts are referred to sparingly in the Irish Health Eating Guidelines. Nuts are considered to be part of the meat, poultry, fish, and/or alternatives food group, and consumers are advised to "choose lean meat and poultry; include fish (oily is best), and remember that peas, beans, and lentils are good alternatives." Nuts are also not specifically referred to in the detailed overview of the food groups, which provides recommendations on types of foods to include from each food group, as well as suggested cooking methods. Consumers are specifically advised to limit their intake of salted nuts, in order to reduce sodium intake. Thus, consideration of another nutrient, sodium, comes into play, and in association with food processing rather than the inherent nutritional composition of raw nuts.

As with a number of other guidelines globally, Ireland's Healthy Eating Guidelines recommend consumption levels by age and gender groups. Males aged between 15–50 years are advised to consume one "main meal" serving of foods from the meat, poultry, fish, and/or alternatives food group and 1–2 "light meal" servings

per day, whilst all other age and gender groups are recommended to consume one "main meal" and one "light meal" serving per day. Unsalted nuts are recommended as a potential option for a "light meal," with the serving size listed as a handful, or 1–2 teaspoons of peanut butter. This combines the consideration of the nuts as a single food group and culinary elements, bringing into play the concept of a meal.

In this set of guidelines from English speaking countries, the position of nuts can be seen to be somewhat variable and possibly ambiguous, particularly where concerns are present for energy and fat consumption. Challenges for guidelines development will remain with untangling the inter-relationships between dietary qualities, reflected in overall nutrient and total energy intakes, while still appreciating the unique nutritional package and the evidence of the health benefits of the consumption of nuts.

12.3.2 Dietary Guidelines in the Mediterranean Region

Rather than limit dietary fat, the Mediterranean cuisine can be seen to embrace it, but only as a result of commitment to naturally fat-rich plant foods, notably olive oil and nuts. Thus, there is a greater emphasis on foods themselves and then the type of fat they provide.

The Greek Dietary Guidelines were released in 1999 [64]. The guidelines specifically highlight nuts as a source of MUFA, vitamin E, and fiber. As a result, along with seeds, they are recommended as a healthy snack choice. A Greek version of the Harvard Mediterranean diet pyramid accompanies the guidelines and recommends consumption of 3–4 servings of olives, pulses, and nuts per week. One serving is considered to be equal to approximately half the portion size served in restaurants. With a largely plant-based diet, the inclusion of significant servings of these fat-rich foods would still maintain an overall balance in nutrient and energy intakes.

More recently, the Dietary Guidelines for Maltese Adults [65] was released in 2016. The guidelines and their accompanying food selection guide, the Healthy Plate, were developed following a review of the literature. Like many dietary guidelines in Europe, the Maltese dietary guidelines promote consumption of a Mediterranean dietary pattern. Nuts are considered to be part of the "meat and alternative products" food group, which also includes lean meat, fish, poultry, eggs, legumes, and seeds, although the guidelines also highlight nuts as a source of omega-3 fatty acids. The dietary guidelines recommend adults consume approximately 20 g of nuts 4–5 times a week (for a total of 80–90 g per week). Nuts are encouraged as a healthy snack option, and guidelines recommend the consumption of raw or roasted and otherwise unsalted nuts, rather than fried or salted varieties. Nuts are also promoted as an alternative to meat to promote sustainability. This introduced another dimension to the attribution of value to nuts. In addition the reference to cuisine, guidance on snacks and the limitation of added sodium reflect considerations beyond macronutrient composition.

The Food-Based Dietary Guidelines for Lebanese Adults were released in 2013 [66]. Nuts are classified in the "protein-rich foods" group, with lean red and white meat, eggs, legumes, and seeds. In the context of a 2,000 kcal diet, consumers are recommended to have 5–6 ½ servings of this group per day, with a serving of nuts considered to be 15 g. The 6th Guideline also specifically refers to nuts, recommending that individuals "consume legume-based dishes regularly and enjoy

some unsalted nuts and seeds," with the goal of increasing intakes of protein, fiber, and micronutrients. The Food-Based Dietary Guidelines for Lebanese Adults also include cuisine-based suggestions for increasing the intake of legumes, nuts, and seeds, including adding nuts to breakfast cereals, rice dishes, salads, homemade puddings, and fruit salads. Raw unsalted nuts are also suggested as a healthy option for snacking. In addition to the guideline recommending increased consumption of legumes, nuts, and seeds, the Lebanese Dietary Guidelines also highlight walnuts as an alternative source of omega-3 fatty acids for those who do not consume fish or fish oil supplements. Thus, the value of nuts is considered for an essential fatty acid as opposed to just protein, traditionally seen in its categorization with meats and similar foods.

12.3.3 Dietary Guidelines in Northern European Regions

The Nordic Nutrition Recommendations 2012 [59] are the basis for a number of dietary guidelines in Northern Europe, including Denmark, Estonia, Finland, Iceland, Norway, and Sweden. The recommendations were developed based on a number of comprehensive systematic reviews of the literature, with reference to additional scientific reports and recommendations from other expert bodies nationally and internationally.

The Nordic Nutrition Recommendations emphasize the important of consuming a dietary pattern rich in plant-based foods, featuring vegetables, fruits, pulses, nuts, seeds, and whole grains. The recommendations also encourage consumption of fish and seafood, vegetable oils and spreads, and reduced fat from dairy foods. Nuts are specifically highlighted as one of the foods consumers should eat more of in order to promote health. In reviewing the evidence for the effects of consumption of specific food groups on health, nuts are discussed with other plant foods such as vegetables, fruits, and berries. Significantly, nuts are promoted as a fiber-rich food and are also encouraged as a strategy for improving dietary fat quality.

In 2015, the Netherlands released their updated dietary guidelines, which had last been updated in 2006 [48]. The development of the 2015 Dutch Dietary Guidelines was informed by the body of evidence from background documents, such as pooled analyses, meta-analyses, and systematic reviews, on the relationships between nutrients, foods, and dietary patterns and chronic diseases. The Dutch Dietary Guidelines recommend the consumption of a plant-based dietary pattern, with reduced consumption of animal foods such as red meat. The guidelines specifically refer to increasing nut consumption, due to the relationship between nut intake and reduction of CHD risk. Unlike many other guidelines globally, the Dutch Dietary Guidelines include a guideline solely concerning nuts, where consumers are advised to "eat at least 15 g of unsalted nuts daily." This demonstrates an emergence of nuts being considered as a distinct food group.

12.3.4 Dietary Guidelines in South Asia and Asia

The revised version of the Dietary Guidelines for Indians was released in 2011, building on the first version which was initially published in 1998 [44]. The guidelines were revised following shifts to the socio-economic situation in India, which in

turn with globalization have resulted in an increased prevalence of obesity and other chronic diseases, although protein-energy malnutrition continues to be an issue for much of the population [67]. Within the Dietary Guidelines for Indians, nuts are considered to be part of the "Oils, fats, nuts, and oilseeds" group, a position seen in other countries. Nuts are highlighted as being useful to increase the energy density of the diet, and are also stated to be rich in protein, calcium, riboflavin, and folate. Nuts are also emphasized as a source of omega-3 fatty acids, with consumers being advised to substitute nuts in place of visible and invisible fat from animal products. Despite their energy density, nuts are still considered to a valuable component in the dietary prevention of obesity, with a diet rich in fruits, vegetables, legumes, nuts, and whole grains advised to consumers. Thus, the broader nutritional contribution of nuts remains important in this context.

The Malaysian Dietary Guidelines were updated in 2010 to include an expanded list of recommendations with more comprehensive information than the first version, published in 1999 [68]. Background information underpinning the guidelines was developed based on reviews of the literature. Within the Malaysian Dietary Guidelines, nuts are grouped with other protein-rich foods such as fish, meat, poultry, eggs, and legumes. Nuts are highlighted as being rich in fiber, protein, unsaturated fatty acids, and other vitamins and minerals, and are recommended to be consumed as alternatives to other protein-rich foods from animal sources, such as meat. However, the guidelines warn against excessive consumption due to the energy content of nuts, and limited consumption of salted nuts is recommended. The guidelines recommend that nuts and seeds be consumed in a weekly diet, with cuisine-based suggestions given such as the inclusion of nuts in vegetarian stir-fries. The Malaysian food pyramid also provides quantitative recommendations for other foods in this food group (for example ½–2 servings of meat, poultry, and eggs per day). Although specific recommendations regarding nuts are not provided, their presence in culinary guidance is similar to that seen elsewhere.

The revised version of the Food Based Dietary Guidelines for Sri Lankans [46] was released in 2011. Nuts are classified in the "nuts and oil seed" group, and adults are recommended to eat 2–4 servings from this food group per day (one serving is considered to be 15 g or one tablespoon of nuts). Nuts are emphasized as being good sources of fiber, folate, vitamin E, selenium, and MUFA. These nutrients would become available in their recommendation as a healthy snack.

12.3.5 Dietary Guidelines in South American, Caribbean, and African Regions

The Dietary Guidelines for the Brazilian Population, updated in 2014 [69], specifically highlight the importance of considering whole foods and dietary patterns, rather than focusing solely on individual nutrients. The guidelines were developed in a joint initiative of the Ministry of Health and the Center for Epidemiological Research in Nutrition and Health of the University of São Paulo and were supported by the Brazilian Pan American Health Organization Office. The development process used in the guidelines was highly participatory, using working groups made up of a range of experts, with stages of evaluation and public consultation. Rather than prescribing amounts of foods to consume, the Dietary Guidelines for the Brazilian

Population recommends ten steps to achieving a healthy diet. A distinguishing feature of these guidelines is seen with the initial focus on consuming a variety of natural or minimally processed foods, with a particular emphasis on plant foods. Nuts without the addition of salt or sugar are categorized as a natural or minimally processed food in the guidelines. The addition of salt or sugar to nuts results in them being considered to be processed and, as a result, consumption of these varieties are not encouraged. The Brazilian Dietary Guidelines also emphasize the importance of considering the role of individual foods within the wider cuisine. As such, the guidelines contain suggestions and images depicting healthy meal options. Nuts are recommended as components of salads, sauces, and other dishes, or as a snack. The importance of cuisine and the foods contained therein is reflected in these guidelines.

The Food-Based Dietary Guidelines for Jamaica were released in 2015 [70]. The guidelines were developed following focus group discussions, household trials, and consultations with stakeholders. The guidelines are aimed at those aged 2 years and older and are designed to address health problems associated with under and over-nutrition, including chronic diseases such as CVD and T2D. Of the eight food-based dietary guidelines, one guideline recommends Jamaicans include peas, beans, and nuts in their daily meals as a way of increasing fiber intake, providing dietary variety, and improving satiety. Unsalted nuts are also highlighted as a healthy snack. Quantitative recommendations for nut consumption vary by age, gender, and activity. In the context of a 2,200 kcal/day diet, consumers are recommended to eat three servings of legumes and nuts per day, with a serving proving 73 kcal (listed as being equivalent to 16 peanuts, 7 cashews, or 10 almonds). This is a substantial consideration for this food group, reflecting their significance in the local diet.

In Africa, the Sierra Leone Food-Based Dietary Guidelines for Healthy Eating were published in 2016 [45], with technical guidance and supervision from the Food and Agriculture Organization of the United Nations. The Sierra Leone guidelines were designed to address the prevention and management of both under-nutrition and overweight/obesity. Unlike a number of other guidelines worldwide, due to differences in nutrient profile, nuts are not grouped with protein foods but are instead classified with other dietary sources of fat such as oils and seeds. The nutrient-dense nature of nuts is highlighted, and consumption of nuts is recommended. For example, in mixed dishes, the role of nuts is highlighted as a source of protein and nutrients, without which individuals could risk nutrient inadequacy or deficiency. Within the Sierra Leone guidelines, an example of a serving of nuts given is half a cup of shelled groundnuts, and when used in mixed dishes it is recommended that each individual consume enough nuts and seeds to fill their palm. Again, the positioning of nuts is substantial in this population where problems of both under-nutrition and obesity are present.

12.4 Descriptive Consumption of Nuts

The consumption of nuts reported within a given population is a consideration for their inclusion in dietary guidelines. National surveys indicate that nut consumption may fall short of recommendations in a number of countries, suggesting a disconnection between dietary guidance and consumer behavior. For example, the 2011–2013

Australian Health Survey identified that only 15.6% of individuals reported consuming nuts or nut products on the day of the survey [71]. Mean consumption of nuts and nut products between 2011 and 2013 in the Australian Health Survey was 5.2 g, likely due to the large proportion of the population who did not consume nuts. The 2008–2009 New Zealand Adult Diet Survey also reported similar mean intakes of total nuts to that found in Australia, although a higher proportion of nut consumers were identified in New Zealand, with 28.9% of the population consuming nuts on the day of the survey [72]. This variation may in part be due to differences in survey methodology, as the New Zealand survey considered "nuts from hidden sources" such as muesli bars to contribute to total nut intake, whereas the Australian survey did not. It should also be noted that available data from both the Australian and New Zealand surveys represent a single day's consumption, which may have resulted in under-estimation of the proportion of nut consumers.

Results from other national surveys also suggest a low proportion of nut consumers in other countries. For example, O'Neil et al. [32] explored nut consumption reported in the National Health and Nutrition Examination Survey in the United States in 2005–2010. In adults aged over 19 years, those consuming tree nuts (considered to be those reporting a usual nut intake of more than ¼ ounce per day) made up only 6% of the population. Due to the low proportion of consumers, mean usual intake of nuts in the population overall was approximately 3 g per day, whereas mean usual intake in nut consumers was 44.3 g per day. Whilst a relatively small proportion of the population reported consuming nuts, these results suggest that those who did were likely to meet recommended intake quantities. This suggests scope for targeting individuals currently not consuming nuts to promote intakes which are in line with dietary guidelines.

12.5 Conclusion

From a traditionalist nutrition perspective, nuts provide substantive amounts of protein, fat, and energy in the diet, along with a range of essential micronutrients and bioactive compounds. Thus, the inclusion of nuts in the total diet contributes to the overall nutritional quality. The energy and fat content of the diet reflects the combination of foods consumed, and nuts can be important contributors to the overall balance achieved. Research involving habitual consumption of nuts provides evidence of a range of favorable health effects, particularly cardiovascular benefits. Nuts form part of a number of healthy dietary patterns, and emerging evidence now suggests that their inclusion may further improve the quality of a dietary pattern.

Dietary guidelines are developed based on evidence of nutritional benefits. The considerations apparent in the statements of guidelines from various regions of the world suggest that the nutrient contributions remain important. Nuts may be categorized with other protein-rich or fat-rich foods or treated as a discrete food group. Emergent considerations now appear as nuts as a source of plant protein and an alternative source of desirable fatty acids. Cuisine is an important element, with educational support materials moving beyond reference simply to snacks, a protein source in meals, and inclusion in traditional dishes to include established serving sizes for nuts and recommended frequency of consumption. Processing is also emerging as a concern, particularly with the caution expressed around the addition of salt and sugar to nut products. Most guidelines recommend regular nut consumption,

although evidence from representative surveys suggests that consumers may not be complying with these recommendations. To find ways of encouraging nut consumption to ensure intakes align with dietary recommendations presents a public health challenge. Further research is also required on the complementary role of including nuts as a strategy for promoting healthy dietary patterns and should continue to investigate the effect of nuts on a range of emerging health outcomes, such as novel biomarkers of health.

References

1. Luo, C., Zhang, Y., Ding, Y., Shan, Z., Chen, S., Yu, M., Hu, F.B. et al., Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: A systematic review and meta-analysis. *Am. J. Clin. Nutr.*, 100, 256–269, 2014.
2. Aune, D., Keum, N., Giovannucci, E., Fadnes, L.T., Boffetta, P., Greenwood, D.C., Tonstad, S. et al., Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review and dose-response meta-analysis of prospective studies. *BMC Med.*, 14, 207, 2016.
3. Sabaté, J., and Ang, Y., Nuts and health outcomes: New epidemiologic evidence. *Am. J. Clin. Nutr.*, 89, 1643S–1648S, 2009.
4. Barbour, J.A., Howe, P.R., Buckley, J.D., Bryan, J., and Coates, A.M., Nut consumption for vascular health and cognitive function. *Nutr. Res. Rev.*, 27, 131–158, 2014.
5. Ros, E., Health benefits of nut consumption. *Nutrients*, 2, 652–682, 2010.
6. Grundy, M.M., Grassby, T., Mandalari, G., Waldron, K.W., Butterworth, P.J., Berry, S.E., and Ellis, P.R., Effect of mastication on lipid bioaccessibility of almonds in a randomized human study and its implications for digestion kinetics, metabolizable energy, and postprandial lipemia. *Am. J. Clin. Nutr.*, 101, 25–33, 2015.
7. Mandalari, G., Grundy, M.M.L., Grassby, T., Parker, M.L., Cross, K.L., Chessa, S., Bisignano, C. et al., The effects of processing and mastication on almond lipid bioaccessibility using novel methods of *in vitro* digestion modelling and micro-structural analysis. *Br. J. Nutr.*, 112, 1521–1529, 2014.
8. Jacobs, D.R., and Tapsell, L.C., Food, not nutrients, is the fundamental unit in nutrition. *Nutr. Rev.*, 65, 439–450, 2007.
9. Willett, W.C., Sacks, F., Trichopoulou, A., Drescher, G., Ferro-Luzzi, A., Helsing, E., and Trichopoulos, D., Mediterranean diet pyramid: A cultural model for healthy eating. *Am. J. Clin. Nutr.*, 61, 1402S–1406S, 1995.
10. Estruch, R., Ros, E., Salas-Salvadó, J., Covas, M.-I., Corella, D., Arós, F., Gómez-Gracia, E. et al., Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N. Engl. J. Med.*, 378, e34, 2018.
11. Martínez-González, M.A., García-Arellano, A., Toledo, E., Salas-Salvadó, J., Buil-Cosiales, P., Corella, D., Covas, M.I. et al., A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: The PREDIMED Trial. *PLoS One*, 7, e43134, 2012.
12. Toledo, E., Hu, F.B., Estruch, R., Buil-Cosiales, P., Corella, D., Salas-Salvadó, J., Covas, M.I. et al., Effect of the Mediterranean diet on blood pressure in the PREDIMED trial: Results from a randomized controlled trial. *BMC Med.*, 11, 207, 2013.

13. Salas-Salvadó, J., Bulló, M., Babio, N., Martínez-González, M.Á., Ibarrola-Jurado, N., Basora, J., Estruch, R. et al., Reduction in the incidence of type 2 diabetes with the Mediterranean diet: Results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care*, 34, 14–19, 2011.
14. Ruiz-Canela, M., Estruch, R., Corella, D., Salas-Salvadó, J., and Martínez-González, M.A., Association of Mediterranean diet with peripheral artery disease: The PREDIMED randomized trial. *JAMA*, 311, 415–417, 2014.
15. Casas, R., Sacanella, E., Urpí-Sardà, M., Corella, D., Castañer, O., Lamuela-Raventos, R.-M., Salas-Salvadó, J. et al., Long-term immunomodulatory effects of a Mediterranean diet in adults at high risk of cardiovascular disease in the PREvención con DIeta MEDiterránea (PREDIMED) Randomized Controlled Trial. *J. Nutr.*, 146, 1684–1693, 2016.
16. Appel, L.J., and Van Horn, L., Did the PREDIMED trial test a Mediterranean diet? *N. Engl. J. Med.*, 368, 1353–1354, 2013.
17. Schröder, H., Salas-Salvadó, J., Martínez-González, M., Fito, M., Corella, D., Estruch, R., and Emilio, R., Baseline adherence to the Mediterranean diet and major cardiovascular events: Prevención con Dieta Mediterránea trial. *JAMA Intern. Med.*, 174, 1690–1692, 2014.
18. Yokoyama, Y., Nishimura, K., Barnard, N.D., Takegami, M., Watanabe, M., Sekikawa, A., Okamura, T. et al., Vegetarian diets and blood pressure: A meta-analysis. *JAMA Intern. Med.*, 174, 577–587, 2014.
19. Dinu, M., Abbate, R., Gensini, G.F., Casini, A., and Sofi, F., Vegetarian, vegan diets and multiple health outcomes: A systematic review with meta-analysis of observational studies. *Crit. Rev. Food Sci. Nutr.*, 57, 3640–3649, 2017.
20. Song, M.Y., Fung, T.T., Hu, F.B., Willett, W.C., Longo, V.D., Chan, A.T., and Giovannucci, E.L., Association of animal and plant protein intake with all-cause and cause-specific mortality. *JAMA Intern. Med.*, 176, 1453–1463, 2016.
21. Viguiliouk, E., Stewart, S., Jayalath, V., Ng, A., Mirrahimi, A., de Souza, R., Hanley, A. et al., Effect of replacing animal protein with plant protein on glycemic control in diabetes: A systematic review and meta-analysis of randomized controlled trials. *Nutrients*, 7, 5509, 2015.
22. Richter, C.K., Skulas-Ray, A.C., Champagne, C.M., and Kris-Etherton, P.M., Plant protein and animal proteins: Do they differentially affect cardiovascular disease risk? *Adv. Nutr.*, 6, 712–728, 2015.
23. Appel, L.J., Moore, T.J., Obarzanek, E., Vollmer, W.M., Svetkey, L.P., Sacks, F.M., Bray, G.A. et al., A clinical trial of the effects of dietary patterns on blood pressure. *N. Engl. J. Med.*, 336, 1117–1124, 1997.
24. Sacks, F.M., Obarzanek, E., Windhauser, M.M., Svetkey, L.P., Vollmer, W.M., McCullough, M., Karanja, N. et al., Rationale and design of the dietary approaches to stop hypertension trial (DASH). *Ann. Epidemiol.*, 5, 108–118, 1995.
25. Svetkey, L.P., Sacks, F.M., Obarzanek, E.V.A., Vollmer, W.M., Appel, L.J., Lin, P.-H., Karanja, N.M. et al., The DASH diet, sodium intake and blood pressure trial (DASH-Sodium). *J. Acad. Nutr. Diet.*, 99, S96–S104, 1999.
26. Lin, P.-H., Aickin, M., Champagne, C., Craddick, S., Sacks, F.M., McCarron, P., Most-Windhauser, M.M. et al., Food group sources of nutrients in the dietary patterns of the DASH-Sodium trial. *J. Am. Diet. Assoc.*, 103, 488–496, 2003.
27. Sacks, F.M., Svetkey, L.P., Vollmer, W.M., Appel, L.J., Bray, G.A., Harsha, D., Obarzanek, E. et al., Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N. Engl. J. Med.*, 344, 3–10, 2001.

28. Azadbakht, L., Fard, N.R.P., Karimi, M., Baghaei, M.H., Surkan, P.J., Rahimi, M., Esmaillzadeh, A. et al., Effects of the dietary approaches to stop hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients. *Diabetes Care*, 34, 55–57, 2011.
29. Siervo, M., Lara, J., Chowdhury, S., Ashor, A., Oggioni, C., and Mathers, J.C., Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: A systematic review and meta-analysis. *Br. J. Nutr.*, 113, 1–15, 2015.
30. Schwingshackl, L., Bogensberger, B., and Hoffmann, G., Diet quality as assessed by the healthy eating index, alternate healthy eating index, dietary approaches to stop hypertension score, and health outcomes: An updated systematic review and meta-analysis of cohort studies. *J. Acad. Nutr. Diet.*, 118, 74–100.e11, 2018.
31. O'Neil, C.E., Keast, D.R., Fulgoni, V.L., and Nick, T.A., Tree nut consumption improves nutrient intake and diet quality in US adults: An analysis of National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Asia Pac. J. Clin. Nutr.*, 19, 142–150, 2010.
32. O'Neil, C.E., Nicklas, T.A., and Fulgoni, V.L., Tree nut consumption is associated with better nutrient adequacy and diet quality in adults: National Health and Nutrition Examination Survey 2005–2010. *Nutrients*, 7, 595–607, 2015.
33. Guasch-Ferre, M., Bullo, M., Martinez-Gonzalez, M.A., Ros, E., Corella, D., Estruch, R., Fito, M. et al., Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. *BMC Med.*, 11, 2013.
34. Njike, V., Ayettey, R., Petraro, P., Treu, J., and Katz, D., Walnut ingestion in adults at risk for diabetes: Effects on diet quality, body composition, and cardiac risk measures. *FASEB J.*, 29, 2015.
35. Wibisono, C., Probst, Y., Neale, E., and Tapsell, L., Changes in diet quality during a 12 month weight loss randomised controlled trial. *BMC Nutr.*, 3, 38, 2017.
36. Njike, V.Y., Yarandi, N., Petraro, P., Ayettey, R.G., Treu, J.A., and Katz, D.L., Inclusion of walnut in the diets of adults at risk for type 2 diabetes and their dietary pattern changes: A randomized, controlled, cross-over trial. *BMJ Open Diabetes Res. Care.*, 4, e000293, 2016.
37. Tapsell, L.C., Neale, E.P., Satija, A., and Hu, F.B., Foods, nutrients, and dietary patterns: Interconnections and implications for dietary guidelines. *Adv. Nutr.*, 7, 445–454, 2016.
38. Schwingshackl, L., Missbach, B., König, J., and Hoffmann, G., Adherence to a Mediterranean diet and risk of diabetes: A systematic review and meta-analysis. *Public Health Nutr.*, 18, 1292–1299, 2014.
39. Ndanuko, R.N., Tapsell, L.C., Charlton, K.E., Neale, E.P., and Batterham, M.J., Dietary patterns and blood pressure in adults: A systematic review and meta-analysis of randomized controlled trials. *Adv. Nutr.*, 7, 76–89, 2016.
40. Neale, E.P., Batterham, M.J., and Tapsell, L.C., Consumption of a healthy dietary pattern results in significant reductions in C-reactive protein levels in adults: A meta-analysis. *Nutr. Res.*, 36, 391–401, 2016.
41. Eichelmann, F., Schwingshackl, L., Fedirko, V., and Aleksandrova, K., Effect of plant-based diets on obesity-related inflammatory profiles: A systematic review and meta-analysis of intervention trials. *Obes. Rev.*, 17, 1067–1079, 2016.
42. Schwingshackl, L., and Hoffmann, G., Mediterranean dietary pattern, inflammation and endothelial function: A systematic review and meta-analysis of intervention trials. *Nutr. Metab. Cardiovasc. Dis.*, 24, 929–939, 2014.

43. Food and Agriculture Organization of the United Nations, Food-based Dietary Guidelines. Published online at: http://www.fao.org/nutrition/education/food-dietary-guidelines/home/en/ (accessed April 24, 2017).
44. National Institute of Nutrition, *Dietary Guidelines for Indians – A Manual*, National Institute of Nutrition, Hyderabad, India, 2011.
45. Sierra Leone Food, *Sierra Leone Food-Based Dietary Guidelines for Healthy Eating*, Food and Agriculture Organization of the United Nations, Rome, Italy, 2016.
46. Nutrition Division Ministry of Health, *Food Based Dietary Guidelines for Sri Lankans*, Nutrition Division Ministry of Health, Colombo, Sri Lanka, 2011.
47. Public Health England, *Eatwell Guide*, Public Health England, London, UK, 2016.
48. Kromhout, D., Spaaij, C., de Goede, J., and Weggemans, R., The 2015 Dutch food-based dietary guidelines. *Eur. J. Clin. Nutr.*, 70, 869–878, 2016.
49. U.S. Department of Agriculture (USDA), *Scientific Report of the 2015 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Health & Human Services and the Secretary of Agriculture*, U.S. Department of Agriculture, U.S. Department of Health & Human Services, Washington, DC, 2015.
50. U.S. Department of Health and Human Services and U.S. Department of Agriculture, *2015–2020 Dietary Guidelines for Americans*, U.S. Department of Health and Human Services, U.S. Department of Agriculture, Washington, DC, 2015.
51. Health Canada, *Eating Well with Canada's Food Guide*, Health Canada, Ottawa, ON, Canada, 2007.
52. Health Canada, *Eating Well with Canada's Food Guide: A Resource for Educators and Communicators*, Health Canada, Ottawa, ON, Canada, 2007.
53. Department of Health and Ageing and National Health and Medical Research Council, *Australian Dietary Guidelines*, Department of Health and Ageing, National Health and Medical Research Council, Canberra, Australia, 2013.
54. Department of Health and Ageing and National Health and Medical Research Council, *A Modelling System to Inform the Revision of the Australian Guide to Healthy Eating*, Department of Health and Ageing, National Health and Medical Research Council, Canberra, Australia, 2011.
55. Ministry of Health, *Eating and Activity Guidelines for New Zealand Adults*, Ministry of Health, Wellington, New Zealand, 2015.
56. Ministry of Health, *Food and Nutrition Guidelines for Adults*, Ministry of Health, Wellington, New Zealand, 2003.
57. Sport and Recreation New Zealand and Ministry of Health, *Movement = Health*, Sport and Recreation New Zealand and Ministry of Health, Wellington, New Zealand, 2007.
58. Department of Health and Ageing and National Health and Medical Research Council, *A Review of the Evidence to Address Targeted Questions to Inform the Revision of the Australian Dietary Guidelines*, Department of Health and Ageing, National Health and Medical Research Council, Canberra, Australia, 2011.
59. Nordic Council of Ministers, *Nordic Nutrition Recommendations 2012*, Nordic Council of Ministers, Copenhagen, Denmark, 2014.
60. World Health Organization (WHO), *Sugars Intake for Adults and Children*, World Health Organization, Geneva, Switzerland, 2015.

61. World Cancer Research Fund and American Institute for Cancer Research, Food, *Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*, World Cancer Research Fund, American Institute for Cancer Research, Washington, DC, 2007.
62. Public Health England, *From Plate to Guide: What, Why and How for the Eatwell Model*, Public Health England, London, UK, 2016.
63. Food Safety Authority of Ireland, *Scientific Recommendations for Healthy Eating Guidelines in Ireland*, Food Safety Authority of Ireland, Dublin, Ireland, 2011.
64. Supreme Scientific Health Council and Hellenic Ministry of Health, *Dietary Guidelines for Adults in Greece*, Supreme Scientific Health Council, Hellenic Ministry of Health, Athens, Greece, 1999.
65. Ministry of Health, *Dietary Guidelines for Maltese Adults*, Ministry of Health, Malta, 2016.
66. American University of Beirut, *The Food-Based Dietary Guideline Manual for Promoting Healthy Eating in the Lebanese Adult Population*, The Faculty of Agricultural and Food Sciences, American University of Beirut, Beirut, Lebanon, 2013.
67. Wang, Y., Chen, H.J., Shaikh, S., and Mathur, P., Is obesity becoming a public health problem in India? Examine the shift from under- to overnutrition problems over time. *Obes. Rev.*, 10, 456–474, 2009.
68. Ministry of Health Malaysia, *Malaysian Dietary Guidelines*, Ministry of Health Malaysia, Putrajaya, Malaysia, 2010.
69. Ministry of Health of Brazil, *Dietary Guidelines for the Brazilian Population*, Ministry of Health of Brazil, Brasilia, Brazil, 2014.
70. Ministry of Health Jamaica, *Food Based Dietary Guidelines for Jamaica 2015*, Ministry of Health Jamaica, Kingston, Jamaica, 2015.
71. Australian Bureau of Statistics, *4364.0.55.007—Australian Health Survey: Nutrition First Results – Foods and Nutrients,* 2011–12, Canberra, Australia, 2014.
72. Brown, R.C., Tey, S.L., Gray, A.R., Chisholm, A., Smith, C., Fleming, E., Blakey, C. et al., Patterns and predictors of nut consumption: Results from the 2008/9 New Zealand Adult Nutrition Survey. *Br. J. Nutr.*, 112, 2028–2040, 2014.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 13

Nuts

Gut Health and Microbiota

Serena Galiè, Mònica Bulló, Alessandro Atzeni, Pablo Hernández-Alonso, Jananee Muralidharan, and Jordi Salas-Salvadó

13.1 Introduction 313
13.2 The Effect of Diet on Gut Microbiota 314
13.3 Modulation of Gut Microbiota by Nut Consumption 316
13.3.1 Methodological Issues of *In Vitro* and *In Vivo* Studies 316
13.3.2 Animal Models 317
13.3.3 *In Vitro* Experimental Models 318
13.3.4 Human Intervention Studies 319
13.4 Putative Mechanisms: Gut Microbiota, Nuts, and Health Axes 324
13.5 Conclusion 326
References 326

13.1 Introduction

The impact of nut consumption on human health is widely recognized. The beneficial effects of nuts have been mainly attributed to their specific fatty acid profiles, high fiber content, and richness in bioactive compounds with antioxidant and anti-inflammatory properties. However, the prebiotic properties of nuts as substrates for gut microbiota and their potential impact on health have been much less explored.

In this chapter, we focus on the overall effect of plant-based diets on gut microbiota and specifically in the modulatory role of nut consumption. We summarize the evidence provided by *in vitro* and *in vivo* animal studies using gnotobiotic mice

and multi-stage fermentation models, as well as recent evidence from clinical trials. Finally, we propose an overview of putative mechanisms explaining these findings, albeit further mechanistic studies are required to help unravel the underlying mechanisms linking nut consumption, gut microbiota, and health benefits.

13.2 The Effect of Diet on Gut Microbiota

It is now well established that dietary habits influence the composition of gut microbiota. The traditional view of the beneficial effects attributed to single nutrients has been shifting towards synergy of multiple food components and dietary patterns. Based on long-term dietary habits, the gut microbial profile is divided broadly into two enterotypes: (i) *Prevotella enterotype*, found predominantly in individuals consuming carbohydrate-based or vegetarian diets; and (ii) *Bacteroidetes phylum*, found in diets high in protein and/or animal products [1]. There are several well-known diet patterns based on different cultures and geographical locations; however, the three most common dietary patterns followed around the world are the Western diet, Mediterranean diet (MedDiet), and Asian diet. Vegetarian (lacto ovo-vegetarian [LOV] and pesco-vegetarian) and vegan diets emphasize consumption of plant-based food, which are also present in Mediterranean and Asian diets. The microbiome may be key to understanding mechanisms explaining the protective effects of vegetarian diets against chronic diseases such as type-2 diabetes (T2D), hypertension, cardiovascular disease (CVD), and different types of cancer [2–4]. In contrast, the Western diet is characterized by high refined carbohydrates and meat intake [5]. Macronutrient content could vary highly among these diets. For example, the total fat content in an omnivorous diet (34%–36%) is higher than in the LOV (30%–34%) and the vegan diets (28%–32%) [6].

The MedDiet, widely acknowledged to be a healthy dietary pattern, is characterized by a high consumption of fruits, vegetables, legumes, fish, whole grains, nuts, and olive oil; moderate consumption of dairy products and wine; and low intake of red and processed meats and foods that contain high amounts of added sugars. Therefore, the MedDiet is rich in fat, especially monounsaturated fat, which abounds in olive oil and nuts, but also in antioxidants and polyphenols from all sources of vegetables. However, the synergistic effect of the MedDiet components on gut microbiota has been little explored. High adherence to the MedDiet has been associated with beneficial changes in the gut microbiome and their metabolome, such as abundance of fiber-degrading *Prevotella* and *Firmicutes* and raised production of fecal short-chain fatty acids (SCFAs) [7]. Higher adherence to the MedDiet was also found to be characterized by lower counts of pathogenic *Escherichia coli* and higher frequency of beneficial *Bifidobacteria* [8]. Conversely, lower adherence to the MedDiet was linked to higher urinary trimethylamine *N*-oxide levels, a microbial metabolite believed to be a marker for cardiovascular risk [9]. Consumption of MedDiet with up to 22% monounsaturated fat in an obese population has also been shown to increase counts of the beneficial *Roseburia* genus [10]. An interesting study comparing the effect of a vegan diet rich in seaweed, wholegrain, legumes, and fermented products (the Ma-Pi 2 diet) to a control MedDiet was conducted in 12 participants with reactive hypoglycemia for 3 days. The diets did not induce significant changes in gut microbiota, but fecal SCFAs increased significantly after the vegan diet [11].

The vegan diet is similar to the vegetarian diet but is completely devoid of animal products, including dairy, which is commonly included in the vegetarian diet. More than three decades ago, van Faassen et al. [12] conducted one of the first studies analyzing gut microbiota, wherein they compared three diets for 20 days each (vegan, LOV, and mixed Western diet) in 12 healthy men. The genera *Lactobacillus* and *Enterococcus* were found to be reduced among participants consuming the vegan diet. A large-scale trial compared the gut microbiome from vegans (n = 105) and vegetarians (n = 144) to that of age and gender-matched controls consuming an omnivorous diet. The four most important taxonomical groups of gut bacteria (*Bacteroides*, *Bifidobacterium*, *E. coli*, and *Enterobacteriaceae*) did not differ significantly between omnivores, vegans, and vegetarians. However, vegan samples differed the most from omnivores for the aforementioned bacterial genera [13]. It was also noted that the stool pH was significantly reduced in vegans compared to omnivore controls. The reduced pH could be related to the higher microbial production of SCFAs that occurs when more microbial substrates, such as the ones derived from vegan diet, are available [13]. This lowering in pH was also strongly correlated with reduced counts of *Enterobacteriacea* and, specifically, *E. coli*.

A study conducted in Slovenia observed the differences amongst healthy individuals with long term consumption of omnivorous *versus* vegan or lacto-vegetarian dietary patterns. This study included 31 omnivores, who were compared with 20 vegan or 11 lacto-vegetarian participants. Proportions of *Bacteroides* to *Prevotella* were found to be higher among the vegan/lacto-vegetarian group in comparison to omnivores. In addition, a higher proportion (percent of group-specific DNA in relation to all bacterial DNA) of *Bacteroides thetaiotaomicron*, *Clostridium clostridioforme*, and *Faecalibacterium prausnitzii*, and a lower proportion of *Clostridium cluster* XIVa, that is, an overall healthier gut microbiota profile, was observed in vegetarians compared to omnivores. Similar to the Slovenian study, another study conducted in Thailand compared the stool microbiome of six non-vegetarians to seven vegetarians, showing a high proportion of *Bacteroides* in non-vegetarian participants and higher proportion of *Prevotella* in vegetarians [14]. Similar results have been reported in African children from Burkina Faso, where the most abundant genus in the gut microbiota of vegetarians was *Prevotella*, whereas in children living in urban Florence (Italy) who primarily consume non-vegetarian foods, *Bacteroides* was the most abundant genus [15].

High consumption of dietary fiber typically from plant-based diets has received maximum attention in relation to positive changes in gut microbiota [16]. Shifting from a high fat diet to a high fiber diet in 20 middle-aged African Americans for 2 weeks showed changes in microbiota and their pathways with increased butyrogenesis and beneficial changes in mucosal biomarkers of colon cancer [17]. Plant-based diets such as vegetarian and MedDiet are not only rich in fiber, with recognized effects on gut microbiome, but also contain high amounts of polyphenols, which are mainly found in fruits, vegetables, legumes, nuts, wholegrain cereals, tea, coffee, cocoa, and wine [18]. Tea polyphenols have shown the ability to inhibit the growth of pathogens such as *Helicobacter pylori*, *Staphylococcus aureus*, *Listeria monocytogenes*, and *Pseudomonas aeruginosa* [19]; hence plant-based diets rich in polyphenols have the potential to modify the gut microbiome profile and its metabolic effects.

Other than the major recognized dietary patterns, people also follow different diets for specific aims and lengths of time. For the purpose of this chapter, it

is worth mentioning ketogenic and gluten free diets, which are usually rich in fat. The ketogenic diet has been used as a nutritional therapy for a wide range of neuro-related diseases, such as epilepsy [20], Parkinson's disease [21], and autism [22], but also to treat obesity [23,24]. One *in vivo* study conducted in mice demonstrated that the ketogenic diet increased beneficial gut microbiota and improved neurovascular function. In addition, it reduced the pro-inflammatory genera *Desulfovibrio* and *Turicibacter*, while increasing the beneficial *Akkermensia municiphila* [25]. However, exploration of the ketogenic diet's mechanisms of action based on gut microbiota has been limited thus far. Another diet followed by patients with celiac disease and frequently by individuals who believe they are gluten intolerant is the gluten-free diet. This diet has been associated with reduction in the diversity of *Bifidobacterium* and *Lactobacillus* [26,27].

It is undisputed that different dietary patterns have a varied impact on gut microbiota and health. Starting from understanding the role of single nutrient or individual food components would allow us to look better into the combined effect of different dietary elements. In the following sections of this chapter, the role of nuts – a key component of such dietary patterns – on gut microbiota is explored.

13.3 Modulation of Gut Microbiota by Nut Consumption

13.3.1 Methodological Issues of In Vitro *and* In Vivo *Studies*

Since the beginning of the twenty-first century, the majority of human studies have been based on the use of fecal samples to identify the microbial species of the gastrointestinal tract and to correlate microbiota composition with host phenotype [28]. The use of 16S rRNA sequencing has been established as the main technique to provide taxonomic information about the microbiota [29]. Despite the creation of 16S rRNA-based catalogues *via* high-throughput sequencing platforms, little is understood about the functionality of the species identified [30].

Human studies have utilized valid approaches to address research questions about the effects of specific nutrients on gut microbial composition or to confirm effects observed or mechanisms implied in simplified models; there are, however, important limitations to consider:

i. To investigate the effects of nutritional compounds on the gut microbiota sometimes requires the administration of high doses of test ingredients, which could lead to undesirable side effects and entails difficulty monitoring and achieving good compliance to the interventions [28].
ii. There is an inherent difficulty in obtaining samples from different areas of the gastrointestinal tract [31].
iii. It is crucial to consider the microbial community of the mucus layer, formed by the secretions of the gut epithelial cells, which separates the gut lumen and host tissue [32], but sampling is invasive, and fecal samples do not represent the community of this mucus layer [33].
iv. The adaptability of colonic microbiota to changes in substrate availability and inter-individual variability between samples resulting from genetic background, diet, health status, lifestyle, and environmental conditions, are important constraints [34].

v. In the context of the impact of prebiotics and probiotics on gut microbiota composition, it is difficult to determine if their effects are driven by direct growth stimulation or by the decrease in pH caused by the SCFAs produced by microbial fermentation [35].
vi. The complexity of host–microbiota interactions is an added hindrance in focusing on gut microbial activity and interpret the results [36].

13.3.2 Animal Models

The use of animal models makes it possible to modulate and investigate host–microbe interactions in highly controlled conditions while reducing interferences that can be encountered in human studies [37]. In gnotobiotic systems, animals born in aseptic conditions are exposed to a specific single bacterium or a known consortia of bacteria, allowing researchers to explore their effects on host functions [38]. Once animals are sacrificed, it is possible to examine the colonic contents wherein bacterial metabolites have not been absorbed by the host, which allows the collection of valid information on the metabolic activity of the gut microbiota compared to studies using analyses of spot feces. For the screening of nutritional interventions, such as pre- and probiotics, and to examine mechanisms of action and effects on the host and identifying relevant biomarkers, the use of animal models represents a more advantageous approach compared with human studies [39].

In vivo studies are useful to describe the activity of prebiotics, especially when targeting specific bacterial species as *Bifidobacteria* and *Lactobacilli* by promoting the fermentation of prebiotic carbohydrates with ensuing selective enrichment in the gastrointestinal tract [40]. These species are able to inhibit pathogenic bacteria through the production of SCFAs and antimicrobial compounds, as well as by competition for growth substrate and adhesion sites [41]. In fact, approaches combining *in vitro* and *in vivo* studies were used to examine differences between raw and roasted almonds promoting potential prebiotic effects [42]. After digestion *in vitro*, the fermentation profile of raw and roasted almonds by three typical intestinal bacterial species (*Lactobacillus acidophilus*, *Bifidobacterium breve*, and *E. coli*) was determined. Wistar rats were exposed to different diets supplemented with raw or roasted almonds. Fecal samples were also used for the determination of bacterial and digestive enzymes. This set of experiments showed the potential prebiotic effect of raw and roasted almonds, including regulation of intestinal bacteria and improved metabolic activities. The roasting process may negatively affect the prebiotic effects of almonds but significantly improves their metabolic effects [42].

Supplementation with walnuts in mouse models was used to investigate their potential cancer-protective properties. Fecal samples were collected and analyzed to determine diet-induced changes in gut microbiota. Results demonstrated that walnut consumption reduces colon tumor development, and alterations in the microbiome were associated with a tumor-suppressive effect [43]. Additional *in vivo* experiments were performed to identify gut microbiome changes after inclusion of walnuts in the diet [44]. Male Fischer rats were exposed to one of two different diets: (i) a diet supplemented with walnuts, or (ii) a diet in which fat, fiber, and protein from walnuts were matched with corn oil, casein, and a cellulose fiber source. The isolation of bacterial DNA from colon samples and subsequent sequencing permitted the distinction of microbial communities between the two different diet groups. Animals

consuming walnuts showed significantly greater species diversity, with increased abundance of probiotic-type bacteria, including *Lactobacillus*, *Ruminococcaceae*, and *Roseburia*, suggesting a health-promoting change in the gut microbial community. However, there are limitations in the use of animal models, such as high costs and labor-intensive procedures, and they do not fully represent human metabolism. Therefore, translating findings from animal models to conditions in humans still remains a complicated issue.

13.3.3 In Vitro *Experimental Models*

In vitro experimental models to study the impact of nutrients on gut microbiota often consist of fermentation techniques, which are based on the anaerobic processes that generate energy by the breakdown of organic compounds or any process that generates bacterial metabolites as end-products [45]. This technique avoids the disadvantages of *in vivo* models and allows the characterization of the gut microbiota under controlled physiological conditions (e.g., anaerobiosis, retention time, culture media, temperature, and pH) to better simulate the different regions of the colon. The cultivation of aerobic and anaerobic human gut microorganisms derived from fecal samples takes place in chambers called *bioreactors* or *fermenters*, mirroring enzymatic digestive activity, mucous production, and host-microbiota interactions [46].

The simplest and most frequently used *in vitro* model is the batch culture fermentation system, suitable for performing short-term experiments (24–48 hours). The growth of a pure or mixed bacterial suspension occurs in a carefully selected medium without the further addition of nutrients. Continuous culture fermentation models, as single-stage, are used to simulate proximal colon function and metabolic activity. The simulation of proximal, transverse, and distal colon regions is achieved by using multi-stage fermentation models [47]. More complex models simulate the gastrointestinal tract from the stomach through the small intestine, reproducing human digestive functions such as bile secretion, motility, pH, and absorption capacities of the upper intestine [48] and also including other host functions such as peristaltic mixing and uptake of metabolites [49].

In 2008, Mandalari et al. [50] investigated the potential prebiotic effect of two almond products – finely ground almonds and defatted finely ground almonds – by using a full model of intestinal digestion. Results showed that finely ground almonds significantly increased the populations of *Bifidobacteria* and *Eubacterium rectale*, while no significant differences in the proportions of gut bacterial species were detected in response to defatted ground almonds. Of note, the increased growth of these bacterial species during fermentation of finely ground almonds correlated with increased butyrate production.

Other studies were performed to evaluate the prebiotic effect endurance of chestnut components by examining the viability of selected lactic acid bacteria strains after exposure to simulated gastric secretions of the stomach and to the bile salts released into the duodenum [51]. Some strains were selected according to their tolerance to low pH values and bile salts and were exposed to simulated gastric or bile juice in presence of chestnut extract with or without immobilization in chestnut fiber. Chestnut extract improved gastric tolerance to *Lactobacilli* through a protective effect due to specific hydrophobic peptides or oligopeptides.

A more recent study examined the chemopreventive effects of walnuts on colon cancer through an *in vitro* simulated digestion and fermentation system using human fecal samples [52]. The results demonstrated the ability of human fecal microbiota to convert fatty acids from walnuts to potential chemopreventive metabolites. In addition, the production of butyrate and reduction in potential carcinogens such as secondary bile acids and lipid peroxidation products might have contributed to the protective effects of nuts in the development of colon cancer.

In vitro gut fermentation models represent an innovative technological approach which permits investigations into both the existence of gut microbial species and their related functionality. The design of an ultimate approach to investigate gut microbiota functionality must, therefore, include a combination of *in vitro* and *in vivo* models, to deepen the complex relationship between the intestinal microbial community, diet, and host, and to further elucidate the role of gut flora in health and disease [53].

Research findings obtained from all these *in vitro* and *in vivo* studies assessing the gut microbiota modulation by nut consumption were further applied to clinical studies that will be addressed in the next section.

13.3.4 Human Intervention Studies

The role of nut consumption on changes in gut microbiota have been described in several clinical feeding trials [54–60] (Table 13.1). In 2014, Ukhanova et al. [54] performed two separate randomized, controlled, cross-over feeding studies in healthy subjects who were assigned to diets enriched with 42 or 84 g/day of either almonds ($n = 18$) or pistachios ($n = 16$) or a control nut-free diet, each dietary period lasting 18 days. The results showed that both nut types had a significant modulatory role on the microbiota, although there was a greater overall prebiotic effect on gut microbiota composition with the pistachio diet compared with the almond diet. Moreover, pistachios' microbiota modulation specifically increased the number of butyrate-producing bacteria – widely identified as potentially beneficial – whereas the numbers of *Bifidobacteria* remained unaffected [54]. Also, by assessing gut-derived metabolites in 24-hour urine after a pistachio diet or a control diet, a 4-month, randomized clinical trial (RCT) conducted in 49 subjects with pre-diabetes found a shift towards a healthier gut microbiota following the pistachio diet [59]. Three metabolites related to gut microbiota metabolism (hippurate, *p*-cresol sulfate, and dimethylamine) decreased after the pistachio diet compared with the nut-free control intervention.

Three clinical studies have examined the specific effects of almonds or almond products on the intestinal microbiome. Liu et al. [58] reported a 6-week feeding trial with 48 volunteers randomly assigned to one of three different intervention groups, who took half the test food at lunch and half at dinner. Groups were divided into i) a control group supplied with 8 g/day of fructo-oligosaccharides, ii) an intervention group supplemented with 10 g/day of almond skins, and iii) an intervention group supplemented with 56 g/day of roasted, unsalted, whole almonds. Significant increases in the proportion of *Bifidobacterium spp.* and *Lactobacillus spp.* in both almond groups were observed. The populations of *E. coli* mildly changed and the growth of *Clostridium perfringens* was significantly repressed in both almond groups. Motivated by their previous findings [54], the same research group designed a 3-week short-term crossover study with 29 parents and their children

Table 13.1 Summary of Clinical Trials Evaluating Nut Consumption on Outcomes Related to Gut Microbiota Modulation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*Methodology(ies) for Microbiota Analysis*	*Microbiota-Related Outcome(s)*	*Other Outcome(s)*	*References*
48 (24/24) Healthy subjects (Re: 18–22)	Almonds Feeding trial (6 weeks)	No control diet Positive control diet: 8 g/day of FOS	56 g/day of roasted almonds 10 g/day of almond skins	Analysis for microbiota composition and indicators of microbial activity (enzyme assays). Selective media for: *Bifidobacterium spp.*, *Lactobacillus spp.*, *Escherichia coli*, and *Clostridium perfringens*.	Significant increases in the populations of *Bifidobacterium spp.* and *Lactobacillus spp.* after both almond groups. *Escherichia coli* populations did not change significantly, while the growth of the pathogen *Clostridium perfringens* was significantly repressed.	Modulated microbiota induced changes in bacterial enzyme activities (e.g., significant increase in fecal β-galactosidase activity).	[58]
18 (10/8) Healthy subjects (56 ± 8.6 (SEM) 16 (8/8) Healthy subjects (50; Re: 29–64)	Almonds or pistachios Crossover feeding trial (18 day, 3 weeks per period)	Nut-free diet	42 or 84 g/day of almonds 42 or 84 g/day of pistachios	16S rRNA with universal primers 27F and 533R. qPCR to validate and confirm results for LAB and bifidobacteria.	Different OTUs appeared to be affected by nut consumption. The effect of pistachio consumption on gut microbiota composition was much stronger than that of almond consumption and included an increase in the number of potentially beneficial butyrate-producing bacteria.		[54,83, 84]

(*Continued*)

Table 13.1 (Continued) Summary of Clinical Trials Evaluating Nut Consumption on Outcomes Related to Gut Microbiota Modulation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*Methodology(ies) for Microbiota Analysis*	*Microbiota-Related Outcome(s)*	*Other Outcome(s)*	*References*
Parents: 29 (5/24) Healthy subjects (35 ± 0.6) Children: 29 (15/14) Healthy subjects (4 ± 0.2)	Almonds Crossover (3 weeks per period)	Almond-free diet	42 g/day of almonds (adults) 14 g/day of almonds (children including almond butter)	16S rRNA (V1–V3 region) sequencing clustered with a 95% and 98% similarity into OTUs.	Microbiota was stable at the phylum and family level, but genus-level changes occurred with nut intake, especially in children.	Consuming almonds increased total HEI score in parents and children.	[60]
194 (60/134)* Healthy subjects (63 ± 7)	Walnuts Crossover (8 weeks per period)	Nut-free diet	43 g/day of walnuts	16S rRNA (V3-V4 region) sequencing clustered with a 97% similarity into OTUs.	Generalized UniFrac distance shows that walnut consumption significantly affects microbiome composition and diversity.		[56]
18 (10/8) Healthy subjects (56.7 ± 10.2 (SD)	Almonds Crossover (3 weeks per period)	Nut-free diet	42 g/day of: i) whole almonds ii) whole, roasted almonds iii) roasted, chopped almonds iv) almond butter	16S rRNA bacterial (V4 region), archaeal, and fungal genes were sequenced and clustered with a 97% similarity into OTUs.	Almond consumption increased the relative abundances of *Lachnospira*, *Roseburia*, and *Dialister*. Comparisons between control and the four almond treatments revealed specific modulations.		[57]

(*Continued*)

Table 13.1 (Continued) Summary of Clinical Trials Evaluating Nut Consumption on Outcomes Related to Gut Microbiota Modulation

Number of Participants (M/F) Characteristics (Age in Years)	*Nut Study Design (Length of the Intervention)*	*Control Group*	*Intervention Group(s)*	*Methodology(ies) for Microbiota Analysis*	*Microbiota-Related Outcome(s)*	*Other Outcome(s)*	*References*
18 (10/8) Healthy subjects (53.1 ± 2.2 (SEM)	Walnuts Crossover (3 weeks per period)	Isocaloric nut-free diet	42 g/day of walnuts	Bacterial (16S rRNA V4 region), archaeal, and fungal. Clustered with a 97% similarity into OTUs.	Compared with after the control period, walnut consumption resulted in a 49%–160% higher relative abundance of *Faecalibacterium*, *Clostridium*, *Dialister*, and *Roseburia* and 16%–38% lower relative abundances of *Ruminococcus*, *Dorea*, *Oscillospira*, and *Bifidobacterium*.	Serum LDL-C concentration and fecal secondary bile acids (deoxycholic acid and lithocholic acid) were 7%, 25%, and 45% lower, respectively, after the walnut diet compared with the control diet.	[55]

Note: *, 135 subjects analyzed.

Abbreviations: F, female; FOS, fructooligosaccharides; HEI, healthy eating index; LAB, lactic acid bacteria; LDL-C, low-density lipoprotein cholesterol; M, male; OTU, operational taxonomic unit; qPCR, quantitative polymerase chain reaction; Re, range; SD, standard deviation; SEM, standard error of the mean; V, variable region number.

(n = 29) to examine gut microbiota modulation by almonds. Parents consumed 42 g/day of almonds and encouraged their children to consume 14 g/day of almonds (including almond butter). Significant changes at overall genus levels after almond consumption *versus* control intervention were observed, particularly in children [60]. However, no modulation at the species level was reported. The third study, a 3-week RCT conducted in 18 healthy subjects, also assessed the beneficial effect of almond consumption on gut microbiota composition compared to an almond-free control diet [55]. Almond intervention included the consumption of 42 g/day of raw or processed (roasted and/or chopped) almonds or almond butter. The results showed that almond consumption increased the relative abundances of *Lachnospira*, *Roseburia*, and *Dialister*. Particularly, compared to controls, chopped almonds increased the abundance of *Lachnospira*, *Roseburia*, and *Oscillospira*, while whole almonds increased counts of *Dialister*. Thus, almond consumption – and the nuts' degree of processing – had a significant impact on the relative abundances of intestinal microbiota species.

Two RCTs of different duration assessed changes in gut microbiota due to walnut consumption [56,57]. In a crossover RCT, 135 normal-weight or overweight healthy individuals consumed 43 g/day of walnuts or a nut-free diet for 8 weeks [56]. Generalized UniFrac distance (a parameter for comparing microbial communities) showed that walnut consumption significantly modulated both microbiome composition and diversity. By using a multidimensional scaling approach, authors reported dissimilarities of approximately 5% between walnut and control diet interventions. Specifically, the abundance of the family *Ruminococcaceae* and genus *Bifidobacteria* increased significantly, while the genera *Blautia* and *Anaerostipes* decreased significantly during walnut consumption. Holscher et al. [57] conducted a 3-week crossover study to evaluate the effects of the consumption of 42 g/day of walnuts *versus* no consumption in 18 overweight but otherwise healthy men and women. Compared with the control period, walnut consumption resulted in a 49%–160% higher relative abundance of the genera *Faecalibacterium*, *Clostridium*, *Dialister*, and *Roseburia* and 16%–38% lower relative abundance of *Ruminococcus*, *Dorea*, *Oscillospira*, and *Bifidobacterium*. Microbiota modulation following walnut consumption was accompanied by improvements in the lipid profiles. These results are supported by experimental *in vivo* studies indicating that walnuts increased the relative abundances of *Firmicutes*, including the genera *Clostridium* [43] and *Roseburia* [44]. Specifically, walnuts showed mild colonic protection against a potent carcinogenic insult partially due to walnut-induced changes to the gut microbiome [43]. In fact, diets rich in nuts have been associated with a reduced risk of total and cause-specific mortality from cancer [61]. Thus, gut microbiota could also have a potential beneficial role in tumorigenesis. Moreover, both *Faecalibacterium* and *Roseburia* have been reported to be negatively associated with age, whereas *Oscillospira* may be positively associated with age [62,63]. Therefore, it has been suggested that the consumption of walnuts may help to slow age-related changes in the microbiota. Nevertheless, additional research is necessary to assess the effects of walnut consumption on gut microbiota in the context of aging and cancer development.

Thus, increasing evidence supports the notion that healthy individuals consuming 1–2 servings/day of nuts may significantly benefit from improvements in the intestinal microbiota characterized by the enhancement of probiotic and butyric acid–producing species. However, the importance of the modulation of other not so well-known bacteria is still pending. Importantly, a common issue shared by most

RCTs assessing intestinal microbiota changes in response to dietary interventions is that a "healthy microbiota" has not been unequivocally defined [64]. The methodology for microbiota analysis has also varied among studies (Table 13.1), from targeting specific genera to sequencing specific variable 16S rRNA region(s) (e.g., V1-V3), thus limiting the comparisons among them. Therefore, further studies are needed to determine whether microbial modulation is maintained during longer nut consumption periods, affects subjects with cardiometabolic diseases, and is associated with improvements in other disease-related parameters.

13.4 Putative Mechanisms: Gut Microbiota, Nuts, and Health Axes

Several epidemiological and clinical studies have evaluated the beneficial effect of nut consumption on different health outcomes, including a reduced risk of CVD, metabolic syndrome, and cancer [65–68], with particular reference to their effect in decreasing the inflammatory status in atherogenesis [65]. In this regard, bioactive compounds of nuts, such as tocopherols, phytosterols, polyphenols, folic acid, selenium, and magnesium, are reported to have antioxidant and anti-inflammatory properties, which could explain in part the decreased risk of both CVD and T2D in individuals with high nut consumption. However, apart from the direct antioxidant and anti-inflammatory effects of bioactive compounds of nuts affecting different health outcomes, it is important to consider the prebiotic effect they exert directly on gut microbiota and indirectly into intestinal homeostasis [69].

The prebiotic effect of nuts is mainly related to dietary fiber (non-digestible polysaccharides) and polyphenols (polymerized compounds). Dietary fiber (cellulose, hemicelluloses, pectin, etc.) are fermented by the intestinal bacteria to SCFA, especially butyrate, while polyphenols are only partially absorbed in the small intestine during the digestion process, although when reaching the colon they are bioactivated by the microbiota [70].

The product of bacterial fermentation butyrate, for example, enhances adenosine monophosphate kinase (AMPK) activity in liver and muscle by increasing the adenosine monophosphate/adenosine triphosphate ratio, as observed in *in vitro* studies [71]. AMPK is an enzyme that plays a great role in cellular energy homeostasis and is involved in lipid and glucose metabolism. Additionally, butyrate stimulates the expression of peptide YY *via* the G-protein-coupled receptors leading to inhibition of gut motility and suppression of appetite [72] and also inhibits hydroxymethyl-glutaryl-CoA reductase activity [73], the limiting enzyme for the cholesterol synthetic pathway, which explains in part the hypocholesterolemic effect of nuts [74]. Therefore, a butyrogenic microbiota composition is currently a common unit of measurement for gut microbiome health.

The cited *in vitro* studies with almonds of Mandalari et al. [50] showed an increase in the levels of lactic, acetic, propionic, and butyric acids produced by bacterial fermentation. Similarly, the cited clinical studies of Ukhanova et al. [54], with almonds and pistachios, showed that the main fermenters of polysaccharides from nuts are SCFA-producing bacteria. At the same time, polyphenols need to be bioactivated by microbiota to express their beneficial effects on health. Bioaccessible polyphenols are involved in decreasing the synthesis of fatty acids in the liver and delaying their intestinal absorption [75]. They slow down digestion of carbohydrates

through the inhibition of digestive enzymes or modulation of glucose uptake [76]. For instance, bacterial species including *Lactobacillus plantarum*, *L. paraplantarum*, and *L. pentosus* express the enzymes that promote the intestinal bioavailability of polyphenols.

The nuts with highest contents of polymerized polyphenols are hazelnuts and pecans, followed by pistachios, almonds, and walnuts. On the other hand, walnuts are the richest plant source of ellagitannins (approximately 1600 mg/100 g) [77], a particularly active type of polyphenols included within the so-called "hydrolysable tannins" group. Ellagic acid is metabolized by gut microbiota into highly bioactive urolithins, which are absorbed and appear in the circulation following nut consumption and may influence cardiometabolic health through a variety of mechanisms, as reviewed [78]. In reference to intestinal health, *in vitro* assays have shown that the prebiotic properties of ellagitannins increase the growth of *Lactobacillus* and *Bifidobacterium* [79], together with improved insulin sensitivity and decreased DNA damage [80].

Despite differences in the evidences linking nut consumption to a beneficial overall gut microbiota composition (Figure 13.1), mechanistic studies are still needed in order to understand the complex interplay between nuts' components and selective microbiota modulation and function. In this regard, omics platforms are presently the gold standard methodologies in gut microbiota analysis. A general understanding about both its composition and metabolic function is given respectively from metagenomics and metabolomics techniques in stool samples. However,

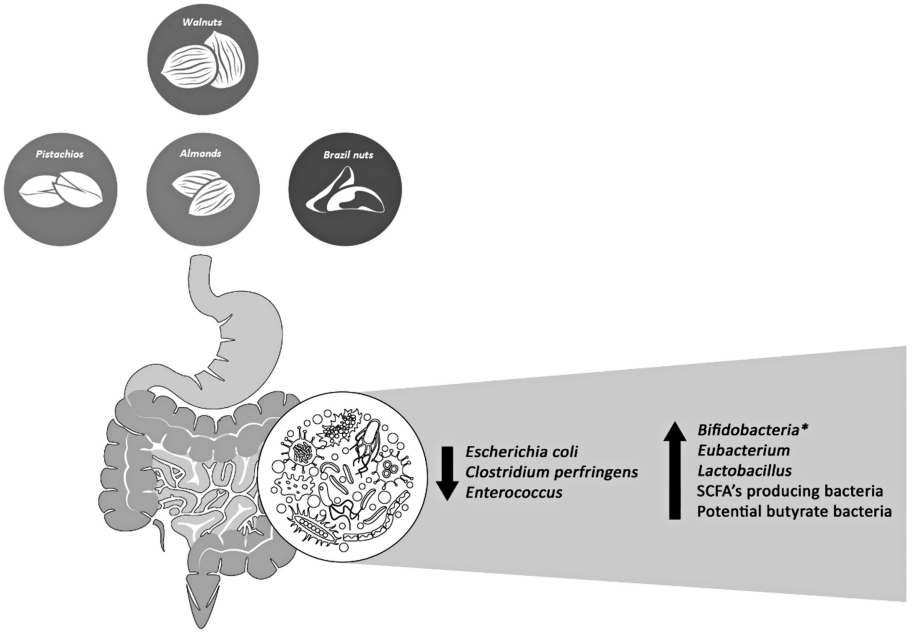


Figure 13.1 Summary of the effects of nuts and/or their constituents on microbiota modulation observed in experimental *in vitro* an *in vivo* models and in clinical studies. * Inconsistent results have been found; thus, the most common modulatory outcome was reported. *Abbreviation*: SCFAs, short chain fatty acids.

since gut microbiota is a recent area of research, a consensus about analytical procedures is still lacking. For example, metagenomics is strictly dependent on a uniform and reliable method of microbial DNA extraction, which is one of the most important critical points for further analysis [81]. At the same time, the possibility of analyzing more accurately different microbial metabolites also depends on the possibility of sharing different methods of analysis, which include nuclear magnetic resonance, liquid chromatography-mass spectrometry (MS), gas chromatography-MS, and high-performance liquid chromatography-MS, among others [82].

13.5 Conclusion

Little is known about the impact of nuts on the gut microbiome, but the available evidence strongly suggests that tree nuts alter gut microbial communities in different animal and human studies. This is supported by some *in vitro* studies showing the ability of nut consumption to change microbiota composition and activity. It is unclear whether microbial changes are preserved during long periods of nut supplementation and if they are causally related to the observed changes of gut function and host metabolism. Long-term human RCTs investigating the effect of different types and amounts of nuts would be useful to understand the possible mechanisms by which nuts could have beneficial effects on health and disease through the modulation of the human gut microbiome. More studies using multiple omics methodologies (metagenomics, metabolomics, and proteomics) are warranted in the future to better understand the underlying mechanisms of nut effects on microbiota in relation to various health outcomes.

References

1. Wu, G.D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.-Y., Keilbaugh, S.A., Bewtra, M. et al., Linking long-term dietary patterns with gut microbial enterotypes. *Science*, 334, 105–108, 2011.
2. Dinu, M., Abbate, R., Gensini, G.F., Casini, A., and Sofi, F., Vegetarian, vegan diets and multiple health outcomes: A systematic review with meta-analysis of observational studies. *Crit. Rev. Food Sci. Nutr.*, 57, 3640–3649, 2017.
3. Huang, T., Yang, B., Zheng, J., Li, G., Wahlqvist, M.L., and Li, D., Cardiovascular disease mortality and cancer incidence in vegetarians: A meta-analysis and systematic review. *Ann. Nutr. Metab.*, 60, 233–240, 2012.
4. Craig, W.J., Health effects of vegan diets. *Am. J. Clin. Nutr.*, 898(Suppl.), 1627S–1633S, 2009.
5. Ogce, F., Ceber, E., Ekti, R., and Oran, N.T., Comparison of Mediterranean, Western and Japanese diets and some recommendations. *Asian Pacific J. Cancer Prev.*, 9, 351–356, 2008.
6. Davis, B.C., and Kris-Etherton, P.M., Achieving optimal essential fatty acid status in vegetarians: Current knowledge and practical implications. *Am. J. Clin. Nutr.*, 788(Suppl.) 640S–646S, 2003.
7. De Filippis, F., Pellegrini, N., Vannini, L., Jeffery, I.B., La Storia, A., Laghi, L., Serrazanetti, D.I. et al., High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut*, 65, 1812LP–1821LP, 2016.

8. Mitsou, E.K., Kakali, A., Antonopoulou, S., Mountzouris, K.C., Yannakoulia, M., Panagiotakos, D.B., and Kyriacou, A., Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population. *Br. J. Nutr.*, 117, 1645–1655, 2017.
9. Tang, W.H.W., Wang, Z., Levison, B.S., Koeth, R.A., Britt, E.B., Fu, X., Wu, Y. et al., Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N. Engl. J. Med.*, 368, 1575–1584, 2013.
10. Haro, C., Montes-Borrego, M., Rangel-Zúñiga, O.A., Alcalã-Diaz, J.F., Gamez-Delgado, F., Pérez-Martinez, P., Delgado-Lista, J. et al., Two healthy diets modulate gut microbial community improving insulin sensitivity in a human obese population. *J. Clin. Endocrinol. Metab.*, 101, jc20153351, 2015.
11. Quercia, S., Turroni, S., Fiori, J., Soverini, M., Rampelli, S., Biagi, E., Castagnetti, A. et al., Gut microbiome response to short-term dietary interventions in reactive hypoglycemia subjects. *Diabetes. Metab. Res. Rev.*, 33, e2927, 2017.
12. van Faassen, A., Bol, J., van Dokkum, W., Pikaar, N.A., Ockhuizen, T., and Hermus, R.J., Bile acids, neutral steroids, and bacteria in feces as affected by a mixed, a lacto-ovovegetarian, and a vegan diet. *Am. J. Clin. Nutr.*, 46, 962–967, 1987.
13. Zimmer, J., Lange, B., Frick, J.-S., Sauer, H., Zimmermann, K., Schwiertz, A., Rusch, K. et al., A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *Eur. J. Clin. Nutr.*, 66, 53–60, 2012.
14. Ruengsomwong, S., Korenori, Y., Sakamoto, N., Wannissorn, B., Nakayama, J., and Nitisinprasert, S., Senior Thai fecal microbiota comparison between vegetarians and non-vegetarians using PCR-DGGE and real-time PCR. *J. Microbiol. Biotechnol.*, 24, 1026–1033, 2014.
15. De Filippo, C., Cavalieri, D., Di Paola, M., Ramazzotti, M., Poullet, J.B., Massart, S., Collini, S. et al., Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc. Natl. Acad. Sci. U.S.A.*, 107, 14691–14696, 2010.
16. So, D., Whelan, K., Rossi, M., Morrison, M., Holtmann, G., Kelly, J.T., Shanahan, E.R. et al., Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis. *Am. J. Clin. Nutr.*, 107, 965–983, 2018.
17. O'Keefe, S.J.D., Li, J.V., Lahti, L., Ou, J., Carbonero, F., Mohammed, K., Posma, J.M. et al., Fat, fibre and cancer risk in African Americans and rural Africans. *Nat. Commun.*, 6, 6342–6371, 2015.
18. Gorzynik-Debicka, M., Przychodzen, P., Cappello, F., Kuban-Jankowska, A., Gammazza, A.M., Knap, N., Wozniak, M. et al., Potential health benefits of olive oil and plant polyphenols. *Int. J. Mol. Sci.*, 19, 547–686, 2018.
19. Duda-Chodak, A., Tarko, T., Satora, P., and Sroka, P., Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: A review. *Eur. J. Nutr.*, 54, 325–341, 2015.
20. Barañano, K.W., and Hartman, A.L., The ketogenic diet: Uses in epilepsy and other neurologic illnesses. *Curr. Treat. Options Neurol.*, 10, 410–419, 2008.
21. Vanitallie, T.B., Nonas, C., Di Rocco, A., Boyar, K., Hyams, K., and Heymsfield, S.B., Treatment of parkinson disease with diet-induced hyperketonemia: A feasibility study. *Neurology*, 64, 728–730, 2005.
22. Evangeliou, A., Vlachonikolis, I., Mihailidou, H., Spilioti, M., Skarpalezou, A., Makaronas, N., Prokopiou, A. et al., Application of a ketogenic diet in children with autistic behavior: Pilot study. *J. Child Neurol.*, 18, 113–118, 2003.

23. Moreno, B., Bellido, D., Sajoux, I., Goday, A., Saavedra, D., Crujeiras, A.B., and Casanueva, F.F., Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. *Endocrine*, 47, 793–805, 2014.
24. Choi, H.R., Kim, J., Lim, H., and Park, Y.K., Two-week exclusive supplementation of modified ketogenic nutrition drink reserves lean body mass and improves blood lipid profile in obese adults: A randomized clinical trial. *Nutrients*, 10, 1895, 2018.
25. Ma, D., Wang, A.C., Parikh, I., Green, S.J., Hoffman, J.D., Chlipala, G., Murphy, M.P. et al., Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice. *Sci. Rep.*, 8, 6670–6680, 2018.
26. Nistal, E., Caminero, A., Vivas, S., Ruiz de Morales, J.M., Saenz de Miera, L.E., Rodriguez-Aparicio, L.B., and Casqueiro, J., Differences in faecal bacteria populations and faecal bacteria metabolism in healthy adults and celiac disease patients. *Biochimie*, 94, 1724–1729, 2012.
27. De Palma, G., Nadal, I., Collado, M.C., and Sanz, Y., Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. *Br. J. Nutr.*, 102, 1154–1160, 2009.
28. Pham, V.T., and Mohajeri, M.H., The application of *in vitro* human intestinal models on the screening and development of pre-and probiotics. *Benef. Microbes*, 9, 725–742, 2018.
29. Graham, E.A., Mallet, J.-F., Jambi, M., Alsadi, N., and Matar, C., The role of fibers and bioactive compounds in gut microbiota composition and health, in *Dietary Fibre Functionality in Food and Nutraceuticals: From Plant to Gut*, Hosseinian, F., Oomah, B.D., and Campos-Vega, R., Eds., Wiley-Blackwell, Oxford, UK, 2017, pp. 205–262.
30. Bianchi, F., Rossi, E.A., Sakamoto, I.K., Adorno, M.A.T., Van de Wiele, T., and Sivieri, K., Beneficial effects of fermented vegetal beverages on human gastrointestinal microbial ecosystem in a simulator. *Food Res. Int.*, 64, 43–52, 2014.
31. Van Den Abbeele, P., Marzorati, M., Derde, M., De Weirdt, R., Joan, V., Possemiers, S., and Van De Wiele, T., Arabinoxylans, inulin and *Lactobacillus reuteri* 1063 repress the adherent-invasive *Escherichia coli* from mucus in a mucosa-comprising gut model. *NPJ Biofilms Microbiomes*, 2, 16016–16024, 2016.
32. Schroeder, B.O., Fight them or feed them: How the intestinal mucus layer manages the gut microbiota. *Gastroenterol. Rep.*, 7, 3–12, 2018.
33. Donaldson, G.P., Lee, S.M., and Mazmanian, S.K., Gut biogeography of the bacterial microbiota. *Nat. Rev. Microbiol.*, 14, 20–32, 2015.
34. David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., Ling, A.V. et al., Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, 505, 559–563, 2014.
35. Chung, W.S.F., Walker, A.W., Louis, P., Parkhill, J., Vermeiren, J., Bosscher, D., Duncan, S.H. et al., Modulation of the human gut microbiota by dietary fibres occurs at the species level. *BMC Biol.*, 14, 1–13, 2016.
36. Van Den Abbeele, P., Grootaert, C., Marzorati, M., Possemiers, S., Verstraete, W., Gérard, P., Rabot, S. et al., Microbial community development in a dynamic gut model is reproducible, colon region specific, and selective for bacteroidetes and *Clostridium cluster* IX. *Appl. Environ. Microbiol.*, 76, 5237–5246, 2010.
37. Kostic, A.D., Howitt, M.R., and Garrett, W.S., Exploring host-microbiota interactions in animal models and humans. *Genes Dev.*, 27, 701–718, 2013.
38. Grover, M., and Kashyap, P.C., Germ-free mice as a model to study effect of gut microbiota on host physiology. *Neurogastroenterol. Motil.*, 26, 745–748, 2014.

39. Charbonneau, M.R., O'Donnell, D., Blanton, L.V., Totten, S.M., Davis, J.C.C., Barratt, M.J., Cheng, J. et al., Sialylated milk oligosaccharides promote microbiota-dependent growth in models of infant undernutrition. *Cell*, 164, 859–871, 2016.
40. Gibson, G.R., and Roberfroid, M.B., Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J. Nutr.*, 125, 1401–1412, 1995.
41. Gibson, G.R., and Wang, X., Regulatory effects of Bifidobacteria on the growth of other colonic bacteria. *J. Appl. Bacteriol.*, 77, 412–420, 1994.
42. Liu, Z., Wang, W., Huang, G., Zhang, W., and Ni, L., *In vitro* and *in vivo* evaluation of the prebiotic effect of raw and roasted almonds (*Prunus amygdalus*). *J. Sci. Food Agric.*, 96, 1836–1843, 2016.
43. Nakanishi, M., Chen, Y., Qendro, V., Miyamoto, S., Weinstock, E., Weinstock, G.M., and Rosenberg, D.W., Effects of walnut consumption on colon carcinogenesis and microbial community structure. *Cancer Prev. Res.*, 9, 692–703, 2016.
44. Byerley, L.O., Samuelson, D., Blanchard, E., Luo, M., Lorenzen, B.N., Banks, S., Ponder, M.A. et al., Changes in the gut microbial communities following addition of walnuts to the diet. *J. Nutr. Biochem.*, 48, 94–102, 2017.
45. van Hylckama Vlieg, J.E., Veiga, P., Zhang, C., Derrien, M., and Zhao, L., Impact of microbial transformation of food on health from fermented foods to fermentation in the gastro-intestinal tract. *Curr. Opin. Biotechnol.*, 22, 211–219, 2011.
46. Macfarlane, G.T., and Macfarlane, S., Models for intestinal fermentation: Association between food components, delivery systems, bioavailability and functional interactions in the gut. *Curr. Opin. Biotechnol.*, 18, 156–162, 2007.
47. Macfarlane, G.T., Macfarlane, S., and Gibson, G.R., Validation of a three-stage compound continuous culture system for investigating the effect of retention time on the ecology and metabolism of bacteria in the human colon. *Microb. Ecol.*, 35, 180–187, 1998.
48. Minekus, M., Marteau, P., Havenaar, R., and Huisintveld, J.H.J., A multicompartmental dynamic computer-controlled model simulating the stomach and small intestine. *Altern. Lab. Anim.*, 23, 197–209, 1995.
49. Payne, A.N., Zihler, A., Chassard, C., and Lacroix, C., Advances and perspectives in *in vitro* human gut fermentation modeling. *Trends Biotechnol.*, 30, 17–25, 2012.
50. Mandalari, G., Nueno-Palop, C., Bisignano, G., Wickham, M.S.J., and Narbad, A., Potential prebiotic properties of almond (*Amygdalus communis* L.) seeds. *Appl. Environ. Microbiol.*, 74, 4264–4270, 2008.
51. Blaiotta, G., La Gatta, B., Di Capua, M., Di Luccia, A., Coppola, R., and Aponte, M., Effect of chestnut extract and chestnut fiber on viability of potential probiotic *Lactobacillus* strains under gastrointestinal tract conditions. *Food Microbiol.*, 36, 161–169, 2013.
52. Schlörmann, W., Birringer, M., Lochner, A., Lorkowski, S., Richter, I., Rohrer, C., and Glei, M., *In vitro* fermentation of nuts results in the formation of butyrate and c9,t11 conjugated linoleic acid as chemopreventive metabolites. *Eur. J. Nutr.*, 55, 2063–2073, 2016.
53. Lacroix, C., de Wouters, T., and Chassard, C., Integrated multi-scale strategies to investigate nutritional compounds and their effect on the gut microbiota. *Curr. Opin. Biotechnol.*, 32, 149–155, 2015.
54. Ukhanova, M., Wang, X., Baer, D.J., Novotny, J.A., Fredborg, M., and Mai, V., Effects of almond and pistachio consumption on gut microbiota composition

in a randomised cross-over human feeding study. *Br. J. Nutr.*, 111, 2146–2152, 2014.
55. Holscher, H.D., Guetterman, H.M., Swanson, K.S., An, R., Matthan, N.R., Lichtenstein, A.H., Novotny, J.A. et al., Walnut consumption alters the gastrointestinal microbiota, microbially derived secondary bile acids, and health markers in healthy adults: A randomized controlled trial. *J. Nutr.*, 148, 861–867, 2018.
56. Bamberger, C., Rossmeier, A., Lechner, K., Wu, L., Waldmann, E., Fischer, S., Stark, R.G. et al., A walnut-enriched diet affects gut microbiome in healthy Caucasian subjects: A randomized, controlled trial. *Nutrients*, 10, 244–258, 2018.
57. Holscher, H.D., Taylor, A.M., Swanson, K.S., Novotny, J.A., and Baer, D.J., Almond consumption and processing affects the composition of the gastrointestinal microbiota of healthy adult men and women: A randomized controlled trial. *Nutrients*, 10, 126–136, 2018.
58. Liu, Z., Lin, X., Huang, G., Zhang, W., Rao, P., and Ni, L., Prebiotic effects of almonds and almond skins on intestinal microbiota in healthy adult humans. *Anaerobe*, 26, 1–6, 2014.
59. Hernández-Alonso, P., Cañueto, D., Giardina, S., Salas-Salvadó, J., Cañellas, N., Correig, X., and Bulló, M., Effect of pistachio consumption on the modulation of urinary gut microbiota-related metabolites in prediabetic subjects. *J. Nutr. Biochem.*, 45, 48–53, 2017.
60. Burns, A.M., Zitt, M.A., Rowe, C.C., Langkamp-Henken, B., Mai, V., Nieves, C., Ukhanova, M. et al., Diet quality improves for parents and children when almonds are incorporated into their daily diet: A randomized, crossover study. *Nutr. Res.*, 36, 80–89, 2016.
61. Bao, Y., Han, J., Hu, F.B., Giovannucci, E.L., Stampfer, M.J., Willett, W.C., and Fuchs, C.S., Association of nut consumption with total and cause-specific mortality. *N. Engl. J. Med.*, 369, 2001–2011, 2013.
62. Wang, F., Yu, T., Huang, G., Cai, D., Liang, X., Su, H., Zhu, Z. et al., Gut microbiota community and its assembly associated with age and diet in Chinese centenarians. *J. Microbiol. Biotechnol.*, 25, 1195–1204, 2015.
63. Biagi, E., Franceschi, C., Rampelli, S., Severgnini, M., Ostan, R., Turroni, S., Consolandi, C. et al., Gut microbiota and extreme longevity. *Curr. Biol.*, 26, 1480–1485, 2016.
64. Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G., Gasbarrini, A., and Mele, M., What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. *Microorganisms*, 7, 1–22, 2019.
65. Nash, S.D., and Nash, D.T., Nuts as part of a healthy cardiovascular diet. *Curr. Atheroscler. Rep.*, 10, 529–535, 2008.
66. Coates, A., Hill, A., and Tan, S., Nuts and cardiovascular disease prevention. *Curr. Atheroscler. Rep.*, 20, 48, 2018.
67. Aune, D., Keum, N., Giovannucci, E., Fadnes, L.T., Boffetta P., Greenwood, D.C., Tonstad, S. et al., Nut consumption and risk of cardiovascular disease, total cancer, all-cause and causespecific mortality: A systematic review and dose-response meta-analysis of prospective studies. *BMC Med.*, 14, 207–221, 2016.
68. Ros, E., Nuts and CVD. *Br. J. Nutr.*, 113(Suppl. 2), S111–S120, 2015.
69. Sugizaki, C.S.A., and Naves, M.M.V., Potential prebiotic properties of nuts and edible seeds and their relationship to obesity. *Nutrients*, 10, 1645–1659, 2018.

70. Lamuel-Raventos, R.M., and Onge, M.P.S., Prebiotic nut compounds and human microbiota. *Crit. Rev. Food Sci. Nutr.*, 57, 3154–3163, 2017.
71. Ye, J., Martin, R.J., Gao, Z., Zhang, J., Ward, R.E., Yin, J., Lefevre, M. et al., Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes*, 58, 1509–1517, 2009.
72. Kaji, I., Karaki, S.I., and Kuwahara, A., Short-chain fatty acid receptor and its contribution to glucagon-like peptide-1 release. *Digestion*, 89, 31–36, 2014.
73. den Besten, G., van Eunen, K., Groen, A.K., Venema, K., Reijngoud, D.J., and Bakker, B.M., The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J. Lipid Res.*, 54, 2325–2340, 2013.
74. Kim, Y., Keogh, J.B., and Clifton, P.M., Benefits of nut consumption on insulin resistance and cardiovascular risk factors: Multiple potential mechanisms of actions. *Nutrients*, 9, 1271–1310, 2017.
75. Bloemen, J.G., Venema, K., van de Poll, M.C., Olde, Damink, W., Buurman, W.A., and Dejong, C.H., Short chain fatty acids exchange across the gut and liver in humans measured at surgery. *Clin. Nutr.*, 28, 657–661, 2009.
76. Ozdal, T., Sela, D.A., Xiao, J., Boyacioglu, D., Chen, F., and Capanoglu, E., The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. *Nutrients*, 8, 1–36, 2016.
77. García-Conesa, M.T., Chambers, K., Combet, E., Pinto, P., Garcia-Aloy, M., Andrés-Lacueva, C., de Pascual-Teresa, S. et al., Meta-analysis of the effects of foods and derived products containing ellagitannins and anthocyanins on cardiometabolic biomarkers: Analysis of factors influencing variability of the individual responses. *Int. J. Mol. Sci.*, 19, 694–727, 2018.
78. Tomás-Barberán, F.A., González-Sarrías, A., García-Villalba, R., Núñez-Sánchez, M.A., Selma, M.V., García-Conesa, M.T., and Espín, J.C., Urolithins, the rescue of "old" metabolites to understand a “new” concept: Metabotypes as a nexus among phenolic metabolism, microbiota dysbiosis, and host health status. *Mol. Nutr. Food Res.*, 61, 1–36, 2017.
79. Li, Z., Summanen, P.H., Komoriya, T., Henning, S.M., Lee, R.P., Carlson, E., Heber, D. et al., Pomegranate ellagitannins stimulate growth of gut bacteria *in vitro*: Implications for prebiotic and metabolic effects. *Anaerobe*, 34, 164–168, 2015.
80. Tulipani, S., Llorach, R., Jáuregui, O., López-Uriarte, P., Garcia-Aloy, M., Bulló, M., Salas-Salvadó, J. et al., Metabolomics unveils urinary changes in subjects with metabolic syndrome following 12-week nut consumption. *J. Proteome Res.*, 10, 5047–5058, 2011.
81. Thomas, V., Clark, J., and Doré, J., Fecal microbiota analysis: An overview of sample collection methods and sequencing strategies. *Future Microbiol.*, 10, 1485–1504, 2015.
82. Moosmang, S., Pitscheider, M., Sturm, S., Seger, C., Tilg, H., Halabalaki, M., and Stuppner, H., Metabolomic analysis – addressing NMR and LC-MS related problems in human feces sample preparation. *Clin. Chim. Acta*, 489, 169–176, 2019.
83. Novotny, J.A., Gebauer, S.K., and Baer, D.J., Discrepancy between the Atwater factor predicted and empirically measured energy values of almonds in human diets. *Am. J. Clin. Nutr.*, 96, 296–301, 2012.
84. Baer, D.J., Gebauer, S.K., and Novotny, J.A., Measured energy value of pistachios in the human diet. *Br. J. Nutr.*, 107, 120–125, 2012.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Section II

DRIED FRUITS

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 14

Dried Fruits

Nutrients, Natural Antioxidants, and Phytochemicals

Cesarettin Alasalvar, Sui Kiat Chang, and Fereidoon Shahidi

14.1 Introduction 336
14.2 Nutrient Profiles of Dried Fruits 338
14.2.1 Proximate Composition 338
14.2.1.1 Carbohydrates 338
14.2.1.2 Lipids 343
14.2.1.3 Proteins 343
14.2.2 Minerals 343
14.2.3 Vitamins 344
14.2.4 Amino Acids 344
14.2.5 Health Claims for Dried Fruits 344
14.2.6 Daily Intake Values of Minerals from Dried Fruits 345
14.2.7 Daily Intake Values of Vitamins from Dried Fruits 345
14.3 Antioxidant Activities of Dried Fruits 350
14.4 Phytochemicals in Dried Fruits 351
14.4.1 Carotenoids 351
14.4.2 Phytoestrogens 352
14.4.3 Phenolics 352
14.4.3.1 Flavonoids 353
14.4.3.2 Phenolic Acids 363
14.4.3.3 Tannins 364

14.4.3.4 Stilbenes 364
14.4.3.5 Chalcones/Dihydrochalcones 364
14.5 Conclusion 364
References 364

14.1 Introduction

Most of the common fruits are produced on a seasonal basis and hence may not be available in fresh form throughout the year. Thus, in order to prolong their shelf life, fresh fruits are processed using various techniques to make dried fruits. Dried fruits are a concentrated form of fresh fruits, albeit with lower moisture content than that of their fresh counterparts since a large proportion of their moisture content has been removed through sun-drying or through various modern drying techniques [1,2].

Fruits can be dried whole (e.g., grapes, berries, apricots, and plums), in halves, or as slices (e.g., mangoes, papayas, and kiwis). Dates, figs, prunes, raisins, apricots, peaches, apples, and pears are referred to as *conventional* or *traditional* dried fruits. Meanwhile, some fruits, such as blueberries, cranberries, cherries, strawberries, and mangoes, are usually infused with sugar solutions or fruit-juice concentrates prior to drying [2]. Some products sold as dried fruit, such as papayas and pineapples, are actually candied fruits [3].

Considering the 2017/2018 global production of commercially important dried fruits (Table 14.1), raisins rank first on a global basis with a production of 1,216,500 metric tons (MT), followed by dates (1,025,000 MT), prunes (240,808 MT), apricots (226,760 MT), and figs (139,400). However, statistics on the global production of other died fruits are generally scarce [4].

Dried fruits serve as important healthful snack items worldwide. They provide a concentrated form of fresh fruits. Dried fruits, with their unique combination of flavor (taste and aroma), essential nutrients, fiber, and phytochemicals, are convenient for healthy eating and bridge the gap between recommended intake of fruits and actual consumption. Dried fruits are nutritionally equivalent to fresh fruits in smaller serving sizes, ranging from 30 to 43 g depending on the fruit, in current dietary recommendations in different countries. Numerous scientific evidences suggest that individuals who regularly consume generous amounts of dried fruits have lower rates of cardiovascular disease (CVD), obesity, various types of cancer, type-2 diabetes, and other chronic diseases, although for certain diseases some controversies exist. Therefore, daily consumption of dried fruits is recommended in order to get the full benefit of the nutrients and health-promoting phytochemicals, including antioxidants, that they contain, together with their desirable taste and aroma. Dried fruits also have the advantage of being easy to store and distribute, available around the year, readily incorporated into other foods and recipes, and a healthy alternative to salty or sugar-coated snacks [1,2].

This chapter provides a comprehensive overview of nutrients, natural antioxidants, and phytochemical compositions of commercially important dried fruits. Percentages of recommended dietary allowances (RDA) or adequate intake (AI) of vitamins and minerals provided by dried fruits in adult men and women (aged 19–50 years) are also provided.

Table 14.1 World Dried Fruits Production (Metric Tons)

Production	*2010/2011*	*2011/2012*	*2012/2013*	*2013/2014*	*2014/2015*	*2015/2016*	*2016/2017*	*2017/2018*
Apricots	159,100	198,917	239,018	170,945	87,829	150,746	169,450	226,760
Dates	670,800	659,800	747,250	753,900	781,000	836,500	929,000	1,025,000
Figs	107,562	107,000	145,250	117,800	135,744	142,505	131,500	139,400
Prunes	244,030	230,703	293,400	197,977	224,920	266,572	225,775	240,808
Raisins	1,038,547	1,206,999	1,328,405	1,225,635	1,328,844	1,217,000	1,278,000	1,216,500

Source: Adapted from International Nut and Dried Fruit Council (INC), Nuts and Dried Fruits, Statistical Yearbook 2017/2018 and Nutfruit Magazine July 2018, INC, Reus, Spain, 2018.

14.2 Nutrient Profiles of Dried Fruits

Dried fruits are rich sources of essential nutrients. Compositional and nutritional characteristics of 12 dried fruits (apples, apricots, dates, figs, peaches, pears, prunes, raisins, blueberries, cranberries, currants, and mangoes) are compared and presented in Table 14.2. Complete nutrient profiles of other dried fruits (such as açai fruits, bananas, blackberries, blackcurrants, cherries, dried citrus fruits, goji berries, guavas, mulberries, nectarines, papayas, passion fruits, raspberries, and strawberries, among others) are not available in the United States Department of Agriculture (USDA) database or elsewhere, and therefore they are not discussed in this section.

14.2.1 Proximate Composition

Dried fruits are a nutrient-dense component of the diet. Their proximate composition varies considerably depending on the dried fruit type being considered. Based on the data provided in Table 14.2, carbohydrate is the predominant component (61.33–82.80 g/100 g; being lowest in peaches and highest in cranberries), followed by moisture (water) (14.80–31.80 g/00 g; being lowest in blueberries and highest in peaches), protein (0.17–4.08 g/100 g; being lowest in cranberries and highest in currants), lipid (fat) (0.27–1.18 g/100 g; being lowest in currants and highest in mangoes), and ash (0.15–2.64 g/100 g; being lowest in cranberries and highest in prunes). Dried fruits are a good source of energy due to their high carbohydrate content. The most calorie-rich fruits are mangoes (319 kcal/100 g), followed by blueberries (317 kcal/100 g), cranberries (308 kcal/100 g), and raisins (299 kcal/100 g). In other words, dried fruits are rich in carbohydrate and mainly devoid of lipid and protein [5].

14.2.1.1 Carbohydrates

Carbohydrates are essentially composed of sugars, fibers, and starches. The dominant carbohydrate in dried fruits is sugars. Based on the USDA database in Table14.2, dried fruits contain natural sugars, ranging from 38.13 g/100 g in prunes to 72.56 g/100 g in cranberries. Fructose and glucose are the main sugars found in all dried fruits, except dates and peaches where sucrose is most abundant (23.84 and 15.42 g/100 g, respectively) (Figure 14.1). Trace amounts of maltose (in dates and prunes), galactose (figs), and lactose (sweetened cranberries) are also found in some dried fruits [5]. Levels of sugar may differ according to the drying methods, growing conditions, region, fruit maturity, and cultivar, among others (Table 14.1 and Figure 14.1) [5,6].

Their content of dietary fiber (2.4–9.8 g/100 g) makes dried fruit an important source of it that makes it easier to reach the recommended daily intake (14 g of fiber for every 1,000 calories of food consumed each day). This provides between 25 and 38 g of fiber per day, depending on age [7]. On a per serving basis, 40 g of dried fruits deliver over 9% of the recommended daily intake of fiber, depending on the fruit [5]. It has been reported that dried fruits (40 g serving) compare favorably in their fiber content with commonly consumed fresh fruits (one cup or one fruit serving) [5,8].

The majority of dried fruits do not contain starch; the exceptions are prunes (5.11 g/100 g), figs (5.07 g/100 g), raisins (2.70 g/100 g), and apricots (0.35 g/100 g)

Table 14.2 Compositional and Nutritional Characteristics of Selected Dried Fruits (per 100 g)

Nutrient	*Unit*	*Apples*	*Apricots*	*Dates*[a]	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*[b]	*Blueberries*[c]	*Cranberries*[d]	*Currats*[e]	*Mangoes*[f]
Proximate composition													
Water	g	31.76	30.89	20.53	30.05	31.80	26.69	30.92	15.43	14.80	15.79	19.21	16.60
Energy	kcal	243	241	282	249	239	262	240	299	317	308	283	319
Protein	g	0.93	3.39	2.45	3.30	3.61	1.87	2.18	3.07	2.50	0.17	4.08	2.45
Lipid (fat)	g	0.32	0.51	0.39	0.93	0.76	0.63	0.38	0.46	2.50	1.09	0.27	1.18
Ash	g	1.10	2.57	1.60	1.86	2.50	1.11	2.64	1.85	0.73	0.15	2.36	1.19
Carbohydrate	g	65.89	62.64	75.03	63.87	61.33	69.70	63.88	79.18	80.00	82.80	74.08	78.58
Dietary fiber	g	8.7	7.3	8.0	9.8	8.2	7.5	7.1	3.7	7.5	5.3	6.8	2.4
Sugars	g	57.19	53.44	63.35	47.92	41.74	62.20	38.13	59.19	67.50	72.56	67.28	66.27
Starch	g	na	0.35	na	5.07	na	na	5.11	2.70	na	na	na	na
Minerals													
Calcium	mg	14	55	39	162	28	34	43	50	19	9.0	86	na
Copper	mg	0.19	0.34	0.21	0.29	0.36	0.37	0.28	0.32	0.16	0.06	0.47	0.30
Fluoride	µg	nd	nd	nd	nd	nd	nd	4.0	234	nd	nd	nd	nd
Iron	mg	1.40	2.66	1.02	2.03	4.06	2.10	0.93	1.88	0.90	0.39	3.26	0.23
Magnesium	mg	16	32	43	68	42	33	41	32	18	4.0	41	20

(*Continued*)

Table 14.2 (Continued) Compositional and Nutritional Characteristics of Selected Dried Fruits (per 100 g)

Nutrient	*Unit*	*Apples*	*Apricots*	*Dates*[a]	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*[b]	*Blueberries*[c]	*Cranberries*[d]	*Currats*[e]	*Mangoes*[f]
Manganese	mg	0.09	0.24	0.26	0.51	0.31	0.33	0.30	0.30	nd	0.18	0.47	10
Phosphorus	mg	38	71	62	67	119	59	69	101	36	8.0	125	50
Potassium	mg	450	1162	656	680	996	533	732	749	214	49	892	279
Selenium	µg	1.3	2.2	3.0	0.6	0.5	0.2	0.3	0.6	0.6	0.6	0.7	2.1
Sodium	mg	87	10	2.0	10	7.0	6.0	2.0	11	3.0	5.0	8.0	162
Zinc	mg	0.20	0.39	0.29	0.55	0.57	0.39	0.44	0.22	0.49	0.10	0.66	0.30
Vitamins													
Betaine	mg	nd	0.30	0.4	0.7	nd	nd	0.4	0.3	nd	nd	nd	nd
Choline	mg	17.6	13.9	6.3	15.8	12.7	23	10.1	11.1	18.5	8.3	10.6	23.7
Folate (DFE)	µg	nd	10.0	19.0	9.0	nd	nd	4.0	5.0	12	nd	10	68
Niacin	mg	0.93	2.59	1.27	0.62	4.38	1.37	1.88	0.77	1.15	0.55	1.62	2.0
Pantothenic acid	mg	0.25	0.52	0.59	0.43	0.56	0.15	0.42	0.10	nd	nd	0.05	nd
Pyridoxine (B-6)	mg	0.13	0.14	0.17	0.11	0.07	0.07	0.21	0.17	0.15	0.04	0.30	0.33
Riboflavin	mg	0.16	0.07	0.07	0.08	0.21	0.15	0.19	0.13	0.13	0.03	0.14	0.09
Thiamin	mg	nd	0.02	0.05	0.09	0.002	0.01	0.05	0.11	0.09	0.01	0.16	0.06
Vitamin A (RAE)	µg	nd	180	nd	nd	108	nd	39	nd	7.0	2.0	4.0	67
Vitamin C	mg	3.9	1.0	0.4	1.2	4.8	7.0	0.6	2.3	23.8	0.2	4.7	42.3

(*Continued*)

Table 14.2 (Continued) Compositional and Nutritional Characteristics of Selected Dried Fruits (per 100 g)

Nutrient	*Unit*	*Apples*	*Apricots*	*Dates*[a]	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*[b]	*Blueberries*[c]	*Cranberries*[d]	*Currats*[e]	*Mangoes*[f]
Vitamin E (ATE)	mg	0.53	4.33	0.05	0.35	0.19	0.06	0.43	0.12	2.35	2.10	0.11	4.02
Vitamin K	µg	3.0	3.1	2.7	15.6	15.7	20.4	59.5	3.5	59.4	7.6	3.3	13.2
Amino acids													
Alanine	g	0.033	0.110	0.083	0.134	0.215	0.062	0.066	0.105	na	na	na	na
Arginine	g	0.029	0.066	0.136	0.077	0.092	0.032	0.037	0.413	na	na	na	na
Aspartic acid	g	0.162	0.937	0.213	0.645	0.602	0.368	0.801	0.110	na	na	na	na
Cystine	g	0.012	0.019	0.067	0.036	0.029	0.018	0.011	0.019	na	na	na	na
Glutamic acid	g	0.097	0.188	0.359	0.295	0.548	0.135	0.114	0.164	na	na	na	na
Glycine	g	0.037	0.070	0.101	0.108	0.126	0.054	0.047	0.080	na	na	na	na
Histidine[g]	g	0.015	0.047	0.032	0.037	0.067	0.020	0.027	0.072	na	na	na	na
Isoleucine[g]	g	0.037	0.063	0.049	0.089	0.104	0.054	0.041	0.057	na	na	na	na
Leucine[g]	g	0.057	0.105	0.084	0.128	0.204	0.094	0.066	0.096	na	na	na	na
Lysine[g]	g	0.058	0.083	0.066	0.088	0.116	0.066	0.050	0.084	na	na	na	na
Methionine[g]	g	0.009	0.015	0.022	0.034	0.087	0.022	0.016	0.021	na	na	na	na
Phenylalanine[g]	g	0.026	0.062	0.050	0.076	0.114	0.049	0.052	0.065	na	na	na	na
Proline	g	0.032	0.821	0.130	0.610	0.152	0.051	0.130	0.254	na	na	na	na
Serine	g	0.038	0.087	0.057	0.128	0.167	0.067	0.059	0.070	na	na	na	na
Threonine[g]	g	0.033	0.073	0.043	0.085	0.141	0.049	0.049	0.077	na	na	na	na

(*Continued*)

Table 14.2 (Continued) Compositional and Nutritional Characteristics of Selected Dried Fruits (per 100 g)

Nutrient	*Unit*	*Apples*	*Apricots*	*Dates*[a]	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*[b]	*Blueberries*[c]	*Cranberries*[d]	*Currats*[e]	*Mangoes*[f]
Tryptophan[g]	g	0.009	0.016	0.012	0.020	0.010	nd	0.025	0.050	na	na	na	na
Tyrosine	g	0.017	0.039	0.015	0.041	0.094	0.016	0.021	0.012	na	na	na	na
Valine[g]	g	0.043	0.078	0.071	0.122	0.197	0.066	0.056	0.083	na	na	na	na

Source: Adapted from the U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed June 20, 2018).

Note: Some numbers are rounded to the second digit after decimal point.

Abbreviations: ATE, alpha-tocopherol equivalents; DFE, dietary folate equivalents; na, not available; nd, not detected; RAE, retinol activity equivalents.

[a] Deglet noor.
[b] Seedless.
[c] Dried, sweetened.
[d] Dried, sweetened.
[e] Zante, dried.
[f] Dried, sweetened.
[g] Indispensable amino acids.

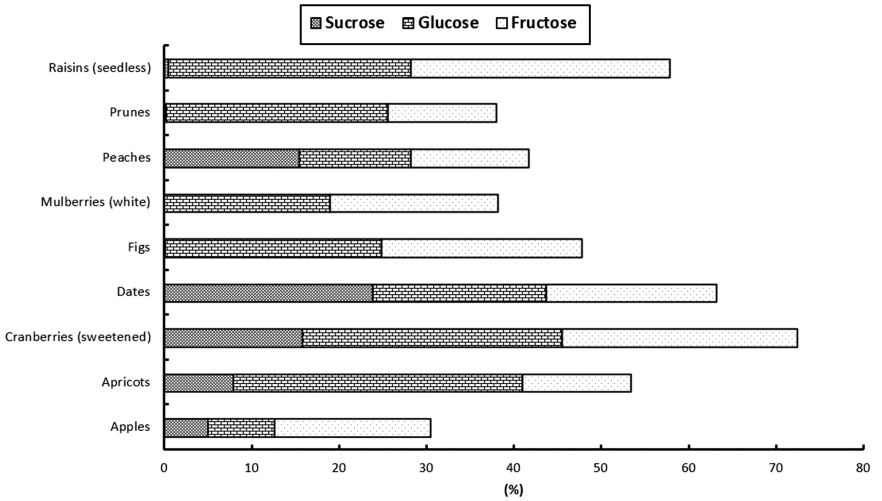


Figure 14.1 Sugar content of selected dried fruits. *Source:* Adapted from the U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed June 20, 2018) and from Turkish Food Composition Database, TürKomp. Published online at http://www.turkomp.gov.tr/?locale=en (accessed August 28, 2018).

(Table 14.2). As expected, dried fruits, unlike other plant foods, such as cereals, nuts, and tubers, do not contain large amounts of starch [5].

14.2.1.2 Lipids

Dried fruits are very low in their lipid content (ranging from 0.27 g/100 g in currants to 1.18 g/100 g in mangoes) (Table 14.2). Lipid contributes to a very small portion of the energy obtained from dried fruits. Therefore, detailed information on lipid content and profiles (e.g., fatty acids, phytosterols, and tocols) of dried fruits are not discussed in this section. Again, cultivar type, geographical location, and growing conditions influence the lipid content of dried fruits. However, the seeds of fruits may serve as a good source of specialty lipid, often with high tocol content.

14.2.1.3 Proteins

Dried fruits contain a low content of protein, ranging from 0.17 to 4.08 g/100 g. Among the 12 dried fruits listed in Table 14.2, apricots, figs, peaches, raisins, and currants appear to have the highest (between 3.07 and 4.08 g/100 g), whereas others contain the lowest (less than 2.5 g/100 g) amount of protein.

14.2.2 Minerals

A total of 11 minerals have been reported in dried fruits by the USDA [5]. In general, potassium is the most abundant mineral, followed by phosphorus, calcium, and/or

magnesium. Among the 12 dried fruits listed in Table 14.2, all contain 11 minerals, albeit to a different extent, except for fluoride, which is only reported in prunes and raisins. The content of the antioxidant mineral selenium in dates (3.0 μg/100 g) is much higher than that in other dried fruits (range from 0.2 μg/100 g in pears to 2.2 μg/100 g in apricots). Daily requirement of minerals at suggested consumption level of dried fruits is discussed in detail in Section 14.2.6.

14.2.3 Vitamins

Dried fruits contain both water-soluble vitamins (betaine, choline, folate, niacin, pantothenic acid, pyridoxine, riboflavin, thiamine, and vitamin C) and fat-soluble vitamins (A, E, and K) at different levels. Among them, vitamins A, C, and E are known as antioxidant vitamins.

With respect to water-soluble vitamins, mangoes and blueberries have the highest amounts of vitamin C (42.3 and 23.8 mg/100 g, respectively) among the 12 dried fruits listed in Table 14.2. Dried fruits, in general, contain a small amount of vitamin C due to the drying process such as drying under sunlight. Moreover, certain dried fruits are good sources of folate, such as mangoes (68 μg dietary folate equivalents [DFE]/100 g); niacin, such as peaches (4.38 mg/100 g); and pyridoxine, such as currants (0.30 mg/100 g) and mangoes (0.33 mg/100 g) [2,5].

Regarding fat-soluble vitamins, prunes and blueberries are the richest sources of vitamin K (59.5 and 59.4 μg/100 g), whereas apricots and peaches are the richest sources of vitamin A (180 and 108 μg retinol activity equivalents [RAE]/100 g) among the 12 dried fruits listed (Table 14.2). In addition, vitamin E is most abundant in apricots (4.33 mg alpha-tocopherol equivalents [ATE]/100 g) and mangoes (4.02 mg ATE/100 g). Although certain dried fruits are rich in some fat-soluble vitamins, they are in general poor sources of these vitamins due to the low fat content of the products [5]. Daily requirement of vitamins at suggested consumption level of dried fruits is discussed in detail in Section 14.2.7.

14.2.4 Amino Acids

The amino acid compositions of eight major dried fruits are summarized in Table 14.2. Values for dried blueberries, cranberries, currants, and mangoes are not available in the literature. Even though dried fruits contain all indispensable amino acids (except tryptophan in pears), in general, they are not good sources of amino acids due to their low protein content. Therefore, detailed information on amino acid profiles of dried fruits are not discussed in this section.

14.2.5 Health Claims for Dried Fruits

The European Food Safety Authority (EFSA) authorizes health claims provided that they are based on scientific evidence and can be easily understood by consumers. At this time, there is only one health claim approved by the EFSA with regard to dried fruits, which refers to prunes and digestive health [9]. Due to the scientific evidence published in 2006 about prunes and constipation, the EFSA authorized the

health claim: "*dried plums/prunes can contribute to normal bowel function*." In order to obtain the claimed effect, about 100 g of prunes should be consumed daily.

14.2.6 Daily Intake Values of Minerals from Dried Fruits

With respect to nutritional aspects of dried fruits, percentage of RDA or AI of minerals for adult men and women (aged 19–50 years) are given in Table 14.3 [5,10–13]. Consuming 40 g (on a per-serving basis) of dried fruits supplies 0.4%–6.5% (men and women) of calcium, 2.7%–20.9% (men and women) of copper, tr-2.3% (men) and tr-3.1% (women) of fluoride, 2.0%–20.3% (men) and 0.9%–9.0% (women) of iron, 0.4%–6.6% (men) and 0.6%–8.6% (women) of magnesium, 3.1%–174% (men) and 4.0%–222% (women) of manganese, 0.5%–7.1% (men and women) of phosphorus, 0.4%–9.9% (men and women) of potassium, 0.1%–2.2% (men and women) of selenium, 0.1%–4.3% (men and women) of sodium, and 0.4%–2.4% (men) and 0.5%–3.3% (women) of zinc for RDA or AI, respectively.

Based on the RDA or AI values among the 12 dried fruits listed in Table 14.3, mangoes are an excellent source of manganese. Figs are high in calcium, magnesium, and manganese, whereas currants are good source of copper and phosphorus. Peaches are an important source of iron and phosphorus. Moreover, apricots are an important source of potassium among the 12 dried fruits listed in Table 14.3. In general, dried fruits contribute to small amounts of daily intake values of minerals, such as fluoride, selenium, sodium, and zinc, with the exception of a few dried fruits. On a per-serving basis (40 g or about ¼ cup), dried fruits rank among the top potassium sources in diets around the world [8]. Moreover, on a per-serving basis, different dried fruits such as apricots, currants, dates, figs, peaches, prunes, and raisins (40 g serving), compare positively within potassium content of the 10 most common fresh fruits (apples, bananas, grapes, mangos, oranges, peaches, pears, pineapples, strawberries, and watermelons [one cup or one fruit serving]) [5,8].

14.2.7 Daily Intake Values of Vitamins from Dried Fruits

With respect to nutritional aspects of dried fruits, percentage of RDA or AI of vitamins for adult men and women (aged 19–50 years) are given in Table 14.4 [5,11,13,14]. Consuming 40 g (on a per-serving basis) of dried fruits supplies 0.5%–1.7% (men) and 0.6%–2.2% (women) of choline, 0.4%–6.8% (men and women) of folate, 1.4%–11.0% (men) and 1.6%–12.5% (women) of niacin, 0.4%–4.7% (men and women) of pantothenic acid, 1.2%–10.2% (men and women) of pyridoxine, 0.9%–6.5% (men) and 1.1%–7.6% (women) of riboflavin, 0.1%–5.3% (men) and 0.1%–5.8% (women) of thiamin, tr-8.0% (men) and tr-10.3% (women) of vitamin A, 0.1%–18.8% (men) and 0.1%–22.6% (women) of vitamin C, 0.1%–11.5% (men and women) of vitamin E, and 0.9%–19.8% (men) and 1.2%–26.4% (women) of vitamin K for RDA or AI, respectively.

Based on the RDA or AI values among the 12 dried fruits listed in Table 14.4, mangoes contain higher levels of choline, folate, pyridoxine, and vitamin C than other dried fruits, whereas prunes and blueberries are the richest sources of vitamin K. While vitamin A and E are most abundant in apricots, peaches are good sources of niacin and riboflavin. In general, dried fruits contribute to small amounts of daily intake values of choline, folate, and thiamin and vitamins A, C, E, and K.

Table 14.3 Percentage of RDA Values of Minerals in Selected Dried Fruits (for adults aged 19–50 years; based on 40 g serving basis)

Mineral	*RDA or AI**	*Apples*	*Apricots*	*Dates*[a]	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*[b]	*Blueberries*[c]	*Cranberries*[d]	*Currants*[e]	*Mangoes*[f]	*References*
Men														
Calcium	1000 mg/day*	0.6	2.2	1.6	6.5	1.1	1.4	1.7	2.0	0.8	0.4	3.4	nd	[5,10]
Copper	0.9 mg/day	8.4	15.1	9.3	12.9	16.0	16.4	12.4	14.2	7.1	2.7	20.9	13.3	[5,11]
Fluoride	4000 µg/day*	nd	nd	nd	nd	nd	nd	tr	2.3	nd	nd	nd	nd	[5,10]
Iron	8 mg/day	7.0	13.3	5.1	10.2	20.3	10.5	4.7	9.4	4.5	2.0	16.3	1.2	[5,11]
Magnesium	400–420 mg/day	1.6	3.1	4.2	6.6	4.1	3.2	4.0	3.1	1.8	0.4	4.0	2.0	[5,10]
Manganese	2.3 mg/day*	1.6	4.2	4.5	8.9	5.4	5.7	5.2	5.2	nd	3.1	8.2	174	[5,11]
Phosphorus	700 mg/day	2.2	4.1	3.5	3.8	6.8	3.4	3.9	5.8	2.1	0.5	7.1	2.9	[5,10]
Potassium	4700 mg/day	3.8	9.9	5.6	5.8	8.5	4.5	6.2	6.4	1.8	0.4	7.6	2.4	[5,12]
Selenium	55 µg/day	0.9	1.6	2.2	0.4	0.4	0.1	0.2	0.4	0.4	0.4	0.5	1.5	[5,13]
Sodium	1500 mg/day	2.3	0.3	0.1	0.3	0.2	0.2	0.1	0.3	0.1	0.1	0.2	4.3	[5,12]
Zinc	11 mg/day	0.7	1.4	1.1	2.0	2.1	1.4	1.6	0.8	1.8	0.4	2.4	1.1	[5,11]
Women														
Calcium	1000 mg/day*	0.6	2.2	1.6	6.5	1.1	1.4	1.7	2.0	0.8	0.4	3.4	nd	[5,10]
Copper	0.9 mg/day	8.4	15.1	9.3	12.9	16.0	16.4	12.4	14.2	7.1	2.7	20.9	13.3	[5,11]
Fluoride	3000 µg/day*	nd	nd	nd	nd	nd	nd	tr	3.1	nd	nd	nd	nd	[5,10]
Iron	18 mg/day	3.1	5.9	2.3	4.5	9.0	4.7	2.1	4.2	2.0	0.9	7.2	0.5	[5,11]
Magnesium	310–320 mg/day	2.0	4.1	5.5	8.6	5.3	4.2	5.2	4.1	2.3	0.5	5.2	2.5	[5,10]
Manganese	1.8 mg/day*	2.0	5.3	5.8	11.3	6.9	7.3	6.7	6.7	nd	4.0	10.4	222	[5,11]

(*Continued*)

Table 14.3 (Continued) Percentage of RDA Values of Minerals in Selected Dried Fruits (for adults aged 19–50 years; based on 40 g serving basis)

Mineral	*RDA or AI**	*Apples*	*Apricots*	*Dates*[a]	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*[b]	*Blueberries*[c]	*Cranberries*[d]	*Currants*[e]	*Mangoes*[f]	*References*
Phosphorus	700 mg/day	2.2	4.1	3.5	3.8	6.8	3.4	3.9	5.8	2.1	0.5	7.1	2.9	[5,10]
Potassium	4700 mg/day	3.8	9.9	5.6	5.8	8.5	4.5	6.2	6.4	1.8	0.4	7.6	2.4	[5,12]
Selenium	55 µg/day	0.9	1.6	2.2	0.4	0.4	0.1	0.2	0.4	0.4	0.4	0.5	1.5	[5,13]
Sodium	1500 mg/day	2.3	0.3	0.1	0.3	0.2	0.2	0.1	0.3	0.1	0.1	0.2	4.3	[5,12]
Zinc	8 mg/day	1.0	2.0	1.5	2.8	2.9	2.0	2.2	1.1	2.5	0.5	3.3	1.5	[5,11]

Abbreviations: AI*, adequate intake; nd, not detected; RDA, recommended dietary allowances; tr, trace.

[a] Deglet noor.
[b] Seedless.
[c] Dried, sweetened.
[d] Dried, sweetened.
[e] Zante, dried.
[f] Dried, sweetened.

Table 14.4 Percentage of RDA Values of Vitamins in Selected Dried Fruits (for adults aged 19–50 years; based on 40 g serving basis)

Vitamin	*RDA or AI**	*Apples*	*Apricots*	*Dates*[a]	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*[b]	*Blueberries*[c]	*Cranberries*[d]	*Currants*[e]	*Mangoes*[f]	*References*
Men														
Choline	550 mg/day*	1.3	1.0	0.5	1.1	0.9	1.7	0.7	0.8	1.3	0.6	0.8	1.7	[5,14]
Folate (DFE)	400 µg/day	nd	1.0	1.9	0.9	nd	nd	0.4	0.5	1.2	nd	1.0	6.8	[5,14]
Niacin	16 mg/day	2.3	6.5	3.2	1.6	11.0	3.4	4.7	1.9	2.9	1.4	4.1	5.0	[5,14]
Pantothenic acid	5 mg/day*	2.0	4.2	4.7	3.4	4.5	1.2	3.4	0.8	nd	nd	0.4	nd	[5,14]
Pyridoxine	1.3 mg/day	4.0	4.3	5.2	3.4	2.2	2.2	6.5	5.2	4.6	1.2	9.2	10.2	[5,14]
Riboflavin	1.3 mg/day	4.9	2.2	2.2	2.5	6.5	4.6	5.8	4.0	4.0	0.9	4.3	2.8	[5,14]
Thiamin	1.2 mg/day	nd	0.7	1.7	3.0	0.1	0.3	1.7	3.7	3.0	0.3	5.3	2.0	[5,14]
Vitamin A (RAE)	900 µg/day	nd	8.0	tr	tr	4.8	nd	1.7	nd	0.3	0.1	0.2	3.0	[5,11]
Vitamin C	90 mg/day	1.7	0.4	0.2	0.5	2.1	3.1	0.3	1.0	10.6	0.1	2.1	18.8	[5,13]
Vitamin E (ATE)	15 mg/day	1.4	11.5	0.1	0.9	0.5	0.2	1.1	0.3	6.3	5.6	0.3	10.7	[5,13]
Vitamin K	120 µg/day*	1.0	1.0	0.9	5.2	5.2	6.8	19.8	1.2	19.8	2.5	1.1	4.4	[5,11]
Women														
Choline	425 mg/day*	1.7	1.3	0.6	1.5	1.2	2.2	1.0	1.0	1.7	0.8	1.0	2.2	[5,14]
Folate (DFE)	400 µg/day	nd	1.0	1.9	0.9	nd	nd	0.4	0.5	1.2	nd	1.0	6.8	[5,14]
Niacin	14 mg/day	2.7	7.4	3.6	1.8	12.5	3.9	5.4	2.2	3.3	1.6	4.6	5.7	[5,14]
Pantothenic acid	5 mg/day*	2.0	4.2	4.7	3.4	4.5	1.2	3.4	0.8	nd	nd	0.4	nd	[5,14]
Pyridoxine	1.3 mg/day	4.0	4.3	5.2	3.4	2.2	2.2	6.5	5.2	4.6	1.2	9.2	10.2	[5,14]
Riboflavin	1.1 mg/day	5.8	2.5	2.5	2.9	7.6	5.5	6.9	4.7	4.7	1.1	5.1	3.3	[5,14]

(*Continued*)

Table 14.4 (Continued) Percentage of RDA Values of Vitamins in Selected Dried Fruits (for adults aged 19–50 years; based on 40 g serving basis)

Vitamin	*RDA or AI**	*Apples*	*Apricots*	*Dates*[a]	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*[b]	*Blueberries*[c]	*Cranberries*[d]	*Currants*[e]	*Mangoes*[f]	*References*
Thiamin	1.1 mg/day	nd	0.7	1.8	3.3	0.1	0.4	1.8	4.0	3.3	0.4	5.8	2.2	[5,14]
Vitamin A (RAE)	700 µg/day	nd	10.3	tr	tr	6.2	nd	2.2	nd	0.4	0.1	0.2	3.8	[5,11]
Vitamin C	75 mg/day	2.1	0.5	0.2	0.6	2.6	3.7	0.3	1.2	12.7	0.1	2.5	22.6	[5,13]
Vitamin E (ATE)	15 mg/day	1.4	11.5	0.1	0.9	0.5	0.2	1.1	0.3	6.3	5.6	0.3	10.7	[5,13]
Vitamin K	90 µg/day*	1.3	1.4	1.2	6.9	7.0	9.1	26.4	1.6	26.4	3.4	1.5	5.9	[5,11]

Abbreviations: AI*, adequate intake; ATE, alpha-tocopherol equivalents; DFE, dietary folate equivalents; nd, not detected; RAE, retinol activity equivalents; RDA, recommended dietary allowances; tr, trace.

[a] Deglet noor.
[b] Seedless.
[c] Dried, sweetened.
[d] Dried, sweetened.
[e] Zante, dried.
[f] Dried, sweetened.

14.3 Antioxidant Activities of Dried Fruits

A comprehensive review of the antioxidant efficacies of dried fruits such as apples, apricots, cranberries, dates, figs, peaches, pears, prunes, and raisins has already been reported by Chang et al. [1]. Various assays (*in vitro* and biological) have been used to determine the antioxidant activities of different dried fruits [1,15–19]. In this chapter, only oxygen radical absorbance capacity (ORAC) values of selected dried fruits are compared (Table 14.5). Raisins (golden seedless) have the highest ORAC value (10,450 μmol trolox equivalents [TE]/100 g fresh weight [fw]), followed by pears, prunes, apples, peaches, dates (Deglet noor), figs, and apricots. Interestingly, dates (Medjool) have the lowest ORAC value (2,387 μmol TE/100 g fw) among the 11 dried fruits listed [15,20]. The antioxidant activities of different dried fruits vary widely based on the assay type or cultivar.

Various studies have reported the bioactive compounds and corresponding antioxidant activities of dried fruits (e.g., peaches and dates), which are always higher than those of their corresponding fresh counterparts [16,18,21,22]. This is because antioxidants become concentrated after the dehydration process. There is a loss of or change in some phytochemicals during drying. However, the antioxidant activity and total phenolic content (TPC) of dried fruits remain relatively unaffected during the process, although many of the phenolic compounds are still to be identified [23].

Table 14.5 Antioxidant Activity, Total Phenolics, and Total Phytoestrogens in Selected Dried Fruits (Values in per 100 g edible portion)

Dried fruit	*ORAC (μmol of TE/100 g)*	*Total phenolics (mg of GAE/100 g)*	*Total phytoestrogens (μg/100 g)*	*References*
Apples[a]	6681	324	na	[20,64]
Apricots[a]	3234	248	445[b]	[20,28,64]
Dates (Deglet noor)	3895	661	330[c]	[15,20,28]
Dates (Medjool)	2387	572	na	[15,20]
Figs	3383	960	na	[15,20]
Peaches[a]	4222	283	na	[20,64]
Pears[a]	9496	679	na	[20,64]
Prunes	8578	1195	184[c]	[15,20,28]
Raisins (Golden seedless)	10450	na	na	[20,65]
Raisins (Seedless)	3037	1065	30[d]	[15,20,28]
Raisins (White)[a]	4188	330	na	[20,64]

Abbreviations: GAE, gallic acid equivalents; ORAC, oxygen radical absorbance capacity; na, not available; TE, trolox equivalents; VLDL, very low-density lipoprotein.

[a] Dried to 40% moisture (purchased in Italy).
[b] Turkish.
[c] Whole pitted.
[d] California seedless.

14.4 Phytochemicals in Dried Fruits

Dried fruits have a wide range of bioactive phytochemicals such as phenolic acids, flavonoids, phytoestrogens, and carotenoids, among others, as well as antioxidant activities. Phytochemicals are defined as nonnutritive, naturally occurring, biologically active, and chemically derived compounds found in plants. However, a large percentage of phytochemicals is still unknown and remains to be identified [2]. Phytochemicals can be mainly divided into carotenoids, organosulfur compounds, phenolics, nitrogen-containing compounds, phytoestrogens, and alkaloids [24]. Of these, carotenoids, phytoesterogens, and phenolics, which are most abundant in dried fruits, are discussed in detail below.

14.4.1 Carotenoids

Carotenoids, which are fat-soluble bioactives, are plant pigments responsible for bright red, yellow, and orange hues in many fruits and vegetables. Five carotenoids, namely α-carotene, β-carotene, β-cryptoxanthin, lutein, and zeaxanthin, are present in some dried fruits, albeit to different extents. Of these, β-carotene, which acts as provitamin A, is the most abundant in apricots (2163 μg/100 g), peaches (1074 μg/100 g), mangoes (sweetened) (786 μg/100 g), and prunes (394 μg/100 g). Peaches are also rich in lutein + zeaxanthin (559 μg/100 g) and β-cryptoxanthin (444 μg/100 g) [5]. With regard to total carotenoid content among the 12 dried fruits, apricots have the highest content (2163 μg/100 g), followed by peaches (2080 μg/100 g), mangoes (sweetened) (878 μg/100 g), and prunes (692 μg/100 g). The other dried fruits contain small amounts of carotenoids, ranging from 18 to 292 μg/100 g. No carotenoids have been reported in raisins (seedless) (Figure 14.2).

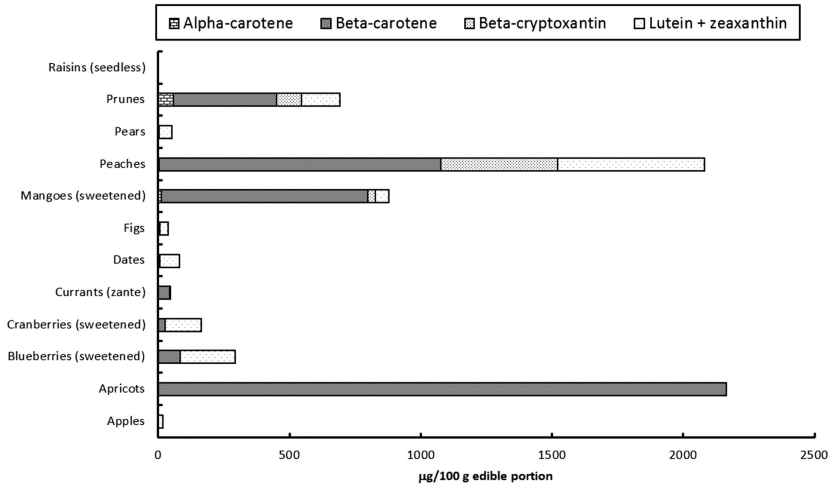


Figure 14.2 Carotenoid content of selected dried fruits. *Source:* Adapted from the U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed June 20, 2018).

The low level of carotenoids in dried fruits may be due to the drying process, since carotenoids are sensitive to heat or sun-drying [25–27]. However, the USDA Nutrient Database [5] reported that drying significantly increased carotenoid concentration (such as β-carotene, β-cryptoxanthin, and lutein) in dried peaches compared to their fresh counterparts. This happens because the removal of water concentrates the carotenoids.

14.4.2 Phytoestrogens

Phytoestrogens comprise three major classes of compounds, namely isoflavones, lignans, and coumestans. Some dried fruits, such as apricots, currants, dates, prunes, and raisins, have been shown to contain isoflavones (formononetin, daidzein, genistein, and glycitein), lignans (matairesinol, lariciresinol, pinoresinol, and secoisolariciresinol), and coumestans (coumestrol). Among the four dried fruits (apricots, dates, prunes, and raisins) reported in Table 14.5, total phytoestrogen contents ranged from 30 μg/100 g in raisins (seedless) to 445 μg/100 g in apricots. Dried fruits have a higher content of lignans (ranging from 22.0 to 401 μg/100 g) than isoflavones (ranging from 4.2 to 39.8 μg/100 g). Coumestan, expressed as coumestrol, is generally present in low concentrations in dried fruits [1,28]. In addition, daidzein, genistein, and biochanin A have been reported in trace amounts in dried apricots [29,30]. Meanwhile, dried figs contain a relatively low amount of isoflavones (5.97 μg/100 g) compared to other dried fruits, except dried apricots (4.27 μg/100 g) [30]. However, there has not to date been any detailed quantitative analysis on different classes of phytoestrogens in different forms and varieties of other dried fruits.

14.4.3 Phenolics

Phenolic compounds may be divided into six groups (phenolic acids, flavonoids, stilbenes, coumarins, lignans, and tannins, among others). Dried fruits contain most of them, albeit to different extents [1,2]. Dried fruits are excellent sources of phenolic compounds. These make up the largest group of plant phytochemicals in the diet and they appear to be, at least in part, responsible for the health benefits associated with diets abundant in fruits and vegetables.

The Folin-Ciocalteau reagent assay is a common method used to determine the TPC of dried fruits. Total phenolics of dried fruits, expressed as mg of gallic acid equivalents (GAE)/100 g fw, range from 248 to 1195, being lowest in apricots and highest in prunes (Table 14.5) [15,20]. It is interesting to note that raisins (seedless) contain ~3-fold higher total phenolics than that of white raisins. In another study conducted by Ishiwata et al. [16], total phenolics (expressed as mg of ascorbic acid equivalents [AAE]/g dried weight [dw]) of dried fruits decreased in the order of apricots > raisins > cranberries > peaches > figs > pears > prunes > apples > dates. However, in another study reported by Vinson et al. [18], dates demonstrated the highest total phenolics (1959 mg catechin equivalents [CE]/100 g fw), while figs had the lowest (320 mg CE/100 g fw) among the six dried fruits studied (apricots, cranberries, dates, figs, plums, and raisins). These results clearly show that total phenolics of dried fruits may differ according to the drying method, growing conditions, region, fruit maturity, and varietal factors, as well as the method used for the

analysis of total phenolics. In the following sections, the most abundant phenolics (such as flavonoids, phenolic acids, tannins, stilbenes, and dihydrochalcones) present in dried fruits are reviewed in detail.

14.4.3.1 Flavonoids

Flavonoids are a group of phenolic compounds that can be classified into seven groups: anthocyanins, flavan-3-ols (flavanols or catechins), flavonols, flavanones, flavones, flavanonols, and isoflavones [24,31]. The major flavonoids reported in dried fruits are anthocyanins, flavan-3-ols, flavonols, and flavones. The reported flavonoids in selected dried fruits are listed in Table 14.6.

Anthocyanins Anthocyanins are only reported in cranberries, dates, figs, peaches, and raisins (Table 14.6). Raisins have been reported to contain the highest number of anthocyanins, followed by cranberries and figs [32–36]. Raisins and cranberries have the most diverse profiles of anthocyanins, while cranberries have the most abundant content of anthocyanins [32,33]. Peonidin-3-*O*-galactoside (2740 mg/g dw) is the most abundant anthocyanin identified in cranberries, followed by cyanidin-3-*O*-galactoside (1951 mg/g dw), cyanidin-3-*O*-arabinoside (1335 mg/g dw), and peonidin-3-*O*-arabinoside (1110 mg/100 g dw) [33].

Eighteen anthocyanins have been reported in raisins [32]. A number of anthocyanins (such as cyanidin-3-glucoside, delphinidin-3-glucoside, malvidin-3-glucoside, pelargonidin-3-glucoside, peonidin-3-glucoside, and petunidin-3-glucoside) and anthocyanin-derived compounds (delphinidin-3-acetylglucoside, malvidin-3-acetylglucoside, malvidin-3-caffeoylglucoside, peonidin-3-acetylglucoside, petunidin-3-acetylglucoside, petunidin-3-caffeoylglucoside, petunidin-3-coumaroylglucoside, vitisin A, vitisin B, A-type vitisin of malvidin-3-acetylglucoside, and B-type vitisin of peonidin-3-glucoside) are present in Spanish *Merlot* and *Syrah* varieties of raisin [32]. Anthocyanin-derived compounds present in raisins are not reported in other dried fruits.

Flavan-3-ols Numerous flavan-3-ols have been characterized in dried fruits, except dates. Apricots have the highest number of flavan-3-ols, followed by raisins and figs (Table 14.6). Lower levels of flavan-3-ols are reported in dried fruits as compared to flavonols, anthocyanins, and phenolic acids.

Catechin and epicatechin are present in all dried fruits except dates and peaches. Gallocatechin is the most abundant flavan-3-ol reported in apricots (2955 mg/100 g dw), followed by polymeric procyanidins (202 mg/100 g dw) and epicatechin (20–133 mg/100 g dw) [37,38]. Catechin (615 μg hyperoside equivalents [HE]/g) is the most abundant flavan-3-ol present in raisins, followed by procyanidin B_1 (346 μg HE/g) and procyanidin B_3 (139 μg HE/g) [39,40].

Epigallocatechin gallate has been reported in apricots, cranberries, and raisins, while procyanidin B_2 is only present in apricots, figs, peaches, prunes, and raisins [33,37–41]. In addition, procyanidin B_1 is only present in apricots, figs, and raisins. Polymeric procyanidins have also been reported only in apricots, peaches, and prunes (Table 14.6).

Flavonols Flavonols have been reported in apples, apricots, cranberries, dates, figs, peaches, prunes, and raisins at varying concentrations [33,35–38,40–47].

Table 14.6 Phenolics in Selected Dried Fruits

Dried Fruit	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
Apples	Flavan-3-ols	Catechin	mg/100 g dw	0.26–18	[42,58]
		Epicatechin		3.1–50.5	
	Flavonols	Cyanidin-3-*O*-galactoside	mg/100 g dw	2.97	[42,43]
		Quercetin-3-*O*-galactoside		36.2	
		Quercetin-3-*O*-glucoside		5.93	
		Quercetin-3-*O*-rhamnoside		9.21	
		Quercetin-3-*O*-rutinoside		1.71	
		Quercetin-3-*O*-xyloside		6.7	
	Phenolic acids	Chlorogenic acid	mg/100 g dw	139–180	[42,58]
	Chalcones/ Dihydrochalcones	Phloridzin	mg/100 g dw	35.4	[42]
		Phloretin		0.32	
Apricots	Flavan-3-ols	Catechin	mg/100 g dw	3.9–47.3	[37,38,41]
		Epicatechin		20–133	
		Epicatechin gallate		13.26	
		Epigallocatechin		8.2	
		Epigallocatechin gallate		8.2	
		Gallocatechin		2955	
		Procyanidin B_2		5.2–9.4	
		Procyanidin B_1		21.3	
		Polymeric procyanidins		202	
	Flavonols	Myricetin		1.29	
		Quercetin		0.30	
		Quercetin-3-*O*-glucoside		8.14	
		Quercetin-3-*O*-rutinoside		30.1	
		Quercetin-3-*O*-galactoside		4.00	
		Rutin		34.6–75	
	Flavones	Luteolin	mg/100 g dw	0.43	[37]
	Phenolic acids	Chlorogenic acid	mg/kg dw	365	
		Neochlorogenic acid		221	[41]
		Caffeic acid	mg/100 g dw	0.36	[38,51]
		Cumaric acid		0.30	
		Gallic acid		35.0	
		Ferulic acid		0.32	
		Protocatechuic acid		12.6	
		Vanillic acid		3.8	
		4-*O*-Caffeoylquinic acid		50.04	
		3-*p*-Feruloylquinic acid		7.13	
	Chalcones/ Dihydrochalcones	Phloridzin	mg/100 g dw	0.17	[37]

(*Continued*)

Table 14.6 (Continued) Phenolics in Selected Dried Fruits

Dried Fruit	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
Cranberries	Anthocyanins	Cyanidin-3-*O*-arabinoside	mg/100 g dw	1335	[33]
		Cyanidin-3-*O*-galactoside		1951	
		Cyanidin-3-*O*-glucoside		62.1	
		Delphinidin-3-*O*-glucoside		16.7	
		Malvidin-3-*O*-arabinoside		7.96	
		Peonidin-3-*O*-arabinoside		1110	
		Peonidin-3-*O*-galactoside		2740	
		Peonidin-3-*O*-glucoside		254	
	Flavan-3-ols	Catechin	mg/100 g fw	0.80–3.80	[33,44]
		Epicatechin		4.5–45.7	
		Epigallocatechin gallate		1.9	
	Flavonols	Myricetin	mg/100 g fw	16.6	
		Quercetin		19.4	
		Methoxyquercetin pentoside	mg/100 g dw	9.11–10.7	[33]
		Methoxyquercetin hexoside		11.1–51.4	
		Myricetin-3-*O*-pentoside		25.2–611	
		Quercetin-3-*O*-galactoside		33.3	
		Quercetin-3-*O*-pentoside		38.6–53.2	
		Quercetin-3-*O*-rhamnoside		124	
		Quercetin-benzoyl-galactoside		5.7	
		Quercetin *p*-coumaroyl-hexoside		3.9	
	Phenolic acids	Caffeic acid	mg/100 g fw	2.31	[52,53]
		Chlorogenic acid		10.3	
		Ferulic acid		2.96	
		Gallic acid		14.5	
		p-Coumaric acid		25.2	
		Protocatechuic acid		51.2	
		3-Hydroxybenzoic acid		1.90	
		3-Hydroxyphenylpropionic acid		1.53	
		4-Hydroxybenzoic acid		3.42	
		4-Hydroxyphenylacetic acid		3.21	
	Proanthocyanidins	A-type PAC dimer	mg/100 g dw	64.7–101	[33]
		A-type PAC trimer		73.9	
		B-type PAC dimer		27.8	
		Procyanidin polymers		1076	

(*Continued*)

Table 14.6 (Continued) Phenolics in Selected Dried Fruits

Dried Fruit	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
		PAC dimers		5.1	[60]
		PAC trimers		4.4	
		PAC 4-6mers		10.1	
		PAC 7-10mers		0.33	
Dates	Anthocyanins	Cyanidin	mg/100 g fw	1.7	[44]
	Flavonols	Quercetin		0.9	
	Phenolic acids	Caffeic acid	mg/100 g fw	2.5	[54]
		Ferulic acid		11.8	
		Gallic acid		1.6	
		o-Coumaric acid		2.9	
		p-Coumaric acid		5.8	
		Protocatechuic acid		4.9	
		Syringic acid		2.9	
		Vanillic acid		2.3	
	Proanthocyanidins	PAC dimers	mg/100 g dw	1.84	[61]
		PAC trimers		3.02	
		PAC 4-6mers		5.9	
Figs	Anthocyanins	Cyanidin-3-*O*-rutinoside	mg/100 g fw	0.19	[34–36]
		Cyanidin-3-glucoside		0.1	
		Cyanidin-3-rutinoside		1.5	
	Flavan-3-ols	Catechin	mg/100 g fw	1.5–8.7	[36,45]
		Epicatechin		0.6–21.83	
		Procyanidin B_1		0.8–1.5	
		Procyanidin B_2		0.5–1.3	
	Flavonols	Kaempferol-3-*O*-glucoside	mg/100 g fw	0.4	[35,36,45]
		Kaempferol rutinoside		0.2–2.0	
		Quercetin		0.6–16	
		Quercetin-3-glucoside		0.2–0.7	
		Quercetin glucoside		2.5	
		Quercetin-3-*O*-glucoside		2.9	
		Quercetin rutinoside		10.2	
		Quercetin acetylglucoside		2.6	
		Rutin		9.0–15	
	Flavones	Apigenin-7-rutinoside	mg/100 g fw	16–32	[35,45]
		Luteolin-3-7-*O*-diglucoside		13–22	
		Luteolin-8-*C*-glucoside		0.14	
	Phenolic acids	Benzoic acid	mg/100 g fw	1.1–2.6	[35,36,50]
		Chlorogenic acid		0.8–3.0	

(*Continued*)

Table 14.6 (Continued) Phenolics in Selected Dried Fruits

Dried Fruit	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
		Cinnamic acid		0.6–2.6	
		m-Coumaric acid		0.13–0.19	
		o-Coumaric acid		0.8–1.05	
		p-Coumaric acid		0.33–9.9	
		Ferulic acid		7.2	
		Gallic acid		0.10	
		Gentisic acid		2.2–2.8	
		p-Hydroxybenzoic acid		0.15–1.5	
		Protocatechuic acid		1.96	
		Salicylic acid		1.3–2.6	
		Syringic acid		0.3–0.43	
		Vanillic acid		2.1–3.3	
	Proanthocyanidins	Total proanthocyanidins	mg CyE/100 g dw	103–180	[62]
Peaches	Anthocyanins	Cyanidin-3-glucoside	mg/100 g fw	5.1	[21]
	Flavan-3-ols	Procyanidin B_2	mg/100 g fw	82.9	[38]
		Polymeric procyanidins		138	
	Flavonols	Quercetin-3-*O*-rutinoside-glucoside		3.9	
		Quercetin-3-*O*-rutinoside		9.11	
		Quercetin-3-*O*-galactoside		2.7	
		Kaempferol-3-*O*-rutinoside		3.11	
		Isorhamnetin-3-*O*-rutinoside		6.52	
	Phenolic acids	Chlorogenic acid	mg/kg fw	151	[59]
		Neochlorogenic acid		85.3	
		4-*O*-Caffeoylquinic acid	mg/100 g fw	114	[38]
Pears	Flavan-3-ols	Catechin	mg/g fw	2.6	[63]
		Epicatechin		15.2	
	Phenolic acids	Caffeoylquinic acid		6.1	
		p-Coumaroylmallic acid		0.7	
	Chalcones/ Dihydrochalcones	Arbutin		7.5	
Prunes	Flavan-3-ols	Epicatechin	mg/kg dw	7.2	[57]
		Procyanidin B_2	mg/100 g fw	88.1	[38]
		Polymeric procyanidins		185	
	Flavonols	Quercetin-3-*O*-rutinoside		26.7	
		Quercetin-3-*O*-galactoside		4.00	
		Isorhamnetin-3-*O*-rutinoside		3.64	

(*Continued*)

Table 14.6 (Continued) Phenolics in Selected Dried Fruits

Dried Fruit	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
	Phenolic acids	Caffeic acid	mg/kg dw	1–35	[55–57]
		Chlorogenic acid		67–562	
		Neochlorogenic acid		928–3045	
		p-Coumaric acid		2–43	
		Protocatechuic acid		0.5–2.0	
		4-*O*-Caffeoylquinic acid	mg/100 g fw	35.1	[38]
		3-*O*-Caffeoylshikimic acid		10.35	
		3-*p*-Feruloylquinic acid		11.12	
Raisins	Anthocyanins	Cyanidin-3-glucoside	mg/kg dw	1.16–1.56	[32]
		Cyanidin-3-acetylglucoside		0.67–0.98	
		Delphinidin-3-glucoside		1.45–1.75	
		Delphinidin-3-acetylglucoside		0.39–0.40	
		Malvidin-3-glucoside		47.2–74.1	
		Malvidin-3-acetylglucoside		14.3–16.7	
		Malvidin-3-caffeoylglucoside		1.56–1.73	
		Pelargonidin-3-glucoside		0.87–1.04	
		Peonidin-3-glucoside		20.0–22.7	
		Peonidin-3-acetylglucoside		3.81–5.57	
		Petunidin-3-glucoside		9.34–11.4	
		Petunidin-3-acetylglucoside		5.17–6.33	
		Petunidin-3-caffeoylglucoside		2.86–2.95	
		Petunidin-3-coumaroylglucoside		2.36–2.54	
		A-type vitisin of malvidin-3-acetylglucoside		0.44–0.53	
		B-type vitisin of peonidin-3-glucoside		0.38–0.75	
		Vitisin A		0.11–0.12	
		Vitisin B		0.76–0.84	
	Flavan-3-ols	Catechin	µg HE/g	615	[39,40]
		Epicatechin		48.1	
		Epicatechin-3-*O*-gallate		10.9	
		Epigallocatechin-3-*O*-gallate		4.9	
		Procyanidin B_1		346	
		Procyanidin B_2		41.8	
		Procyanidin B_3		139	
		Procyanidin C_1		14	

(*Continued*)

Table 14.6 (Continued) Phenolics in Selected Dried Fruits

Dried Fruit	*Types of Phenolic Compounds*		*Unit*	*Content*	*References*
	Flavonols	Isorhamnetin-3-*O*-glucoside	mg/100 g dw	1.25	[40,46,47]
		Isorhamnetin-hexoside		1.8–43	
		Isorhamnetin		0.7–17	
		Kaempferol		3.3–49	
		Kaempferol hexoside		81–213	
		Quercetin		0.8–98	
		Quercetin-3-*O*-glucoside		2.1	
		Quercetin-3-*O*-glucuronide		3.4–42	
		Quercetin-3-*O*-rutinoside		109–260	
	Flavones	Astilbin	µg/100 g dw	0.3–27	[40]
		Apigenin	mg/g dw	0.09–0.47	[48]
		Apigenin-7-glucoside		0.03–0.09	
		Luteolin		0.06–1.32	
		Luteolin-7-glucoside		0.27–1.17	
		Malvine		0.1–0.26	
		Naringenin		0.05–0.2	
	Phenolic acids	Caffeic acid	mg/100 g dw	0.63	[40,47–49]
		Cinnamic acid		0.16	
		Caftaric acid		3.26–19	
		Coutaric acid		0.64–3.5	
		Chlorogenic acid		0.02–0.23	
		Ferulic acid		0.32	
		Gallic acid		0.16–0.69	
		p-Coumaric acid		0.36–8.6	
		p-Hydroxybenzoic acid		0.23	
		p-Hydroxyphenylacetic acid		0.12	
		Protocatechuic acid		0.15–0.44	
		Rosameric acid		0.05–0.15	
		Syringic acid		0.34	
		Vanillic acid		1.21	
		Isovanillic acid		0.15–0.18	
		Salicylic acid		0.06	
		3,4-Dihydroxybenzoic acid		0.51	
		3,4-Dihydroxyphenylacetic acid		0.10	
	Stilbenes	Resveratrol		0.02–0.12	[40,48]
		trans-Resveratrol		2.60	

Abbreviations: CyE, cyanidin equivalents; dw, dry weight; fw, fresh weight; HE, hyperoside equivalents; PAC, proanthocyanidins.

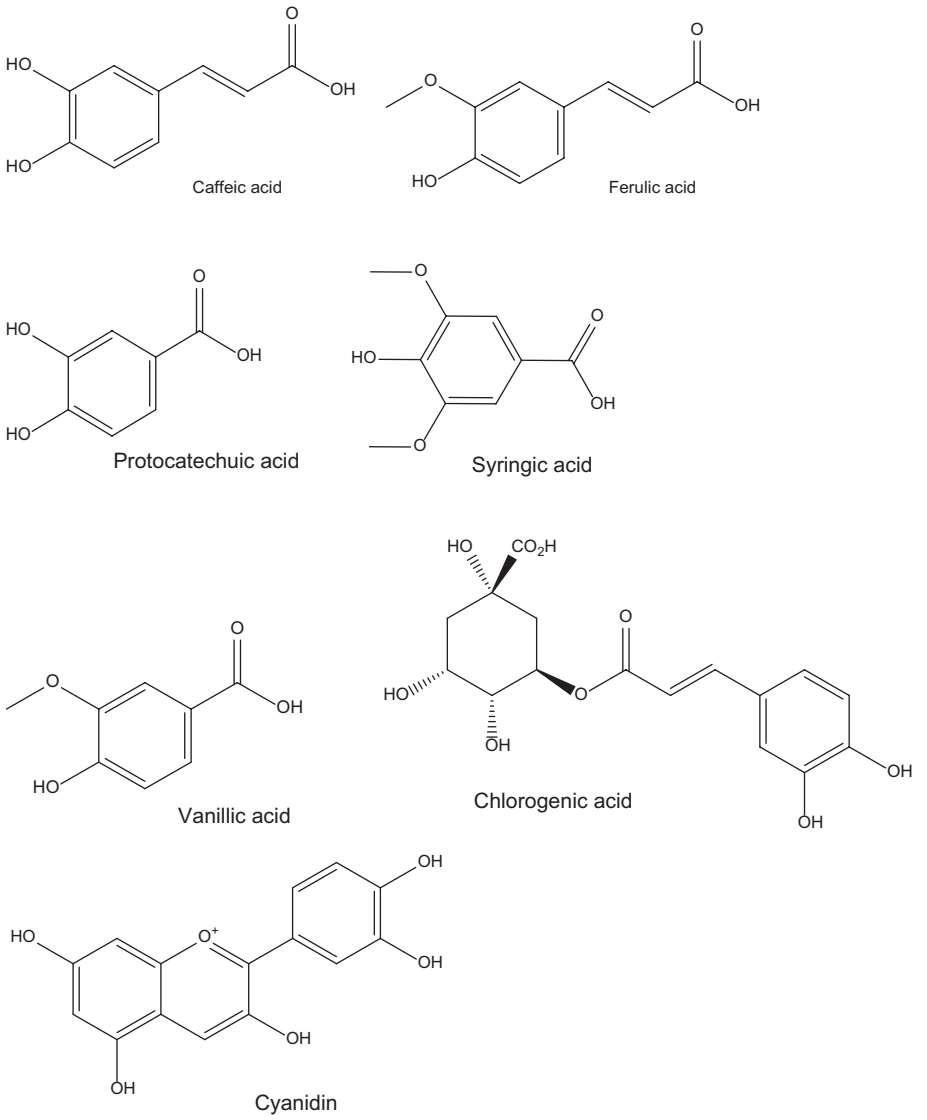


Figure 14.3 Chemical structures of representative phenolic compounds (phenolic acids, flavonoids, and anthocyanidins) present in dried fruits.

Among dried fruits, cranberries, raisins, apples, apricots, and peaches have the most diverse flavonol profiles (Table 14.6).

Rutin is the most abundant flavonol in apricots (34.6–75 mg/100 g dw) [37,38] and figs (9–15 mg/100 g fw) [35,36,45]. While quercetin is present in all dried fruits, except pears, myricetin has only been reported in apricots and cranberries. In addition, kaempferol and its derivatives are present only in figs, peaches, and raisins (Table 14.6)

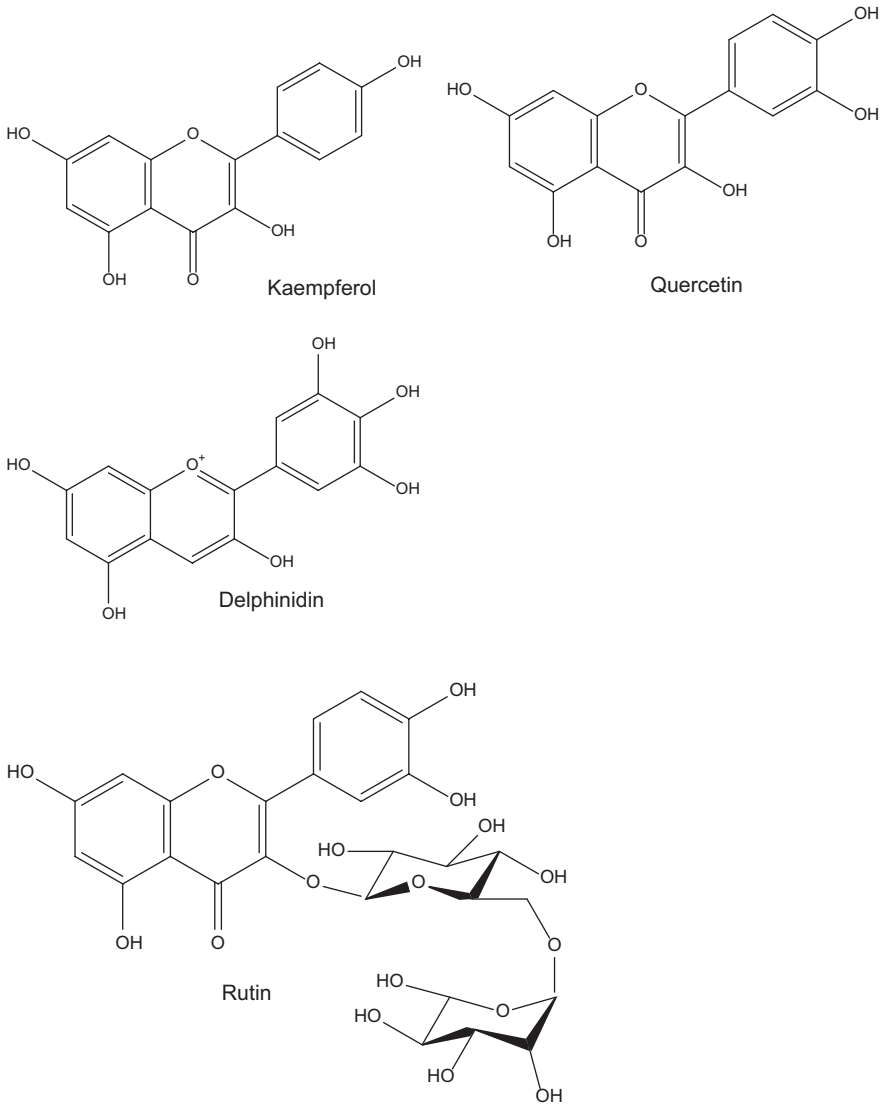


Figure 14.3 (Continued) Chemical structures of representative phenolic compounds (phenolic acids, flavonoids, and anthocyanidins) present in dried fruits.

Quercetin-3-*O*-rutinoside is found in apples, apricots, peaches, prunes, and raisins. Of these, raisins have the highest amount of this compound (109–260 mg/100 g fw) [40]. Meanwhile, quercetin-3-*O*-galactoside (36.2 mg/100 g dw) is the most abundant flavonol present in apples, followed by quercetin-3-*O*-rhamnoside (9.2 mg/100 g dw) [42,43]. Furthermore, myricetin-3-*O*-pentoside (25.2–611 mg/100 g dw) is most abundant flavonol in cranberries, followed by quercetin-3-*O*-rhamnoside (124 mg/100 g dw) and quercetin-3-*O*-pentoside (38.6–53.2 mg/100

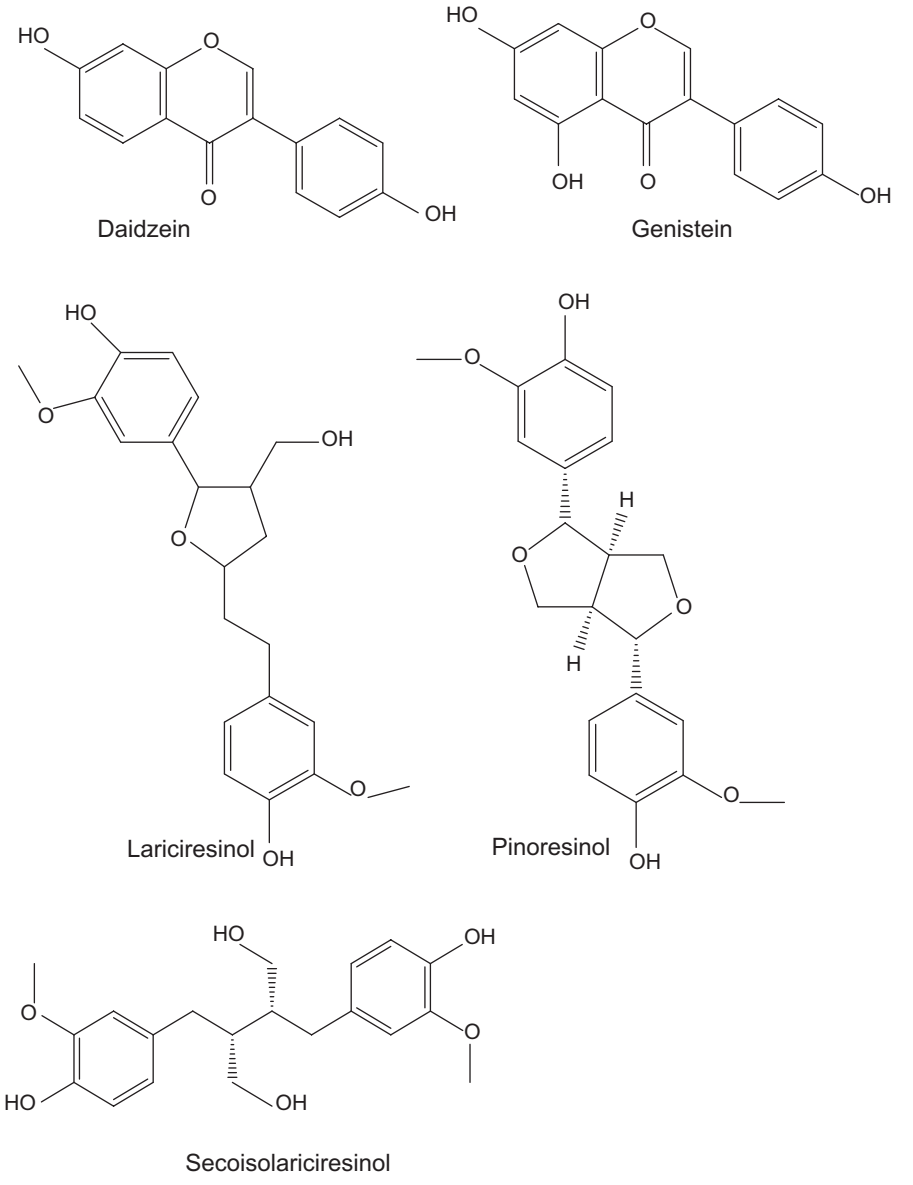


Figure 14.4 Chemical structures of representative phytoestrogens present in dried fruits.

g dw) [33]. Some unique flavonols (such as methoxyquercetin pentoside, methoxyquercetin hexoside, quercetin-benzoyl-galactoside, and quercetin *p*-coumaroyl-hexoside) that are not present in other dried fruits have been reported in cranberries [33]. Moreover, quercetin-3-*O*-rutinoside-glucoside has only been reported in peaches [38].

Flavones Flavones have only been reported in apricots (luteolin) [37], figs (apigenin-7-rutinoside, luteolin-3-7-*O*-diglucoside, and luteolin-8-*C*-glucoside) [35,45], and raisins (astilbin, apigenin, apigenin-7-glucoside, luteolin, luteolin-7-glucoside, malvine, and naringenin) [40,48] (Table 14.6). Apigenin-7-rutinoside (16–32 mg/100 g fw) and luteolin-3-7-*O*-diglucoside (13–22 mg/100 g fw) are the most abundant flavones in figs [35,45]. Among dried fruits, astilbin, naringenin, and malvine are only present in raisins [40,48].

14.4.3.2 Phenolic Acids

Phenolic acids are the second largest group of phenolics after flavonoids and occur in foods in free, esterified, glycoside, and insoluble-bound forms. Free phenolic acids are known to contribute to the taste of foods and include both hydroxycinnamic acids (caffeic, chlorogenic, cinnamic, *trans*-cinnamic, *o*-coumaric, *p*-coumaric, ferulic, caffeoylquinic, *p*-coumaroylquinic, sinapic, and *trans*-*p*-coumaric acids) and hydroxybenzoic acids (gallic, *p*-hydroxybenzoic, 3,4-dihydroxybenzoic, *p*-hydroxyphenylacetic, protocatechuic, syringic, and vanillic acids), both of which have been reported in dried fruits.

Contents and compositions of phenolic acids present in dried fruits are summarized in Table 14.6. Raisins contain the highest number of phenolic acids (18) [40,47–49], followed by figs (14) [35,36,50]; then the same for both apricots (10) [37,38,41,51] and cranberries (10) [52,53]; and finally the same numbers in dates (8) [54] and prunes (8) [38,55–57]. Other dried fruits, such as apples, peaches, and pears, contain between one and three phenolic acids, being lowest in apples [41,58] and highest in peaches [38,59]. Among the identified phenolic acids, chlorogenic acid in apples (139–180 mg/100 g dw), 4-*O*-caffeoylquinic acid in apricots (50.04 mg/100 g dw), protocatechuic acid in cranberries (51.2 mg/100 g fw), ferulic acid in dates (11.8 mg/100 g fw), *p*-coumaric acid in figs (0.33–9.9 mg/100 g fw), 4-*O*-caffeoylquinic acid in peaches (114 mg/100 g fw), caffeoylquinic acid in pears (6.1 mg/g fw), neochlorogenic acid in prunes (928–3045 mg/kg dw), and caftaric acid in raisins (3.26–19 mg/100 g dw) are the most abundant phenolic acids reported (Table 14.6).

Both chlorogenic and neochlorogenic acids are abundantly present in apricots, prunes, and peaches. Caffeic acid is found in all dried fruits, except apples, peaches and pears. Protocatechuic acid is found in most dried fruits, except for apples, figs, peaches, and pears. Both gallic acid and ferulic acid are present in apricots, cranberries, dates, figs, and raisins. 3-Hydroxybenzoic acid, 3-hydroxyphenylpropionic acid, 4-hydroxybenzoic acid, and 4-hydroxyphenylacetic acid are present only in cranberries. Gentisic acid is found only in figs, whereas 4-*O*-caffeoylquinic acid is reported in apricots, peaches, and prunes. Meanwhile, two unique phenolic acids, caffeoylquinic acid and *p*-coumaroylmallic acid, are found only in pears. Finally, while salicylic acid is reported in both figs and raisins, vanillic acid is present in apricots, dates, figs, and raisins (Table 14.6).

Four free phenolic acids (protocatechuic, vanillic, syringic, and ferulic) and nine bound phenolic acids (gallic, protocatechuic, *p*-hydroxybenzoic, vanillic and syringic acids, caffeic, *p*-coumaric, ferulic, and *o*-coumaric acids) have been reported in fresh and sun-dried Omani dates of three native varieties [54]. In addition, there are some unique phenolic acids reported only in raisins, such as caftaric, coutaric, rosameric, isovanillic, 3,4-dihydroxybenzoic, and 3,4-dihydroxyphenylacetic acids [40,48].

14.4.3.3 Tannins

Tannins are defined as proanthocyanidins (also known as condensed tannins) (monomers, dimers, oligomers, and polymers of flavan-3-ols) or hydrolysable tannins (gallotannins and ellagitannins), depending on their structures. Proanthocyanidins have only been reported in cranberries, dates, and figs [33,60–62] (Table 14.6). Proanthocyanidin dimers, trimers, and tetramers to hexamers are present in both dates and figs, while proanthocyanidins heptamers to decamers are only reported in cranberries [33,60,61]. A-type proanthocyanidin dimer, trimer, and B-type proanthocyanidin dimer are only present in cranberries [33]. Procyanidin polymers (1076 mg/100 g dw) are the most abundant proanthocyanidins reported in cranberries, followed by A-type proanthocyanidin dimer (64.7–101 mg/100 g dw) and A-type proanthocyanidin trimer (73.9 mg/100 g dw) [33]. Figs have been reported to contain 103–180 cyanidin equivalents (CyE)/100 g dw of total proanthocyanidins [62].

14.4.3.4 Stilbenes

There are two stilbenes that have been reported in raisins, *trans*-resveratrol (2.60 mg/g dw) and resveratrol (0.02–0.12 mg/g dw) [40,48]. No stilbenes have been reported in other dried fruits.

14.4.3.5 Chalcones/Dihydrochalcones

Chalcones/dihydrochalcones have been reported in apples (phloridzin and phloretin) [42], apricots (phloridzin) [37], and pears (arbutin) [63] (Table 14.6). Among them, phloridzin is the most abundant of the chalcones/dihydrochalcones in apples (35.4 mg/100 g dw) [42].

14.5 Conclusion

Dried fruits are good sources of fiber, carbohydrate, micronutrients, and phytochemicals, with low sodium content and only trace amounts of fat. In fact, consuming dried fruits in the same amount as their fresh counterparts provides more nutrients, calories, and sugar, although they may be lower in some heat-sensitive nutrients such as vitamin C and carotenoids. Despite their high sugar content, dried fruits have low-to-moderate glycemic index, which is beneficial for controlling blood glucose level for diabetic patients. Dried fruits, which contain an abundance of phytochemicals as well as nutrient and nonnutrient antioxidants, is an excellent choice as a snack food and food additive. A detailed and up-to-date summary and scientific review of the available data on nutrient and nonnutrient antioxidant components of dried fruits are reported in this chapter, which indicates that consumption of dried fruits as healthy snacks is a viable way to increase daily fruit consumption.

References

1. Chang, S.K., Alasalvar, C., and Shahidi, F., Review of dried fruits: Phytochemicals, antioxidant efficacies, and health effects. *J. Funct. Foods*, 21, 113–132, 2016.

2. Alasalvar, C., and Shahidi, F., Composition, phytochemicals, and beneficial health effects of dried fruits: An overview, in *Dried Fruits: Phytochemicals and Health Effects*, Alasalvar, C. and Shahidi, F., Eds., John Wiley & Sons, Oxford, UK, 2013, pp. 1–18.
3. Barta, J., Fruit drying principles, in *Handbook of Fruits and Fruit Processing*, Hui, Y.H. Ed., Blackwell Publishing, Oxford, UK, 2006, pp. 81–94.
4. International Nut and Dried Fruit Council (INC), Nuts and Dried Fruits, Statistical Yearbook 2017/2018 and Nutfruit Magazine July 2018, INC, Reus, Spain, 2018.
5. U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed June 20, 2018).
6. TürKomp, Turkish Food Composition Database, TürKomp. Published online at http://www.turkomp.gov.tr/?locale=en (accessed August 28, 2018).
7. U.S. Department of Agriculture (USDA), *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*, The National Academies Press, Washington, DC, 2005.
8. International Nut and Dried Fruit Council (INC), Traditional dried fruits: Valuable tools to meet dietary recommendations for fruit intake, presented at the XXX World Nut and Dried Fruit Congress, Budapest, Hungary, May 20–22, 2011. Dried Fruit Round Table.
9. European Food Safety Authority (EFSA), Scientific opinion on the substantiation of a health claim related to prunes and contribution to normal bowel function pursuant to Article 14 of Regulation (EC) No 1924/2006. *EFSA J.*, 12(11), 3892, 2014.
10. DRIs., *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*, The National Academies Press, Washington, DC, 1997.
11. DRIs., *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, The National Academies Press, Washington, DC, 2001.
12. DRIs., *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*, The National Academies Press, Washington, DC, 2004.
13. DRIs., *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*, The National Academies Press, Washington, DC, 2000.
14. DRIs., *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, The National Academies Press, Washington, DC, 1998.
15. Wu, X., Beecher, G.R., Holden, J.M., Haytowitz, D.B., Gebhardt, S.E., and Prior, R.L., Lipophilic and hydrophilic antioxidant capacities of common foods in the United States. *J. Agric. Food Chem.*, 52, 4026–4037, 2004.
16. Ishiwata, K., Yamaguchi, T., Takamura, H., and Matoba, T., DPPH radical-scavenging activity and polyphenol content in dried fruits. *Food Sci. Technol. Res.*, 10, 152–156, 2004.
17. Pellegrini, N., Serafini, M., Salvatore, S., Del Rio, D., Bianchi, M., and Brighenti, F., Total antioxidant capacity of spices, dried fruits, nuts, pulses, cereals and sweets consumed in Italy assessed by three different *in vitro* assays. *Mol. Nutr. Food Res.*, 50, 1030–1038, 2006.
18. Vinson, J.A., Zubik, L., Bose, P., Samman, N., and Proch, J., Dried fruits: Excellent *in vitro* and *in vivo* antioxidants. *J. Am. Coll. Nutr.*, 24, 44–50, 2005.
19. Kamiloglu, S., Pasli, A.A., Ozcelik, B., and Capanoglu, E., Evaluating the *in vitro* bioaccessibility of phenolics and antioxidant activity during consumption of dried fruits with nuts. *LWT-Food Sci. Technol.*, 56, 284–289, 2014.

20. USDA, *USDA Database for the Oxygen Radical Absorbance Capacity (ORAC of Selected Foods, Release 2.0*, U.S. Department of Agriculture, Beltsville, MD, 2010.
21. Rababah, T.M., Ereifej, K., and Howard, L., Effect of ascorbic acid and dehydration on concentrations of total phenolics, antioxidant capacity, anthocyanins, and color in fruits. *J. Agric. Food Chem.*, 53, 4444–4447, 2005.
22. Threlfall, R., Morris, J., and Meullenet, J.F., Product development and nutraceutical analysis to enhance the value of dried fruit. *J. Food Quality*, 30, 552–566, 2007.
23. Madrau, M.A., Sanguinetti, A., Del Caro, A., Fadda, C., and Piga, A., Contribution of melanoidins to the antioxidant activity of prunes. *J. Food Quality*, 33, 155–170, 2010.
24. Alasalvar, C., and Shahidi, F., Tree nuts: Composition, phytochemicals, and health effects: An overview, in *Tree Nuts: Composition, Phytochemicals, and Health Effects*, Alasalvar, C. and Shahidi, F., Eds., CRC Press, Boca Raton, FL, 2009, pp. 1–10.
25. Al-Farsi, M., and Lee, C.Y., Nutritional and functional properties of dates: A review. *Crit. Rev. Food Sci. Nutr.*, 48, 877–887, 2008.
26. Namitha, K., and Negi, P.S., Chemistry and biotechnology of carotenoids. *Crit. Rev. Food Sci. Nutr.*, 50, 728–760, 2010.
27. Rawson, A., Patras, A., Tiwari, B.K., Noci, F., Koutchma, T., and Brunton, N., Effect of thermal and non-thermal processing technologies on the bioactive content of exotic fruits and their products: Review of recent advances. *Food Res. Int.*, 44, 1875–1887, 2011.
28. Thompson, L.U., Boucher, B.A., Liu, Z., Cotterchio, M., and Kreiger, N., Phytoestrogen content of foods consumption in Canada, including isoflavones, lignans, and coumestan. *Nutr. Cancer*, 54, 184–201, 2006.
29. Kuhnle, G.G.C., Dell' Aquila, C., Aspinall, S.M., Runswick, S.A., Joosen, A.M.C.P., Mulligan, A.A., and Bingham, S.A., Phytoestrogen content of fruits and vegetables commonly consumed in the UK based on LC-MS and 13C-labelled standards. *Food Chem.*, 116, 542–554, 2009.
30. Liggins, J., Bluck, L.J.C., Runswick, S., Atkinson, C., Coward, W.A., and Bingham, S.A., Daidzein and genistein content of fruits and nuts. *J. Nutr. Biochem.*, 11, 326–331, 2000.
31. Shahidi, F., and Ambigaipalan, P., Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects – A review. *J. Funct. Foods*, 18, 820–897, 2015.
32. Marquez, A., Dueñas, M., Serratosa, M.P., and Merida, J., Formation of vitisins and anthocyanin-flavanol adducts during red grape drying. *J. Agric. Food Chem.*, 60, 6866–6874, 2012.
33. Oszmiański, J., Kolniak-Ostek, J., Lachowicz, S., Gorzelany, J., and Matłok, N., Effect of dried powder preparation process on polyphenolic content and antioxidant capacity of cranberry (*Vaccinium macrocarpon* L.). *Ind. Crops Prod.*, 77, 658–665, 2015.
34. Vallejo, F., Marín, J.G., and Tomás-Barberán, F.A., Phenolic compound content of fresh and dried figs (*Ficus carica* L.). *Food Chem.*, 130, 485–492, 2012.
35. Russo, F., Caporaso, N., Paduano, A., and Sacchi, R., Phenolic compounds in fresh and dried figs from Cilento (Italy), by considering breba crop and full crop, in comparison to Turkish and Greek dried figs. *J. Food Sci.*, 79, C1–C7, 2014.

36. Bachir Bey, M., Richard, G., Meziant, L., Fauconnier, M.L., and Louaileche, H. Effects of sun-drying on physicochemical characteristics, phenolic composition and *in vitro* antioxidant activity of dark fig varieties. *J. Food Process. Preserv.*, 9, 337–346, 2016.
37. Erdoğan, S., and Erdemoğlu, S., Evaluation of polyphenol contents in differently processed apricots using accelerated solvent extraction followed by high-performance liquid chromatography-diode array detector. *Int. J. Food Sci. Nutr.*, 62, 729–739, 2011.
38. Nowicka, P., Wojdyło, A., and Samoticha, J., Evaluation of phytochemicals, antioxidant capacity, and antidiabetic activity of novel smoothies from selected Prunus fruits. *J. Funct. Foods*, 25, 397–407, 2016.
39. Di Lorenzo, C., Frigerio, G., Colombo, F., de Sousa, L.P., Altindişli, A., Dell'Agli, M., and Restani, P., Phenolic profile and antioxidant activity of different raisin (*Vitis vinifera* L.) samples, presented at the 39th World Congress of Wine and Wine, Bento Gonçalves, Brazil, October 24–28, 2016, Abstract 04006.
40. Fabani, M.P., Baroni, M.V., Luna, L., Lingua, M.S., Monferran, M.V., Paños, H., Tapia, A. et al., Changes in the phenolic profile of Argentinean fresh grapes during production of sun-dried raisins. *J. Food Comp. Anal.*, 58, 23–32, 2017.
41. Madrau, M.A., Piscopo, A., Sanguinetti, A.M., Del Caro, A., Poiana, M., Romeo, F.V., and Piga, A., Effect of drying temperature on polyphenolic content and antioxidant activity of apricots. *Eur. Food Res. Technol.*, 228, 441–448, 2009.
42. Joshi, A.P.K., Rupasinghe, H.P.V., and Khanizadeh, S., Impact of drying processes on bioactive phenolics, vitamin C and antioxidant capacity of red-fleshed apple slices. *J. Food Process. Preserv.*, 35, 453–457, 2011.
43. Schulze, B., Hubbermann, E.M., and Schwarz, K., Stability of quercetin derivatives in vacuum impregnated apple slices after drying (microwave vacuum drying, air drying, freeze drying) and storage. *LWT*, 57, 426–433, 2014.
44. Harnly, J.M., Doherty, R.F., Beecher, G.R., Holden, J.M., Haytowitz, D.B., Bhagwat, S., and Gebhardt, S., Flavonoid content of US fruits, vegetables, and nuts. *J. Agric. Food Chem.*, 54, 9966–9977, 2006.
45. Slatnar, A., Klancar, U., Stampar, F., and Veberic, R., Effect of drying of figs (*Ficus carica* L.) on the contents of sugars, organic acids, and phenolic compounds. *J. Agric. Food Chem.*, 59, 11696–11702, 2011.
46. Williamson, G., and Carughi, A., Polyphenol content and health benefits of raisins. *Nutr. Res.*, 30, 511–519, 2010.
47. Meng, J., Fang, Y., Zhang, A., Chen, S., Xu, T., Ren, Z., Han, G. et al., Phenolic content and antioxidant capacity of Chinese raisins produced in Xinjiang Province. *Food Res. Int.*, 44, 2830–2836, 2011.
48. Mnari, A.B., Harzallah, A., Amri, Z., Dhaou Aguir, S., and Hammami, M., Phytochemical content, antioxidant properties, and phenolic profile of Tunisian raisin varieties (*Vitis Vinifera* L.). *Int. J. Food Prop.*, 19, 578–590, 2016.
49. Chiou, A., Karathanos, V.T., Mylona, A., Salta, F.N., Preventi, F., and Andrikopoulos, N.K., Currants (*Vitis vinifera* L.) content of simple phenolics and antioxidant activity. *Food Chem.*, 102, 516–522, 2007.
50. Aegean Exporter's Associations, *Report on Food Composition and Clinical Research on Seedless Raisins and Dried Figs*, Aegean Exporter's Associations, Izmir, Turkey, 2009.
51. Čanadanović-Brunet, J.M., Vulić, J.J., Ćetković, G.S., Đilas, S.M., and Tumbas-Šaponjac, V.T., Bioactive compounds and antioxidant properties of dried apricot. *Acta Period. Technol.*, 44, 193–205, 2013.

52. Palikova, I., Vostalova, J., Zdarilova, A., Svobodova, A., Kosina, P., Vecera, R., Stejskal, D. et al., Long-term effects of three commercial cranberry products on the antioxidative status in rats: A pilot study. *J. Agric. Food Chem.*, 58, 1672–1678, 2010.
53. Prior, R.L., Rogers, T.R., Khanal, R.C., Wilkes, S.E., Wu, X., and Howard, L.R., Urinary excretion of phenolic acids in rats fed cranberry. *J. Agric. Food Chem.*, 58, 3940–3949, 2010.
54. Al-Farsi, M., Alasalvar, C., Morris, A., Barron, M., and Shahidi, F., Comparison of antioxidant activity, anthocyanins, carotenoids, and phenolics of three native fresh and sun-dried date (*Phoenix dactylifera* L.) varieties grown in Oman. *J. Agric. Food Chem.*, 53, 7592–7599, 2005.
55. Del Caro, A., Piga, A., Pinna, I., Fenu, P.M., and Agabbio, M., Effect of drying conditions and storage period on polyphenolic content, antioxidant capacity, and ascorbic acid of prunes. *J. Agric. Food Chem.*, 52, 4780–4784, 2004.
56. Kayano, S.-I., Kikuzaki, H., Ikami, T., Suzuki, T., Mitani, T., and Nakatani, N., A new bipyrrole and some phenolic constituents in prunes (*Prunus domestica* L.) and their oxygen radical absorbance capacity (ORAC). *Biosci. Biotechnol. Biochem.*, 68, 942–944, 2004.
57. Kayano, S.-I., Kikuzaki, H., Fukutsuka, N., Mitani, T., and Nakatani, N., Antioxidant activity of prune (*Prunus domestica* L.) constituents and a new synergist. *J. Agric. Food Chem.*, 50, 3708–3712, 2002.
58. Francini, A., Romeo, S., Cifelli, M., Gori, D., Domenici, V., and Sebastiani, L., 1H NMR and PCA-based analysis revealed variety dependent changes in phenolic contents of apple fruit after drying. *Food Chem.*, 221, 1206–1213, 2017.
59. Villarino, M., Sandín-España, P., Melgarejo, P., and De Cal, A., High chlorogenic and neochlorogenic acid levels in immature peaches reduce *Monilinia laxa* infection by interfering with fungal melanin biosynthesis. *J. Agric. Food Chem.*, 59, 3205–3213, 2011.
60. Grace, M.H., Massey, A.R., Mbeunkui, F., Yousef, G.G., and Lila, M.A., Comparison of health–relevant flavonoids in commonly consumed cranberry products. *J. Food Sci.*, 77, H176–H183, 2012.
61. Gu, L., Kelm, M.A., Hammerstone, J.F., Beecher, G., Holden, J., Haytowitz, D., Gebhardt, S. et al., Concentrations of proanthocyanidins in common foods and estimations of normal consumption. *J. Nutr.*, 134, 613–617, 2004.
62. Bey, M.B., and Louaileche, H., A comparative study of phytochemical profile and *in vitro* antioxidant activities of dark and light dried fig (*Ficus carica* L.) varieties. *J. Phytopharmacol.*, 4, 41–48, 2015.
63. Ferreira, D., Guyot, S., Marnet, N., Delgadillo, I., Renard, C.M., and Coimbra, M.A., Composition of phenolic compounds in a Portuguese pear (*Pyrus communis* L. var. S. Bartolomeu) and changes after sun-drying. *J. Agric. Food Chem.*, 50, 4537–4544, 2002.
64. Bacchiocca, M., Biagiotti, E., and Ninfali, P., Nutritional and technological reasons for evaluating the antioxidant capacity of vegetable products. *Ital. J. Food Sci.*, 18, 209–217, 2006.
65. Parker, T.L., Wang, X.-H., Pazmiño, J., and Engeseth, N.J., Antioxidant capacity and phenolic content of grapes, sun-dried raisins, and golden raisins and their effect on *ex vivo* serum antioxidant capacity. *J. Agric. Food Chem.*, 55, 8472–8477, 2007.

Chapter 15

Bioavailability of Nutrients and Phytochemicals from Dried Fruits

Arianna Carughi, Daniel Gallaher, and Giuseppina Mandalari

15.1 Introduction 370
15.2 Bioavailability and Bioaccessibility of Nutrients and Phytochemicals in Dried Fruits 370
15.3 Sugars and Sugar Alcohols in Dried Fruits 370
15.3.1 Glycemic Index as a Measure of Glucose Bioavailability 371
15.3.2 Sorbitol 374
15.4 Vitamin and Mineral Absorption 375
15.4.1 Vitamins 375
15.4.2 Minerals 376
15.5 Carotenoids in Dried Fruits 376
15.6 Phenolic Compounds in Dried Fruits 378
15.7 Gut Microbiota 383
15.7.1 Impact of Dried Fruits on Gut Microbiota 384
15.7.2 Fermentation of Bioactive Compounds in Dried Fruits 385
15.8 Conclusion 387
References 388

15.1 Introduction

Dried fruits provide a unique combination of essential nutrients and health promoting bioactive compounds or phytochemicals. Practically devoid of fat, dried fruits are concentrated sources of sugar, have a high content of dietary fiber, contribute to the daily requirement of key vitamins and minerals, and provide a broad range of phytochemicals, including phenolic acids, flavonoids, and carotenoids. Limited information, however, is available on the bioavailability of vitamins and essential minerals and of phytochemicals from dried fruits. In this chapter, we summarize the current literature regarding this topic.

15.2 Bioavailability and Bioaccessibility of Nutrients and Phytochemicals in Dried Fruits

Epidemiological studies have shown that diets rich in fruits and vegetables are associated with a lower risk of chronic diseases such as cardiovascular disease (CVD), diabetes, and cancer. Their protective effect has been attributed, in part, to their content of bioactive compounds or phytochemicals. However, the biological properties of these compounds depend on the ease by which they are released from the food matrix (bioaccessibility), their bioavailability, and, in some cases, their metabolism by colonic microbiota. The term *bioaccessibility* is defined as "the fraction of the compound that is released from its matrix in the gastrointestinal tract and thus becomes available for absorption," whereas *bioavailability* generally refers to the fraction of an oral dose from a parent compound of active metabolite that is absorbed and reaches the systemic circulation [1]. In these terms, bioavailability is strictly dependent on bioaccessibility [2]. Only carotenoids and phenolic compounds will be discussed in this section, as they are the most investigated compounds in relation to health benefits of dried fruits. In nutritional sciences, the term *relative bioavailability* is commonly used to describe the bioavailability of a compound from one source compared to another. Figure 15.1 illustrates the basic events describing the fate of ingested nutrients and phytochemicals in the body [3].

15.3 Sugars and Sugar Alcohols in Dried Fruits

Fruits are concentrated sources of simple sugars and, in some cases, certain sugar alcohols, primarily sorbitol. Dried fruits, consequently, can have very high concentrations of sugars. As reported in the United States Department of Agriculture (USDA) Food Composition Database (Table 15.1), the total sugar concentration of many dried fruits exceeds 50% of the weight of the dried fruits. Dried plums and peaches have the lowest sugar concentration. In the majority of dried fruits where individual sugars were reported, glucose and fructose are the major sugars. Only in dates and dried peaches does sucrose constitute the major sugar. In prunes, figs, and raisins, sucrose is present in low concentrations.

Of the dried fruits for which the sorbitol concentration has been reported, or can be extrapolated from values in fresh fruits, prunes have the greatest concentration, although dried pears also have a significant concentration. Raisins and dried

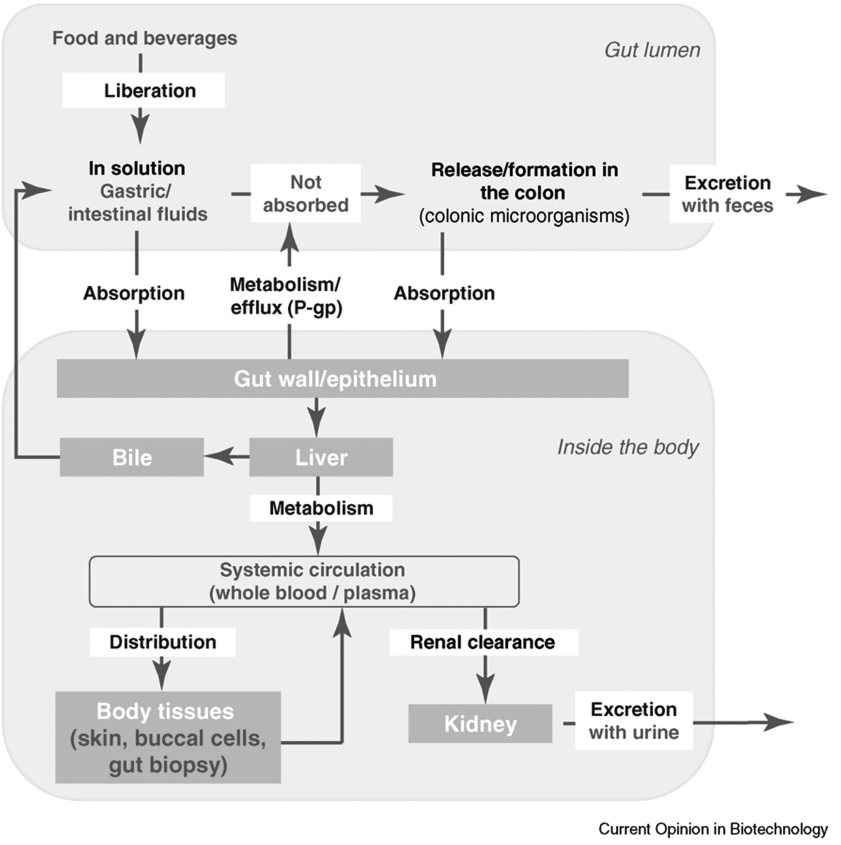


Figure 15.1 Basic events describing the fate of nutrients and phytochemicals. (1) Liberation: the release and dissolution of a compound to become available for absorption (bioaccessibility); (2) absorption: the movement of compounds from the site of administration to the blood circulation; (3) distribution: the process by which a compound diffuses or is transferred from the blood to the body tissues; (4) metabolism: the biochemical conversion or transformation of a compound into a form that is easier to eliminate; and (5) excretion: the elimination of unchanged compound or metabolites from the body, mainly *via* renal, biliary, or pulmonary pathways. *Source*: Adapted from Holst and Williamson, *Curr. Opin. Biotechnol.*, 19, 73, 2008. With permission.

apricots would be expected to have no sorbitol, based on the lack of sorbitol in the fresh fruit. More detail information about nutritional characteristics of dried fruits is given in Chapter 14.

15.3.1 Glycemic Index as a Measure of Glucose Bioavailability

Plasma glucose increases after ingestion of glucose-containing foods, or foods containing starch or sucrose. The magnitude of this postprandial increase, both in

Table 15.1 Sugars and Sugar Alcohol Concentrations in Dried Fruits (g/100 g edible portion)

	Apples	*Apricots*	*Cranberries*	*Currants*	*Dates*	*Figs*	*Peaches*	*Pears*	*Prunes*	*Raisins*	*References*
Glucose	nr	33.1	29.7	nr	19.9	24.8	12.8	nr	25.5	27.8	[116]
Fructose	nr	12.5	27.0	nr	19.6	22.9	13.5	nr	12.4	29.7	[116]
Sucrose	nr	7.9	15.8	nr	23.8	0.10	15.4	nr	0.15	0.50	[116]
Total sugars	57.2	53.4	72.6	67.3	63.4	47.9	41.7	62.2	38.1	59.2	[116]
Sorbitol	1.5	0.00	nr	nr	nr	0.20	0.30	5.6	10.8	0.00	[117]

Abbreviation: nr, not reported.

terms of its amplitude and the duration of its increase relative to fasting glucose concentrations, has long been of interest in terms of its association with diabetes and coronary heart disease (CHD). As an attempt to quantify the postprandial increase in plasma glucose caused by foods, relative to some standard, the glycemic index (GI) was proposed by Jenkins et al. [4]. Operationally, the GI is measured as the area under the curve of the plasma glucose response to a food, measured multiple times over 2 hours, expressed as a percentage of the area under the plasma glucose curve for a reference carbohydrate, which is either a glucose solution or white bread. Thus, the GI can be considered a measure of the bioavailability of glucose (as glucose or products that give rise to glucose when hydrolyzed, such as starch or sucrose) from a food. In normal individuals, the postprandial glucose response to oral fructose is minimal [5], as is the glucose response to sorbitol [6]. Thus, the GI of an individual dried fruit largely depends on the bioaccessibility of glucose and sucrose from the dried fruits. GI values ≥ 70 are considered high. Intermediate values are 55–70, and a low GI is ≤ 55.

The GI has been determined for a number of different dried fruits. As shown in Figure 15.2, dried apricots and prunes have the lowest GI, with values of approximately 30. Dates also have a low GI of approximately 42, although this value varies considerably depending on the type of dates. For example, the Bahri variety of dates has a GI of 50, whereas the GI of the Bo ma'an variety has a value of 31. Sweetened dried cranberries, dried figs, and raisins have GI values considered to be medium (62, 61, and 58, respectively), although in the case of dried cranberries, the GI was

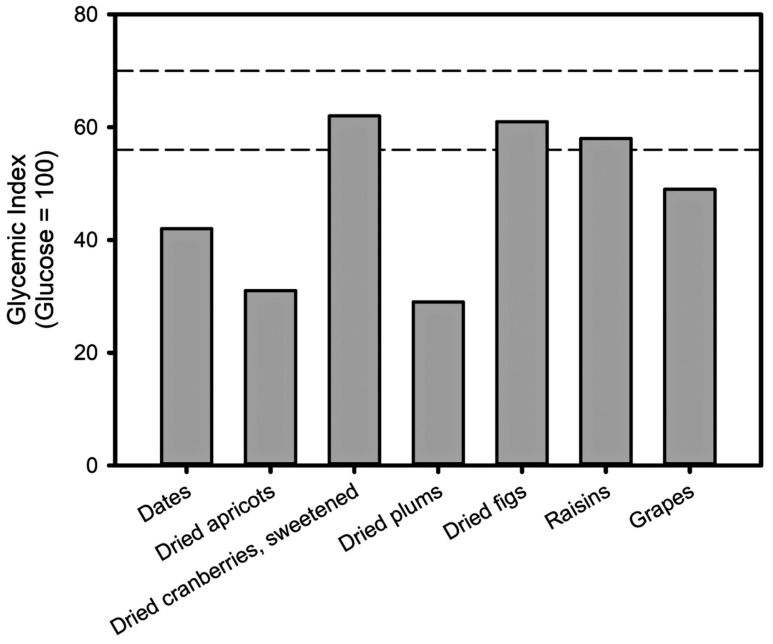


Figure 15.2 Glycemic index for a number of dried fruits and for grapes, using glucose as the reference. Values are taken from the University of Sydney Glycemic Index Database (http://www.glycemicindex.com/index.php). When multiple values existed for the same dried fruit, the values were averaged.

likely influenced by the sweetener. Overall, dried fruits have a low to intermediate GI. This is consistent with the study by Miller et al. [7], who concluded that foods high in simple sugars, such as fruits, generally have a lower GI than starchy foods.

Grapes, the one fruit listed with a dried fruit counterpart (e.g., raisins) has an average GI of 49, somewhat lower than the value for raisins. This might suggest greater bioavailability of the sugars from raisins than grapes. However, in a study comparing the blood glucose response of a 100 kcal serving of raisins to a 100 kcal serving of Thompson Seedless grapes, the variety of grapes used to make commercial raisins, it was found that raisins had a somewhat lower glycemic response than grapes (Table 15.2) [8]. In another study, the glycemic response to the recommended serving size of raisins (36 g, 109 kcal, and 27 g carbohydrate) and Thompson seedless grapes (151 g, 104 kcal, and 26 g carbohydrate) were compared. With blood collections at 30, 60, and 120 minutes, there were no differences ($P > 0.05$) in blood glucose levels between the treatments at any time point [9].

15.3.2 Sorbitol

The sugar alcohol sorbitol (also called D-glucitol) is present in several dried fruits, as shown in Table 15.1. Prunes have the greatest concentration, followed by dried pears. Dried apples, figs, and peaches have low concentrations of sorbitol, whereas dried apricots and raisins would be expected to have no sorbitol, based on the lack of detection of sorbitol in the fresh fruits. Although sorbitol is known to be incompletely absorbed, the majority does seem to be taken up by the small intestine. In ileostomy patients, only about 26.8 ± 2.8% of a dose of sorbitol could be recovered in the ileal effluent, indicating that about three-quarters of the dose was absorbed [10]. Based on these findings, the metabolizable energy value was estimated to be 2.8 kcal/g. Similar results were found in normal subjects in which the distal ileal contents were aspirated after a meal containing sorbitol. Absorption of sorbitol was estimated at 79 ± 4%, and subsequently the energy value was estimated at 3.58 kcal/g [11]. Sorbitol that is not absorbed in the small intestine is completely fermented in the large intestine [12].

There appear to be no studies of sorbitol absorption from fruits, fresh or dried, or indeed from any other whole food. However, it has been shown that a solution of sorbitol is better absorbed when containing either glucose or lipids, compared to

Table 15.2 Glycemic Response to 100 kcal Serving of Raisins and Thompson Seedless Grapes

Time (min)	*Raisins*	*Thompson Seedless Grapes*
	Plasma glucose (mg/dL)	
0	150.8 ± 10.1	154.4 ± 15.2
30	180.5 ± 12.7	204.6 ± 16.2
60	167.3 ± 13.2	181.3 ± 18.2
120	143.7 ± 11.4	149.5 ± 14.9

Source: Adapted from Wilson, T. et al., *Food Nutr. Sci.*, 3, 1162, 2012. Open access journal.

the sorbitol solution alone [13]. The improved absorption of sorbitol with co-administration of glucose or lipids was attributed to a slowing of gastric emptying by the glucose or lipids. Since sorbitol is passively absorbed in the small intestine [14], a slower presentation of gastric contents to the small intestine allows for a greater absorption. Thus, it would be expected that sorbitol absorption would be greater from a food, including dried fruits, compared to pure solutions of this sugar alcohol.

15.4 Vitamin and Mineral Absorption

15.4.1 Vitamins

Fruits, including dried fruits, are considered a good food source of only a few vitamins. They are not, for example, a source of vitamins A, D, or E, as vitamins A and D are only found in animal products, and vitamin E is associated with oil-rich foods, such as nuts and seeds. However, fruits are often an excellent source of ascorbic acid (vitamin C) and carotenoids, some of which have pro-vitamin A activity, as discussed in the following section. However, none of the commonly consumed dried fruits in the United States are a particularly good source of vitamin C. This is unsurprising, as drying processes lead to significant degradation of vitamin C [15]. Of the dried fruits, only prunes are a good source of vitamin K (phylloquinone) (Table 15.3), providing about 28 μg vitamin K per serving size of 5 prunes, which is 23% of the daily adequate intake for men and 31% for women. More detailed information about daily requirements of vitamins of dried fruits is given in Chapter 14.

There are no studies of bioavailability of vitamin C from dried fruits. However, it has been shown that vitamin C is equally well absorbed from whole oranges,

Table 15.3 Vitamin K, Potassium, and Iron Content of Dried Fruits

Dried fruits	*Serving size*	*Vitamin K (μg)*	*Potassium (mg)*	*Iron (mg)*
Apples	6 rings (38.4 g)	1.2	173	0.54
Apricots	10 halves (35 g)	1.1	407	0.93
Dates	2 (48 g)	1.3	334	0.43
Figs	5 (42 g)	6.6	286	0.85
Peaches	3 halves (39 g)	6.1	388	1.58
Pears	2 halves (36 g)	7.3	533	0.76
Prunes	5 (47.5 g)	28.3	348	0.44
Raisins	Small box (42.5 g)	1.5	322	0.81

Source: Adapted from U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Release 28, 2016. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed April 1, 2018).

Notes: Adequate Intake of vitamin K is 120 μg/day for men and 90 μg/day for women. The Adequate Intake for potassium is 4.7 g/day. The Recommended Dietary Intake for iron is 8 mg/day for men and postmenopausal women and 18 mg/day for premenopausal women.

orange juice, and synthetic vitamin C in humans [16]. This suggests that the food matrix has little if any effect on the bioavailability of vitamin C. Based on these findings, one would suspect that the modest amount of vitamin C present in some dried fruits would be as available for absorption as from the fresh fruits it is derived from.

Since green leafy vegetables are the major dietary source of vitamin K [17], and fruits, with the exception of prunes, are low in vitamin K, it is understandable that no bioavailability studies have been conducted with fruits, fresh or dried. However, one point about vitamin K bioavailability worth noting is that vitamin K absorption is greatly increased in the presence of some dietary fat. For example, the vitamin K in spinach was absorbed to a 3-fold greater extent when consumed with butter compared to without butter [18]. Thus, consuming prunes in the absence of fat, such as alone as a snack, may result in a relatively low absorption of their vitamin K.

15.4.2 Minerals

All dried fruits are a good source of potassium, with dried pears having the most potassium per standard serving, and dried apples the least (Table 15.3). There appear to be no studies of the bioavailability of potassium from dried fruits. However, potassium is generally efficiently absorbed from the small intestine, typically around 85%, although there is considerable individual variation [19]. Thus, it is likely that potassium is well absorbed from dried fruits and therefore would be a significant dietary source of the mineral. Since a high sodium-potassium ratio is associated with a significant increase in risk for CVD as well as all-cause mortality in the US population [20], increased consumption of dried fruits would provide a means to reduce the sodium-potassium ratio, therefore potentially reducing CVD risk.

Iron deficiency is the most common nutrient deficiency in the world, leading to anemia and associated symptoms, such as fatigue. Although dried fruits would not be considered a rich source of dietary iron, several dried fruits have sufficient iron that they could make a significant contribution to total iron intake. Dried peaches have notable iron content, but dried apricots and raisins also have sufficient iron to make a worthwhile contribution to iron status in some circumstances, particularly for men and postmenopausal women. However, the bioavailability of the iron may be low in at least some dried fruits. When examined using an *in vitro* digestion/Caco-2 cell culture model, the iron bioavailability of raisins was quite low [21], a finding attributed to the high concentration of iron-binding phenolic compounds in raisins, which are known to decrease iron absorption [22]. Thus, dried fruits with a high concentration of phenolic compounds are likely to have low iron bioavailability. The carotenoids and phenolic compounds of dried fruits are discussed in the following sections.

15.5 Carotenoids in Dried Fruits

Carotenoids are natural plant pigments responsible for most of the yellow, orange, and red colors of fruits and vegetables. Depending on their structural characteristics, they can be categorized as provitamin A carotenoids (e.g., α-, β-, and γ-carotene, β-cryptoxanthin) or non-pro-vitamin A carotenoids (e.g., lycopene, lutein, zeaxanthin, astaxanthin, and neoxanthin). Carotenoids exert significant antioxidant

activity by singlet-oxygen quenching and free-radical scavenging, mechanisms that may explain their protective effect on human health. They have been shown to play a role in the prevention of degenerative disease, especially CHD, age-related macular degeneration, and certain cancers. Before exerting health effects, however, carotenoids need to be released from the food matrix, dispersed, and solubilized into mixed micelles in the small intestine and then absorbed by the enterocytes into the blood stream (Figure 15.1). The effectiveness of this process depends on many factors, both dietary and physiologic. The main determinants include the food matrix in which the carotenoid is incorporated and the interaction of carotenoids with other dietary components [23]. The type and amount of carotenoid consumed in the meal, host nutrient status, and genetic factors all influence absorption [24]. Excellent reviews on carotenoid bioavailability and bioaccessibility are available [24,25].

Dried fruits are a source of an array of carotenoids, notably α- and β-carotene, β-cryptoxanthin, lutein, and zeaxanthin. Of these, β-carotene is particularly high in dried apricots, peaches, mangos, and papayas [26]. Dried peaches provide lutein + zeaxanthin and β-cryptoxanthin, prunes provide β-carotene, and red-fleshed dried papayas provide lycopene [27]. Dates are rich in lutein and neoxanthin [28]. Traditional dried fruits have a higher carotenoid content than their fresh counterparts do, as they are concentrated by the removal of water. On the other hand, the exposure of the fruit to high temperatures in the presence of oxygen induces oxidation, which affects carotenoid content and profiles [29].

The major physical barriers to carotenoid bioaccessibility in plant foods, and probably of the greatest relevance to dried fruits, are the thickness and fibrous structure of cell walls and the morphology of the chromoplast wherein carotenoids are localized [30]. Mastication disrupts the cellular matrix, but the impact of cell walls on bioaccessibility is not limited to the ease with which cellular contents are released. The fruit's fiber content (cell wall material) can increase the viscosity of intestinal content, thus entrapping carotenoids and bile salts and decreasing the activity of digestive enzymes. This would reduce the efficiency of micelle formation [31]. Pectin, a viscous dietary fiber, has been shown to inhibit carotenoid absorption [32]. Thermal processing or dehydration can affect carotenoid bioaccessibility by making mastication less effective, by hardening cell walls, and by concentrating fiber.

In vitro digestion approaches have been used to assess the impact of food matrix factors on carotenoid bioaccessibility from fruits, vegetables, and nuts but not from dried fruits. Very few studies have assessed the bioavailability of carotenoids from dried fruits. Gouado et al. [27] measured systemic levels of carotenoids after consuming fresh, dried, or juiced mangoes and papayas. Two groups of healthy volunteers ate meals containing bread, yogurt, and one of the three forms of fruit on different days. Meals were served after an overnight fast, and blood samples were collected before the meal (T0 – Control) and 4 hours (T4) and 8 hours (T8) after the test meal. Subjects received 100 g of the dried fruit or 565, 568, 532, and 513 g of the juiced mango, fresh mango, juiced papaya, and fresh papaya, respectively. Dried fruits were prepared by slicing fresh fruits and drying on a gas drier (starting at 80 °C and ending at 40 °C) until residual moisture content was 12%. The carotenoid content of the dried fruits was significantly lower than those of the juiced and fresh fruits. This is because exposure to light and excessive heat led to oxidative destruction of the carotenoids. Carotenoids from dried mangoes and papayas were absorbed at a slower rate than from their fresh counterparts. The authors hypothesized that

drying hardens cell walls, making the liberation of carotenoids from the cellular matrix more difficult. Carotenoids from dried mango slices were absorbed slower than from dried papayas. The authors attributed this to the higher fiber content of mangoes. It is interesting to note that Jeffrey et al. [33], using an *in vitro* model of gastric and small intestinal digestion, estimated bioaccessibility to be 48.5 ± 13.3% and 37.3% ± 52.5 for β-carotene and lutein, respectively, in fresh papayas and 31.8 ± 3.7% and 13.5 ± 11.9 % for these carotenoids in fresh mangoes.

15.6 Phenolic Compounds in Dried Fruits

Phenolic compounds are characterized by having hydroxyl groups on aromatic rings, and are common plant secondary metabolites involved in defense against ultraviolet radiation or physiological damage by pathogens. Several hundred phenolics have been identified in fruits and vegetables, which may be classified into phenolic acids, flavonoids, stilbenes, and lignans, among others, according to the number of phenol rings they have and the structural elements that bind these rings to one another.

Polyphenols are probably the most investigated phytochemicals of nutritional interest. Prospective epidemiological studies, as well as cross-sectional observations and interventions, have linked these compounds to beneficial effects in human health by reducing the incidence of several chronic diseases, including CVD, stroke, type-2 diabetes, and several types of cancer, among others. In mechanistic studies, they have been shown to inhibit the proliferation of cancer cells, reduce vascularization, protect neurons against oxidative stress, lower markers of inflammation and oxidative stress, stimulate vasodilation, and improve insulin secretion [34].

Dried fruits provide a wide range of polyphenols and phenolic acids. The major flavonoids found in dried fruits are anthocyanidins, dehydrochalcones, flavonols, flavones, and flava-3-ols. The common phenolic acids present are chlorogenic acid, caffeic, ferulic, *p*-coumaric acid, protocatechuic acid, and gallic acid [28,35,36]. The total phenolic content (TPC) of dried fruits (apples, apricots, cranberries, dates, peaches, pears, prunes, and raisins), expressed as ascorbic acid equivalents (AAE)/100 g of dry weight (dw), has been reported to range from 916 to 2414 [37]. In this analysis, raisins had the highest TPC, and dates had the lowest. However, this ranking was not replicated in another study [28]. Drying concentrates the phenolic compounds in fruits but has variable effects on the phenolic profiles and the TPC, depending on the type of drying process and the fruit [38,39]. The drying process can also alter the microstructure of the fruits and thus affect the bioaccessibility and bioavailability of phenolic compounds after intestinal digestion.

Polyphenol bioavailability involves the following digestive and metabolic processes (Figure 15.3):

1. Release of polyphenol from the food matrix.
2. Changes in polyphenols during the gastric/small intestinal digestion including cleavage of sugar moieties in glycosides.
3. Cellular uptake of aglycones and some conjugated polyphenols by enterocytes.
4. Microbiological fermentation of non-absorbed polyphenols or those excreted *via* bile to yield additional metabolites.

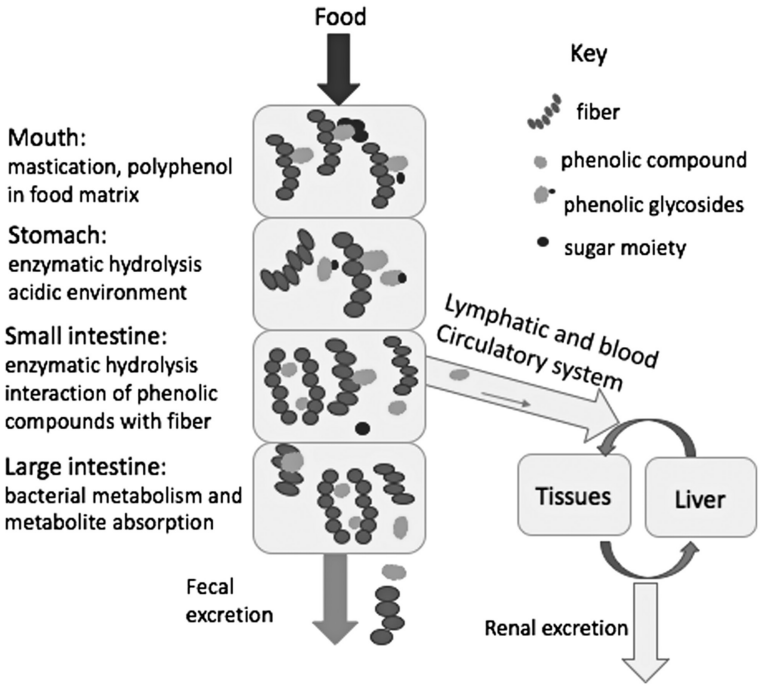


Figure 15.3 **(See color insert.)** General pathway of absorption of phenolic compounds contained in foods rich in dietary fiber, such as fruits and vegetables. *Source*: Adapted from Palafox-Carlos, H. et al., *J. Food Sci.*, 76, R6, 2011. Open access journal.

5. Phase I/II enzymatic modification that occur upon uptake in small intestine and colon; transport to the bloodstream and tissue redistribution.
6. Excretion *via* the kidney [40].

As is the case with carotenoids, several factors may impact polyphenol bioaccessibility and bioavailability, including the food matrix; the amount of fiber, protein, carbohydrate and antioxidant vitamins co-ingested; and the molecular structure of the polyphenol itself. Many excellent reviews on polyphenol bioavailability are available [40–42].

Of special relevance to dried fruits is the influence of dietary fiber on polyphenol bioaccessibility. A large proportion of polyphenols is associated with dietary fiber. Extractable polyphenols (easily extracted with methanol or water) should be differentiated from non-extractable (or insoluble-bound) polyphenols (NEPPs), which are mostly attached to the cell wall. While many of the low-molecular weight polyphenols, such as phenolic acids, are released during digestion in the gastric phase or in the small intestine, higher-molecular-weight compounds, such as tannins and proanthocyanidins, which are typically covalently bound to dietary fiber or proteins, would be expected to reach the colon. NEPPS can range from 80% to 90% in commonly consumed fruits. In a recent review of dietary fiber as a carrier of antioxidants, it was suggested that, although NEPPs may not be available in the small intestine, they may be released into the colon by microbiological fermentation.

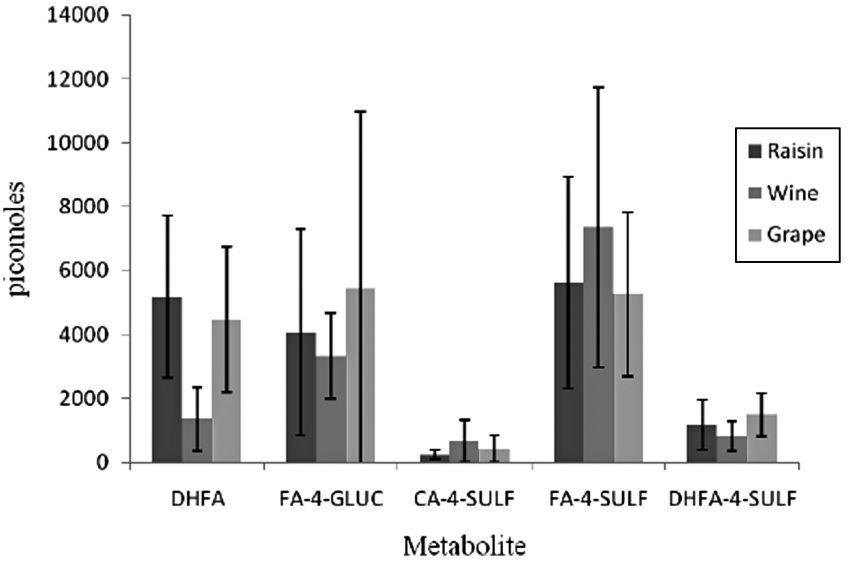


Figure 15.4 **(See color insert.)** Total urinary excretion of phenolic acid metabolites from raisins, white wine, and grapes per 24 hours. *Source*: Adapted from Carughi, A., *Ann. Nutr. Metab.*, 62, 14, 2013. With permission.

Using an *in vitro* model of digestion and colonic fermentation, it has been estimated that 48% of polyphenols are bioaccessible in the small intestine, while 42% become bioaccessible in the large intestine, and only small amounts (about 10%) are inaccessible and remain in the food matrix after the whole digestion process [43]. In the Spanish diet, it has been estimated that 197 mg/person/day of polyphenols from fruits are bioaccessible in the small intestine, 346 mg/person/day are bioaccessible in the large intestine, and 74 mg/person/day are non-bioaccessible [43]. Other than the effect of NEPPs, fiber *per se* may decrease bioavailability, as in the case of carotenoids, by physical entrapment, increased viscosity, and increased bulk [40].

In vitro models simulating gastrointestinal digestion have been developed to assess bioaccessibility of phenolic compounds from fruits and vegetables [1,44,45]. These methods are fast and safe, and they do not have the ethical restrictions of the *in vivo* methods. Although results cannot predict the human *in vivo* condition, they are a tool for investigating the effect of food matrix and enzymes on polyphenol bioavailability. Even so, very limited information is available on dried fruits. Kamiloglu et al. [46] measured antioxidant activity, proanthocyanidin content, and major phenolic compounds in yellow and purple fresh and dried Turkish figs at different phases of simulated gastrointestinal digestion. TPC was determined using the Folin-Ciocalteau reagent, and total antioxidant capacity (TAC) was estimated from four different assays. Phases included post gastric digestion, intestinal digestion, and a dialyzed fraction after intestinal digestion. Dialysis through a semi-permeable cellulose membrane allows the study of free soluble fraction of polyphenols potentially available for further uptake as a simplified model of the epithelial barrier, thus, an indication of bioavailability. They found that after intestinal digestion, in both fresh and dried yellow and purple figs, chlorogenic acid and rutin values were much

lower in the dialyzed fraction, indicating that the amount of these compounds available for absorption under the conditions of the small intestine is quite low. They also found that the amount of chlorogenic acid was higher in the dialyzed fraction from dried figs than from fresh figs, which may indicate that sun-drying had a positive effect on its bioaccessibility. The results were reversed for rutin; drying may have an adverse effect on rutin bioaccessibility, as lower values for this compound were seen in the dialyzed fraction after intestinal digestion. The amounts of both cyanidin-3-glucoside and cyanidin-3-rutinoside of dried purple figs were higher than those of their fresh fig counterparts in the gastric digestion fraction. However, no anthocyanins were detected in yellow and purple dried figs, indicating low bioaccessibility. As mentioned above, this does not mean that they have no role in health protection; if they are not absorbed in the small intestine, they can reach the large intestine, where they can be transformed by the colon microbiota. The metabolites generated can have a beneficial effect on the large intestinal cells, the microbiota itself or be absorbed and exert a biological action elsewhere in the body. In fact, Matsumura et al. [47] measured the antioxidant activity of the non-extractable fraction of dried persimmons and found that the non-extractable fraction may possess significant antioxidant potential *in vivo*, as measured by plasma oxygen radical absorbance capacity values of experimental animals, and retain bioactivity by inducing changes in plasma triacylglycerols and high-density lipoprotein cholesterol.

In another study, using the same model, Kamiloglu et al. [48] assessed the impact of gastrointestinal digestion on the TPC and TAC of dried apricots, figs, and raisins. As with the study above, there was an increase in TPC for all samples after PG. TAC also increased. However, TPC after intestinal digestion in the dialyzed fraction was only a part of the initial phenolic content. Comparable results were found for apple phenolics, using a similar *in vitro* model of digestion [45]. In this study, about 65% of phenolics and flavonoids were released during gastric digestion, with less than 10% released during intestinal digestion. Anthocyanins present after gastric digestion were not detectable after intestinal digestion. Free-soluble phenolics crossing the semi-permeable cellulose membrane, and thus potentially available for further uptake, were significantly lower than after intestinal digestion. TAC followed the concentration of TPC and flavonoids. Results are consistent with those of Tagliazucchi et al., [44] who assessed the bioaccessibility of phenolic compounds in grapes using a model of *in vitro* gastrointestinal digestion. The amount of bioaccessible polyphenols, flavonoids, and anthocyanins increased during gastric digestion. The transition to the intestinal environment caused a decrease in all the analyzed classes of polyphenols followed by a renewal in the extraction of polyphenols and flavonoids but not of anthocyanins. The authors concluded that the gastrointestinal tract might act as an extractor, wherein polyphenols are progressively released from a solid matrix and made available for absorption. Similar results were observed by Zhao et al., [49] who investigated the effects of three thermal drying methods on the phenolic profiles and their bioaccessibility and the antioxidant activity of *Rhodomyrtus tomentosa* berries using a similar *in vitro* gastrointestinal digestion model. Release of phenolics from the food matrix mainly occurred in the stomach.

Kamiloglu et al. [48] evaluated the *in vitro* bioaccessibility of phenolics and antioxidant activity during the consumption of dried fruits (figs, apricots, and raisins) with nuts (almonds, walnuts, and hazelnuts) using the *in vitro* model described above. Consumption of fig–nut and apricot–walnut/hazelnut mixtures instead of consuming them alone results in higher TAC recoveries in the dialyzed fraction,

which may reflect greater bioavailability. For all samples, co-digestion of dried fruits with nuts reduced the TPC in the dialyzed fraction. The authors suggested that dietary fiber in dried fruits might decrease bioaccessibility by acting as an entrapping matrix and restricting the diffusion of the enzymes to their substrates in the *in vitro* system. Physiologically, this would suggest that a large fraction of the polyphenols bound to the fiber end up in the large intestine. Considering that the Folin-Ciocalteu assay for total phenolics is subject to interference from amino acids and purines that are released from the proteins and nucleic acid by enzymatic action in the *in vitro* digestion procedure, this assay may not be sufficient to reflect changes in phenolics during co-digestion.

Very few studies have examined bioavailability of dried-fruit phenolic compounds. A liquid chromatography-mass spectrometry method was developed to measure the concentration of caffeic acid, ferulic acid, and chlorogenic acid in human plasma and urine. This method was tested in plasma and urine samples collected from three healthy volunteers after they ingested a single dose of 100 g of dried plums [50]. While no chlorogenic acid was detected in the plasma (limit of detection 10 nmol/L), small amounts were recovered in the urine, particularly 2–4 hours after ingestion. Caffeic acid in free and conjugated forms in urine increased from between 1.5-fold to 3-fold after dried-plum ingestion. Plasma levels of ferulic and caffeic acid also increased 2 hours after dried-plus ingestion. It is well known that dried-plum consumption increases serum levels and urinary excretion of hippuric acid within 48 hours after ingestion. This could reflect the bacterial metabolism and absorption of quinic acid and phenolic compounds in the digestive tract, as quinic acid is excreted in the urine as hippuric acid [51].

A recent study examined the antioxidant effect and the bioavailability of phenolic compounds from Corinthian raisins in 15 healthy subjects [52]. Subjects consumed 144 g raisins, and blood samples were collected at 0, 1, 2, 3, and 4 hours following consumption. Plasma TPC (μg gallic acid equivalents [GAE]/mL plasma) and serum resistance to copper-induced oxidation peaked at 1 hour after raisin consumption ($P < 0.05$) and correlated strongly with each other (Table 15.4).

Table 15.4 Plasma Total Polyphenols and Total Serum Oxidizability after Ingestion of 144 g Raisins

Time (Hours)	*Total Polyphenols (μg GAE/mL Plasma)*	*Total Serum Oxidizability (tLAG in Seconds)*
0	290 ± 13	1630 ± 172
1	316 ± 20*	3011 ± 641*
2	296 ± 23	2216 ± 542
3	308 ± 20	1933 ± 382
4	309 ± 21	2378 ± 559

Source: Adapted from Kanellos, P.T. et al., *Plant Foods Hum. Nutr.*, 68, 411, 2013. With permission.

Note: Values are means ± SEM, *$P < 0.05$ at different time points measured.

Abbreviations: GAE, gallic acid equivalents, tLAG, lag-time in sec. preceding copper-induced oxidation.

Sixteen phenolic compounds were identified and quantified in subjects' plasma by gas chromatography-mass spectrometry analysis, most reaching highest levels at 1 hour after consumption. A second rise in many phenolic compounds in plasma was observed 4 hours after consumption, possibly due to enterohepatic recycling of phenolic compounds and reabsorption. This study also measured plasma level of triterpenoid oleanolic acid and found that it peaked 4 hours after consumption. The results suggest that raisins influence antioxidant potential *in vivo,* and that phytochemicals are bioavailable. Repeated measures, however, did not display any significant difference in plasma concentrations of individual compounds measured at different times.

A pilot human cross-over intervention study wherein subjects consumed 100 g raisins, 400 g grapes, and 300 mL non-alcoholic white wine (equivalent weight of fresh grapes) suggests that microbial metabolism in the colon plays an important role in the bioavailability of phenolic acids [53]. Despite the lower content of phenolic compounds in raisins as compared to grapes, subjects consuming raisins and grapes had a significantly higher level of the metabolite dihydroferulic acid in their urine compared to non-alcoholic white wine. Other phenolic metabolites were present in the urine at comparable levels for all three treatments, showing that the bioavailability of phenolic compounds, as estimated from content in 24-hour urine, is very similar for these grape-derived products despite substantial differences in processing (Figure 15.4). The data suggests that microbial metabolism in the colon plays an important role in the bioavailability of phenolics from raisins.

15.7 Gut Microbiota

The human gut microbiota is a complex and dynamic ecosystem made of thousands of different bacterial species, of which more than 90% belong to the phyla *Bacteroidetes* and *Firmicutes* [54,55]. The gut microbiota is now recognized as a critical factor in nutrition and health, affecting the bioavailability and the metabolism of many food ingredients [56]. The integrity of the gut mucosal barrier is essential for maintaining a host energy balance, which could preclude the onset of certain chronic metabolic diseases, including intestinal inflammation and metabolic syndrome [57,58].

Dysfunction of the gut barrier and dysbiosis have been reported in typical Western diets that are high in saturated fats and low in fiber and phytochemicals, which could lead to a range of pathologies, such as inflammatory bowel disease and increased permeability of bacterial lipopolysaccharide (LPS) [59]. LPS plays an important role in inflammatory responses related to acute infections and is found in blood and tissues with postprandial and chronic inflammation [60]. Intestinal inflammation and disturbed colonic fermentation in subjects suffering from irritable bowel syndrome have been found to be associated with (a) microbiomes limited in the abundance and diversity of *Bacteroidetes* and *Firmicutes* and (b) reduced numbers of *Clostridium coccoides* [61]. A high-fat, high-sugar diet was found to increase intestinal permeability and tumor necrosis factor-alpha (TNF-α) secretion, resulting in a greater ability of invasive *Escherichia coli* to colonize the gut mucosa and induce inflammation in transgenic mice [62].

There is growing interest in the contributions of diet-mediated changes in the gut microbiota, and advances in molecular analysis techniques allow efficient microbiota,

profiling in animal and human studies. The composition of the intestinal microbiota is highly individual: molecular 16S rDNA-based microbiota analysis techniques including denaturing gradient gel electrophoresis, fluorescent *in situ* hybridization, and quantitative PCR have been very beneficial in identifying new species [63–66].

A variety of plant foods and nuts have been reported to selectively and positively influence the growth of the gut microbial ecology [67–69]. Gibson and Roberfroid [70] first described prebiotics as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving the health of the host." It has been demonstrated that functional foods rich in dietary fiber, polyphenols, or both were able to exert a prebiotic effect through the modulation of the human gut microbiota, which resulted in an increase of beneficial bacteria such as *Bifidobacteria* and *Lactobacilli* [71–73].

15.7.1 Impact of Dried Fruits on Gut Microbiota

The microbial fermentation of certain dietary components present in dried fruits, such as dietary fiber and polyphenols, could improve host health. Dried grapes (e.g., raisins, *Vitis vinifera* L.) are rich in both simple sugars and fructo-oligosaccharides, known for their prebiotic potential [74–76]. We have recently demonstrated that sun-dried raisins exhibit the potential to promote the colonization and proliferation of beneficial bacteria in the human gastrointestinal tract, and stimulate the production of advantageous organic acids [69]. Wijayabahu et al. [77] conducted a pilot human feeding study to determine how consumption of three oz. (~85 g) servings of sun-dried raisins per day affected composition and activities of the microbiota. Fecal samples were collected at baseline and days 7 and 14 of the study. Based on high throughput 16S rRNA sequence analysis, they observed stability in microbiota diversity indexes and in the proportions of bacterial phyla. Individual bacterial signature sequences suggested that the prevalence of up to 16 Operational Taxonomic Units (OTUs) changed during the first week of raisin consumption compared to only 11 OTUs that changed during the second week of raisin consumption. They also detected a significant reduction in an OTU closest to *Klebsiella* spp., potentially an enteric pathogen. The findings suggested that while adding raisins to the diet does not distort overall microbiota composition, it might potentially be beneficial to the host by reducing enteric inflammation associated with sub-clinical infections with an enteric pathogen. The anti-inflammatory effect of grape-seed proanthocyanindin extract in high-fat diet-induced obesity and the contribution of the effects of grape-seed proanthocyanindin extract on the gut microbiota metabolism has recently been evaluated. The results demonstrated that supplementation with grape-seed proanthocyanindin extract significantly decreased plasma levels of inflammatory factors such as TNF-α, interleukin 6, and monocyte chemoattractant protein-1, accompanied by increased macrophage infiltration in epididymal fat and liver tissues [78]. Furthermore, grape-seed proanthocyanindin extract also reduced epididymal fat mass and improved insulin sensitivity. The 16S rDNA analyses revealed that grape-seed proanthocyanindin extract supplementation modulated the gut microbiota composition and certain bacteria, including *Clostridium* XIVa, *Roseburia*, and *Prevotella*. More importantly, depleting gut microbiota by antibiotic treatment abolished the beneficial effects of grape-seed proanthocyanindin extract on inflammation and

adiposity. A polyphenol-rich fraction obtained from table grapes decreased adiposity, insulin resistance, and markers of inflammation and affected the gut microbiota in high-fat-fed mice, thus attenuating many of the adverse health consequences associated with consuming a high-fat diet [79].

The relationship between the intestinal microbiota and the hypocholesterolemic and anti-obesity effects of whole grape-seed flour from white and red winemaking was evaluated by Kim et al. [80]. The results suggested that the beneficial health effects of Chardonnay grape-seed flour on high-fat-induced metabolic disease related to the modulation of the intestinal microbiota and their metabolic processes.

Two reports have indicated that dates affected the gut microbiota. A fruit extract significantly increased the growth of *Bifidobacteria* and production of short-chain fatty acids *in vitro*, whereas an *in vivo* study showed beneficial changes in terms of increased stool frequency, reduction of stool ammonia concentrations, and reduced genotoxicity in human fecal water after consumption of dates for 21 days [81,82]. Blumberg et al. [56] have recently reviewed the impact of cranberries on gut microbiota and cardiometabolic health. Bioactives present in cranberries, particularly the proanthocyanidins, flavonols, and hydroxycinnamic acids, may act against a range of bacterial, fungal, and viral pathogens such as *Escherichia coli* [83], *Helicobacter pylori* [84,85], *Streptococcus mutans* [86], *Porphyromonas gingivalis* [87], *Staphylococcus aureus* [88], *Pseudomonas aeruginosa* [89], *Cryptococcus neoformans* [84], *Haemophilus influenzae* [90], and *Candida albicans* [91]. Furthermore, Anhe et al. [92] demonstrated that a polyphenol-rich cranberry extract protected against chronic inflammation associated with gut barrier dysfunction, with reduction in plasma LPS, cyclo-oxygenase-2, and TNF-α in mice. Polyphenols from cranberries had positive effects on oxidative stress, proinflammatory cytokines, nuclear factor-kappa B activation, and nuclear factor E2-related factor 2 [93]. A prune-essence concentrate may positively regulate the intestinal microbiota and effectively act as a hypocholesterolemic agent. This was demonstrated in a placebo-controlled, randomized study with 60 healthy mild hypercholesterolemic subjects, who showed a significant increase in the numbers of beneficial bacteria such as *Bifidobacterium* spp. and *Lactobacillus* spp., whereas the numbers of *Clostridium perfringens* and *Escherichia coli* decreased [94]. The shift in microbiota composition correlated with a reduction in total cholesterol and LDL-cholesterol levels.

Patrignani et al. [95] evaluated the combined effects of an aroma compound (citral, used at a concentration of 50 mg/L) and high pressure homogenization treatments (performed at 100 MPa for 1–8 successive passes) on the inactivation dynamics of *Saccharomyces cerevisiae* SPA strain inoculated in apricot juices at level of about 4.5 log CFU/mL. Results demonstrated that yeast cell viability decreased with the increase of passes at 100 MPa and the relationship between yeast cell loads and number of passes at 100 MPa followed a linear trend. In addition, the effect of high pressure homogenization treatment can be potentiated throughout the presence of citral and ethanol, increasing the time necessary to reach a spoilage threshold during storage.

15.7.2 Fermentation of Bioactive Compounds in Dried Fruits

It is well established that dried fruits contain bioactive compounds, including polyphenols as well as other phytochemicals such as terpenes, organic acids, complex

carbohydrates, and sugars, among others [96,97]. The two major classes of polyphenols are hydroxycinnamic acids and flavonoids, which account for around one half and one quarter of our dietary polyphenol intake, respectively [98]. Caffeic acid, the most abundant hydroxycinnamic acid, is commonly esterified with quinic acid to form chlorogenic acid [99]. Amongst flavonoids, quercetin is the most common flavonol, often present as glycosides, such as the rutinoside conjugate rutin [100].

Due to their low bioavailability, only a small proportion of polyphenols (about 10%) are directly absorbed in the small intestine, whereas as much as 90% enter the colon where they can be metabolized by intestinal bacteria [67]. Therefore, the gut microbiota plays a crucial role in the bioconversion of polyphenols into lower molecular weight metabolites, which can be absorbed and are responsible for the health benefits associated with consumption of polyphenol-rich foods. Caffeic acid is much better absorbed than chlorogenic acid, which is fermented in the colon into caffeic acid [101]. Quercetin aglycone has a very high bioavailability, with a peak in urine 24 hours after intake, whereas most of the rutin reaches the colon where it is fermented and liberates quercetin, some of which is absorbed in the colon and the remainder biotransformed into simpler phenolic acids [102].

The fermentation in the large bowel through anaerobic microbial metabolism usually generates production of short-chain fatty acids, such as acetate, propionate, and butyrate [103,104]. A recent *in vitro* investigation suggested that the effect of phenolic compounds is dependent on the absorption and metabolism in the gastrointestinal tract [105]. The biological activities related to consumption of dried fruits may also be due to the synergistic interaction of different polyphenols rather than to the action of an individual or single phenolic group [106]. Parkar et al. [107] investigated the fermentation of four dietary polyphenols, rutin, quercetin, chlorogenic acid, and caffeic acid, using an *in vitro* mixed culture model of human gut microbiota. All four compounds were biotransformed rapidly, disappearing from the medium within half an hour and later replaced by phenolic acid breakdown products (hydrocaffeic acid, dihydroxyphenylpropionic acid, 3-hydroxyphenylacetic acid, 4-hydroxyphenylpropionic acid, 3- hydroxyphenylpropionic acid, and phenylpropionic acid). Fermentation of polyphenols stimulated proliferation of *Bifidobacteria* and decreased the ratio of *Firmicutes* to *Bacteroidetes*, relative to controls.

The red cranberry is rich in several groups of phenolic compounds, especially flavonols (200–400 mg/kg), anthocyanins (136–1710 mg/kg), and proanthocyanidins (4,188 mg/kg (96). Proanthocyanidins are oligomers and polymers of flavan-3-ol monomers (mainly [epi]afzelechin, [epi]catechin, and[epi]galocatechin) joined by B-type (4b-8 or 4b-6) and additional A-type (2b-O-7 or 2b-O-5) linkages. Sanchez-Patan et al. [108] reported the *in vitro* degradation of cranberry polyphenols by the human gut microbiota and its subsequent modulation by polyphenols and their metabolites. The results showed the formation of phenylacetic (3,4-dihydroxy-, 3-hydroxy-, 4-hydroxy-, and phenylacetic), phenyl-propionic (3-[3',4'-dihydroxy-phenyl]-, 3-[3'-hydroxy-phenyl]-, 3-[4'-hydroxy-phenyl]-, and 3-[phenyl]propionic acid), and benzoic (3,4-dihydroxy-, 4-hydroxy,2-hydroxy-, and benzoic acid) acids, as well as phenols such as catechol and its derivatives (4-methy- and 4-ethyl), derived from the action of colon microbiota on cranberry polyphenols. Wang et al. [106] found a significant increase in the content of 4-hydroxyphenylacetic, 4-hydroxybenzoic acid, 2-hydroxybenzoic, and benzoic acids, among other metabolites, in urine samples of healthy subjects after a 3-week administration of cranberry juice. Khanal et al. [109] demonstrated that a diet containing cranberries significantly increased the excretion

of 3,4-dihydroxyphenylacetic, 3-hydroxyphenylacetic, 3-(3'-hydroxyphenyl)-propionic, and 3,4-dihydroxybenzoic in the urine of rats. In comparison to fermentation of grape-seed polyphenols, microbial degradation of cranberry polyphenols produced a different phenolic fingerprint, characterized by a relatively higher production of 3,4-dihydroxyphenylacetic, 3-(3',4'-dihydroxyphenyl)-propionic, 3-(4'-hydroxyphenyl)-propionic, and phenylpropionic acids [110]. Microbial fermentation of grape-seed extracts, which are rich in B-type proanthocyanidins, induced formation of intermediate metabolites, such as 5-(3',4-dihydroxyphenyl)-γ-valerolactone and 4-hydroxy-5-(3',4'-dihydroxyphenyl)-valeric acid, and of several phenolic acids, including 3-(3,4-dihydroxyphenyl)-propionic acid, 3,4-dihydroxyphenylacetic acid, 4-hydroxymandelic acid, and gallic acid.

When comparing the effect of grape-seed and cranberry extracts on the growth of lactic acid bacteria pure cultures, a higher reduction in growth parameters was detected after incubation with grape-seed extract compared to cranberry extract [111,112]. These findings demonstrated that procyanidin B2 (B-type linkage) has a higher inhibitory capacity than procyanidin A2 (A-type linkage). Interestingly, *Lactobacillus plantarum* cleaved the heterocyclic ring of monomeric flavan-3-ols, originating 1-(3',4'-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)propan-2-ol. This activity was exhibited by a few human intestinal bacteria only.

In vitro fermentation of grape-seed extracts with different flavon-3-ol compositions showed an increase in the growth of *Lactobacillus* spp. and a decrease in the *Clostridium hystolyticum* group [110]. A recent study reported that the extraction and *in vitro* fermentation of polyphenols from grape seeds resulted in a significant increase in the numbers of *Bifidobacterium* and *Lactobacillus* spp. as well as an inhibition of the growth of the *Clostridium histolyticum* group and the *Bacteroides-Prevotella* group [113]. Raisins contain flavonols (such as quercetin and kaempferol) and phenolic acids (such as caftaric and coutaric acid) [97]. In 2010, Williamson and Carughi [35] reported that raisins are richer in certain acids, such as protocatechuic and oxidized cinnamic acids, than their hydrated counterparts. A recent study reported that polyphenols contained in red wine altered the intestinal *Bacteroidetes/Firmicutes* balance and significantly increased the concentration of *Firmicutes* and *Bacteroidetes* found in stool samples [114]. Polyphenol consumption resulted in no discernable effect on *Lactobacillus* spp. abundance. In addition, raisins are known to contain significant amounts (2.0–3.5 g/100 g) of tartaric acid (TA), which in and of itself could influence the composition of the colonic microbiome. A study demonstrated that the inclusion of TA in the diet has a positive impact on colonic health; the work compared the effect of a low-fiber, grape-free diet to one including either 120 g of sun-dried raisins or 5 g cream of tartar (roughly equivalent to the amount of TA in the raisins) on intestinal function in healthy adults [115]. The authors found that both diets effectively minimized intestinal transit time. Unlike other fruit acids (e.g., malic and citric acids), TA is not absorbed in the small intestine and is fermented by colonic bacteria into short-chain fatty acids. As was discussed above, these acids play a significant role in maintaining colonic well-being.

15.8 Conclusion

Dried fruits provide a broad range of nutrients and health-promoting bioactive compounds. However, few studies using dried fruits qualitatively and/or

quantitatively describe their uptake into the body and bioavailability. Simple sugars are well absorbed, but the more compact food matrix and concentration of fiber, a result of the drying process, may impact absorption rate and therefore lower the GI. Studies using simulated *in vitro* gastrointestinal tract digestion models indicate that there is a limited absorption of phytochemicals from dried fruits after intestinal digestion. It has been postulated that unabsorbed phytochemicals may be active in the digestive tract, rather than systemically. As the digestive tract is a major organ involved in the immune response, effects within it may still contribute to its overall health indirectly, but significantly. Reaching the colon, phytochemicals are metabolized by gut microbiota to form a wide range of bioactive metabolites. Some of these could be responsible for health benefits attributed to the parent compound. Measuring nutrient bioavailability from dried fruits is an open area of investigation. More research should be conducted on dried fruits to determine metabolites of bioactive compounds after urinary excretion, and to compare metabolite excretion after ingestion of dried fruits to fresh fruit counterparts. Studies of bioaccessibility using *in vitro* gastrointestinal tract models cannot directly mimic the *in vivo* absorption process but are important mechanistic approaches. This research is critical to demonstrate the significance of these compounds present in dried fruits for disease prevention and maintaining optimal health.

References

1. Fernandez-Garcia, E., Carvajal-Lerida, I., and Perez-Galvez, A., *In vitro* bioaccessibility assessment as a prediction tool of nutritional efficiency. *Nutr. Res.*, 29, 751–760, 2009.
2. Palafox-Carlos, H., Ayala-Zavala, J.F., and Gonzalez-Aguilar, G.A., The role of dietary fiber in the bioaccessibility and bioavailability of fruit and vegetable antioxidants. *J. Food Sci.*, 76, R6–R15, 2011.
3. Holst, B., and Williamson, G., Nutrients and phytochemicals: From bioavailability to bioefficacy beyond antioxidants. *Curr. Opin. Biotechnol.*, 19, 73–82, 2008.
4. Jenkins, D.J., Wolever, T.M., Taylor, R.H., Barker, H., Fielden, H., Baldwin, J.M., Bowling, A.C. et al., Glycemic index of foods: A physiological basis for carbohydrate exchange. *Am. J. Clin. Nutr.*, 34, 362–366, 1981.
5. Crapo, P.A., Kolterman, O.G., and Olefsky, J.M., Effects of oral fructose in normal, diabetic, and impaired glucose tolerance subjects. *Diabetes Care*, 3, 575–581, 1980.
6. Livesey, G., Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. *Nutr. Res. Rev.*, 16, 163–191, 2003.
7. Miller, J.B., Pang, E., and Broomhead, L., The glycaemic index of foods containing sugars: Comparison of foods with naturally-occurring *versus* added sugars. *Br. J. Nutr.*, 73, 613–623, 1995.
8. Wilson, T., Anderson, J.A., Andersen, K.F., Heimerman, R.A., Larson, M.M., Freeman, M.R., Baker, S.E. et al., Glycemic response of type 2 diabetics to raisins. *Food Nutr. Sci.*, 3, 1162–1166, 2012.
9. Anderson, J.A., Huth, H.A., Larson, M.M., Colby, A.J., and Wilson, T.A., Glycemic and insulin response to raisins, grapes and bananas in college aged students. *FASEB J.*, 25, 587–584, 2011.

10. Langkilde, A.M., Andersson, H., Schweizer, T.F., and Wursch, P., Digestion and absorption of sorbitol, maltitol and isomalt from the small bowel: A study in ileostomy subjects. *Eur. J. Clin. Nutr.*, 48, 768–775, 1994.
11. Beaugerie, L., Flourie, B., Marteau, P., Pellier, P., Franchisseur, C., and Rambaud, J.C., Digestion and absorption in the human intestine of three sugar alcohols. *Gastroenterology*, 99, 717–723, 1990.
12. Livesey, G., The energy values of dietary fibre and sugar alcohols for man. *Nutr. Res. Rev.*, 5, 61–84, 1992.
13. Beaugerie, L., Lemann, M., Jian, R., Flourie, B., Rain, J.D., and Rambaud, J.C., Effect of glucose and lipids on intestinal absorption of sorbitol: Role of gastric emptying. *Neurogastroenterol. Motil.*, 8, 235–239, 1996.
14. Wilson, T.H., and Landau, B.R., Specificity of sugar transport by the intestine of the hamster. *Am. J. Physiol.*, 198, 99–102, 1960.
15. Santos, P.H.S., and Silva, M.A., Retention of vitamin C in drying processes of fruits and vegetables—A review. *Dry. Technol.*, 26, 1421–1437, 2008.
16. Mangels, A.R., Block, G., Frey, C.M., Patterson, B.H., Taylor, P.R., Norkus, E.P., and Levander, O.A., The bioavailability to humans of ascorbic acid from oranges, orange juice and cooked broccoli is similar to that of synthetic ascorbic acid. *J. Nutr.*, 123, 1054–1061, 1993.
17. Booth, S.L., and Suttie, J.W., Dietary intake and adequacy of vitamin K. *J. Nutr.*, 128, 785–788, 1998.
18. Gijsbers, B.L.M.G., Jie, K.-S.G., and Vermeer, C., Effect of food composition on vitamin K absorption in human volunteers. *Br. J. Nutr.*, 76, 223–229, 1996.
19. Holbrook, J.T., Patterson, K.Y., Bodner, J.E., Douglas, L.W., Veillon, C., Kelsay, J.L., Mertz, W. et al., Sodium and potassium intake and balance in adults consuming self-selected diets. *Am. J. Clin. Nutr.*, 40, 786–793, 1984.
20. Yang, Q.H., Liu, T.B., Kuklina, E.V., Flanders, W.D., Hong, Y.L., Gillespie, C., Chang, M.H. et al., Sodium and potassium intake and mortality among us adults: Prospective data from the third national health and nutrition examination survey. *Arch. Intern. Med.*, 171, 1183–1191, 2011.
21. Yeung, C.K., Glahn, R.P., Wu, X., Liu, R.H., and Miller, D.D., *In vitro* iron bioavailability and antioxidant activity of raisins. *J. Food Sci.*, 68, 701–705, 2003.
22. Tuntawiroon, M., Sritongkul, N., Brune, M., Rossander-Hulten, L., Pleehachinda, R., Suwanik, R., and Hallberg, L., Dose-dependent inhibitory effect of phenolic compounds in foods on nonheme-iron absorption in men. *Am. J. Clin. Nutr.*, 53, 554–557, 1991.
23. Yonekura, L., and Nagao, A., Intestinal absorption of dietary carotenoids. *Mol. Nutr. Food Res.*, 51, 107–115, 2007.
24. Cervantes-Paz, B., Victoria-Campos, C.I., and de Jesús Ornelas-Paz, J., Absorption of carotenoids and mechanisms involved in their health-related properties, in *Carotenoids in Nature*, Stange, C., Ed., Springer, Berlin, Germany, 2016, pp. 415–454.
25. Priyadarshani, A.M., A review on factors influencing bioaccessibility and bioefficacy of carotenoids. *Crit. Rev. Food Sci. Nutr.*, 57, 1710–1717, 2017.
26. Alasalvar, C., and Shahadi, F., Composition, phytochemicals, and beneficial health effects of dried fruits: An overview, in *Dried Fruits, Phytochemicals and Health Effects*., Alasalvar, C., and Shahadi, F., Eds., Wiley-Blackwell, Oxford, UK, 2013, pp. 1–18.
27. Gouado, I., Schweigert, F.J., Ejoh, R.A., Tchouanguep, M.F., and Camp, J.V., Systemic levels of carotenoids from mangoes and papaya consumed in three forms (juice, fresh, and dry slice). *Eur. J. Clin. Nutr.*, 61, 1180–1188, 2007.

28. Chang, S.K., Alasalvar, C., and Shahidi, F., Review of dried fruits: Phytochemicals, antioxidant efficacies, and health benefits. *J. Funct. Foods*, 21, 113–132, 2016.
29. Fratianni, A., Albanese, D., Mignogna, R., Cinquanta, L., Panfili, G., and Di Matteo, M., Degradation of carotenoids in apricot (*Prunus armeniaca* L.) during drying process. *Plant Foods Hum. Nutr.*, 68, 241–246, 2013.
30. Schweiggert, R.M., and Carle, R., Carotenoid deposition in plant and animal foods and its impact on bioavailability. *Crit. Rev. Food Sci. Nutr.*, 57, 1807–1830, 2017.
31. Rodriguez-Roque, M.J., de Ancos, B., Sanchez-Vega, R., Sanchez-Moreno, C., Cano, M.P., Elez-Martinez, P., and Martin-Belloso, O., Food matrix and processing influence on carotenoid bioaccessibility and lipophilic antioxidant activity of fruit juice-based beverages. *Food Funct.*, 7, 380–389, 2016.
32. Bohn, T., Bioavailability of non-provitamin A carotenoids. *Curr. Nutr. Food Sci.*, 4, 240–258, 2008.
33. Jeffery, J.L., Turner, N.D., and King, S.R., Carotenoid bioaccessibility from nine raw carotenoid-storing fruits and vegetables using an *in vitro* model. *J. Sci. Food Agric.*, 92, 2603–2610, 2012.
34. Fraga, C.G., Galleano, M., Verstraeten, S.V., and Oteiza, P.I., Basic biochemical mechanisms behind the health benefits of polyphenols. *Mol. Aspects Med.*, 31, 435–445, 2010.
35. Williamson, G., and Carughi, A., Polyphenol content and health benefits of raisins. *Nutr. Res.*, 30, 511–519, 2010.
36. Kundu, J.K., and Surh, Y.-J. Cancer chemopreventive effects of selected dried fruits, in *Dried Fruits, Phytochemicals and Health Effects*, Alasalvar, C., and Shahadi, F., Eds., Wiley-Blackwell, Oxford, UK, 2013, pp. 19–51.
37. Ishiwata, K., Yamaguchi, T., Takamura, H., and Matoba, T., DPPH radical-scavenging activity and polyphenol content in dried fruits. *Food Sci. Technol. Res.*, 10, 152–156, 2007.
38. Cermak, R., Durazzo, A., Maiani, G., Bohm, V., Kammerer, D.R., Carle, R., Wiczkowski, W. et al., The influence of postharvest processing and storage of foodstuffs on the bioavailability of flavonoids and phenolic acids. *Mol. Nutr. Food Res.*, 53(Suppl. 2), S184–S193, 2009.
39. Bennett, L.E., Jegasothy, H., Konczak, I., Frank, D., Sudharmarajan, S., and Clingeleffer, P.R., Total polyphenolics and anti-oxidant properties of selected dried fruits and relationships to drying conditions. *J. Funct. Foods*, 3, 115–124, 2011.
40. Bohn, T., Dietary factors affecting polyphenol bioavailability. *Nutr. Rev.*, 72, 429–452, 2014.
41. Manach, C., Williamson, G., Morand, C., Scalbert, A., and Remesy, C., Bioavailability and bioefficacy of polyphenols in humans: I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.*, 81(Suppl. 1), 230S–242S, 2005.
42. Scholz, S., and Williamson, G., Interactions affecting the bioavailability of dietary polyphenols *in vivo*. *Int. J. Vitam. Nutr. Res.*, 77, 224–235, 2007.
43. Saura-Calixto, F., Serrano, J., and Goni, I., Intake and bioaccessibility of total polyphenols in a whole diet. *Food Chem.*, 101, 492–501, 2007.
44. Tagliazucchi, D., Verzelloni, E., Bertolini, D., and Conte, A., *In vitro* bio-accessibility and antioxidant activity of grape polyphenols. *Food Chem.*, 120, 599–606, 2010.
45. Bouayed, J., Hoffmann, L., and Bohn, T., Total phenolics, flavonoids, anthocyanins and antioxidant activity following simulated gastro-intestinal digestion

and dialysis of apple varieties: Bioaccessibility and potential uptake. *Food Chem.*, 128, 14–21, 2011.
46. Kamiloglu, S., and Capanoglu, E., Investigating the *in vitro* bioaccessibility of polyphenols in fresh and sun-dried figs (*Ficus carica* L.). *Int. J. Food Sci. Technol.*, 48, 2621–2629, 2013.
47. Matsumura, Y., Ito, T., Yano, H., Kita, E., Mikasa, K., Shibata, M., Nishii, Y. et al., Antioxidant potential in non-extractable fractions of dried persimmon. *Food Chem.*, 202, 99–103, 2016.
48. Kamiloglu, S., Pasli, A.A., Ozcelik, B., and Capanoglu, E., Evaluating the *in vitro* bioaccessibility of phenolics and antioxidant activity during consumption of dried fruits with nuts. *LWT—Food Sci. Technol.*, 56, 284–289, 2014.
49. Zhao, G., Zhang, R., Liu, L., Deng, Y., Wei, Z., Zhang, Y., Ma, Y. et al., Different thermal drying methods affect the phenolic profiles, their bioaccessibility and antioxidant activity in *Rhodomyrtus tomentosa* (Ait.) Hassk berries. *LWT—Food Sci. Technol.*, 79, 260–266, 2017.
50. Cremin, P., Kasim-Karakas, S., and Waterhouse, A.L., LC/ES-MS detection of hydroxycinnamates in human plasma and urine. *J. Agric. Food Chem.*, 49, 1747–1750, 2001.
51. Stacewicz-Sapuntzakis, M., Dried plums and their products: Composition and health effects – An updated review. *Crit. Rev. Food Sci. Nutr.*, 53, 1277–1302, 2013.
52. Kanellos, P.T., Kaliora, A.C., Gioxari, A., Christopoulou, G.O., Kalogeropoulos, N., and Karathanos, V.T., Absorption and bioavailability of antioxidant phytochemicals and increase of serum oxidation resistance in healthy subjects following supplementation with raisins. *Plant Foods Hum. Nutr.*, 68, 411–415, 2013.
53. Carughi, A., Murphy, D., and Williamson, G., Polyphenols from raisins have similar bioavailability to those from grapes and white wine: A human intervention study. *Ann. Nutr. Metab.*, 62, 14, 2013.
54. Ley, R.E., Peterson, D.A., and Gordon, J.I., Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*, 124, 837–848, 2006.
55. Marchesi, J.R., Human distal gut microbiome. *Environ. Microbiol.*, 13, 3088–3102, 2011.
56. Blumberg, J.B., Basu, A., Krueger, C.G., Lila, M.A., Neto, C.C., Novotny, J.A., Reed, J.D. et al., Impact of cranberries on gut microbiota and cardiometabolic health: Proceedings of the Cranberry Health Research Conference 2015. *Adv. Nutr.*, 7, 759s–770s, 2016.
57. Costabile, A., Santarelli, S., Claus, S.P., Sanderson, J., Hudspith, B.N., Brostoff, J., Ward, J.L. et al., Effect of breadmaking process on *in vitro* gut microbiota parameters in irritable bowel syndrome. *PLoS One*, 9, e111225, 2014.
58. Turnbaugh, P.J., Backhed, F., Fulton, L., and Gordon, J.I., Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe*, 3, 213–223, 2008.
59. Buttó, L.F., and Haller, D., Dysbiosis in intestinal inflammation: Cause or consequence. *Int. J. Med. Microbiol.*, 306, 302–309, 2016.
60. Martinez-Medina, M., Denizot, J., Dreux, N., Robin, F., Billard, E., Bonnet, R., Darfeuille-Michaud, A. et al., Western diet induces dysbiosis with increased *E. coli* in CEABAC10 mice, alters host barrier function favouring AIEC colonisation. *Gut*, 63, 116–124, 2014.
61. Ponnusamy, K., Choi, J.N., Kim, J., Lee, S.-Y., and Lee, C.H., Microbial community and metabolomic comparison of irritable bowel syndrome faeces. *J. Med. Microbiol.*, 60, 817–827, 2011.

62. Martinez-Medina, M., and Garcia-Gil, L.J., *Escherichia coli* in chronic inflammatory bowel diseases: An update on adherent invasive *Escherichia coli* pathogenicity. *World J. Gastrointest. Pathophysiol.*, 5, 213–227, 2014.
63. Tannock, G.W., Analysis of the intestinal microflora: A renaissance, in *Lactic Acid Bacteria: Genetics, Metabolism and Applications*, Konings, W.N., Kuipers, O.P., and Huis. In 't Veld, J.H.J. Eds., Springer, Berlin, Germany, 1999, pp. 265–278.
64. Vaughan, E.E., Schut, F., Heilig, H.G., Zoetendal, E.G., de Vos, W.M., and Akkermans, A.D., A molecular view of the intestinal ecosystem. *Curr. Issues Intest. Microbiol.*, 1, 1–12, 2000.
65. Mai, V., Colbert, L.H., Perkins, S.N., Schatzkin, A., and Hursting, S.D., Intestinal microbiota: A potential diet-responsive prevention target in ApcMin mice. *Mol. Carcinog.*, 46, 42–48, 2007.
66. Zoetendal, E.G., Collier, C.T., Koike, S., Mackie, R.I., and Gaskins, H.R., Molecular ecological analysis of the gastrointestinal microbiota: A review. *J. Nutr.*, 134, 465–472, 2004.
67. Tuohy, K.M., Conterno, L., Gasperotti, M., and Viola, R., Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. *J. Agric Food Chem.*, 60, 8776–8782, 2012.
68. Mandalari, G., Nueno-Palop, C., Bisignano, G., Wickham, M.S., and Narbad, A., Potential prebiotic properties of almond (*Amygdalus communis* L.) seeds. *Appl. Environ. Microbiol.*, 74, 4264–4270, 2008.
69. Mandalari, G., Chessa, S., Bisignano, C., Chan, L., and Carughi, A., The effect of sun-dried raisins (*Vitis vinifera* L.) on the *in vitro* composition of the gut microbiota. *Food Funct.*, 7, 4048–4060, 2016.
70. Gibson, G.R., and Roberfroid, M.B., Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J. Nutr.*, 125, 1401–1412, 1995.
71. Mandalari, G., Nueno Palop, C., Tuohy, K., Gibson, G.R., Bennett, R.N., Waldron, K.W., Bisignano, G. et al., *In vitro* evaluation of the prebiotic activity of a pectic oligosaccharide-rich extract enzymatically derived from bergamot peel. *Appl. Microbiol. Biotechnol.*, 73, 1173–1179, 2007.
72. Filocamo, A., Bisignano, C., Mandalari, G., and Navarra, M., *In vitro* antimicrobial activity and effect on biofilm production of a white grape juice (*Vitis vinifera*) extract. *Evid. Based Complement. Alternat. Med.*, 856243, 2015.
73. Costabile, A., Klinder, A., Fava, F., Napolitano, A., Fogliano, V., Leonard, C., Gibson, G.R. et al., Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: A double-blind, placebo-controlled, crossover study. *Br. J. Nutr.*, 99, 110–120, 2008.
74. Carughi, A., Raisins as a source of prebiotic compounds in the diet. *FASEB J.*, 23, 716.719–716.719, 2009.
75. Camire, M.E., and Dougherty, M.P., Raisin dietary fiber composition and *in vitro* bile acid binding. *J. Agric. Food Chem.*, 51, 834–837, 2003.
76. Muir, J.G., Shepherd, S.J., Rosella, O., Rose, R., Barrett, J.S., and Gibson, P.R., Fructan and free fructose content of common Australian vegetables and fruit. *J. Agric. Food Chem.*, 55, 6619–6627, 2007.
77. Wijayabahu, A., Waugh, S., Ukhanova, M., Carughi, A., and Mai, V., Effect of sun-dried raisins consumption on fecal microbiota composition. *FASEB J.*, 31, 965–967, 2017.
78. Liu, W., Zhao, S., Wang, J., Shi, J., Sun, Y., Wang, W., Ning, G. et al., Grape seed proanthocyanidin extract ameliorates inflammation and adiposity by modulating gut microbiota in high-fat diet mice. *Mol. Nutr. Food Res.*, 61, 1601082, 2017.

79. Collins, B., Hoffman, J., Martinez, K., Grace, M., Lila, M.A., Cockrell, C., Nadimpalli, A. et al., A polyphenol-rich fraction obtained from table grapes decreases adiposity, insulin resistance and markers of inflammation and impacts gut microbiota in high-fat-fed mice. *J. Nutr. Biochem.*, 31, 150–165, 2016.
80. Kim, H., Kim, D.-H., Seo, K.-H., Chon, J.-W., Nah, S.-Y., Bartley, G.E., Arvik, T. et al., Modulation of the intestinal microbiota is associated with lower plasma cholesterol and weight gain in hamsters fed chardonnay grape seed flour. *J. Agric. Food Chem.*, 63, 1460–1467, 2015.
81. Eid, N., Enani, S., Walton, G., Corona, G., Costabile, A., Gibson, G., Rowland, I. et al., The impact of date palm fruits and their component polyphenols, on gut microbial ecology, bacterial metabolites and colon cancer cell proliferation. *J. Nutr. Sci.*, 3, e46, 2014.
82. Eid, N., Osmanova, H., Natchez, C., Walton, G., Costabile, A., Gibson, G., Rowland, I. et al., Impact of palm date consumption on microbiota growth and large intestinal health: A randomised, controlled, cross-over, human intervention study. *Br. J. Nutr.*, 114, 1226–1236, 2015.
83. Feliciano, R.P., Krueger, C.G., and Reed, J.D., Methods to determine effects of cranberry proanthocyanidins on extraintestinal infections: Relevance for urinary tract health. *Mol. Nutr. Food Res.*, 59, 1292–1306, 2015.
84. Shmuely, H., Ofek, I., Weiss, E.I., Rones, Z., and Houri-Haddad, Y., Cranberry components for the therapy of infectious disease. *Curr. Opin. Biotechnol.*, 23, 148–152, 2012.
85. Zhang, L., Ma, J., Pan, K., Go, V.L., Chen, J., and You, W.C., Efficacy of cranberry juice on *Helicobacter pylori* infection: A double-blind, randomized placebo-controlled trial. *Helicobacter*, 10, 139–145, 2005.
86. Bodet, C., Grenier, D., Chandad, F., Ofek, I., Steinberg, D., and Weiss, E.I., Potential oral health benefits of cranberry. *Crit. Rev. Food Sci. Nutr.*, 48, 672–680, 2008.
87. Gu, X.J., Li, Y.B., Mu, J., and Zhang, Y., A new phenolic glycoside from *Prunella vulgaris*. *Yao Xue Xue Bao*, 46, 561–563, 2011.
88. LaPlante, K.L., Sarkisian, S.A., Woodmansee, S., Rowley, D.C., and Seeram, N.P., Effects of cranberry extracts on growth and biofilm production of *Escherichia coli* and *Staphylococcus* species. *Phytother. Res.*, 26, 1371–1374, 2012.
89. Ulrey, R.K., Barksdale, S.M., Zhou, W., and van Hoek, M.L., Cranberry proanthocyanidins have anti-biofilm properties against *Pseudomonas aeruginosa*. *BMC Complement. Altern. Med.*, 14, 499, 2014.
90. Weiss, E.I., Houri-Haddad, Y., Greenbaum, E., Hochman, N., Ofek, I., and Zakay-Rones, Z., Cranberry juice constituents affect influenza virus adhesion and infectivity. *Antiviral Res.*, 66, 9–12, 2005.
91. Rane, H.S., Bernardo, S.M., Howell, A.B., and Lee, S.A., Cranberry-derived proanthocyanidins prevent formation of *Candida albicans* biofilms in artificial urine through biofilm-and adherence-specific mechanisms. *J. Antimicrob. Chemother.*, 69, 428–436, 2013.
92. Anhe, F.F., Roy, D., Pilon, G., Dudonne, S., Matamoros, S., Varin, T.V., Garofalo, C. et al., A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. *Gut*, 64, 872–883, 2015.
93. Denis, M.C., Desjardins, Y., Furtos, A., Marcil, V., Dudonne, S., Montoudis, A., Garofalo, C. et al., Prevention of oxidative stress, inflammation and

mitochondrial dysfunction in the intestine by different cranberry phenolic fractions. *Clin. Sci. (Lond)*, 128, 197–212, 2015.
94. Chiu, H.F., Huang, Y.C., Lu, Y.Y., Han, Y.C., Shen, Y.C., Golovinskaia, O., Venkatakrishnan, K. et al., Regulatory/modulatory effect of prune essence concentrate on intestinal function and blood lipids. *Pharm. Biol.*, 55, 974–979, 2017.
95. Patrignani, F., Tabanelli, G., Siroli, L., Gardini, F., and Lanciotti, R., Combined effects of high pressure homogenization treatment and citral on microbiological quality of apricot juice. *Int. J. Food Microbiol.*, 160, 273–281, 2013.
96. Pappas, E., and Schaich, K.M., Phytochemicals of cranberries and cranberry products: Characterization, potential health effects, and processing stability. *Crit. Rev. Food Sci. Nutr.*, 49, 741–781, 2009.
97. Karadeniz, F., Durst, R.W., and Wrolstad, R.E., Polyphenolic composition of raisins. *J. Agric. Food Chem.*, 48, 5343–5350, 2000.
98. Clifford, M., Diet-derived phenols in plasma and tissues and their implications for health. *Planta Med.*, 70, 1103–1114, 2004.
99. Clifford, M.N., Chlorogenic acids and other cinnamates–nature, occurrence, dietary burden, absorption and metabolism. *J. Sci. Food Agric.*, 80, 1033–1043, 2000.
100. Manach, C., Scalbert, A., Morand, C., Remesy, C., and Jimenez, L., Polyphenols: Food sources and bioavailability. *Am. J. Clin. Nutr.*, 79, 727–747, 2004.
101. Gonthier, M.P., Verny, M.A., Besson, C., Remesy, C., and Scalbert, A., Chlorogenic acid bioavailability largely depends on its metabolism by the gut microflora in rats. *J. Nutr.*, 133, 1853–1859, 2003.
102. Aura, A.-M., O'Leary, K., Williamson, G., Ojala, M., Bailey, M., Puupponen-Pimiä, R., Nuutila, A. et al., Quercetin derivatives are deconjugated and converted to hydroxyphenylacetic acids but not methylated by human fecal flora *in vitro*. *J. Agric. Food Chem.*, 50, 1725–1730, 2002.
103. Wong, J.M., de Souza, R., Kendall, C.W., Emam, A., and Jenkins, D.J., Colonic health: Fermentation and short chain fatty acids. *J. Clin. Gastroenterol.*, 40, 235–243, 2006.
104. Roy, C.C., Kien, C.L., Bouthillier, L., and Levy, E., Short-chain fatty acids: Ready for prime time? *Nutr. Clin. Pract.*, 21, 351–366, 2006.
105. Guergoletto, K.B., Costabile, A., Flores, G., Garcia, S., and Gibson, G.R., *In vitro* fermentation of jucara pulp (*Euterpe edulis*) by human colonic microbiota. *Food Chem.*, 196, 251–258, 2016.
106. Wang, C.J., Zuo, Y.G., Vinson, J.A., and Deng, Y.W., Absorption and excretion of cranberry-derived phenolics in humans. *Food Chem.*, 132, 1420–1428, 2012.
107. Parkar, S.G., Trower, T.M., and Stevenson, D.E., Fecal microbial metabolism of polyphenols and its effects on human gut microbiota. *Anaerobe*, 23, 12–19, 2013.
108. Sanchez-Patan, F., Barroso, E., van de Wiele, T., Jimenez-Giron, A., Martin-Alvarez, P.J., Moreno-Arribas, M.V., Martinez-Cuesta, M.C. et al., Comparative *in vitro* fermentations of cranberry and grape seed polyphenols with colonic microbiota. *Food Chem.*, 183, 273–282, 2015.
109. Khanal, R., Howard, L.R., and Prior, R.L., Urinary excretion of phenolic acids in rats fed cranberry, blueberry, or black raspberry powder. *J. Agric. Food Chem.*, 62, 3987–3996, 2014.
110. Cueva, C., Sanchez-Patan, F., Monagas, M., Walton, G.E., Gibson, G.R., Martin-Alvarez, P.J., Bartolome, B. et al., *In vitro* fermentation of grape seed flavan-3-ol

fractions by human faecal microbiota: Changes in microbial groups and phenolic metabolites. *FEMS Microbiol. Ecol.*, 83, 792–805, 2013.
111. Sánchez-Patán, F., Tabasco, R., Monagas, M.A., Requena, T., Peláez, C., Moreno-Arribas, M.V., and Bartolomé, B.A., Capability of *Lactobacillus plantarum* IFPL935 to catabolize flavan-3-ol compounds and complex phenolic extracts. *J. Agric. Food Chem.*, 60, 7142–7151, 2012.
112. Tabasco, R., Sanchez-Patan, F., Monagas, M., Bartolome, B., Victoria Moreno-Arribas, M., Pelaez, C., and Requena, T., Effect of grape polyphenols on lactic acid bacteria and bifidobacteria growth: Resistance and metabolism. *Food Microbiol.*, 28, 1345–1352, 2011.
113. Zhou, L., Wang, W., Huang, J., Ding, Y., Pan, Z., Zhao, Y., Zhang, R. et al., *In vitro* extraction and fermentation of polyphenols from grape seeds (*Vitis vinifera*) by human intestinal microbiota. *Food Funct.*, 7, 1959–1967, 2016.
114. Queipo-Ortuno, M.I., Boto-Ordonez, M., Murri, M., Gomez-Zumaquero, J.M., Clemente-Postigo, M., Estruch, R., Cardona Diaz, F. et al., Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *Am. J. Clin. Nutr.*, 95, 1323–1334, 2012.
115. Spiller, G.A., Story, J.A., Furumoto, E.J., Chezem, J.C., and Spiller, M., Effect of tartaric acid and dietary fibre from sun-dried raisins on colonic function and on bile acid and volatile fatty acid excretion in healthy adults. *Br. J. Nutr.*, 90, 803–807, 2003.
116. U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Release 28, 2016. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed April 1, 2019).
117. Yao, C., Tan, H.L., Langenberg, D., Barrett, J., Rose, R., Liels, K., Gibson, P. et al., Dietary sorbitol and mannitol: Food content and distinct absorption patterns between healthy individuals and patients with irritable bowel syndrome. *J. Hum. Nutr. Diet.*, 27, 263–275, 2014.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 16

Effect of Dried Fruits on Lipid Profiles (Dose–Response, Effects on Different Groups and Different Dried Fruits, and Cardiovascular Diseases)

Chelsea Garcia and Christopher N. Blesso

16.1 Introduction 397
16.2 Health Effects of Dried Fruits 399
16.2.1 Pre-Clinical Evidence of Effects on Serum Lipid and Lipoprotein Profiles 399
16.2.2 Clinical Evidence for Effects on Serum Lipid and Lipoprotein Profiles 403
16.3 Conclusion 408
References 409

16.1 Introduction

Coronary heart disease (CHD) continues to be the largest cause of death in the United States, contributing to over 600,000 deaths per year, which is more than all forms of cancer combined [1]. Atherosclerosis, a key contributor to CHD, is characterized by the hardening and thickening of the artery wall caused by an

accumulation of fatty plaques [2]. Atherosclerosis is considered to be not only an inflammatory disease characterized by infiltration of immune cells, but also a lipid disorder. The accumulations of lipids from plasma-derived lipoproteins, such as low-density lipoprotein-cholesterol (LDL-C), are major contributors to plaque development [2]. Oxidized lipids can accumulate in macrophages residing in the sub-endothelial layer of the artery wall, forming foam cells and contributing to lesion formation [2]. Therefore, managing blood lipid levels is recommended as a primary prevention strategy [3]. Elevated serum concentrations of total cholesterol (TC), triacylglycerols (TAG), and especially LDL-C are well-known to increase the development of CHD [3]. As a result, LDL-C is a primary target of therapy for CHD prevention [3]. In contrast, low concentrations of high-density lipoprotein-cholesterol (HDL-C) are associated with worse CHD outcomes and may explain, in part, the residual risk of patients with well-controlled LDL-C [4]. The main function of HDL that is thought to be responsible for its protective function is its critical role in reverse cholesterol transport. Based on epidemiological data, a 1 mg/dL increase in HDL-C is predicted to result in a 2–3% decrease in CHD risk [5]. Lifestyle modifications, such as changing dietary habits, are recommended as the first strategy in the management of abnormal serum lipid profiles [3]. Dietary fat and cholesterol are widely recognized to influence fasting plasma lipids [6,7]. Saturated fats appear to be the major dietary component responsible for the elevated serum cholesterol associated with Western diets [7,8]. Pharmacological agents, such as statins, efficiently reduce plasma LDL-C and lower CHD risk; however, as with most drugs, undesirable side effects may occur. Therefore, it is important to consider how foods, such as dried fruits, may influence serum lipid profiles.

The 2015–2020 Dietary Guidelines for Americans [9] recommends the consumption of a variety of fruits, including dried fruits, as part of a healthy eating pattern. Traditional methods of dehydrating fruits include sun-drying and air-drying to prevent spoilage and preserve the quality of the food [10]. More modern methods of drying, such as freeze-drying, have also been used to better preserve the nutritional and sensory qualities of fruits [10]. It is estimated that approximately 7% of the US adult population regularly consumes dried fruits [11]. Considering that the consumption of fruits has been shown to reduce the risk of CHD by 7% for each additional portion of fruit per day, dried fruits may be incorporated into dietary patterns as convenient snacks or consumed with meals to meet dietary recommendations [12]. The consumption of dried fruits was associated with improvements in diet quality and reductions in body weight, body mass index, and waist circumference based on data from the National Health and Nutrition Examination Survey [11]. Dried fruits provide a variety of nutrients and natural bioactive compounds which may improve serum lipid profiles and thus lower CHD risk. The intake of dietary fiber from fruits has been shown to be inversely associated with cardiovascular disease (CVD) and CHD risk [13]. Soluble fiber in fruits may lower serum cholesterol through binding with bile acids in the intestinal tract, thereby inhibiting their reabsorption and promoting cholesterol catabolism to bile acids [14]. Soluble fiber may also be fermented in the gut to produce short-chain fatty acids, some of which have been shown to regulate hepatic lipid metabolism [14]. The intake of soluble fibers, including pectin, is associated with reductions in plasma TC and LDL-C concentrations, without changes of HDL-C or TAG [15]. Dried fruits also contain small amounts of phytosterols [16], which have positive effects on serum cholesterol. Phytosterols are compounds of the sterol lipid class that include both plant sterols

and plant stanols, and are found in any food of plant origin. These sterol compounds have cholesterol-lowering properties, especially seen in LDL-C concentrations, as they reduce the intestinal absorption of cholesterol [17]. In addition, the various flavonoids found in dried fruits are bioactive components that may influence lipid metabolism [18]. The consumption of flavonoids has shown to be protective against CVD in observational studies [19]. Based on the variety of components in dried fruits that may impact lipid metabolism, the purpose of this chapter is to summarize pre-clinical and clinical research data investigating the effects of consuming dried fruits on lipid profiles.

16.2 Health Effects of Dried Fruits

16.2.1 Pre-Clinical Evidence of Effects on Serum Lipid and Lipoprotein Profiles

There is considerable evidence in animal studies for the improvement of serum and hepatic lipid profiles with the consumption of various dried fruits (Table 16.1). Freeze-dried apples have been shown to have a significant effect on the lipid profiles of Wistar and Zucker rats, particularly under hyperlipidemic conditions. Three studies [20–22] have shown that freeze-dried apples notably decrease plasma cholesterol in male Wistar rats and obese Zucker rats. Aprikian et al. [20] analyzed the effects of lyophilized Gala apples in male Wistar rats. The rats were fed either a diet containing 15% (w/w) lyophilized Gala apple or a control diet matched in carbohydrates and sugar content. After 3 weeks, plasma cholesterol was lowered by 9.3% in rats fed the apple diet compared with control rats. However, the Gala apple diet did not alter the liver cholesterol content or TAG concentrations in the experimental animals. Similarly, Aprikian et al. [21] found in a second study that a 20% (w/w) lyophilized apple diet had similar effects on plasma cholesterol in obese Zucker rats. The rats were either fed a control diet containing 0.25% (w/w) cholesterol or the same diet containing the lyophilized apple for 3 weeks. Plasma TC and LDL-C concentrations were reduced in the apple-fed obese rats compared with control obese rats. Liver TAG accumulation was also reduced by 50% in the obese rats fed the apple diet. However, in the same study, the same dosage of freeze-dried apples did not impact plasma or liver lipid profiles in lean rats. One other study tested the effects of a 10% (w/w) lyophilized apple diet on male Wistar rats over the course of 4 weeks [22]. Plasma cholesterol concentrations were reduced by 20% in apple-fed rats compared with a control group fed a high-cholesterol diet. Liver cholesterol content was reduced by 30% in apple-fed rats compared with control rats. It is important to note that reductions in plasma cholesterol were most pronounced during hyperlipidemic conditions. Two out of the three animal studies conducted with dried apples revealed comparable effects on liver lipids under hyperlipidemic conditions [21,22].

Besides apples, other commonly consumed dried fruits have shown the potential to modify lipid metabolism in animal studies. Consumption of prunes, peaches, pears, or figs by rodents have all been demonstrated to positively affect plasma and hepatic lipid profiles. Lucas et al. [23] studied the effects of prune supplementation on serum and liver lipid profiles in ovariectomized (OVX) female rats. OVX rats were fed a control diet or diets containing either 5% (w/w) or 25% (w/w) prunes for

Table 16.1 Effects of Dried Fruits on Serum Lipids in Animal Studies

Fruit	*Model*	*Duration*	*Study Design*	*Results*	*References*
Prunes	Ovariectomy-induced hypercholesterolemic rats (*n* = 12 per group)	45 days	Sham operation + control diet* OVX + control diet OVX + 5% prunes OVX + 25% prunes *All diets matched for caloric density, macronutrient profiles, and fiber.	OVX + 25% prunes *vs* OVX: ↓ Serum TC, serum non-HDL-C, and total liver lipids ↔ Serum TAG OVX + 5% prunes *vs* OVX: ↔ Serum or liver lipids	[23]
Gala apples	Male Wistar rats (*n* = 12 per group)	3 weeks	Control# 15% Lyophilized Gala apple diet #All diets matched in carbohydrate and sugar content.	Apple diet *vs* control: ↓ Plasma TC ↔ Plasma & liver TAG and liver TC ↓ Lipoprotein cholesterol corresponding to apoB-lipoprotein fractions ↑ HDL density range and HDL-C: TGRLP-C ratio	[20]
Apples	Lean and obese Zucker rats (*n* = 8 per group)	3 weeks	Lean Zucker rats + control diet¥ Obese Zucker rats + control diet Lean Zucker rats + 20% lyophilized apple diet Obese Zucker rats + 20% lyophilized apple diet ¥All diets matched in carbohydrate and sugar content.	Obese Zucker rats + 20% lyophilized apple diet *vs* Obese Zucker rats + control diet: ↓ Plasma TC, liver TAG, heart TAG, LDL-C fraction, HDL-C fraction, and LDL/HDL ratio Lean Zucker rats + 20% lyophilized apple diet *vs* Lean Zucker rats + control diet: ↔ Plasma TC, TAG, FFA, liver TC, liver TAG, heart TC, and heart TAG	[21]

(*Continued*)

Table 16.1 (Continued) Effects of Dried Fruits on Serum Lipids in Animal Studies

Fruit	*Model*	*Duration*	*Study Design*	*Results*	*References*
Apples, peaches, and pears	Male Wistar rats (*n* = 10 per group)	4 weeks	Control diet HCD 10% apple diet HCD + 10% apples 10% pear diet HCD + 10% pears 10% peach diet HCD + 10% peaches	HCD + 10% apples, HCD + 10% pears, and HCD + 10% peaches *vs* HCD: ↓ Plasma TC, LDL-C, TAG, liver TC, and total plasma phospholipids ↑ HDL-phospholipids 10% apple diet, 10% pear diet, and10% peach diet *vs* control: ↔ TC, LDL-C, TAG, and liver TC	[22]
Freeze-dried cranberry powder	Male Sprague Dawley rats (*n* = 7 per group)	6 weeks	Control diet HCD HCD + 2% FDCP HCD + 5% FDCP	HCD + 2% FDCP and HCD + 5% FDCP *vs* HCD: ↔ Serum TC, LDL-C, and HDL-C/LDL-C ratio HCD + 5% FDCP *vs* HCD: ↑ HDL-C	[26]
Plums	Apolipoprotein E-deficient mice (*n* = 12 per group)	5 months	Control diet[c] HCD HCD + 4.75% dried plum powder HCD + 9.5% dried plum powder [c]All diets matched for moisture, protein, carbohydrate, fat, total dietary fiber, and total energy.	HCD + 4.75% dried plum powder *vs* HCD: ↔ Fasting or non-fasting TC except modest decrease in non-fasting TC at 15 weeks ↔ Aortic arch lesions (by Oil Red O staining) HCD + 9.5% dried plum powder *vs* HCD: ↓ Aortic arch lesions (by Oil Red O staining) ↔ Serum cholesterol	[25]

(*Continued*)

Table 16.1 (Continued) Effects of Dried Fruits on Serum Lipids in Animal Studies

Fruit	*Model*	*Duration*	*Study Design*	*Results*	*References*
Figs	Male albino rats (*n* = 7 per group)	6 weeks	HCD HCD + 3% dried figs HCD + 5% dried figs HCD + 3% sycamore HCD + 5% sycamore	HCD + 3% dried figs, HCD + 5% dried figs, HCD + 3% sycamore, and HCD + 5% sycamore *vs* HCD: ↓ Plasma TC, TAG, VLDL-C, LDL-C, and LDL/HDL-C ↑ HDL-C	[24]

Abbreviations: apoB, apolipoprotein B; HCD, high cholesterol diet; FDCP, freeze-dried cranberry powder; FFA, free fatty acids; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; OVX, ovariectomized; TAG, triacylglycerols; TC, total cholesterol; TGRLP-C, triglyceride-rich lipoprotein-cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

45 days. At the end of the study, rats fed the high-dose prune diet had decreased serum TAC, specifically lower non-HDL-C, as well as a reduction in total liver lipids. However, the rats fed the lower dose had no significant differences in serum or hepatic lipids compared with OVX control rats. In a study conducted by Leontowicz et al. [22], male Wistar rats were fed either a control diet, a high-cholesterol diet, 10% (w/w) lyophilized peach/pear diets, or 10% (w/w) lyophilized peach/pear diets with added cholesterol for 4 weeks. In rats fed the peach or pear diets containing 1% (w/w) non-oxidized cholesterol, plasma TC, LDL-C, TAG, liver cholesterol, and plasma phospholipids were reduced, while HDL-phospholipids increased compared with the high cholesterol control group. In contrast, the rats that were fed the peach or pear diets without added cholesterol did not have significantly altered serum or liver lipids compared with control rats.

In addition, Mahmoud et al. [24] fed male albino rats five different diets for 6 weeks in order to analyze the effects on lipid metabolism. The diets included 3% (w/w) low and 5% (w/w) high doses of dried figs, 3% low and 5% high doses of sycamore figs, and a control diet, all containing 2% (w/w) cholesterol. All rats that were fed the fig and sycamore-containing diets experienced improvements in lipid profiles. Plasma TC, TAG, very-low density lipoprotein-cholesterol (VLDL-C), LDL-C, and LDL-C/HDL-C ratio decreased, while HDL-C increased in all fruit groups compared with the high-cholesterol diet. However, other dried fruits, such as dried plums and cranberries, have had minimal effects on lipid profiles in rodents.

Gallaher and Gallaher [25] used apolipoprotein E (apoE)-deficient mice as a model to determine the effects of dried plum powder on lipid profiles and atherosclerosis. Mice were fed a 0.15% (w/w) cholesterol diet, or the same diet containing either 4.75% (w/w) or 9.5% (w/w) dried plum powder, for 5 months. Blood cholesterol was not affected by either of the diets, except for a slight decrease in non-fasting plasma TC at week 15 in the group of mice fed the high-dose plum diet. Interestingly, it was the lower dose plum diet, not the higher dose, which significantly reduced atherosclerotic lesion area, despite no changes in serum lipids.

Kim et al. [26] evaluated the effects of freeze-dried cranberry powder on male Sprague-Dawley rats for 6 weeks. Rats were fed a control, a 2% (w/w) low dose, or a 5% (w/w) high dose cranberry diets, each containing 1% (w/w) cholesterol. Neither the low dose nor high dose of cranberry had any effect on serum TC, LDL-C, or the HDL-C/LDL-C ratio. However, serum HDL-C increased significantly in the group of rats fed the high-dose cranberry diet, suggesting that freeze-dried cranberries had a modest but positive effect on the serum lipid profiles.

Overall, various dried fruits have been shown to improve serum and hepatic lipid profiles in rodent models. However, while there is strong evidence of lipid-lowering effects with dried fruit in pre-clinical studies, benefits seen in animal studies must translate to humans to be of practical significance.

16.2.2 Clinical Evidence for Effects on Serum Lipid and Lipoprotein Profiles

Although there is evidence for improvements in lipid profiles with dried fruit consumption in animal studies, findings in human studies have not been as strong (Table 16.2). This is possibly related to the much lower dosages that are used in clinical studies. Raisins have been the most commonly studied dried fruit in human

Table 16.2 Effects of Dried Fruits on Serum Lipids in Human Clinical Trials

Fruit	*Model*	*Duration*	*Study Design*	*Results*	*References*
Freeze-dried grape polyphenol powder	Pre- (mean age 40 years) and post-menopausal (mean age 58 years) women (n = 44)	4 weeks crossover with 3 weeks washout	Placebo* 36 g/day grape powder *Designed to match the grape powder in terms of look, feel, taste, and macronutrients but without any polyphenols.	36 g/day grape powder *vs* placebo: ↓ LDL-C, TAG, apoB, apoE, and CETP activity ↔ TC, HDL-C, LDL oxidation, and LCAT activity	[31]
Raisins	Men and post-menopausal women (aged 50-70 years)	6 weeks parallel	Walk (n = 12) 1 Cup raisin/day (n = 12) Raisin + walk (n = 10)	Raisin + walk *vs* walk: ↔ TC, HDL-C, LDL-C, and TAG	[27]
Dried California Mission figs	Men and women (aged 30–75 years) with elevated LDL-C levels (n = 88)	5 weeks crossover without washout period	Usual diet for 5 weeks 120 g (12–15) figs paired with 3 daily meals	120 g (12–15) figs paired with 3 daily meals *vs* usual diet for 5 weeks: ↑ TC ↔ LDL-C, HDL-C, and TAG	[36]
Freeze-dried grape polyphenol powder	Men with metabolic syndrome (aged 30–70 years (n = 24)	30 days crossover with 3 weeks washout	Placebo# 46 g/day grape powder #Designed to match the grape powder in terms of look, feel, taste, and macronutrients but without any polyphenols.	46 g/day grape powder *vs* placebo: ↔ Plasma TC, LDL-C, HDL-C, and TAG	[32]
Apples	Post-menopausal women (aged 50–61 years; n = 100)	12 months parallel	100 g/day dried plums-control 75 g/day dried apples	75 g/day dried apples *vs* 100 g/day dried plums-control: ↔ LDL-C, HDL-C, TAG, and HDL/LDL ratio ↓ TC	[37]

(Continued)

Table 16.2 (Continued) Effects of Dried Fruits on Serum Lipids in Human Clinical Trials

Fruit	*Model*	*Duration*	*Study Design*	*Results*	*References*
Freeze-dried strawberries	Men and women (aged 39–59 years) with abdominal adiposity and elevated serum lipids (n = 60)	12 weeks parallel	Low dosage control beverage High dosage control beverage 25 g FDS/day[¥] 50 g FDS/day[¥] [¥]Calorie and fiber matched to respective control.	25 g FDS/day *vs* low dosage control beverage: ↔ TC, LDL-C, HDL-C, VLDL-C, TAG, NMR-VLDL-C, NMR-LDL-C (total, IDL-C, and large small), and NMR-HDL-C 50 g FDS/day *vs* high dosage control beverage: ↓ TC, LDL-C, and NMR-small LDL-C ↔ HDL-C, VLDL-C, and TAG	[39]
Raisins	Men and women (mean age 60 years; n = 46)	12 weeks parallel	Conventional snacks 1 oz (~28.3 g) raisins 3 × before meal	1 oz raisins 3 × before meal *vs* conventional snacks: ↔ TC, LDL-C, and TAG ↓ HDL-C	[28]
Corinthian raisins	Men and post-menopausal women with type-2 diabetes (aged 54–71 years; n = 48)	24 weeks parallel	Usual diet 36 g raisin daily	36 g raisin daily *vs* usual diet: ↔ TC, HDL-C, LDL-C, and TAG	[30]
Grapes	Obese men and women (aged 20–60 years; n = 24)	3 weeks crossover with 3 weeks washout	Placebo powder[¢] 46 g/day grape powder [¢]Designed to match the grape powder in terms of look, taste, and macronutrients but without any polyphenols.	46 g/day grape powder *vs* placebo powder: ↔ TC, LDL-C, HDL-C, and TAG ↓ large NMR-LDL-C particles and large LDL-C after 3 weeks	[33]

(Continued)

Table 16.2 (Continued) Effects of Dried Fruits on Serum Lipids in Human Clinical Trials

Fruit	*Model*	*Duration*	*Study Design*	*Results*	*References*
Raisins	Adult men and women with type-2 diabetes (mean age 58 years)	12 weeks parallel	Conventional snacks (100 kcal/) (n = 15) 1 oz (~28.3 g) raisins 3 × before meal (90 kcal/day) (n = 31)	1 oz raisins 3 × before meal (90 kcal/day) *vs* conventional snacks (100 kcal/): ↔ TC, HDL-C, LDL-C, and TAG	[29]
Ajwa dates	Healthy adult men and women (aged 18–55 years; n = 22)	3 weeks crossover with 2 weeks washout	Control diet Seven dates daily± ±Matched with control for energy and sugar content.	Seven dates daily *vs* control diet: ↔ TC, HDL-C, LDL-C, and TAG	[38]
Freeze-dried grape powder	Men and women with metabolic syndrome (aged 32–70 years; n = 20)	4 weeks crossover with 3 weeks washout	Placebo† 60 g/day grape powder †Designed to match the grape powder in terms of look, feel, taste, and macronutrients but without any polyphenols.	60 g/day grape powder *vs* placebo: ↓ TAG ↔ Plasma TC, LDL-C, HDL-C, and NMR-HDL particles	[35]

Abbreviations: ApoB, apolipoprotein B; ApoE, apolipoprotein E; CETP, cholesteryl ester transfer protein; FDS, freeze-dried strawberries; HDL-C, high-density lipoprotein-cholesterol; IDL-C, intermediate-density lipoprotein-cholesterol; LCAT, lecithin-cholesterol acyltransferase; LDL-C, low-density lipoprotein-cholesterol; NMR, nuclear magnetic resonance; TAG, triacylglycerols; TC, total cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

intervention trials. Puglisi et al. [27] studied the effects of the addition of one cup of raisins per day to an exercise regimen (walking) over 6 weeks in men and post-menopausal women (aged 50–70 years). Compared with exercise alone, the addition of raisins to exercise had no significant effects on plasma TC, LDL-C, HDL-C, or TAG. Daily raisin intake has also been compared with conventional snack intake in both non-diabetic [28] and diabetic [29] adults. The addition of 85 g raisins (3 oz) per day for 12 weeks lowered serum HDL-C but did not change other serum lipids compared with a conventional snack control in non-diabetic men and women (mean age 60 years) [28]. Furthermore, the intake of 85 g raisins (3 oz) per day for 12 weeks did not significantly alter serum lipids compared with control snacks in men and women with type-2 diabetes (mean age 58 years) [29]. A study of longer duration, where men and post-menopausal women with type-2 diabetes (aged 54–71 years) consumed 36 g of Corinthian raisins per day or their usual diet for 24 weeks, also showed no significant effects on serum lipid profiles [30].

Besides being studied as raisins, grapes have also been examined in freeze-dried form. In a study conducted in pre- and post-menopausal women, the consumption of 36 g/day of freeze-dried grape powder (equivalent to 1.5 servings/day of grapes) for 4 weeks resulted in significant reductions in plasma LDL-C, TAG, apoB, apoE, and cholesteryl ester transfer protein activity compared with a matched placebo powder [31]. There were no differences in plasma TC, HDL-C, LDL oxidation rate, or lecithin-cholesterol acyltransferase activity. However, compared with a placebo powder, the daily consumption of 46 g/day of freeze-dried grape powder (equivalent to two servings/day of grapes) for 30 days was shown to have no significant effects on plasma TC, LDL-C, HDL-C, and TAG in men with metabolic syndrome [32]. Consistent with this finding, the consumption of freeze-dried grape powder (46 g/day) for 3 weeks did not alter the serum lipid panel (TC, LDL-C, HDL-C, and TAG) in obese men and women [33]. Although lipoprotein particle analysis by nuclear magnetic resonance (NMR) spectroscopy revealed significant reductions in the number of large LDL particles and large LDL-C concentrations in plasma, there were no significant changes in small LDL particle and small LDL-C concentrations [33]. Large LDL is not as detrimental as small LDL in regards to CHD [34]; thus, the impact of these changes on heart disease risk is unclear. In contrast, we have recently reported that the daily consumption of 60 g/day of freeze-dried grape powder (equivalent to 2.5 servings/day of grapes) for 4 weeks significantly reduced plasma TAG in adult men and women with metabolic syndrome compared with consuming a matched placebo powder [35]. However, no other changes in plasma lipids or NMR lipoprotein particle characteristics were observed. Overall, dried grapes in the form of raisins or as a freeze-dried powder did not consistently affect traditional serum lipid profiles. However, freeze-dried grapes did lower LDL-C and TAG concentrations in one study which included only women [31] and lowered TAG concentrations in one study which included men and women with metabolic syndrome [35]. Data which show that freeze-dried grapes impact LDL particle characteristics is intriguing, and this area warrants further research.

As well as raisins, other conventional dried fruits have been examined in clinical studies, including apples, dates, and figs. Peterson et al. [36] examined the effects of consuming dried Mission figs in men and women with elevated LDL-C (aged 30–75 years). Participants consumed either 120 g/day of dried figs for 5 weeks or their usual diet in a crossover study design. Interestingly, consumption of the fig diet resulted in elevated serum TC, with no changes in LDL-C, HDL-C, or TAG

compared with the usual diet. The lack of a washout period is a limitation of this study due to potential carryover effects. Although soluble fiber intake increased with the addition of figs, total energy and sugar intake also increased and may have contributed to the study findings.

Chai et al. [37] compared the consumption of dried apples (75 g/day) with dried plums (100 g/day) (comparative control) for 12 months in post-menopausal women (aged 50–61 years). Dried apples significantly reduced plasma TC and LDL-C concentrations over time, although differences compared with dried plums were only observed for plasma TC after 6 months. Eid et al. [38] studied the effects of Ajwa dates in healthy men and women (aged 18–55 years). Participants consumed either seven dates daily (~50 g/day) or matched control powder (maltodextrin-dextrose) for 3 weeks, separated by a 2-week washout period. Compared with control, the consumption of dates did not significantly impact serum TC, LDL-C, HDL-C, or TAG concentrations.

Although not traditionally consumed as a dried fruit, strawberries have been shown to impact serum lipids when consumed in freeze-dried form. Basu et al. [39] examined the effects of consuming freeze-dried strawberry (FDS) beverages in men and women with increased abdominal adiposity and elevated serum lipids (aged 39–59 years). Participants were randomized to consume either 25 g/day FDS (low dosage FDS), 50 g/day FDS (high dosage FDS), or their respective control beverages for 12 weeks. Compared with its respective control beverage, the consumption of high dosage FDS significantly reduced serum TC, LDL-C, and NMR-measured small-LDL concentrations. No other significant changes in serum lipids or plasma NMR lipoprotein profiles were observed with high dosage FDS. The low dosage FDS did not significantly alter serum lipids and lipoprotein particle characteristics compared with its control beverage.

Overall, clinical studies examining dried fruit intake have shown some positive effects on lipoprotein particle characteristics. However, compared with animal studies, changes in serum lipid profiles are less evident.

16.3 Conclusion

Dried fruits contain several components which would be expected to improve lipid profiles, including fiber, flavonoids, and phytosterols. Based on pre-clinical studies using rodent models, various dried fruits appear to improve serum and hepatic lipid profiles (Figure 16.1). However, the amount/dosages of the dried fruits fed in animal studies may be difficult to achieve in a human diet. Thus, the benefits seen in animal studies may not translate to humans, who consume dried fruits mainly as snacks or add them in small amounts to meals. In clinical studies, some dried forms of fruit (apples, strawberries, and freeze-dried grapes) have been shown to improve serum lipid or lipoprotein profiles in typically older, overweight populations, while other dried fruits (raisins, figs, and dates) have not shown much effect in various adult populations. More clinical research is warranted to examine lipid profile responses to the intake of dried fruits in a wider variety of populations. This is especially true in regards to lipoprotein particle characteristics, as important effects on lipoprotein metabolism may be missed when measuring only the traditional serum lipid panel.

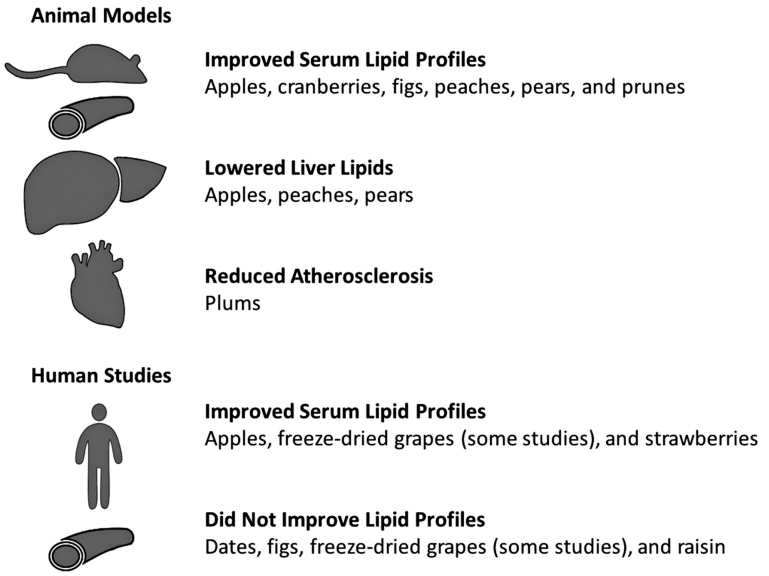


Figure 16.1 Overview of the effects of various dried fruits on lipid profiles in both animal and human studies.

References

1. Xu, J.Q., Murphy, S.L., Kochanek, K.D., and Bastian, B.A., Deaths: Final data for 2013. *Natl. Vital Stat. Rep.*, 16, 1–119, 2016.
2. Hansson, G.K., Inflammation, atherosclerosis, and coronary artery disease. *N. Engl. J. Med.*, 352, 1685–1695, 2005.
3. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*, 285, 2486–2497, 2001.
4. Barter, P., Gotto, A.M., LaRosa, J.C., Maroni, J., Szarek, M., Grundy, S.M., Kastelein, J.J. et al., HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N. Engl. J. Med.*, 357, 1301–1310, 2007.
5. Gordon, D.J., Probstfield, J.L., Garrison, R.J., Neaton, J.D., Castelli, W.P., Knoke, J.D., Jacobs, D.R., Jr. et al., High-density lipoprotein cholesterol and cardiovascular disease. Four Prospective American Studies. *Circulation*, 79, 8–15, 1989.
6. Howell, W.H., McNamara, D.J., Tosca, M.A., Smith, B.T., and Gaines, J.A., Plasma lipid and lipoprotein responses to dietary fat and cholesterol: A meta-analysis. *Am. J. Clin. Nutr.*, 65, 1747–1764, 1997.
7. Mensink, R.P., Zock, P.L., Kester, A.D., and Katan, M.B., Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: A meta-analysis of 60 controlled trials. *Am. J. Clin. Nutr.*, 77, 1146–1155, 2003.

8. Lin, J., Yang, R., Tarr, P.T., Wu, P.H., Handschin, C., Li, S., Yang, W. et al., Hyperlipidemic effects of dietary saturated fats mediated through pgc-1beta coactivation of srebp. *Cell*, 120, 261–273, 2005.
9. U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015–2020 Dietary Guidelines for Americans, 8th Edition. Published online at http://health.gov/dietaryguidelines/2015/guidelines/ (accessed June 4, 2018).
10. Sagar, V.R., and Suresh Kumar, P., Recent advances in drying and dehydration of fruits and vegetables: A review. *J. Food Sci. Technol.*, 47, 15–26, 2010.
11. Keast, D.R., O'Neil, C.E., and Jones, J.M., Dried fruit consumption is associated with improved diet quality and reduced obesity in US adults: National Health and Nutrition Examination Survey, 1999–2004. *Nutr. Res.*, 31, 460–467, 2011.
12. Dauchet, L., Amouyel, P., Hercberg, S., and Dallongeville, J., Fruit and vegetable consumption and risk of coronary heart disease: A meta-analysis of cohort studies. *J. Nutr.*, 136, 2588–2593, 2006.
13. Threapleton, D.E., Greenwood, D.C., Evans, C.E., Cleghorn, C.L., Nykjaer, C., Woodhead, C., Cade, J.E., Dietary fibre intake and risk of cardiovascular disease: Systematic review and meta-analysis. *Br. Med. J.*, 347, f6879, 2013.
14. Gunness, P., and Gidley, M.J., Mechanisms underlying the cholesterol-lowering properties of soluble dietary fibre polysaccharides. *Food Funct.*, 1, 149–155, 2010.
15. Brown, L., Rosner, B., Willett, W.W., and Sacks, F.M. Cholesterol-lowering effects of dietary fiber: A meta-analysis. *Am. J. Clin. Nutr.*, 69, 30–42, 1999.
16. Jiménez-Escrig, A., Santos-Hidalgo, A.B., and Saura-Calixto, F. Common sources and estimated intake of plant sterols in the Spanish diet. *J. Agric. Food Chem.*, 54, 3462–3471, 2006.
17. Ras, R.T., Geleijnse, J.M., and Trautwein, E.A., LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: A meta-analysis of randomised controlled studies. *Br. J. Nutr.*, 112, 214–219, 2014.
18. Millar, C.L., Duclos, Q., and Blesso, C.N., Effects of dietary flavonoids on reverse cholesterol transport, HDL metabolism, and HDL function. *Adv. Nutr.*, 8, 226–239, 2017.
19. Wang, X., Ouyang, Y.Y., Liu, J., and Zhao, G., Flavonoid intake and risk of CVD: A systematic review and meta-analysis of prospective cohort studies. *Br. J. Nutr.*, 111, 1–11, 2014.
20. Aprikian, O., Levrat-Verny, M.-A., Besson, C., Busserolles, J., Rémésy, C., and Demigné, C., Apple favourably affects parameters of cholesterol metabolism and of anti-oxidative protection in cholesterol-fed rats. *Food Chem.*, 75, 445–452, 2001.
21. Aprikian, O., Busserolles, J., Manach, C., Mazur, A., Morand, C., Davicco, M.J., Besson, C. et al., Lyophilized apple counteracts the development of hypercholesterolemia, oxidative stress, and renal dysfunction in obese zucker rats. *J. Nutr.*, 132, 1969–1976, 2002.
22. Leontowicz, H., Gorinstein, S., Lojek, A., Leontowicz, M., Čížž, M., Soliva-Fortuny, R., Park, Y.-S. et al., Comparative content of some bioactive compounds in apples, peaches and pears and their influence on lipids and antioxidant capacity in rats. *J. Nutr. Biochem.*, 13, 603–610, 2002.
23. Lucas, E.A., Juma, S., Stoecker, B.J., and Arjmandi, B.H., Prune suppresses ovariectomy-induced hypercholesterolemia in rats. *J. Nutr. Biochem.*, 11, 255–259, 2000.

24. Mahmoud, M.H., Qura, A.Z.E., Badawy, I.H., Yehya, A.A., and Assmaaa, G.M., Hypocholesterolemic effect of antioxidant containing fruits in rats fed on high-cholesterol and fat diet *J. Appl. Sci. Res.*, 9, 4233–4244, 2013.
25. Gallaher, C.M., and Gallaher, D.D., Dried plums (prunes) reduce atherosclerosis lesion area in apolipoprotein e-deficient mice. *Br. J. Nutr.*, 101, 233–239, 2009.
26. Kim, M.J., Jung, H.N., Kim, K.N., and Kwak, H.K., Effects of cranberry powder on serum lipid profiles and biomarkers of oxidative stress in rats fed an atherogenic diet. *Nutr. Res. Pract.*, 2, 158–164, 2008.
27. Puglisi, M.J., Vaishnav, U., Shrestha, S., Torres-Gonzalez, M., Wood, R.J., Volek, J.S., and Fernandez, M.L., Raisins and additional walking have distinct effects on plasma lipids and inflammatory cytokines. *Lipids Health Dis.*, 7, 14, 2008.
28. Anderson, J.W., Weiter, K.M., Christian, A.L., Ritchey, M.B., and Bays, H.E., Raisins compared with other snack effects on glycemia and blood pressure: A randomized, controlled trial. *Postgrad Med.*, 126, 37–43, 2014.
29. Bays, H., Weiter, K., and Anderson, J., A randomized study of raisins *versus* alternative snacks on glycemic control and other cardiovascular risk factors in patients with type 2 diabetes mellitus. *Phys. Sportsmed.*, 43, 37–43, 2015.
30. Kanellos, P.T., Kaliora, A.C., Tentolouris, N.K., Argiana, V., Perrea, D., Kalogeropoulos, N., Kountouri, A.M. et al., A pilot, randomized controlled trial to examine the health outcomes of raisin consumption in patients with diabetes. *Nutrition*, 30, 358–364, 2014.
31. Zern, T.L., Wood, R.J., Greene, C., West, K.L., Liu, Y., Aggarwal, D., Shachter, N.S. et al., Grape polyphenols exert a cardioprotective effect in pre- and postmenopausal women by lowering plasma lipids and reducing oxidative stress. *J. Nutr.*, 135, 1911–1917, 2005.
32. Barona, J., Aristizabal, J.C., Blesso, C.N., Volek, J.S., and Fernandez, M.L., Grape polyphenols reduce blood pressure and increase flow-mediated vasodilation in men with metabolic syndrome. *J. Nutr.*, 142, 1626–1632, 2012.
33. Zunino, S.J., Peerson, J.M., Freytag, T.L., Breksa, A.P., Bonnel, E.L., Woodhouse, L.R., and Storms, D.H., Dietary grape powder increases IL-1beta and IL-6 production by lipopolysaccharide-activated monocytes and reduces plasma concentrations of large LDL and large LDL-cholesterol particles in obese humans. *Br. J. Nutr.*, 112, 369–380, 2014.
34. Koba, S., Yokota, Y., Hirano, T., Ito, Y., Ban, Y., Tsunoda, F., Sato, T. et al. Small LDL-cholesterol is superior to LDL-cholesterol for determining severe coronary atherosclerosis. *J. Atheroscler. Thromb.*, 15, 250–260, 2008.
35. Millar, C.M., Duclos, Q., Garcia, C., Norris, G.H., Lemos, B.S., DiMarco, D.M., Fernandez, M.L. et al., Effects of freeze-dried grape powder on HDL function in adults with metabolic syndrome: A randomized controlled pilot study. *Metab. Syndr. Relat. Disord.*, 2018, 16, 464–469.
36. Peterson, J.M., Montgomery, S., Haddad, E., Kearney, L., and Tonstad, S., Effect of consumption of dried California mission figs on lipid concentrations. *Ann. Nutr. Metab.*, 58, 232–238, 2011.
37. Chai, S.C., Hooshmand, S., Saadat, R.L., Payton, M.E., Brummel-Smith, K., and Arjmandi, B.H., Daily apple *versus* dried plum: Impact on cardiovascular disease risk factors in postmenopausal women. *J. Acad. Nutr. Diet.*, 112, 1158–1168, 2012.

38. Eid, N., Osmanova, H., Natchez, C., Walton, G., Costabile, A., Gibson, G., Rowland, I. et al., Impact of palm date consumption on microbiota growth and large intestinal health: A randomised, controlled, cross-over, human intervention study. *Br. J. Nutr.*, 114, 1226–1236, 2015.
39. Basu, A., Betts, N.M., Nguyen, A., Newman, E.D., Fu, D., and Lyons, T.J., Freeze-dried strawberries lower serum cholesterol and lipid peroxidation in adults with abdominal adiposity and elevated serum lipids. *J. Nutr.*, 144, 830–837, 2014.

Chapter 17

Dried Fruits and Cardio-Metabolic Syndrome (Endothelial Function, Inflammation, and Blood Pressure)

Valerie Sullivan, Kristina Petersen, and Penny Kris-Etherton

17.1 Introduction 414
17.2 Epidemiological Studies 415
17.2.1 Endothelial Function 415
17.2.2 Circulating Markers of Endothelial Function 415
17.2.3 Inflammation 416
17.2.4 Blood Pressure 417
17.3 *In Vitro* and *In Vivo* Animal Models 418
17.3.1 Nitric Oxide Mediated Effects 418
17.3.2 Polyphenols and Lipid Absorption 419
17.3.3 Antioxidants and Oxidative Stress 419
17.3.4 Polyphenols and Blood Pressure 420
17.3.5 Angiotensin Converting Enzyme Inhibition 421
17.4 Human Intervention Studies 421
17.4.1 Endothelial Function 426
17.4.2 Inflammation 427
17.4.3 Blood Pressure 428
17.5 Conclusion 430
References 431

17.1 Introduction

Cardiovascular disease (CVD) is the number one cause of death and disability worldwide. Poor diet is a leading risk factor for cardiovascular mortality; 72% and 53% of deaths from ischemic heart disease and stroke, respectively, are attributable to poor diet [1]. Diabetes also contributes significantly to global death and disability, with dietary factors accounting for over one-third of diabetes-related mortality [1].

Cardio-metabolic syndrome is a constellation of physiological impairments associated with the development of diabetes and CVD. Contributing factors include visceral obesity, insulin resistance, dyslipidemia, elevated blood pressure, increased inflammation, and hypercoagulability. An estimated one-quarter of the adult population worldwide [2] and 35% of the United States adult population [3] are afflicted by cardio-metabolic syndrome.

Impairments in the vascular system are both contributors to and consequences of cardio-metabolic syndrome. A healthy vascular system regulates hemodynamics, thrombosis, and inflammation in response to and recovery from biochemical and mechanical stressors. Any imbalance in these activities is termed *endothelial dysfunction*, a pathophysiological condition that precedes and may be independently predictive of atherosclerosis. Interventions that protect endothelial function may reduce the risk of cardio-metabolic syndrome.

Diets high in fruits and vegetables have been associated with reduced risk of cardio-metabolic syndrome. As only 13.1% of Americans meet daily fruit intake recommendations [4], strategies to increase consumption are needed. Dried fruit comprises 2.6% of Americans' whole fruit intake [5], and only 6.9% of the population consumes one-eighth of a cup-equivalent of fruit (1 tablespoon) or more per day [6]. The current low consumption in the United States represents an opportunity to increase fruit consumption and potentially improve health. An analysis of 1999–2004 National Health and Nutrition Examination Survey (NHANES) data showed that dried-fruit consumers have higher intakes of several shortfall nutrients identified by the 2015 Dietary Guidelines Advisory Committee (DGAC), including vitamin A, fiber, and potassium. They also have lower intakes of over-consumed unhealthy nutrients, namely sodium and saturated fatty acids [6]. Therefore, inclusion of dried fruits in the usual diet may help individuals achieve recommended nutrient intake levels. In the 2015-2020 Dietary Guidelines for Americans (DGA), each half cup of dried fruit is counted as one cup-equivalent, and it is recommended that two cup-equivalents of fruit be consumed per day [7].

Of particular interest is the effect of dried fruits on vascular health. Concern regarding the adverse effect of high fructose intake, including contributions from dried fruits, may discourage consumption. However, fructose only represents between one-third and one-half of the sugar in dried fruits [8]. Furthermore, they are sources of a rare monosaccharide, D-allulose (previously D-psicose), which has anti-hyperlipidemic and anti-hyperglycemic properties [9]. Dried fruits, while a source of intrinsic sugars, are also nutrient dense and may have vascular benefits. Many dried fruits are also good sources of fiber and potassium, nutrients that support vascular health [10–12]. The nutritional characteristics of dried fruits are presented in detail in Chapter 14.

This chapter examines current evidence regarding the effect of dried fruits on measures of vascular health. Epidemiological evidence, *in vitro* and *in vivo* animal

studies, and human intervention trials are reviewed to assess the effects of dried fruits on endothelial function, inflammation, and blood pressure.

17.2 Epidemiological Studies

17.2.1 Endothelial Function

Vascular homeostasis is largely regulated by the vascular endothelium, a single layer of cells lining blood vessels that separates the smooth muscle beneath from circulating blood. Beyond serving as a barrier, the endothelium actively secretes various substances that influence vasodilation, vascular smooth-muscle cell growth, clot formation, and leukocyte adhesion and activation. Chief among these substances is nitric oxide (NO), a soluble gas produced in the conversion of L-arginine to L-citrulline by NO synthase. An imbalance between relaxing factors, such as NO, and contracting factors, such as endothelin-1 and angiotensin, results in endothelial dysfunction.

Endothelial dysfunction is associated with increased large artery stiffness, which is an independent predictor of cardiovascular events and all-cause mortality [13]. Assessment of pulse wave velocity (PWV) provides a measure of regional arterial stiffness, with higher velocity indicating stiffer arteries. A longitudinal study that followed children into adulthood reported associations between fruit consumption and PWV [14]. Childhood and adulthood fruit intake, ranked by quintile, were inversely associated with adulthood PWV (P for trend across quintiles of childhood and adulthood intake = 0.04 and 0.03, respectively), and fruit consumption in adulthood was predictive of PWV ($\beta = -0.06$, $P = 0.03$). Individuals with high consumption of fruits tracking from childhood through adulthood had significantly slower PWV than those with persistently low consumption grouped by quintiles (difference 0.46 m/s, $P = 0.03$). Dried fruit consumption was not specifically evaluated, so it is uncertain whether this association exists for dried fruits as well.

17.2.2 Circulating Markers of Endothelial Function

Circulating levels of cellular adhesion molecules expressed by endothelial cells increase in response to endothelial damage. Elevations in endothelial activation may promote atherosclerosis [15]. These molecules include soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), and endothelial-leukocyte adhesion molecule, also known as E-selectin. Evaluating associations between dietary factors and serum levels of these molecules helps to understand the relationship between diet and endothelial health.

Based on available evidence, the association between fruit and vegetable consumption and markers of endothelial function is uncertain. In cross-sectional studies, dietary patterns high in fruits and vegetables have been inversely associated with sICAM-1 [16] and E-selectin levels [17]. A dietary pattern rich in fruits and vegetables was also prospectively associated with lower E-selectin and sICAM-1, but not sVCAM-1 at 15-year follow-up [18]. However, these dietary patterns were also high in other foods such as fish, nuts, and whole grains; the individual components

of these diets were not evaluated. The association between fruit intake, specifically, and adhesion molecules was investigated in a small subsample of the Prevención con Dieta Mediterránea (PREDIMED) participants [19]. Higher total fruit intake was not significantly associated with peripheral concentrations of sICAM-1 or sVCAM-1 in adults at increased risk for CVD.

17.2.3 Inflammation

Inflammation contributes to the development of endothelial dysfunction through activation of endothelial cells. The inflammatory response is characterized by the release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), which induce expression of cell adhesion molecules and monocyte chemoattractant protein-1 (MCP-1) by endothelial cells [15]. These substances promote rolling and adhesion in the recruitment of monocytes, which are essential steps preceding endothelial transmigration. Acutely, this response serves a protective role, but it can become maladaptive and harmful to the endothelium in the context of chronic inflammation [20].

Associations between dietary patterns rich in fruits and peripheral levels of the inflammatory cytokines TNF-α and IL-6 have been examined. High fruit and vegetable consumption was associated with lower TNF-α in adults, which persisted after adjustment for body mass index (BMI) [21]. Higher consumption of fruits and vegetables was associated with lower IL-6 in adolescents [22] and adults [21]. High fruit and vegetable consumption in a large ethnically diverse adult population was also associated with lower IL-6 concentrations, but the association was no longer significant after adjustment for waist circumference [16]. Fruit consumption, specifically, was inversely related to IL-6 in adults at high CVD risk, and the association remained significant after adjustment for BMI [19].

The observed inverse relationship between IL-6 and fruit and vegetable consumption would predict a similar inverse relationship for C-reactive protein (CRP). Associations with CRP are generally consistent with this expectation, but findings are not uniform. Lower CRP was observed among adolescents [22], women [17], and adult men and women [23] consuming diets high in fruits and vegetables, and the associations persisted after adjustment for BMI. Adherence to a dietary pattern higher in fruit and vegetables was also inversely associated with CRP in an ethnically diverse adult population, and the association remained significant after adjustment for waist circumference [16]. Lower CRP was predicted with increasing fruit and vegetable consumption in adults, after adjustments for age, race/ethnicity, and sex [24]. Further adjustments for BMI and energy intake, however, attenuated the relationship. Likewise, a significant inverse association between fruit and vegetable consumption and CRP was detected among community-dwelling adults, but the association was no longer significant after adjustment for multiple covariates, including BMI [21].

Diet components other than fruit may influence these associations. Therefore, some scientists have attempted to tease apart the specific effects of fruit consumption. Greater fruit consumption has been significantly inversely associated with CRP, independent of BMI, in men [25–27] and in both men and women [28]. A cross-sectional study of individuals with type-2 diabetes found that, relative to the lowest tertile of fruit consumption, those in the highest fruit intake tertile – a mean

difference of only 20 g/day – had 31% lower high sensitivity CRP (hs-CRP; $P < 0.001$) after adjustment for potential confounders, including total energy and vegetable intake [29]. However, Salas-Salvadó et al. [19] did not find any relationship between fruit consumption and hs-CRP among individuals at elevated risk for CVD.

Associations between consumption of dried fruits, specifically, and inflammatory markers have not been evaluated. Rather, dried fruits are counted toward total fruit intake [22] or as a component of a dietary pattern [30]. In a cross-sectional analysis of adolescents' (n = 285) dietary intake assessed by food frequency questionnaire and fasting inflammatory markers, fruit consumption – including fresh and dried fruits but excluding fruit juices – was negatively associated with serum CRP and IL-6, but not TNF- α [22]. A large cross-sectional study of Italian adults (≥ 35 years of age; n =7,646) used principal factor analysis to identify an "Olive Oil and Vegetables" dietary pattern, with which intake of dried fruits was positively correlated [30]. Greater adherence to this diet pattern was negatively associated with CRP (P for trend 0.018). However, the relationship of dried fruits with this marker, compared to other components of the dietary pattern, was not evaluated.

Bhupathiraju et al. [31] demonstrated lower CRP with increasing variety, but not quantity, of fruits and vegetables consumed. Consuming a wide array of fruits and vegetables increases exposure to nutrients and phytochemicals that may be absent or only found in low concentrations in commonly consumed types. Fruits infrequently consumed in their fresh forms, such as figs and dates, may be more accessible and acceptable to consumers as dried fruits. Dried fruits thus offer opportunities for dietary diversification and may support lower inflammation.

17.2.4 Blood Pressure

Elevated blood pressure is the leading metabolic risk factor for global deaths and disability. High systolic blood pressure (SBP) contributes to 10.4 million deaths and 208.1 million disability adjusted life years [1]. A reduction in blood pressure of 10 mmHg systolic or 5 mmHg diastolic is associated with a 22% decrease in coronary heart disease (CHD) events and 41% decrease in stroke [32].

Endothelial dysfunction is closely associated with high blood pressure, although the direction of causation is unclear. Perturbation of endothelial function may increase blood pressure due to impaired vascular relaxation from inadequate NO release or activity. However, in a prospective study of a large ethnically diverse population, endothelial dysfunction was not predictive of hypertension [33]. High blood pressure in adolescent men was, instead, predictive of endothelial dysfunction in adulthood [34]. The relationship is likely bidirectional and may vary by population [35].

Adherence to diets rich in fruits has been inversely associated with blood pressure. A cross-sectional analysis of dietary patterns and blood pressure among overweight adults revealed a significant inverse association between adherence to a dietary pattern high in nuts, seeds, fruits, and fish and both SBP and diastolic blood pressure (DBP) [36]. Dietary sodium intake, a potential confounder in associations between diet and blood pressure, was not significantly different in individuals who did not adhere to this pattern. Combined fruit and vegetable consumption was significantly inversely associated with SBP among French adults after adjustment for multiple covariates, including total energy intake ($\beta = -0.33$, $P = 0.03$) [37].

Associations between dried fruit consumption, specifically, and various health endpoints were examined in the National Health and Nutrition Examination Survey (1999–2004) dataset [6]. Adult dried-fruit consumers, defined by consumption of at least one-eighth of a cup-equivalent per day reported on a 24-hour diet recall, were found to have significantly lower blood pressure [6]. After adjustment for BMI and energy intake, the association remained significant, with mean SBP and DBP in consumers and non-consumers assessed as 121.4 ± 0.7 *versus* 122.9 ± 0.3 mm Hg and 71.1 ± 0.6 *versus* 72.1 ± 0.2 mm Hg, respectively (both $P < 0.05$).

The epidemiological evidence generally supports an association between fruit consumption and vascular health. However, the association between vascular outcomes and dried-fruit consumption, specifically, has only been examined in one known large-scale study [6], and daily consumption in this population is relatively low. Examining various indicators of vascular health among populations with greater usual dried-fruit consumption may provide stronger evidence for the role of dried fruit in population health.

17.3 *In Vitro* and *In Vivo* Animal Models

17.3.1 Nitric Oxide Mediated Effects

Animal and *in vitro* models may help to explain how dried fruits mechanistically alter vascular health, likely through the action of polyphenols (Figure 17.1). Vasodilation

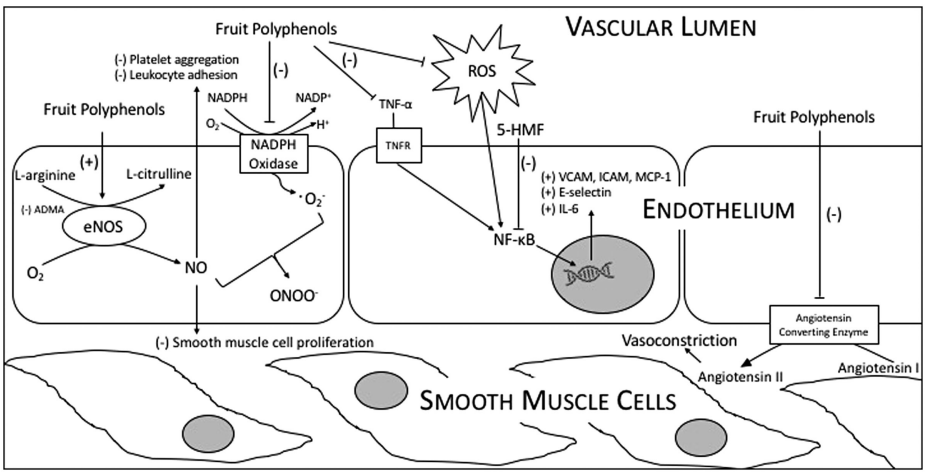


Figure 17.1 Mechanisms through which dried fruit–derived polyphenols and 5-HMF influence vascular function. *Abbreviations*: 5-HMF, 5-hydroxymethylfurfural; ADMA, asymmetric dimethylarginine; eNOS, endothelial nitric oxide synthase; E-selectin, endothelial-leukocyte adhesion molecule 1; ICAM, intercellular adhesion molecule; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ROS, reactive oxygen species; TNFR, tumor necrosis factor receptor; TNF-α, tumor necrosis factor- α; VCAM, vascular cell adhesion molecule.

is largely controlled by release of NO, which diffuses from the endothelium to inhibit platelet aggregation, leukocyte adhesion, and smooth-muscle cell proliferation. A balance between NO production by nitric oxide synthase (NOS) and inactivation by reactive oxygen species (ROS) underlies endothelial function.

Raisins appear to support NO production when a cholesterol-rich diet is consumed. A high cholesterol diet fed to male Wistar rats for 13 weeks resulted in very weak NOS expression in the left ventricular cardiac muscle fibers and the endothelial lining of cardiac blood vessels, whereas expression was moderate in control rats fed a standard diet [38]. When mice on a high cholesterol diet were concomitantly administered a raisin homogenate *via* a nasogastric tube, NOS expression at these sites was significantly greater than in mice fed a high cholesterol diet without raisins, whereas raisins had no significant effect on standard diet-fed rats. The physiological implications of these changes were not evaluated, but attenuation of the decrease in endothelial NOS expression would be expected to preserve endothelial function. Along with decreased NOS expression, the high cholesterol diet significantly increased fasting triacylglycerols (TAG) and low-density lipoprotein (LDL)-cholesterol concentrations [38]. LDL-cholesterol increases endogenous production of an NOS inhibitor, asymmetric dimethylarginine (ADMA) [39]. Functional impairments may result from this inhibition, as evidenced by the inverse correlation between fasting LDL-cholesterol and flow-mediated brachial artery dilation [40]. Elevated post-prandial TAG has been shown to impair endothelial function [40]. The addition of raisins to the high cholesterol diet prevented the increase in TAG and LDL-cholesterol [38], and it is likely that this protected NOS activity.

17.3.2 Polyphenols and Lipid Absorption

Lower TAG was also reported in guinea pigs fed lyophilized grape powder [41]. The decrease in serum TAG was speculated to result from polyphenol interference with lipid absorption [41], and other studies have supported this hypothesis [42]. Polyphenols are a diverse group of compounds in plants involved in defense against environmental and biological stressors. Many have been investigated for their potential benefit to human health. Polyphenols from red wine have been shown to decrease secretion of hepatic and intestinal apolipoprotein B (apo B) and upregulate expression and activity of LDL receptors [43,44]. The polyphenol content of raisins could potentially explain the observed reductions in lipids and, thereby, their influence in NOS expression.

In addition, the high cholesterol diet increased fasting insulin and glucose concentrations [38], likely increasing insulin resistance. Insulin-induced stimulation of endothelial NO production is attenuated in insulin resistance, while production of the vasoconstrictor endothelin-1 is enhanced [45]. Raisins prevented the increase in insulin and glucose resulting from the high cholesterol diet, a finding suggestive of preserved insulin sensitivity and thereby protection of endothelial function.

17.3.3 Antioxidants and Oxidative Stress

Hypertriglyceridemia and hyperglycemia increase generation of ROS, resulting in increased oxidative stress and endothelial dysfunction [40]. Antioxidants from dried

fruits could potentially oppose the damage induced by acute hypertriglyceridemia and hyperglycemia by quenching ROS.

In vivo antioxidant activity of dried fruits has been demonstrated in a rabbit model of atherosclerosis. Rabbits were fed a standard or cholesterol-enriched diet with or without currants (*Vitis vinifera* L., var. Apyrena) for 8 weeks, and measures of serum oxidative stress, plasma phenolic compounds, and aortic intimal thickness were compared [46]. Currants inhibited formation of atherosclerotic lesions in rabbits fed the high cholesterol diet, resulting in significantly lower intimal thickness in the abdominal portion of the aortic vessel. Oxidative stress, assessed by serum thiobarbituric acid reactive substances (TBARS) concentration, increased in rabbits fed high cholesterol diets, but was significantly lower in those supplemented with currants. No changes in these endpoints were observed in rabbits fed the standard diet, with or without currants. Interestingly, total and non-high-density lipoprotein (HDL)-cholesterol concentrations increased significantly on both cholesterol-enriched diets, with no differences between currant-supplemented and non-supplemented groups. TAG and glucose concentrations remained unchanged. It appears that the vascular benefits of currants were independent of lipemic or glycemic changes. Instead, currants attenuated the increase in oxidative stress induced by a high cholesterol diet.

Decreasing oxidative stress may be a mechanism by which antioxidant-rich dried fruits reduce endothelial activation and inflammation. Genetic expression of endothelial adhesion molecules and the chemokines MCP-1 and IL-8 is regulated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which is activated in the setting of elevated cellular oxidative stress [47]. Conversely, its activation is inhibited by antioxidants. Oxidative stress contributes to endothelial NOS uncoupling, a state in which NOS shifts from NO production to superoxide anion radical generation from molecular oxygen. NO bioavailability is also reduced in the setting of oxidative stress, as ROS react with NO to form peroxynitrate. Inhibition of oxidative stress thus decreases endothelial activation and favors NO production and bioavailability.

17.3.4 Polyphenols and Blood Pressure

Limited animal and *in vitro* studies support a role of dried fruits in blood pressure reduction. Intravenously administered prune extract dose-dependently decreased SBP and DBP of rats [48]. However, translation to human health is limited by the intravenous route of administration used to achieve the hypotensive effect. In humans, prune bioactives must be digested, absorbed, and circulated in metabolically active forms at sufficient concentrations to obtain their physiological benefits.

Enteral digestion and absorption of dried fruit components that reduce blood pressure were demonstrated with dried fig extract in rats [49]. Oral administration of dried fig extract at several concentrations (250, 500, and 1,000 mg/kg) significantly decreased SBP and DBP in normotensive rats at 1 and 3 hours post-administration, compared to baseline. Dried fig extract (1,000 mg/kg), administered daily, also prevented hyperglycemia-induced rises in SBP and DBP in rats hydrated with a 10% glucose solution instead of water for 21 days. The anti-hypertensive effect of dried figs was hypothesized to result from antioxidant activities of the polyphenols they contain.

Polyphenols are thought to be responsible for the blood pressure–lowering effects of grape products, namely wine and grape juice but also potentially raisins. A red grape skin extract (GSE), administered orally to rats for 28 days, prevented hypertension induced by N(G)-nitro-L-arginine methyl ester (L-NAME), a known inhibitor of NOS [50]. Mechanisms of action were investigated by evaluating vasodilation in isolated mesenteric vascular beds of rats in response to drug and GSE treatment. After treatment of the vascular bed with the cytotoxic bile acid deoxycholic acid to remove the endothelium, vasodilation in response to GSE was significantly reduced, whereas endothelium-independent vasodilation in response to nitroglycerin was not affected. The vasodilator effect of GSE was unaffected by pretreatment of the vascular bed with inhibitors of prostanoids or calcium- or adenosine triphosphate (ATP)-dependent potassium channels, whereas L-NAME significantly reduced GSE-induced vasodilation. Thus, GSE appears to promote vasodilation through increasing endothelial NO production and/or availability, and it may thereby exert antihypertensive effects. The preservation of the bioactive phytochemicals from GSE in raisins, in concentrations sufficient to achieve clinically meaningful improvements in endothelial function and blood pressure, has not been confirmed.

Similarly, freeze-dried strawberry polyphenols have been shown to improve endothelial-dependent relaxation. Rabbit aorta rings pre-contracted with norepinephrine were treated with an aqueous extract of freeze-dried strawberry powder, resulting in dose-dependent relaxation [51]. No effect was observed after removal of the endothelium nor after L-NAME treatment, pointing to NOS as the responsive endothelial relaxation mediator. Through immunoblotting of human umbilical vein endothelial cells treated with strawberry extract, the investigators demonstrated that the extract induced phosphorylation and thereby increased activation of endothelial NOS.

The polyphenols in grapes, and possibly in raisins, may increase levels of NO by augmenting transcription and translation of endothelial NOS. Endothelial cells exposed to dealcoholized red wine polyphenol extract for 18–20 hours were shown to increase NO production, endothelial NOS protein levels, and transcription of NOS [52]. Thus, increased activity and/or expression of endothelial NOS appear to be mechanisms by which fruit polyphenols improve endothelial function.

17.3.5 Angiotensin Converting Enzyme Inhibition

Prune extract [48] and date sugar (finely ground dates) [53] have been shown to inhibit serum angiotensin converting enzyme *in vitro*, elucidating another potential mechanism of action. This mechanism has not been confirmed *in vivo*. The antihypertensive effect of grape-derived bioactives appears to be independent of the renin-angiotensin system, as GSE reduced blood pressure in a low-renin model of hypertension in rats [50]. Different phytochemicals may act through different pathways to influence blood pressure. Further investigations are warranted to determine what components of dried fruits exert these actions and which mechanisms are implicated.

17.4 Human Intervention Studies

Clinical trials evaluating the effect of dried fruits on vascular outcomes are summarized in Table 17.1. The limited evidence points to opportunities for further investigation.

Table 17.1 Summary of Human Intervention Studies and Findings Relevant to the Effects of Fruit and Dried fruits on Vascular Function

Treatment	*Study Design*	*Duration*	*n*	*Participant Characteristics*	*Relevant Endpoints*	*Main Findings*	*References*
1 Oz portion of raisins (90 kcal), three times daily *versus* processed snack (100 kcal), three times daily	Parallel, randomized	12 Weeks	31 Raisins 15 Snacks	Adults. BMI 25–34.9 kg/m^2. ≥ 1 fasting plasma or serum glucose level of 90–150 mg/dL within 4 weeks of initial study visit. BP > 120 mm Hg SBP or > 80 mm Hg DBP but ≤ 160/100 mm Hg.	Blood pressure.	Relative to baseline, raisin intervention significantly reduced SBP at 4, 8, and 12 weeks and DBP at 4 and 12 weeks. Mean 12-week BP change on raisin treatments: –5.4/–4.5 mm Hg. Changes in SBP and DBP were significantly greater on raisin *versus* snack intervention at all time points.	[67]
Polyphenol-rich *versus* polyphenol-poor freeze-dried apples (40 g/day)	Crossover, double-blinded	4 Week treatments, separated by 4 weeks washout	30 Per treatment	Adult males, mean age 53 years. High total (> 6.2 mmol/L) or LDL (> 4.1 mmol/L) cholesterol.	Brachial artery FMD.	No change in FMD post-treatment *versus* baseline. No change in FMD in response to polyphenol-rich *versus* poor treatment.	[56]
1 Oz portion of raisins (90 kcal), three times daily *versus* processed snack (100 kcal), three times per day	Parallel, randomized	12 Weeks	27 Raisins 19 Snacks	Adults. BMI 25–50 kg/m^2. Diagnosis of type-2 diabetes HbA_{1c} 6.5%–10%.	Blood pressure.	Relative to baseline, raisin intervention reduced SBP 4.2 mm Hg (3.7%) at 12 weeks. SBP at week 12 was 8.7 mm Hg (7.5%) lower in raisin treatment, relative to control. DBP did not change significantly.	[68]
Dried apples (75 g/day) *versus* dried plums (100 g/day) *Note*: Serving sizes determined by matching for energy, carbohydrates, fat, and fiber	Parallel, randomized	12 Months	45 Apples 55 Dried plums	Healthy post-menopausal women.	Serum CRP.	Serum CRP was significantly lower in dried plums *versus* dried apples group at 3 months but not at 6 or 12 months. Dried plums non-significantly reduced CRP by 17% at 3 months, relative to baseline, and then remained constant. Dried apples non-significantly reduced CRP by 32% at 12 months.	[65]
Dried plums, 0 g/day *versus* 50 g/day *versus* 100 g/day	Parallel, randomized	6 Months	13 on 0 g/day 16 on 50 g/day 13 on 100 g/day	Post-menopausal women, aged 65-79 years. Osteopenic (bone mineral density T-score -1 to -2.5).	Serum hs-CRP.	No significant changes in hs-CRP at any dose.	[64]

(*Continued*)

Table 17.1 (Continued) Summary of Human Intervention Studies and Findings Relevant to the Effects of Fruit and Dried fruits on Vascular Function

Treatment	*Study Design*	*Duration*	*n*	*Participant Characteristics*	*Relevant Endpoints*	*Main Findings*	*References*
Corinthian raisins (36 g/day) *versus* control (usual diet, abstaining from grape or raisin consumption)	Parallel, randomized	24 Weeks	22 Controls 26 Raisins	Men and post-menopausal women, aged 40–65 years. Type-2 diabetes (diagnosed ≥ 3 years ago; well-controlled, with HbA_{1c} <8%).	Serum hs-CRP, TNF-α, and IL-6. Blood pressure.	No significant difference in hs-CRP, TNF-α, or IL-6 relative to baseline or control. DBP decreased significantly after raisin treatment relative to baseline (76.8 ± 10.5 *versus* 71.4 ± 8 mm Hg). Post-treatment DBP was significantly lower in raisin *versus* control treatment. No significant change in SBP.	[63]
Daily self-selected fruit and vegetable intake (1, 3, or 6 portions)	Parallel, randomized	8 Weeks	112 total (33 on 1/day, 39 on 3/day, and 40 on 6/day)	Males and females, aged 40–65 years. SBP (140–179 mm Hg). DBP (90–109 mm Hg).	Endothelium-dependent vasodilation (maximum forearm blood flow response to intra-arterial acetylcholine).	6.2% improvement in forearm blood flow response per 1-portion increase in reported fruit/vegetable intake.	[54]
Acute intake of 100 g dried dates, apricots, currants, plums, or fruit bread	Crossover, randomized	Acute intake with 5-hour follow-up	75 Per treatment	Healthy adults, aged 20–30 years.	Urinary 8-OHdG, baseline *versus* 5 hours postprandial.	Urinary 8-OHdG decreased after all treatments except dates, but did not reach statistical significance. Urinary 8-OHdG increased significantly after consumption of dates. 5-HMF content of dried fruits was inversely associated with change in 8-OHdG.	[60]

(*Continued*)

Table 17.1 (Continued) Summary of Human Intervention Studies and Findings Relevant to the Effects of Fruit and Dried fruits on Vascular Function

Treatment	*Study Design*	*Duration*	*n*	*Participant Characteristics*	*Relevant Endpoints*	*Main Findings*	*References*
250 g fresh Thompson seedless grapes *versus* 50 g sun-dried raisins *versus* 50 g golden raisins	Crossover, randomized	4 Week treatments, separated by 3 weeks washout	10 Per treatment	Healthy. Non-smoking, aged 18–45 years.	Serum antioxidant capacity (ORAC). Serum *ex vivo* lipoprotein oxidation. Plasma phenolics. Plasma CRP.	Long-term: ORAC increased, relative to baseline, after 2 weeks of grapes and 3 weeks of golden raisin consumption. No change in serum oxidation. Short-term: ORAC increased and serum lipoprotein oxidation decreased 2 hours after sun-dried raisin intake in week 1. ORAC increased 1 and 2 hours after grape intake in weeks 3 and 4. Serum oxidation lag time was significantly shorter at 1 and 2 hours post-grape consumption during week 1 and at 2 hours post-golden raisin consumption at week 4. No significant change in plasma total phenolics or CRP.	[59]
Raisins (1 cup/day) *versus* walking *versus* raisins (1 cup/day) plus walking	Parallel, randomized	6 Weeks	12 Raisins 12 Walking 12 Raisins + walking	Healthy adults, aged 50–70 years.	Plasma IL-8, MCP-1, TNF-α, and sICAM-1. Blood pressure.	Plasma IL-8 and MCP-1 did not change. TNF-α decreased in raisin group. sICAM-1 decreased in all groups. SBP reduced by 2.2% in all groups. DBP did not significantly change.	[66]
100 g/day Medjool dates *versus* 100 g/day Hallawi dates	Crossover	4 Week treatments, separated by 4-Week washout	10 Per treatment	Healthy adults.	Serum oxidative status (lipid peroxidation by TBARS assay and antioxidant potential by FRAP assay).	Significantly decreased TBARS after Hallawi dates, but not Medjool. FRAP unchanged by either treatment.	[58]

(*Continued*)

Table 17.1 (Continued) Summary of Human Intervention Studies and Findings Relevant to the Effects of Fruit and Dried fruits on Vascular Function

Treatment	*Study Design*	*Duration*	*n*	*Participant Characteristics*	*Relevant Endpoints*	*Main Findings*	*References*
Blueberry drink (from freeze-dried blueberries) with varying total polyphenol content (766, 1,278, and 1,791 mg) *versus* blueberry-free control beverage	Crossover, randomized	Acute intake, with 24 hours follow-up *Time-course effects*	10 Per treatment	Healthy men, aged 18–40 years.	Brachial artery FMD. Carotid-femoral PWV. Augmentation index. Blood pressure. Neutrophil NADPH oxidase activity.	FMD increased significantly at 1, 2, and 6 hours post-consumption of blueberry beverage *versus* control. Changes in FMD were not significantly different for different polyphenol contents. Blood pressure, PWV, and augmentation index did not change. NADPH oxidase activity decreased significantly at 1, 2, and 6 hours.	[55]
Blueberry drink (from freeze-dried blueberries) with varying total polyphenol content (319, 639, 766, 1,278, and 1,791 mg) *versus* blueberry-free control beverage	Crossover, randomized	Acute intake, with 1 hour follow-up *Dose-dependency study*	11 Per treatment	Healthy men, aged 18–40 years.	Brachial artery FMD.	FMD increased linearly up to the 766 mg polyphenol concentration. Response plateaued and decreased slightly at higher concentrations.	[55]
240 mL Sprite soda alone (control) or with 40 g dried Mission and Calimyrna figs	Crossover, randomized	Acute intake, with 6 hours follow-up	10 Per treatment	Healthy male and female, aged 25–58 years.	Plasma antioxidant capacity (assessed by TEAC assay).	Plasma antioxidant capacity increased significantly relative to baseline up to 4 hours post-consumption of figs with Sprite. Figs overcame the pro-oxidant effect of Sprite alone, with significantly greater plasma antioxidant capacity at 1, 2, and 4 hours post-consumption.	[57]

Abbreviations: 5-HMF, 5-hydroxymethylfurfural; 8-OHdG, 8-oxo-2'-deoxyguanosine; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; DBP, diastolic blood pressure; FMD, flow-mediated dilation; FRAP, ferric reducing ability of plasma; HbA_{1c}, hemoglobin A1c; hs-CRP, high sensitivity C-reactive protein; IL, interleukin; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; NADPH, reduced nicotinamide adenine dinucleotide phosphate; ORAC, oxygen radical absorbance capacity; PWV, pulse wave velocity; SBP, systolic blood pressure; sICAM-1, soluble intercellular adhesion molecule-1; TBARS, thiobarbituric acid reactive substances; TEAC, trolox equivalents antioxidant capacity; TNF-α, tumor necrosis factor- α.

17.4.1 Endothelial Function

Change in endothelium-dependent forearm blood flow response was evaluated after an 8-week fruit and vegetable intervention [54]. Each one-serving increase in self-selected fruit and vegetable consumption improved maximum response to acetylcholine by 6.2% in hypertensive adults. Endothelium-independent vasodilation, assessed by brachial artery vasodilation response to sodium nitroprusside, remained unchanged, confirming that vasodilation was mediated by endothelial changes related to the dietary intervention. Despite the functional changes observed, circulating markers of endothelial activation, including sICAM-1 and sVCAM-1, did not change. Dried fruits, specifically, were not evaluated in this trial. However, as a concentrated form of fruit, it may be a useful strategy to increase daily fruit intake to promote vasodilation.

A randomized, double-blind, crossover, and controlled trial evaluated temporal changes in brachial flow-mediated dilation (FMD) in healthy men consuming freeze-dried blueberry beverages as well as the dose-dependency of the FMD response by comparing beverages with incrementally greater polyphenol contents [55]. FMD improved significantly at 1, 2, and 6 hours post-blueberry beverage consumption, compared to the control beverage. Response increased linearly with polyphenol content up to 766 mg polyphenols (equivalent to 240 g blueberries), after which response plateaued. The activity of neutrophil-reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a membrane-bound generator of ROS, was significantly decreased at the same time points, whereas activity remained unchanged with the control beverage. The peaks in FMD and decline in NADPH oxidase were correlated with increases in specific plasma polyphenol metabolites, and changes in FMD and NADPH oxidase activity were also significantly correlated. These relationships support the proposed role of polyphenols in mediating vascular changes by inhibiting NADPH oxidase, though further research is needed to identify the specific polyphenols responsible for the effect. Other measures of vascular health, including blood pressure, PWV, and augmentation index, remained unchanged in this acute feeding study.

Significant endothelial benefits may only be realized acutely after polyphenol consumption. A double-blind crossover study evaluating changes in fasting FMD after 4 weeks of daily high- *versus* low-polyphenol freeze-dried apple consumption among hypercholesterolemic men did not detect significant changes in FMD, relative to baseline or between apple varieties [56]. The daily apple dose was 40 g, equivalent to two fresh apples, and provided 214 mg and 1.43 g total polyphenols in the low- and high-polyphenol treatments, respectively. Clearance of these active metabolites from circulation in a fasted state may explain the lack of change in FMD.

Endothelial function may be improved by dietary antioxidants scavenging ROS. Absorption and *in vivo* activity of dried fruit antioxidants are supported by acute and short-term feeding trials. Dried figs overcame the pro-oxidant effect of a high-sugar beverage consumed by 10 healthy adults [57]. Consumed alone, soda decreased plasma antioxidant capacity, as assessed by the trolox equivalents antioxidant assay. When 40 g of dried figs were consumed with the soda, antioxidant capacity increased by 9% relative to baseline. Hallawi dates consumed for 4 weeks (100 g/day) significantly decreased serum oxidative status, analyzed by TBARS assay, by 33% relative to baseline in 10 healthy adults [58]. Medjool dates did not

affect oxidative status in this small pilot study, a finding that investigators attributed to their lower total concentration or different composition of phenolic compounds.

An important antioxidant role of phenolic compounds is supported by studies that have compared raisins processed by different techniques. Golden raisins (50 g) consumed daily for 4 weeks increased serum antioxidant capacity assessed by oxygen radical absorbance capacity (ORAC) assay [59]. Levels peaked at 3 weeks, and serum oxidation lag time increased and reached statistical significance by week 4. Fresh grapes consumption increased antioxidant capacity only at 2 weeks, and neither grapes nor sun-dried raisins affected serum oxidation lag time. The increase in serum antioxidant capacity after golden but not sun-dried raisin consumption was attributed to their retention of phenolic antioxidants in processing, supported by significantly greater *in vitro* ORAC values. Investigators acknowledge that uncontrolled dietary factors or stress may have influenced results.

Dried fruits also contain 5-hydroxymethylfurfural (5-HMF), a browning reaction product. Evidence of a role of 5-HMF mediating *in vivo* protection against oxidative stress is reported in an acute feeding study comparing urinary excretion of 8-hydroxydeoxyguanosine (8-OHdG) before and 5 hours after consumption of 100 g dried dates, apricots, currants, plums, or fruit-enriched bread [60]. Urinary concentrations of 8-OHdG, a product of oxidized DNA, were assessed as a measure of oxidative stress. Concentrations of 5-HMF in the tested dried fruits were inversely associated with changes in 8-OHdG, and urinary concentrations of the 5-HMF metabolite (5-hydroxymethyl-2-furoic acid) were directly associated with urinary 8-OHdG. These associations support an antioxidant role of 5-HMF in humans consuming dried fruits. By protecting NO from oxidative degradation, antioxidant-rich dried fruits may support endothelial function.

17.4.2 Inflammation

The inflammatory cascade directly impacts the vascular wall, including the endothelium. Dietary interventions that decrease inflammation may protect endothelial function. The most commonly examined inflammatory biomarker is CRP, which is not only a marker of systemic inflammation but also may suppress endothelial NO release [61,62].

Clinical trials with dried fruits have not consistently demonstrated changes in inflammatory markers after various dietary interventions. In a randomized crossover study of 15 healthy adults, neither golden nor sun-dried raisins consumed daily (50 g/day) for 4 weeks significantly changed CRP concentrations relative to baseline [59]. Twenty-four weeks of daily raisin consumption (36 g/day) did not change hs-CRP in 26 adults with well-controlled diabetes, relative to baseline [63]. Likewise, dried plums, supplemented at 50 g or 100 g per day for 6 months, did not alter hs-CRP in 16 and 13 healthy post-menopausal women, respectively [64]. Consistent with this finding, daily supplementation of dried apples (75 g/day) or prunes (100 g/day) in 45 and 55 post-menopausal women, respectively, for one year did not significantly change serum CRP [65].

Baseline and intervention diets were not assessed in these studies. Whether dried fruits are substituted for other foods in the diet or added to the usual diet may affect inflammatory response to the intervention. This might explain the observed differences in results. In addition, significant CRP changes in response to diet

interventions may not be seen in a healthy adult population. The effect of dried-fruit interventions on inflammatory measures in individuals with elevated baseline CRP has not been reported. Finally, CRP is a biomarker that can fluctuate appreciably in response to various factors, including illness, stress, and diet. At least two measurements, separated by 2 weeks, are recommended to assess an individual's CRP concentration. Often, only one sample per baseline and endpoint is assessed to compare changes in CRP with dietary intervention studies [63]. Significant variation between and within subjects was reported when weekly CRP was assessed during baseline (4 weeks) and treatment (4 weeks each) periods of a supplemental intervention [59]. Thus, the lack of observed changes in CRP with dried-fruit interventions may reflect the variability of this biomarker due to uncontrolled factors rather than lack of anti-inflammatory benefits.

TNF-α is another commonly measured marker of systemic inflammation and immunological activation. A parallel group randomized controlled trial of healthy adults aged 50–70 years compared the effect of daily raisin consumption (1 cup/day) for 6 weeks, independently (n = 12) or with a prescribed walking intervention (n = 10) *versus* walking alone (n = 12) on TNF-α, sICAM-1, IL-8, and monocyte chemotactic protein-1 [66]. All treatments resulted in comparable reductions in sICAM-1, while plasma IL-8 and MCP-1 remained unchanged. Plasma TNF-α decreased in the raisin-only intervention but remained unchanged in the other arms. The reduction in sICAM-1 after raisin consumption may be mediated through reduced TNF-α, which activates NF-κB and thereby upregulates sICAM-1 expression. Though investigators could not explain why TNF-α did not change in the walking-plus-raisins group, they suggested that exercise lowered sICAM-1 through an alternative mechanism by increasing antioxidant status. In contrast, daily raisin consumption (36 g/day) for 24 weeks by men and post-menopausal women diagnosed with type-2 diabetes (n = 26) did not alter serum concentrations of TNF-α or IL-6 [63]. However, the portion consumed in this study was much smaller. A 36 g portion is approximately one-quarter cup, whereas one cup was consumed daily in the aforementioned trial.

17.4.3 Blood Pressure

The effect of dried-fruit consumption on blood pressure is more consistent based on current evidence. Raisins support blood pressure reductions at varying intake levels and durations. In a parallel design study, overweight and obese adults (BMI 25–34.9 kg/m^2) consumed either an ounce (28.35 g) of raisins (n = 31) or a 100-calorie portion of a processed snack (n = 15), three times daily for 12 weeks. Eligible participants had impaired fasting serum or plasma glucose, defined as 90–150 mg/dL, and elevated blood pressure (SBP >120–160 mm Hg or DBP >80–100 mm Hg) at baseline. Among those consuming raisins, blood pressure significantly decreased from baseline (mean change –5.4 mm Hg for SBP and –4.5 mm Hg for DBP) and relative to the comparator group consuming processed snacks [67]. A similar study was undertaken in adults with type-2 diabetes (BMI 25–50 kg/m^2), comparing the effect of consuming raisins (1 oz, three times daily; n = 27) *versus* processed snacks (100-calorie portions, three times daily; n = 19) for 12 weeks on various metabolic outcomes including blood pressure. The raisin intervention decreased SBP by 8.7 mm Hg relative to the control group, but did not affect DBP [68]. Participants remained weight stable in both studies, supporting the effectiveness of the raisin intervention rather than weight change.

A shorter 6-week intervention in healthy adults 50–70 years of age ($n = 12$) consuming 1 cup of raisins daily decreased SBP by 2.2% relative to baseline ($P = 0.008$). However, the same change was observed for comparator groups assigned to either a walking ($n = 12$) or walking plus 1 cup per day raisins ($n = 10$) intervention [66]. DBP did not change. As weight remained stable in all groups, the change was attributed to the interventions. In contrast, two daily servings (36 g/day) of raisins consumed by adults with type-2 diabetes ($n = 26$) for 24 weeks decreased DBP from baseline (71.4 ± 8 *versus* 76.8 ± 10.5 mm Hg, $P = 0.013$), but not SBP [63].

Phytochemicals or unique properties of nutrients delivered within a food matrix may significantly contribute to blood pressure reduction. This concept is best exemplified by a controlled dietary intervention comparing a Dietary Approaches to Stop Hypertension (DASH)-type diet to a Western-type diet equal in sodium but supplemented with potassium, magnesium, and fiber [69]. The blood pressure–lowering effect of the DASH diet is often attributed to these nutrients. Yet, participants with elevated blood pressure and abdominal obesity had significantly lower SBP and DBP after following a DASH diet for 3 weeks, compared to the supplemented Western-type diet. The DASH diet also improved arterial elasticity and reduced the aortic augmentation index, indicating decreased arterial stiffness. Importantly, sodium was equal across diets.

Polyphenols are speculated to be responsible for the additional blood pressure-lowering benefits of fruits. Post-menopausal women with pre- and stage 1 hypertension supplemented with 22 g freeze-dried blueberries (equivalent to 1 cup fresh) daily for 8 weeks had significantly lower brachial SBP (–5.1%) and DBP (–6.3%) and improved peripheral arterial stiffness, as evidenced by decreased brachial-ankle PMV ($P < 0.01$), compared to placebo [70]. NO concentrations were also significantly increased in the blueberry group after 8 weeks supplementation. The increase in NO after chronic daily blueberry consumption is likely mediated through inhibition of NADPH oxidase by polyphenols [55], which thereby increases NO bioavailability.

Thus, the sum of evidence indicates that dried-fruit consumption is associated with improved measures of endothelial health, inflammation, and blood pressure. Their vascular effects appear to be mediated by supporting NO availability. They may increase production by upregulating NOS expression or activation or by opposing oxidative stress. Several mechanisms may operate simultaneously.

Several components of dried fruits may be responsible for these actions, including polyphenols and browning reaction products. However, dried fruits are also good sources of nutrients with established vascular health benefits. While not entirely responsible for the vascular benefits of fruits, potassium and fiber are likely contributors. Consumers of dried fruits, who have lower blood pressure on average, achieve greater daily intakes of potassium and fiber than non-consumers [6]. Observational and experimental evidence support the role of potassium and fiber in endothelial and vascular function.

A systematic review of controlled intervention studies reports improved endothelial and vascular function with increased potassium intake, particularly among individuals with high sodium intake [12]. Changes in blood pressure may mediate the vascular improvements. An inverse association between potassium intake and blood pressure has been demonstrated, with each 1,000 mg increase in potassium associated with a 1.04 mmHg (95% confidence interval, 0.27–1.82) decrease in SBP and 0.75 mmHg (95% confidence interval, 0.22–1.28) decrease in DBP [71]. A meta-analysis of randomized controlled trials and observational prospective cohort

studies also supports the role of potassium in lowering blood pressure, at least in hypertensive individuals [72]. Many dried fruits contain potassium, though dried apricots and peaches are particularly good sources, containing 465 mg and 398 mg potassium, respectively, per 40 g serving.

Several dried fruits are also good sources of fiber, containing at least 2.5 g per ¼ cup (40 g) serving. Cross-sectional evidence supports an association between higher fiber intake and lower blood pressure. Among adults, the odds of having hypertension were significantly reduced for those consuming the highest *versus* lowest quintile of total dietary fiber (0.71, 95% confidence interval 0.54–0.93; $P < 0.02$) and fiber from dried fruits, specifically (0.76, 95% confidence interval 0.62–0.92; $P < 0.01$) [10]. In middle-aged adults, greater total fiber intake of 6.8 g per 1000 kcal was associated with a 1.69 mmHg lower SBP, after adjustments for lifestyle factors and BMI [11]. The primary source of dietary fiber was fruits, a high potassium food group. After further adjustment for urinary potassium excretion, the association was no longer significant. This finding suggests that, in this population, lower blood pressure associated with high fiber diets may have been confounded by higher potassium intakes. Nonetheless, the benefit of fiber is supported by a meta-analysis of randomized placebo-controlled trials concluding that fiber supplementation significantly reduces DBP, though the decrease in SBP was non-significant [73]. Reductions were greatest for older (>40 years) and for hypertensive populations.

Fiber may benefit vascular health by protecting against arterial stiffening. Elasticity of healthy arteries allows them to respond to changes in blood flow. In contrast, increasing blood flow through stiff arteries increases SBP and cardiac afterload, thereby heightening CVD risk. Blood pressure reciprocally influences vascular stiffening, as remodeling is stimulated in response to vessel wall stress. A 24-year longitudinal study following adolescents into adulthood found fiber to be protective against development of carotid arterial stiffness, as assessed by ultrasound [74]. The association remained significant after adjustment for energy intake, smoking, alcohol consumption, and physical activity. Further adjustment for mean arterial pressure only weakly attenuated the association, indicating that blood pressure was not mediating the relationship between fiber and artery stiffness. Individuals with the stiffest arteries (tertile 3) in adulthood also consumed significantly less fruit (–32.6 g/day) throughout adolescence than those in the lowest tertile of artery stiffness, after adjusting for energy intake and lifestyle factors. The association was greatly attenuated (~65%) by adjusting for fiber, supporting the hypothesis that fiber itself is protective against arterial stiffening. Thus, high fiber intakes may benefit vascular health independently of any observed changes in blood pressure, and dried fruits can contribute valuably to daily fiber intake.

17.5 Conclusion

Cardio-metabolic impairments underlie the vast majority of non-communicable diseases worldwide. Over the past few decades, the importance of vascular health in the etiology of chronic disease has been recognized. Assessment methodology has evolved, yielding techniques to detect preclinical changes predictive of disease risk. Greater implementation will improve our understanding of how diet impacts vascular health.

The available evidence indicates that dried-fruit consumption may improve cardio-metabolic health in the context of a healthy dietary pattern. Fruits, and the nutrients they contain, are under-consumed in the United States. Dried fruits represent convenient, shelf-stable forms of fruits that are options for meeting fruit recommendations in the 2015–2020 Dietary Guidelines for Americans. Further research is needed to clarify the extent to which phytochemicals are altered by processing and whether this affects their bioactivity. Elucidating the mechanisms and phytochemicals responsible can also help to identify processing techniques (e.g., heat-drying *versus* freeze-drying) or particular fruits that best promote vascular health.

References

1. Institute for Health Metrics and Evaluation (IHME), GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2016. Published online at: http://vizhub.healthdata.org/gbd-compare (accessed June 20, 2018).
2. International Diabetes Federation (IDF), IDF Worldwide Definition of the Metabolic Syndrome. Published online at: http://www.idf.org/metabolic-syndrome (accessed June 20, 2018).
3. Aguilar, M., Bhuket, T., Torres, S., Liu, B., and Wong, R.J., Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA*, 313, 1973–1974, 2015.
4. Moore, L.V., and Thompson, F.E., Adults meeting fruit and vegetable intake recommendations – United States, 2013. *MMWR Morb. Mortal. Wkly Rep.*, 64, 709–713, 2015.
5. Bachman, J.L, Reedy, J., Subar, A.F., and Krebs-Smith, S.M., Sources of food group intakes among the US population, 2001–2002. *J. Am. Diet. Assoc.*, 108, 804–814, 2008.
6. Keast, D.R., O'Neil, C.E., and Jones, J.M., Dried fruit consumption is associated with improved diet quality and reduced obesity in US adults: National Health and Nutrition Examination Survey, 1999–2004. *Nutr. Res.*, 31,460–467, 2011.
7. U.S. Department of Agriculture (USDA), 2015–2020 Dietary Guidelines for Americans, 8th Edition. December 2015. Published online at: http://health.gov/dietaryguidelines/2015/guidelines/ (accessed March 28, 2018).
8. U.S. Department of Agriculture (USDA), USDA National Nutrient Database for Standard Reference Legacy Release, 2018. Published online at https://ndb.nal.usda.gov/ndb/search/list (accessed June 20, 2018).
9. Hossain, A., Yamaguchi, F., Matsuo, T., Tsukamoto, I., Toyoda, Y., Ogawa, M., Nagata, Y. et al., Rare sugar D-allulose: Potential role and therapeutic monitoring in maintaining obesity and type 2 diabetes mellitus. *Pharmacol. Ther.*, 155, 49–59, 2015.
10. Lairon, D., Arnault, N., Bertrais, S., Planells, R., Clero, E., Hercberg, S., and Boutron-Ruault, M.C., Dietary fiber intake and risk factors for cardiovascular disease in French adults. *Am. J. Clin. Nutr.*, 82, 1185–1194, 2005.
11. Aljuraiban, G.S., Griep, L.M., Chan, Q., Daviglus, M.L., Stamler, J., Van Horn, L., Elliot, P. et al., Total, insoluble and soluble dietary fibre intake in relation to blood pressure: The INTERMAP Study. *Br. J. Nutr.*, 114, 1480–1486, 2015.
12. Blanch, N., Clifton, P.M., and Keogh, J.B., A systematic review of vascular and endothelial function: Effects of fruit, vegetable and potassium intake. *Nutr. Metab. Cardiovasc. Dis.*, 25, 253–266, 2015.

13. Vlachopoulos, C., Aznaouridis, K., and Stefanadis, C., Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *J. Am. Coll. Cardiol.*, 55, 1318–1327, 2010.
14. Aatola, H., Koivistoinen, T., Hutri-Kähönen, N., Juonala, M., Mikkilä, V., Lehtimäki, T., Viikari, J.S. et al., Lifetime fruit and vegetable consumption and arterial pulse wave velocity in adulthood: The Cardiovascular Risk in Young Finns Study. *Circulation*, 122, 2521–2528, 2010.
15. Järvisalo, M.J., Juonala, M., and Raitakari, O.T., Assessment of inflammatory markers and endothelial function. *Curr. Opin. Clin. Metab. Care*, 9, 547–552, 2006.
16. Nettleton, J.A., Steffen, L.M., Mayer-Davis, E.J., Jenny, N.S., Jiang, R., Herrington, D.M., and Jacobs, D.R. Jr., Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am. J. Clin. Nutr.*, 83, 1369–1379, 2006.
17. Lopez-Garcia, E., Schulze, M.B., Fung, T.T., Meigs, J.B., Rifai, N., Manson, J.E., and Hu, F.B., Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *Am. J. Clin. Nutr.*, 80, 1029–1036, 2004.
18. Sijtsma, F.P., Meyer, K.A., Steffen, L.M., Van Horn, L., Shikany, J.M., Odegaard, A.O., Gross, M.D. et al., Diet quality and markers of endothelial function: The CARDIA study. *Nutr. Metab. Cardiovasc. Dis.*, 24, 632–638, 2014.
19. Salas-Salvadó, J., Garcia-Arellano, A., Estruch, R., Marquez-Sandoval, F., Corella, D., Fiol, M., Gómez-Gracia, E., Viñoles, E. et al., Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur. J. Clin. Nutr.*, 62, 651–659, 2008.
20. Deanfield, J.E., Halcox, J.P., and Rabelink, T.J., Endothelial function and dysfunction: Testing and clinical relevance. *Circulation*, 115, 1285–1295, 2007.
21. Root, M.M., McGinn, M.C., Nieman, D.C., Henson, D.A., Heinz, D.A., Shanley, R.A., Knab, A.M. et al., Combined fruit and vegetable intake is correlated with improved inflammatory and oxidant status from a cross-sectional study in a community setting. *Nutrients*, 4, 29–41, 2012.
22. Holt, E.M., Steffen, L.M., Moran, A., Basu, S., Steinberger, J., Ross, J.A., Hong, C.P. et al., Fruit and vegetable consumption and its relation to markers of inflammation and oxidative stress in adolescents. *J. Am. Diet. Assoc.*, 109, 414–421, 2009.
23. Gao, X., Bermudez, O.I., and Tucker, K.L., Plasma C-reactive protein and homocysteine concentrations are related to frequent fruit and vegetable intake in Hispanic and non-Hispanic white elders. *J. Nutr.*, 134, 913–918, 2004.
24. Fisk, P.S., Middaugh, A.L., Rhee, Y.S., and Brunt, A.R., Few favorable associations between fruit and vegetable intake and biomarkers for chronic disease risk in American adults. *Nutr. Res.*, 31, 616–624, 2011.
25. Esmaillzadeh, A., Kimiagar, M., Mehrabi, Y., Azadbakht, L., Hu, F.B., and Willet, W.C., Fruit and vegetable intakes, C-reactive protein, and the metabolic syndrome. *Am. J. Clin. Nutr.*, 84, 1489–1497, 2006.
26. Oliveira, A., Rodríguez-Artalejo, F., and Lopes, C., The association of fruits, vegetables, antioxidant vitamins and fibre intake with high-sensitivity C-reactive protein: Sex and body mass index interactions. *Eur. J. Clin. Nutr.*, 63, 1345–1352, 2009.

27. Wannamethee, S.G., Lowe, G.D., Rumley, A., Bruckdorfer, K.R., and Whincup, P.H., Associations of vitamin C status, fruit and vegetable intakes, and markers of inflammation and hemostasis. *Am. J. Clin. Nutr.*, 83, 567–574, 2006.
28. Hickling, S., Hung, J., Knuiman, M., Divitini, M., and Beilby, J., Are the associations between diet and C-reactive protein independent of obesity? *Prev. Med.*, 47, 71–76, 2008.
29. Zhu, Y., Zhang, Y., Ling, W., Feng, D., Wei, X., Yang, C., and Ma, J., Fruit consumption is associated with lower carotid intima-media thickness and C-reactive protein levels in patients with type 2 diabetes mellitus. *J. Am. Diet. Assoc.*, 111, 1536–1542, 2011.
30. Centritto, F., Iacoviello, L., di Giuseppe, R., De Curtis, A., Costanzo, S., Zito, F., Grioni, S. et al., Dietary patterns, cardiovascular risk factors and C-reactive protein in a healthy Italian population. *Nutr. Metab. Cardiovasc. Dis.*, 19, 697–706, 2009.
31. Bhupathiraju, S.N., and Tucker, K.L., Greater variety in fruit and vegetable intake is associated with lower inflammation in Puerto Rican adults. *Am. J. Clin. Nutr.*, 93, 37–46, 2011.
32. Law, M.R., Morris, J.K., and Wald, N.J., Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*, 338, b1665, 2009.
33. Shimbo, D., Muntner, P., Mann, D., Viera, A.J., Homma, S., Polak, J.F., Barr, R.G. et al., Endothelial dysfunction and the risk of hypertension: The multiethnic study of atherosclerosis. *Hypertension*, 55, 1210–1216, 2010.
34. Juonala, M., Viikari, J.S., Rönnemaa, T., Helenius, H., Taittonen, L., and Raitakari, O.T., Elevated blood pressure in adolescent boys predicts endothelial dysfunction: The cardiovascular risk in young Finns study. *Hypertension*, 48, 424–430, 2006.
35. Dharmashankar, K., and Widlansky, M.E., Vascular endothelial function and hypertension: Insights and directions. *Curr. Hypertens. Rep.*, 12, 448–455, 2010.
36. Ndanuko, R.N., Tapsell, L.C., Charlton, K.E., Neale, E.P., and Batterham, M.J., Associations between dietary patterns and blood pressure in a clinical sample of overweight adults. *J. Acad. Nutr. Diet.*, 117, 228–239, 2017.
37. Vernay, M., Aïdara, M., Salanave, B., Deschamps, V., Malon, A., Oleko, A., Mallion, J.M. et al., Diet and blood pressure in 18–74-year-old adults: The French Nutrition and Health Survey (ENNS, 2006–2007). *J. Hypertens.*, 30, 1920–1927, 2012.
38. Abdel-Hamid, G.A., and Ayuob, N.N., Can raisins ameliorate the hypercholesterolaemia-induced cardiac affection? *Folia Morphol. (Warsz)*, 74, 106–117, 2015.
39. Böger, R.H., Sydow, K., Borlak, J., Thum, T., Lenzen, H., Schubert, B., Tsikas, D. et al., LDL cholesterol upregulates synthesis of asymmetrical dimethylarginine in human endothelial cells: Involvement of S-adenosylmethionine-dependent methyltransferases. *Circ. Res.*, 87, 99–105, 2000.
40. Vogel, R.A., Corretti, M.C., and Plotnick, G.D., Effect of a single high-fat meal on endothelial function in healthy subjects. *Am. J. Cardiol.*, 79, 350–354, 1997.
41. Zern, T.L., West, K.L., and Fernandez, M.L., Grape polyphenols decrease plasma triglycerides and cholesterol accumulation in the aorta of ovariectomized guinea pigs. *J. Nutr.*, 133, 2268–2272, 2003.

42. Jakobek, L., Interactions of polyphenols with carbohydrates, lipids and proteins. *Food Chem.*, 175, 556–567, 2015.
43. Pal, S., Ho, N., Santos, C., Dubois, P., Mamo, J., Croft, K., and Allister, E., Red wine polyphenolics increase LDL receptor expression and activity and suppress the secretion of ApoB100 from human HepG2 cells. *J. Nutr.*, 133, 700–706, 2003.
44. Pal, S., Ho, S.S., and Takechi, R., Red wine polyphenolics suppress the secretion of ApoB48 from human intestinal CaCo-2 cells. *J. Agric. Food Chem.*, 53, 2767–2772, 2005.
45. Muniyappa, R., and Sowers, J.R., Role of insulin resistance in endothelial dysfunction. *Rev. Endocr. Metab. Disord.*, 14, 5–12, 2013.
46. Yanni, A.E., Efthymiou, V., Lelovas, R., Agrogiannis, G., Kostomitsopoulos, N., and Karathanos, V.T., Effects of dietary Corinthian currants (*Vitis vinifera* L., var. Apyrena) on atherosclerosis and plasma phenolic compounds during prolonged hypercholesterolemia in New Zealand White rabbits. *Food Funct.*, 6, 963–971, 2015.
47. Collins, T., and Cybulsky, M.I., NF-kappaB: Pivotal mediator or innocent bystander in atherogenesis? *J. Clin. Invest.*, 107, 255–264, 2001.
48. Jabeen, Q., Aslam, N., Akram, A., and Iqbal, Z., Evaluation of prunes for hypotensive, angiotensin converting enzyme (ACE) inhibitory and diuretic activities in rats. *J. Med. Plants Res.*, 6, 1361–1366, 2012.
49. Alamgeer, I.S., Asif, H., and Saleem, M., Evaluation of antihypertensive potential of *Ficus carica* fruit. *Pharm. Biol.*, 55, 1047–1053, 2017.
50. Soares De Moura, R., Costa Viana, F.S., Souza, M.A., Kovary, K., Guedes, D.C., Oliveira, E.P., Rubenich, L.M. et al., Antihypertensive, vasodilator and antioxidant effects of a vinifera grape skin extract. *J. Pharm. Pharmacol.*, 54, 1515–1520, 2002.
51. Edirisinghe, I., Burton-Freeman, B., Varelis, P., and Kappagoda, T., Strawberry extract caused endothelium-dependent relaxation through the activation of PI3 kinase/Akt. *J. Agric. Food Chem.*, 56, 9383–9390, 2008.
52. Leikert, J.F., Räthel, T.R., Wohlfart, P., Cheynier, V., Vollmar, A.M., and Dirsch, V.M., Red wine polyphenols enhance endothelial nitric oxide synthase expression and subsequent nitric oxide release from endothelial cells. *Circulation*, 106, 1614–1617, 2002.
53. Ranilla, L.G., Kwon, Y.I., Genovese, M.I., Lajolo, F.M., and Shetty, K., Antidiabetes and antihypertension potential of commonly consumed carbohydrate sweeteners using *in vitro* models. *J. Med. Food*, 11, 337–348, 2008.
54. McCall, D.O., McGartland, C.P., McKinley, M.C., Patterson, C.C., Sharpe, P., McCance, D.R., Young, I.S. et al., Dietary intake of fruits and vegetables improves microvascular function in hypertensive subjects in a dose-dependent manner. *Circulation*, 119, 2153–2160, 2009.
55. Rodriguez-Mateos, A., Rendeiro, C., Bergillos-Meca, T., Tabatabaee, S., George, T.W., Heiss, C., and Spencer, J.P., Intake and time dependence of blueberry flavonoid-induced improvements in vascular function: A randomized, controlled, double-blind, crossover intervention study with mechanistic insights into biological activity. *Am. J. Clin. Nutr.*, 98, 1179–1191, 2013.
56. Auclair, S., Chironi, G., Milenkovic, D., Hollman, P.C., Renard, C.M., Mégnien, J.L., Gariepy, J. et al., The regular consumption of a polyphenol-rich apple does not influence endothelial function: A randomised double-blind trial in hypercholesterolemic adults. *Eur. J. Clin. Nutr.*, 64, 1158–1165, 2010.

57. Vinson, J.A., Zubik, L, Bose, P., Samman, N., and Proch, J., Dried fruits: Excellent *in vitro* and *in vivo* antioxidants. *J. Am. Coll. Nutr.*, 24, 44–50, 2005.
58. Rock, W., Rosenblat, M., Borochov-Neori, H., Volkova, N., Judeinstein, S., Elias, M., and Aviram, M., Effects of date (*Phoenix dactylifera* L., Medjool or Hallawi Variety) consumption by healthy subjects on serum glucose and lipid levels and on serum oxidative status: A pilot study. *J. Agric. Food Chem.*, 57, 8010–8017, 2009.
59. Parker, T.L., Wang, X.H., Pazmiño, J., and Engeseth, N.J., Antioxidant capacity and phenolic content of grapes, sun-dried raisins, and golden raisins and their effect on *ex vivo* serum antioxidant capacity. *J. Agric. Food Chem.*, 55, 8472–8477, 2007.
60. Mousavi, R., Alizadeh, M., and Saleh-Ghadimi, S., Consumption of 5-hydroxymethylfurfural-rich dried fruits is associated with reduction in urinary excretion of 8-hydroxy-2′-deoxyguanosine: A randomized clinical trial. *Eur. Food. Res. Tech.*, 242, 677–684, 2016.
61. Singh, U., Devaraj, S., Vasquez-Vivar, J., and Jialal, I., C-reactive protein decreases endothelial nitric oxide synthase activity *via* uncoupling. *J. Mol. Cell. Cardiol.*, 43, 780–791, 2007.
62. Hein, T.W., Singh, U., Vasquez-Vivar, J., Devaraj, S., Kuo, L., and Jialal, I., Human C-reactive protein induces endothelial dysfunction and uncoupling of eNOS *in vivo*. *Atherosclerosis*, 206, 61–68, 2009.
63. Kanellos, P.T., Kaliora, A.C., Tentolouris, N.K., Argiana, V., Perrea, D., Kalogeropoulos, N., Kountouri, A.M. et al., A pilot, randomized controlled trial to examine the health outcomes of raisin consumption in patients with diabetes. *Nutrition*, 30, 358–364, 2014.
64. Hooshmand, S., Kern, M., Metti, D., Shamloufard, P., Chai, S.C., Johnson, S.A., Payton, M.E. et al., The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic post-menopausal women: A randomized, controlled trial. *Osteoporos. Int.*, 27, 2271–2279, 2016.
65. Chai, S.C., Hooshmand, S., Saadat, R.L., Payton, M.E., Brummel-Smith, K., and Arjmandi, B.H., Daily apple *versus* dried plum: Impact on cardiovascular disease risk factors in post-menopausal women. *J. Acad. Nutr. Diet.*, 112, 1158–1168, 2012.
66. Puglisi, M.J., Vaishnav, U., Shrestha, S., Torres-Gonzalez, M., Wood, R.J., Volek, J.S., and Fernandez, M.L., Raisins and additional walking have distinct effects on plasma lipids and inflammatory cytokines. *Lipids Health Dis.*, 7, 2008.
67. Anderson, J.W., Weiter, K.M., Christian, A.L., Ritchey, M.B., and Bays, H.E., Raisins compared with other snack effects on glycemia and blood pressure: A randomized, controlled trial. *Postgrad. Med.*, 126, 37–43, 2014.
68. Bays, H., Weiter, K., and Anderson, J., A randomized study of raisins *versus* alternative snacks on glycemic control and other cardiovascular risk factors in patients with type 2 diabetes mellitus. *Phys. Sportsmed.*, 43, 37–43, 2015.
69. Al-Solaiman, Y., Jesri, A., Mountford, W.K., Lackland, D.T., Zhao, Y., and Egan, B.M., DASH lowers blood pressure in obese hypertensives beyond potassium, magnesium and fibre. *J. Hum. Hypertens.*, 24, 237–246, 2010.
70. Johnson, S.A., Figueroa, A., Navaei, N., Wong, A., Kalfon, R., Ormsbee, L.T., Feresin, R.G., et al., Daily blueberry consumption improves blood pressure and arterial stiffness in post-menopausal women with pre- and stage 1-hypertension: A randomized, double-blind, placebo-controlled clinical trial. *J. Acad. Nutr. Diet.*, 115, 369–377, 2015.

71. Zhang, Z., Cogswell, M.E., Gillespie, C., Fang, J., Loustalot, F., Dai, S., Carriquiry, A.L. et al., Association between usual sodium and potassium intake and blood pressure and hypertension among U.S. adults: NHANES 2005–2010. *PLoS One*, 8, e75289, 2013.
72. Aburto, N.J., Hanson, S., Gutierrez, H., Hooper, L., Elliott, P., and Cappuccio, F.P., Effect of increased potassium intake on cardiovascular risk factors and disease: Systematic review and meta-analyses. *BMJ*, 346, f1378, 2013.
73. Streppel, M.T., Arends, L.R., van 't Veer, P., Grobbee, D.E., and Geleijnse, J.M., Dietary fiber and blood pressure: A meta-analysis of randomized placebo-controlled trials. *Arch. Intern. Med.*, 165, 150–156, 2005.
74. van de Laar, R.J., Stehouwer, C.D., van Bussel, B.C., te Velde, S.J., Prins, M.H., Twisk, J.W., and Ferreira, I., Lower lifetime dietary fiber intake is associated with carotid artery stiffness: The Amsterdam Growth and Health Longitudinal Study. *Am. J. Clin. Nutr.*, 96, 14–23, 2012.

Chapter 18

Dried Fruits in the Prevention and Control of Diabetes (Insulin Resistance and Prediabetes)

Kristie (Korbua) Srichaikul, Melody Ong, Zoha Prasla, Yakup Kohen, Iris Mandalozano, Melanie Paquette, Sandhya Sahye-Pudaruth, Darshna Patel, Cyril W.C. Kendall, John L. Sievenpiper, and David J.A. Jenkins

18.1 Introduction 438
18.2 Glycemic Index of Dried Fruits 438
18.3 Impaired Fasting Glucose and Type-2 Diabetes 439
18.4 Type-2 Diabetes Related Health Conditions 440
18.4.1 Blood Pressure 440
18.4.2 Blood Lipids 440
18.4.3 Body Weight 441
18.4.4 Antioxidants and Inflammation 441
18.5 Mechanism of Action 442
18.6 Conclusion 442
References 443

18.1 Introduction

Increased fruit intake has been part of dietary advice for many decades, with recommended intakes for fruits and vegetables set at 5–10 servings per day [1]. Recently, the 2015 dietary guidelines for Americans have also advised three dietary patterns (healthy US-style pattern, healthy vegetarian pattern, and healthy Mediterranean pattern) with fruit intake as a shared theme across all three patterns (total fruit consumption approximately 350–440 g/day) [2]. In cohort studies, fruit and vegetable intake has been related to reduced incidence of stroke, total cardiovascular events, cancer, and all-cause mortality [3–5]. In terms of risk factor reduction, benefits from fruits may be related to the higher potassium and magnesium content and the phenolic and phytosterol levels, as well as the dietary fiber and fructose content (low glycemic index [GI]). In low GI diets, the dietary contents of temperate climate fruits have been shown to be a major driving factor in lowering the GI of the diet as they provide a healthy palatable low GI dietary option that is associated with a reduction in hemoglobin A1c (HbA_{1c}) in type-2 diabetes (T2D) [6].

While there are data on the benefits of fresh fruits on health promotion, the current information on dried fruits is significantly less. Possibly the reason for this lack of attention paid to dried fruits is because of the paucity of this food group in the habitual diet of Western populations, with only 6.9% of the adult population consuming dried fruits, raisins being the major dried fruit consumed as reported in the National Health and Nutrition Examination Surveys (NHANES 1999–2004) [7,8].

Nevertheless, although no prospective cohort studies have reported links between dried-fruit consumption and cardiovascular disease (CVD), and T2D, few cohort studies have demonstrated the association between dry fruit consumption and reduction in cancer incidence or mortality [63]. In addition, there are some data on aspects of glycemic control, insulin sensitivity, and carbohydrate metabolism. Multiple clinical studies have also assessed the benefits of dried fruits on changes in blood pressure (BP), blood lipids, body weight, oxidative stress, inflammatory markers (C-reactive protein, CRP), and satiety, among others [9–16]. This chapter highlights the evidence of the benefits of dried fruits on glycemic response, standardized as GI, and their effects on T2D related cardiometabolic health conditions including BP, serum lipids, body weight, and inflammation.

18.2 Glycemic Index of Dried Fruits

Fruits contain fruit sugar (fructose) as well as glucose and sucrose (the disaccharides of fructose and glucose). Fructose is a low GI sugar with a GI on the bread scale of approximately 30 [17]. With the average of all sugars giving a GI lower than bread, some improvement in blood glucose control in diabetes might be expected with the use of dried fruits, as has been seen in the effect of temperate-climate fresh fruits on HbA_{1c} as the clinical marker of glycemic control in diabetes [6]. As can be seen in Figure 18.1, when the more temperate-climate fruits were dried (pears, peaches, apricots, apples, and plums), lower GI values were also seen [18]. For example, in a study with 31 healthy adults, GI values of raisins were found to be moderate (from 49.4 to 62.3, on a glucose scale) in a study where raisins were also found to have a low insulin index [19]. Nonetheless, in the GI Table of Atkinson et al. [18], the mean GI of raisins on the bread scale was 93, which is toward the high end of the moderate

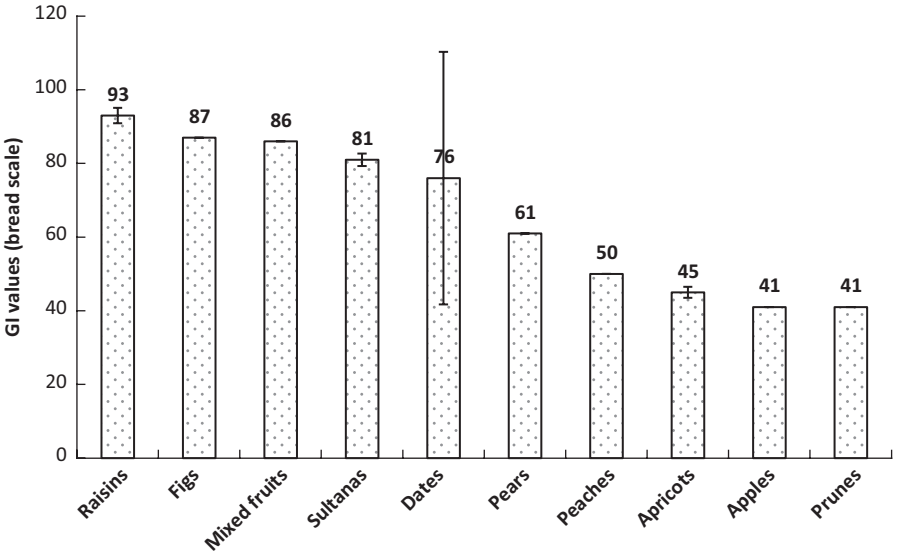


Figure 18.1 Glycemic index values of dried fruits (based on the bread scale) with their respective standard deviations. (Adapted from Atkinson, F.S. et al., *Diabetes Care*, 31, 2281, 2008. With permission.)

range. Only four GI values of fresh fruits were available for comparison with their dried-fruit counterparts (two had GI values above their dried fruit equivalents). Fresh apricots had a GI value of 49 compared to 45 for dried apricots, and fresh apples (Golden delicious) had a GI value of 46 compared to 41 for dried apples. Two comparisons had GI values below their dried fruit equivalents. Black grapes had a GI of 84 compared to a GI of 93 for raisins. Soft, early ripened dates had a GI value of 67 compared to dried dates with a GI of 76 [18].

The low GI fruit sugar, fructose, in soft drinks, however, has been blamed for adverse effects in terms of obesity, especially in the young, and for worsening metabolic syndrome (MetS) [20–23]. Nevertheless, the effects have only been reported in hypercaloric diets or at high levels of fructose intakes [24]. These effects may, therefore, not be relevant when fructose is consumed in the amounts present in a moderate intake of dried fruits.

18.3 Impaired Fasting Glucose and Type-2 Diabetes

When raisins were used as a snack at 1 oz (~28.3 g) three times/day for 12 weeks compared to a non-fruit snack in a study of 46 participants with moderately raised systolic BP (129.2 mmHg) and with moderately raised fasting blood glucose levels, a 0.12% reduction was seen in HbA_{1c} ($P = 0.004$), following consumption of raisins compared to the control group, suggesting significantly greater blood glucose control (10). Similarly, in a study of 36 participants with T2D fed 50 g of freeze-dried strawberries (equal to 500 g fresh strawberries) for 6 weeks, a significant reduction was seen in HbA_{1c} (−0.47% test, +0.15% control). HbA_{1c} reduction was also associated with a reduced low-density lipoprotein (LDL) oxidation (as malondialdehyde) and

a reduced CRP, a marker of inflammation and CVD risk [25]. These data, hence, suggest improved diabetes control and a reduced risk of CVD. These studies were supported by a further 12 weeks raisin feeding trial of 1 oz raisins three times/day in 57 participants with T2D, where significant reductions in fasting and post-prandial glucose response were also seen, together with a non-significant reduction in HbA_{1c} also of 0.12%, possibly due to low statistical power [11]. In these studies, however, reported glucose reductions have been small and often included only lower post-prandial glucose or insulin responses (most studies have not been powered sufficiently to detect the effects on HbA_{1c}) [19,26,27].

18.4 Type-2 Diabetes Related Health Conditions

18.4.1 Blood Pressure

Fresh fruit consumption has well-documented effects in reducing BP. Indeed, the key recommendations of the Dietary Approach to Stop Hypertension (DASH), which have been broadly accepted, especially in North America, focused on increased fruit intake, together with increased vegetable and low-fat dairy intake and reduced intake of meat and salty snack foods [28]. Dried fruits are excellent sources of potassium, which is not lost by drying, in contrary enhanced by this process to be more concentrated per unit weight. On the other hand, when drying, the concentration of sodium remains low on a weight-for-weight basis and also in absolute terms per serving (see Chapter 14, Table 14.2). Dried fruits also contain magnesium and calcium, both minerals being associated with BP reduction. This combination of high potassium, low sodium, and the presence of magnesium and calcium would be expected to lower BP and so be responsible for the BP-lowering effect of dried fruits. This anticipated BP-lowering effect has been demonstrated for raisins of between –6.0 and –10.2 mmHg [10–12,29,30] and also for freeze-dried strawberries, with a substantial reduction in either systolic or diastolic BP [31,32] of as much as –8 mmHg for the test compared to non-fruit control snacks [11]. The observed BP reduction commends the use of dried fruits, along with fresh fruits, in the control of BP. The BP effect is important when considering the effect of dried-fruit consumption in diabetes. We suggest that the lower GI of dried fruits may reduce insulin levels post-prandially, limiting the effect of insulin on the kidney in retaining sodium and hence contributing to a reduction in BP [33]. This reduction in BP may limit glomerular damage, for which those with diabetes are at especially higher risk, and further suggest a role for dried fruits, especially temperate-climate dried fruits.

18.4.2 Blood Lipids

The effect of dried fruits on blood lipids has, in general, been neutral, with no major reduction in total or LDL cholesterol [30,32,34–38]. However, in one study of hyperlipidemic participants, a high dose of 120 g/day of raisins resulted in a 13% reduction in total cholesterol and a 16% reduction in LDL cholesterol [39]. Certainly, dried fruits contain zero saturated fat or cholesterol and so might be predicted to have additional "bad food" displacement potential [40] when large amounts are consumed [39]. Their content of viscous fiber, although small, might also have contributed a

cholesterol-lowering effect. Freeze-dried strawberries at 50 g/day have also been shown to lower serum total and LDL cholesterol and, interestingly, to also reduce another risk factor for CVD, namely small dense LDL particle size [31]. At any rate, no studies have reported increased triacylglycerols (TAG) or lowered high-density lipoprotein (HDL) cholesterol associated with dried-fruit consumption [39] and, therefore, there is no evidence that they would worsen MetS. However, the effects of large intakes of dried fruits have not been reported in vulnerable populations (e.g., subjects with MetS and/or prediabetes) and these data are, therefore, not available to guide clinical decisions. At present, one can conclude that dried fruits can be tried in the management of hyperlipidemic individuals with no deleterious effects and possibly benefits. These data are important in view of the concerns on blood lipid control and the increased risk of CVD seen in individuals with diabetes.

18.4.3 Body Weight

Dried-fruit consumption has been associated with an improvement in diet quality and, in turn, lower rates of overweight and obesity in adults in the United States in the NHANES survey of 1999–2004 [7]. The NHANES survey of 13,292 adults showed that those who consumed more than 20 g of dried fruits daily had a lower body mass index (BMI) and waist circumference, suggesting benefits of dried-fruit consumption for MetS [7]. However, with the average intake of dried fruits approximated at 6 g/day, considerably more dried fruits would have to be consumed at the individual level to lead to a population difference. Furthermore, the pairing of dried fruits with nuts in popular healthy snacks, such as "trail mix," may be a way to increase dried-fruit consumption. This pairing approach, however, may raise the question in population surveys of whether the benefits ascribed to dried fruits may indeed be the result of their pairing with nuts, which have demonstrated multiple benefits in relation to reduced CVD, T2D incidence, improved diabetes control, lower blood lipids, and at least a neutral effect on body weight [8,41–44].

In relatively short-term clinical trials, raisins, prunes, and freeze-dried strawberry powder have not been demonstrated to have any weight-loss benefit in participants but, on the other hand, no weight gain was noted [25,30,37,45]. Since diabetes is a condition where weight gain may result in worsening glycemic control, the neutral effect of dried fruits on body weight, might encourage the use of dried fruits to reduce post-prandial glucose and to reduce BP as it is a weight-neutral source of potassium, calcium, and magnesium while having a low sodium content. Furthermore, the pairing of dried fruits with nuts may enhance the health benefits of dried fruits through additive or, perhaps, synergistic effects [46].

18.4.4 Antioxidants and Inflammation

Fruits are good sources of antioxidants that appear to be present also in dried fruits [16,47,48], and increased antioxidant activity has been reported in the serum of individuals fed grape extract and raisins. In a further trial of 36 T2D participants, reduced LDL oxidation was seen, as assessed by reduced malondialdehyde, after feeding freeze-dried strawberries for 6 weeks. These effects were also associated with reduced CRP levels [25], indicating reduced inflammation and reduced CVD

risk [49]. The exact physiological effects of these changes are beginning to be elucidated. Reduced LDL oxidation is likely to reduce LDL cholesterol uptake by the scavenger system in the arterial wall, reducing foam cell production from mast cells and, hence, cholesterol plaque formation [50]. A reduced level of inflammation associated with lower CRP levels has also been associated with reduced cancer death in addition to lower CVD events [49]. These areas require further exploration in relation to dried fruits.

18.5 Mechanism of Action

In vitro and *in vivo* studies have been conducted to elucidate the mechanisms by which dried fruits may promote improvement in glycemic control and insulin sensitivity. Rodent studies have been conducted to explore these mechanisms, but the findings have been inconsistent and may have limited applicability to the human setting as key differences exist between rodent and human physiology of glucose metabolism [51], including a limited hepatic storage of glycogen and a dependence on gluconeogenesis in mice to maintain higher daylong blood glucose levels compared to larger mammals such as dogs and humans [51].

In vitro and *in vivo* studies using human cell lines have demonstrated the benefits of grape powder extract in reducing the lipopolysaccharide-mediated inflammatory cascade in macrophages [52] and reduction in tumor necrosis factor-α mediated inflammation and insulin resistance in human adipocytes [53].

In rodent studies, grape polyphenol extract or grape skin extract diets have led to decreased muscle TAG content and increased glucose transporter type 4 expression in an *in vitro* analysis [54], and anti-hyperglycemic effects in further studies [55], respectively. In addition to grapes, date fruit extract was also shown to attenuate neurophysiological and behavioral changes induced in a streptozotocin-induced diabetic rat model and was associated with prevention of diabetic neuropathy [56].

In human studies, dried fruits generally have low to moderate GI. Their higher fructose content and their displacement effect may explain the postprandial glucose and HbA_{1c} reductions that have been noted [10,25]. In addition, magnesium has been shown to improve glycemic control [57]. In magnesium deficiency states, alterations of adenosine triphosphate production and utilization, leading to changes in carbohydrate metabolism and insulin resistance, which have been suggested to increase the risk of T2D [58]. Furthermore, the polyphenols in dried fruits have been proposed to protect pancreatic β-cells against oxidative stress, inflammation, and glucose toxicity, which may prevent development of insulin insensitivity and T2D [59–62].

18.6 Conclusion

It can be concluded that dried fruits need further exploration for their therapeutic effects, especially in T2D blood glucose control and BP reduction. Specific dried fruits, such as raisins, have been shown to promote glycemic control and BP reduction in recent studies. Mechanisms which may help to explain the benefits of dried fruits such as raisins may relate to their relatively lower GI and insulin index potential, high mineral content such as potassium and magnesium, increased

fiber content, and high levels of antioxidant and anti-inflammatory compounds. Furthermore, dried-fruit consumption has not been shown to raise body weight or increase TAG levels. Therefore, the use of dried fruits in combination with nuts, with which they are often paired, could be part of a useful dietary strategy to help reduce the risk of T2D, reduce postprandial glycemic, and possibly decrease the risk of CVD.

References

1. Health Canada, Eating Well with Canada's Food Guide. Published online at: https://www.canada.ca/en/health-canada/services/food-nutrition/canada-food-guide/get-your-copy/eating-well-2007.html (accessed June 28, 2018).
2. Hernandez-Alonso, P., Camacho-Barcia, L., Bullo, M., and Salas-Salvado, J., Nuts and dried fruits: An update of their beneficial effects on type 2 diabetes. *Nutrients*, 9, 673, 2017.
3. Wang, X., Ouyang, Y., Liu, J., Zhu, M., Zhao, G., Bao, W., and Hu, F.B., Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: Systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ*, 349, g4490, 2014.
4. Miller, V., Mente, A., Dehghan, M., Rangarajan, S., Zhang, X., Swaminathan, S., Dagenais, G. et al., Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): A prospective cohort study. *Lancet*, 390, 2037–2049, 2017.
5. Larsson, S.C., Virtamo, J., and Wolk, A., Total and specific fruit and vegetable consumption and risk of stroke: A prospective study. *Atherosclerosis*, 227, 147–152, 2013.
6. Jenkins, D.J., Srichaikul, K., Kendall, C.W., Sievenpiper, J.L., Abdulnour, S., Mirrahimi, A., Meneses, C. et al., The relation of low glycaemic index fruit consumption to glycaemic control and risk factors for coronary heart disease in type 2 diabetes. *Diabetologia*, 54, 271–279, 2011.
7. Keast, D.R., O'Neil, C.E., and Jones, J.M., Dried fruit consumption is associated with improved diet quality and reduced obesity in US adults: National Health and Nutrition Examination Survey, 1999–2004. *Nutr. Res.*, 31, 460–467, 2011.
8. Salas-Salvado, J., Casas-Agustench, P., and Salas-Huetos, A., Cultural and historical aspects of Mediterranean nuts with emphasis on their attributed healthy and nutritional properties. *Nutr. Metab. Cardiovasc. Dis.*, 21(Suppl. 1), S1–S6, 2011.
9. Wilson, T., Luebke, J.L., Morcomb, E.F., Carrell, E.J., Leveranz, M.C., Kobs, L., Schmidt, T.P. et al., Glycemic responses to sweetened dried and raw cranberries in humans with type 2 diabetes. *J. Food Sci.*, 75, H218–H223, 2010.
10. Anderson, J.W., Weiter, K.M., Christian, A.L., Ritchey, M.B., and Bays, H.E., Raisins compared with other snack effects on glycemia and blood pressure: A randomized, controlled trial. *Postgrad. Med.*, 126, 37–43, 2014.
11. Bays, H., Weiter, K., and Anderson, J., A randomized study of raisins *versus* alternative snacks on glycemic control and other cardiovascular risk factors in patients with type 2 diabetes mellitus. *Phys. Sportsmed.*, 43, 37–43, 2015.
12. Sivaprakasapillai, B., Edirisinghe, I., Randolph, J., Steinberg, F., and Kappagoda, T., Effect of grape seed extract on blood pressure in subjects with the metabolic syndrome. *Metabolism*, 58, 1743–1746, 2009.

13. Kanellos, P.T., Kaliora, A.C., Liaskos, C., Tentolouris, N.K., Perrea, D., and Karathanos, V.T., A study of glycemic response to Corinthian raisins in healthy subjects and in type 2 diabetes mellitus patients. *Plant Foods Hum. Nutr.*, 68, 145–148, 2013.
14. Kanellos, P.T., Kaliora, A.C., Protogerou, A.D., Tentolouris, N., Perrea, D.N., and Karathanos, V.T., The effect of raisins on biomarkers of endothelial function and oxidant damage; an open-label and randomized controlled intervention. *Food Res. Int.*, 102, 674–680, 2017.
15. Esfahani, A., Lam, J., and Kendall, C.W., Acute effects of raisin consumption on glucose and insulin reponses in healthy individuals. *J. Nutr. Sci.*, 3, e1, 2014.
16. Hokayem, M., Blond, E., Vidal, H., Lambert, K., Meugnier, E., Feillet-Coudray, C., Coudray, C. et al., Grape polyphenols prevent fructose-induced oxidative stress and insulin resistance in first-degree relatives of type 2 diabetic patients. *Diabetes Care*, 36, 1454–1461, 2013.
17. Jenkins, D.J., Wolever, T.M., Taylor, R.H., Barker, H., Fielden, H., Baldwin, J.M., Bowling, A.C. et al., Glycemic index of foods: A physiological basis for carbohydrate exchange. *Am. J. Clin. Nutr.*, 34, 362–366, 1981.
18. Atkinson, F.S., Foster-Powell, K., and Brand-Miller, J.C., International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*, 31, 2281–2283, 2008.
19. Kim, Y., Hertzler, S.R., Byrne, H.K., and Mattern, C.O., Raisins are a low to moderate glycemic index food with a correspondingly low insulin index. *Nutr. Res.*, 28, 304–308, 2008.
20. Schulze, M.B., Manson, J.E., Ludwig, D.S., Colditz, G.A., Stampfer, M.J., Willett, W.C., and Hu, F.B., Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA*, 292, 927–934, 2004.
21. Malik, V.S., Popkin, B.M., Bray, G.A., Despres, J.P., and Hu, F.B., Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*, 121, 1356–1364, 2010.
22. Malik, V.S., Popkin, B.M., Bray, G.A., Despres, J.P., Willett, W.C., and Hu, F.B., Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: A Meta-Analysis. *Diabetes Care*, 33, 2477–2483, 2010.
23. Malik, V.S., Willett, W.C., and Hu, F.B., Sugar-sweetened beverages and BMI in children and adolescents: Reanalyses of a meta-analysis. *Am. J. Clin. Nutr.*, 89, 438–439; author reply 439–440, 2009.
24. Sievenpiper, J.L., de Souza, R.J., Mirrahimi, A., Yu, M.E., Carleton, A.J., Beyene, J., Chiavaroli, L. et al., Effect of fructose on body weight in controlled feeding trials: A systematic review and meta-analysis. *Ann. Intern. Med.*, 156, 291–304, 2012.
25. Moazen, S., Amani, R., Homayouni Rad, A., Shahbazian, H., Ahmadi, K., and Taha Jalali, M., Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: A randomized double-blind controlled trial. *Ann. Nutr. Metab.*, 63, 256–264, 2013.
26. Rasmussen, O., Winther, E., and Hermansen, K., Postprandial glucose and insulin responses to rolled oats ingested raw, cooked or as a mixture with raisins in normal subjects and type 2 diabetic patients. *Diabet. Med.*, 6, 337–341, 1989.
27. Kaliora, A.C., Kanellos, P.T., Gioxari, A., and Karathanos, V.T., Regulation of GIP and ghrelin in healthy subjects fed on sun-dried raisins: A pilot study with a crossover trial design. *J. Med. Food*., 20, 301–308, 2017.

28. Appel, L.J., Moore, T.J., Obarzanek, E., Vollmer, W.M., Svetkey, L.P., Sacks, F.M., Bray, G.A. et al., A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N. Engl. J. Med.*, 336, 1117–1124, 1997.
29. Kaliora, A.C., Kokkinos, A., Diolintzi, A., Stoupaki, M., Gioxari, A., Kanellos, P.T., Dedoussis, G.V. et al., The effect of minimal dietary changes with raisins in NAFLD patients with non-significant fibrosis: A randomized controlled intervention. *Food Funct.*, 7, 4533–4544, 2016.
30. Kanellos, P.T., Kaliora, A.C., Tentolouris, N.K., Argiana, V., Perrea, D., Kalogeropoulos, N., Kountouri, A.M. et al., A pilot, randomized controlled trial to examine the health outcomes of raisin consumption in patients with diabetes. *Nutrition*, 30, 358–364, 2014.
31. Basu, A., Betts, N.M., Nguyen, A., Newman, E.D., Fu, D., and Lyons, T.J., Freeze-dried strawberries lower serum cholesterol and lipid peroxidation in adults with abdominal adiposity and elevated serum lipids. *J. Nutr.*, 144, 830–837, 2014.
32. Djurica, D., Holt, R.R., Ren, J., Shindel, A.W., Hackman, R.M., and Keen, C.L., Effects of a dietary strawberry powder on parameters of vascular health in adolescent males. *Br. J. Nutr.*, 116, 639–647, 2016.
33. DeFronzo, R.A., The effect of insulin on renal sodium metabolism. A review with clinical implications. *Diabetologia*, 21, 165–171, 1981.
34. Vidlar, A., Vostalova, J., Ulrichova, J., Student, V., Stejskal, D., Reichenbach, R., Vrbkova, J. et al., The effectiveness of dried cranberries (*Vaccinium macrocarpon*) in men with lower urinary tract symptoms. *Br. J. Nutr.*, 104, 1181–1189, 2010.
35. Eid, N., Osmanova, H., Natchez, C., Walton, G., Costabile, A., Gibson, G., Rowland, I. et al., Impact of palm date consumption on microbiota growth and large intestinal health: A randomised, controlled, cross-over, human intervention study. *Br. J. Nutr.*, 114, 1226–1236, 2015.
36. Peterson, J.M., Montgomery, S., Haddad, E., Kearney, L., and Tonstad, S., Effect of consumption of dried California mission figs on lipid concentrations. *Ann. Nutr. Metab.*, 58, 232–238, 2011.
37. Chai, S.C., Hooshmand, S., Saadat, R.L., Payton, M.E., Brummel-Smith, K., and Arjmandi, B.H., Daily apple *versus* dried plum: Impact on cardiovascular disease risk factors in postmenopausal women. *J. Acad. Nutr. Diet.*, 112, 1158–1168, 2012.
38. Zunino, S.J., Parelman, M.A., Freytag, T.L., Stephensen, C.B., Kelley, D.S., Mackey, B.E., Woodhouse, L.R. et al., Effects of dietary strawberry powder on blood lipids and inflammatory markers in obese human subjects. *Br. J. Nutr.*, 108, 900–909, 2012.
39. Spiller, G., and Bruce, B., Regular consumption of high fiber carbohydrate foods such as sun dried raisins and whole grain breads does not raise serum triglycerides. *FASEB J.*, 12(Suppl.), A654–A654, 1998.
40. Jenkins, D.J., Mirrahimi, A., Srichaikul, K., Berryman, C.E., Wang, L., Carleton, A., Abdulnour, S. et al., Soy protein reduces serum cholesterol by both intrinsic and food displacement mechanisms. *J. Nutr.*, 140(Suppl.), 2302S–2311S, 2010.
41. Bes-Rastrollo, M., Sabate, J., Gomez-Gracia, E., Alonso, A., Martinez, J.A., and Martinez-Gonzalez, M.A., Nut consumption and weight gain in a Mediterranean cohort: The SUN study. *Obesity (Silver Spring)*, 15, 107–116, 2007.
42. Sabate, J., Nut consumption and body weight. *Am. J. Clin. Nutr.*, 78(Suppl.) 647S–650S, 2003.

43. Sabate, J., Nut consumption and change in weight: The weight of the evidence. *Br. J. Nutr.*, 98, 456–457, 2007.
44. Jenkins, D.J., Kendall, C.W., Lamarche, B., Banach, M.S., Srichaikul, K., Vidgen, E., Mitchell, S. et al., Nuts as a replacement for carbohydrates in the diabetic diet—a re-analysis of a randomized controlled trial. *Diabetologia*, 61, 1734–1747, 2018.
45. Basu, A., Wilkinson, M., Penugonda, K., Simmons, B., Betts, N.M., and Lyons, T.J., Freeze-dried strawberry powder improves lipid profile and lipid peroxidation in women with metabolic syndrome: Baseline and post intervention effects. *Nutr. J.*, 8, 43, 2009.
46. Carughi, A., Feeney, M.J., Kris-Etherton, P., Fulgoni, V., 3rd, Kendall, C.W., Bullo, M., and Webb, D., Pairing nuts and dried fruit for cardiometabolic health. *Nutr. J.*, 15, 23, 2016.
47. Rankin, J.W., Andreae, M.C., Oliver Chen, C.Y., and O'Keefe, S.F., Effect of raisin consumption on oxidative stress and inflammation in obesity. *Diabetes Obes. Metab.*, 10, 1086–1096, 2008.
48. Vinson, J.A., Zubik, L., Bose, P., Samman, N., and Proch, J., Dried fruits: Excellent *in vitro* and *in vivo* antioxidants. *J. Am. Coll. Nutr.*, 24, 44–50, 2005.
49. Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F. et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N. Engl. J. Med.*, 377, 1119–1131, 2017.
50. Steinberg, D., Low density lipoprotein oxidation and its pathobiological significance. *J. Biol. Chem.*, 272, 20963–20966, 1997.
51. Kowalski, G.M., and Bruce, C.R., The regulation of glucose metabolism: Implications and considerations for the assessment of glucose homeostasis in rodents. *Am. J. Physiol. Endocrinol. Metab.*, 307, E859–E871, 2014.
52. Overman, A., Bumrungpert, A., Kennedy, A., Martinez, K., Chuang, C.C., West, T., Dawson, B. et al., Polyphenol-rich grape powder extract (GPE) attenuates inflammation in human macrophages and in human adipocytes exposed to macrophage-conditioned media. *Int. J. Obes. (Lond)*, 34, 800–808, 2010.
53. Chuang, C.C., Bumrungpert, A., Kennedy, A., Overman, A., West, T., Dawson, B., and McIntosh, M.K., Grape powder extract attenuates tumor necrosis factor alpha-mediated inflammation and insulin resistance in primary cultures of human adipocytes. *J. Nutr. Biochem.*, 22, 89–94, 2011.
54. Aoun, M., Michel, F., Fouret, G., Schlernitzauer, A., Ollendorff, V., Wrutniak-Cabello, C., Cristol, J.P. et al., A grape polyphenol extract modulates muscle membrane fatty acid composition and lipid metabolism in high-fat-high-sucrose diet-fed rats. *Br. J. Nutr.*, 106, 491–501, 2011.
55. Soares de Moura, R., da Costa, G.F., Moreira, A.S., Queiroz, E.F., Moreira, D.D., Garcia-Souza, E.P., Resende, A.C. et al., *Vitis vinifera* L. grape skin extract activates the insulin-signalling cascade and reduces hyperglycaemia in alloxan-induced diabetic mice. *J. Pharm. Pharmacol.*, 64, 268–276, 2012.
56. Zangiabadi, N., Asadi-Shekaari, M., Sheibani, V., Jafari, M., Shabani, M., Asadi, A.R., Tajadini, H. et al., Date fruit extract is a neuroprotective agent in diabetic peripheral neuropathy in streptozotocin-induced diabetic rats: A multimodal analysis. *Oxid. Med. Cell Longev.*, 976948, 2011.
57. Martini, L.A., Catania, A.S., and Ferreira, S.R., Role of vitamins and minerals in prevention and management of type 2 diabetes mellitus. *Nutr. Rev.*, 68, 341–354, 2010.
58. Chaudhary, D.P., Sharma, R., and Bansal, D.D., Implications of magnesium deficiency in type 2 diabetes: A review. *Biol. Trace Elem. Res.*, 134, 119–129, 2010.

59. Oboh, G., Ademosun, A.O., and Ogunsuyi, O.B., Quercetin and its role in chronic diseases. *Adv. Exp. Med. Biol.*, 929, 377–387, 2016.
60. Yoshimura, Y., Nishii, S., Zaima, N., Moriyama, T., and Kawamura, Y., Ellagic acid improves hepatic steatosis and serum lipid composition through reduction of serum resistin levels and transcriptional activation of hepatic ppara in obese, diabetic KK-A(y) mice. *Biochem. Biophys. Res. Commun.*, 434, 486–491, 2013.
61. Panchal, S.K., Ward, L., and Brown, L., Ellagic acid attenuates high-carbohydrate, high-fat diet-induced metabolic syndrome in rats. *Eur. J. Nutr.*, 52, 559–568, 2013.
62. Ahad, A., Ganai, A.A., Mujeeb, M., and Siddiqui, W.A., Ellagic acid, an NF-kappaB inhibitor, ameliorates renal function in experimental diabetic nephropathy. *Chem. Biol. Interact.*, 219, 64–75, 2014.
63. Mossine, V.V., Mawhinney, T.P., and Giovannucci, E.L., Dried fruit intake and cancer: A systematic review of observational studies. *Adv. Nutr.*, 2019, Aug 26. doi: 10.1093/advances/nmz085. [Epub ahead of print].

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 19

Dried Fruit Consumption and Cancer

Bradley Bolling, Xiaocao Liu, and Jiyuan Liu

19.1 Introduction 449
19.2 Cancer Chemopreventive Effects of Dried Fruit Consumption 451
19.2.1 Epidemiologic Studies 451
19.2.2 *In Vitro* Experiments and *In Vivo* Animal Studies 452
19.2.2.1 Raisins 452
19.2.2.2 Figs 458
19.2.2.3 Dates 459
19.2.2.4 Prunes 459
19.2.2.5 Apricots 460
19.2.3 Human Intervention Studies 461
19.2.3.1 Raisins 461
19.2.3.2 Prunes 461
19.2.3.3 Dates 462
19.2.3.4 Apricots 462
19.3 Conclusion 462
References 463

19.1 Introduction

Cancer has an immense worldwide burden. It is estimated that cancer will cause 9.6 million deaths globally in 2018, which positions it as the second leading cause of death [1]. Lung, breast, colorectal, prostate, skin, and stomach cancers are the most common forms of cancer [2]. A variety of genetic, environmental, and lifestyle factors influence cancer risk.

The inverse association between fruit consumption and cancer has been well accepted globally. For example, the U.S. Food and Drug Administration has approved health claims for fruits and cancer:

(a) "Low fat diets rich in fiber-containing grain products, fruits, and vegetables may reduce the risk of some types of cancer, a disease associated with many factors" [3].
(b) "Development of cancer depends on many factors. Eating a diet low in fat and high in fruits and vegetables, foods that are low in fat and may contain vitamin A, vitamin C, and dietary fiber, may reduce your risk of some cancers. Oranges are a good source of fiber and vitamin C" [4].

Increasing fruit and vegetable consumption has been identified as a key factor for reducing the burden of cancer and is a component of the World Health Organization Global Strategy on Diet Physical Activity and Health [1]. The World Health Organization (WHO) advises "Eating at least 400 g or 5 servings of fruits and vegetables per day reduces the risk of non-communicable diseases, and helps ensure an adequate daily intake of dietary fiber" [5].

Dried fruits make an important contribution to meeting dietary recommendations for fruit consumption. Dried fruits are rich sources of dietary fiber and other nutrients, as well as various bioactive phytochemicals (Figure 19.1 and see detail in Chapter 14). This chapter focuses on dried-fruit commodities with the highest level

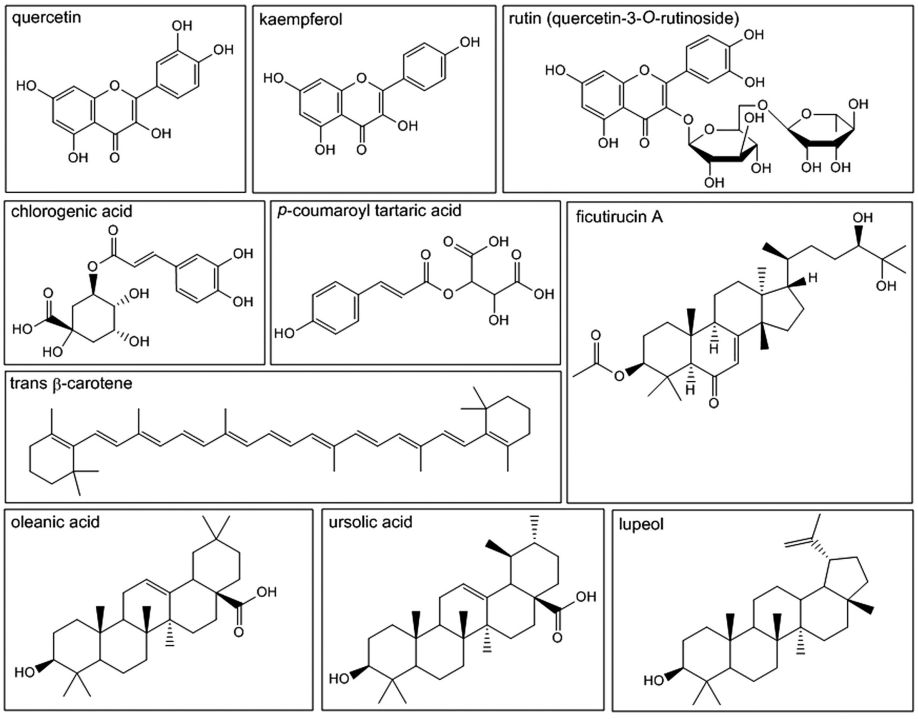


Figure 19.1 Representative bioactives identified in dried fruits.

of production and consumption, namely raisins, dates, figs, prunes, and apricots [6]. It should be noted that a wide variety of lyophilized fruits and fruit extracts have been tested in cell or animal models for cancer prevention. Some of these are emerging products, such as lyophilized black raspberry powder, which have received considerable attention for their therapeutic value and have been reviewed elsewhere [7].

19.2 Cancer Chemopreventive Effects of Dried Fruit Consumption

19.2.1 Epidemiologic Studies

High fruit consumption is inversely associated with all-cause mortality [8]. In an observational study of 65,226 participants in the 2001–2008 Health Surveys for England, dried-fruit consumption reduced the hazard ratio (HR) per portion of all-cause mortality to 0.91 (95% confidence interval [CI]: 0.84-0.99, $P = 0.03$) [9], a level of risk reduction somewhat lower than that observed with fresh fruit, which entails a HR for all-cause mortality per portion of 0.68 (95% CI: 0.58–0.79).

In contrast to all-cause mortality data, the association of fruit intake with total cancer mortality is not strongly supported [8]. This is partly due to the varied causes and types of cancer. For instance, there is limited information on the specific associations between fruit consumption and esophagus, lung, stomach, colorectal, and bladder cancers [10]. A recent dose–response meta-analysis of 95 different prospective studies [11] concluded that combined fruit and vegetable intake was associated with a relative risk (RR) of total cancer of 0.9 (95% CI: 0.87–93). Comparing high to low fruit consumption resulted in a total cancer RR of 0.92 (95% CI: 0.88–0.96). The RR of dried fruit for total cancer was 0.89 (95% CI: 0.61–1.30), a value far from statistical significance. This study highlights the limited prospective data available for dried-fruit consumption and total cancer, as this meta-analysis only included two studies [12,13]. The first was a prospective study of 11,000 health-conscious British adults in the Health Food Shoppers Study [12], which updated an earlier analysis that included dried fruit [14]. Weekly consumption of nuts/dried fruit was not significantly associated with total or site-specific cancer reduction [12]. In contrast, increased fresh fruit consumption was associated with reduced mortality from all cancers (RR 0.78, 95% CI: 0.65–0.95) and specifically lung cancer (RR 0.52, 95% CI: 0.32–0.86) [12]. The second prospective cohort study was the Massachusetts Health Care Panel Study of 1,271 participants above age 66 [13]. Dried-fruit consumption was associated with a non-significant RR for cancer death of 0.6 (95% CL: 0.3–1.4) [13].

Beyond the aforementioned studies, several other epidemiologic studies have evaluated how consumption of dried fruit is associated with mortality and cancer risk. A case-control study performed in Spain, including 354 cases and controls, found and inverse association of increased dried-fruit consumption with gastric cancer, with an odds ratio (OR) of 0.4 (95% CI: 0.2–0.8) [15]. The risk factors for pancreatic cancer were evaluated in the prospective Adventist Health Study ($n = 34{,}000$), which included Seventh-Day Adventists who did not smoke, drink alcohol, or eat pork. In this study, consumption of raisins, dates, and other dried fruits greater than three times/week was inversely associated with pancreatic cancer risk (RR of 0.35, 95% CI: 0.17–0.73; multivariate-adjusted predicted RR of 0.19, 95% CI: 0.04–0.86)

[16]. In the same cohort, consumption of raisins, dates, or other dried fruits more than five times/week was associated with a RR of prostate cancer of 0.62 (95% CI: 0.36–1.06, $P = 0.06$). The age-adjusted reduction in prostate cancer risk for dried-fruit consumption was significant for trend ($P = 0.01$), with a RR of 0.51 (95% CI: 0.31-0.85) at the highest level of consumption [17]. The Netherlands Cohort Study surveyed 58,279 men, 55–69 years old at baseline, with 6.3 median years of follow-up, and it found a non-significant inverse association between the frequency of dried fruit consumption and prostate cancer, with a RR of 0.49 (95% CI: 0.18–1.32) per 25 g increased consumption [18].

In summary, dried-fruit consumption is associated with reduced risk of mortality. However, the epidemiological evidence specific for dried fruits and cancer risk is limited, in part because dried fruits have not been routinely categorized in dietary surveys [19,20], and the amount consumed is scarce in some cohorts. At present, there is limited evidence of an association of increased dried-fruit consumption with reduced risks of gastric, prostate, and pancreatic cancers [15–17]. Including dried fruit intake in dietary surveys is expected to have an important influence on cancer risk estimates.

19.2.2 In Vitro *Experiments and* In Vivo *Animal Studies*

Dried raisins, figs, dates, prunes, and apricots have been investigated for anti-carcinogenic activity using a variety of cell and animal-based research methods (Table 19.1). These studies imply that dried-fruit bioactives may act to inhibit cancer at the stages of initiation, promotion, or progression *via* induction of detoxification enzymes, inhibition of oxidative stress and inflammation, or induction of apoptosis in cancerous or pre-cancerous cells (Figure 19.2). These *in vitro* assays and *in vivo* animal studies are analyzed further in the following subsections.

19.2.2.1 Raisins

Dried grapes (e.g., raisins, sultanas, and currants) are produced in many regions of the world. Grape cultivars include seed-bearing or seedless varieties of white, red, or black grapes [21]. Sultanina grapes (e.g., Thompson seedless, Sultaniye, Sultanine, and Kishmish) are the most popular dried grape product [21]. Raisins are dietary sources of polyphenols, including phenolic acids such as caftaric and coutaric acids, flavonoids such as quercetin and kaempferol, and stilbenes such as resveratrol and *trans*-resveratrol (see details in Chapter 14). Compared to their fresh counterparts, the phenolic contents of raisins are much higher because of concentration during the drying process [22,23].

Polyphenol-rich extracts of raisins have been applied to cancer cells to evaluate their anti-carcinogenic effects. Polyphenol-rich extracts from freeze-dried currants and sultanas were applied to a human gastric adenocarcinoma cell line (AGS), and they suppressed cell proliferation and induced AGS cell apoptosis at 500 μg/mL [24]. This dose also decreased the protein and mRNA levels of intercellular adhesion molecule-1 (ICAM-1) in tumor necrosis factor-α (TNF-α) stimulated AGS cells [24]. Another study evaluated the anti-inflammatory effect of five different sun-dried raisin hydro-alcoholic extracts in AGS cells [25]. Raisin-seed extracts were more potent than raisin extracts at inhibiting TNF-α induced

Table 19.1 Summary of Studies Utilizing Dried Fruits for Anticarcinogenic Activity

Study	*Dried Fruit/Extract*	*Experimental Model*	*Dose*	*Outcome*	*References*
In vitro	Raisins (methanol extract)	Gastric cancer cells (AGS)	500 μg/mL	Inhibited cell proliferation and apoptosis, decreased the protein and mRNA levels of ICAM-1 in TNF-α stimulated AGS cells.	[24]
	Raisins (hydro-alcohol extract)	Gastric cancer cells (AGS)	0.5–100 μg/mL	Inhibited the TNF-α induced IL-8 release in a dose-dependent manner.	[25]
	Raisins (methanol extract)	Human colon cancer cells (HT29)	250–500 μg/mL	Inhibited cell proliferation, suppressed TNF-α induced IL-8, COX-2, GSH, and p65 protein levels.	[26]
	Figs (ethanol extract)	Human breast cancer cells (MCF-7)	~1000 μg/mL	Reduced cell viability in a dose- and time-dependent manner.	[28]
	Figs (hexane, ethyl acetate, and methanol extracts)	Human breast cancer cells (MCF-7)	50 μg/mL	Ethyl acetate extract suppressed cell proliferation with IC_{50} value of 9.8 μg/mL.	[29]
	Figs (triterpenoids, extracted by ethanol)	Human breast cancer cells (MCF-7), liver cancer cells (HepG2), and human osteosarcoma cells (U2OS)	50 μM	Purified compounds (ficutirucins A, B, F, G, and I) were cytotoxic to all three cell lines.	[30]

(*Continued*)

Table 19.1 (Continued) Summary of Studies Utilizing Dried Fruits for Anticarcinogenic Activity

Study	*Dried Fruit/Extract*	*Experimental Model*	*Dose*	*Outcome*	*References*
	Dates (ethanol extract)	Human breast cancer cells (MCF-7)	5 μg/mL	Inhibited cell proliferation and increased cell apoptosis, pro-apoptotic gene expression (p53, Bax, and caspase 3), and DNA fragmentation.	[34]
	Dates (ethyl acetate extract)	Human prostate cancer cells (PC3)	~0.6 mg/mL	Inhibited cell proliferation and increased cell apoptosis by inducing cell-cycle arrest.	[35]
	Prunes (polyphenol extract)	Macrophage cells (RAW264.7)	1000 μg/mL	Inhibited LPS-induced COX-2, NO, and MDA.	[39]
			~30 μg/mL	Inhibited H_2O_2 -induced TNF-α excretion and increased TLR4 and TNF-α expression in LPS-stimulated cells.	[40]
	Prunes (ethanol extract)	Human colon carcinoma cells (Caco-2) andhuman stomach cancer cells (KATO III)	0.25 mg/mL	Inhibited proliferation and increased cellular apoptosis.	[41]
	Apricots (terpenoids, diethyl-ether extract)	Human stomach cancer (Kato-III) andpromyelocytic leukaemia (HL-60)	~5 μL/mL	Inhibited growth of cancer cell lines.	[44]

(*Continued*)

Table 19.1 (Continued) Summary of Studies Utilizing Dried Fruits for Anticarcinogenic Activity

Study	*Dried Fruit/Extract*	*Experimental Model*	*Dose*	*Outcome*	*References*
		Colon cancer (SW48, COLO, and WiDr)	300 μg/mL		[46]
		Breast cancer (MCF-7and MDA-MB-468)	300 μg/mL		[47]
		Hepatocellular carcinoma (HuH7, HepG2)	0.1–1,000 μg/mL		[48]
***In vivo* (rodent)**	Figs	20% ethanol induced oxidative stress and hepatotoxicity rats	10% w/w diet supplementation, 50 days	Prevented lipid oxidation and subchronic liver damage and normalized liver glutathione peroxidase activity.	[32]
	Dates (aqueous extract)	DEN-induced hepatocellular carcinoma rats	0.5 or 1 g/kg body weight, 10 weeks	Alleviated hepatic fibrosis and immunocyte infiltration, inhibited proinflammatory cytokines IL-1α, IL-1β, GM-CSF, IL-6, and hepatic oxidative stress.	[36]
	Prunes	AOM-induced colonic cancer rats	4.75% or 9.5% (w/w), 10 days prior to AOM injection, additional 9 weeks after	Reduced biomarkers of colon cancer risk (decreased fecal bile acids, cecal-β-glucuronidase activity, and cecal 7α-dehydroxylase activity).	[42]
	Apricots (MK615, extraction from Japanese apricots)	FM3A injection mice model	600 μg/day, 25 days	Improved survival and the splenic CD4/CD8 cell ratio relative to the control group.	[49]

(*Continued*)

Table 19.1 (Continued) Summary of Studies Utilizing Dried Fruits for Anticarcinogenic Activity

Study	*Dried Fruit/Extract*	*Experimental Model*	*Dose*	*Outcome*	*References*
	Apricots	AOM-induced colonic cancer rats	20% (w/w)/day, 7 weeks	Alleviated AOM-induced colonic cancer in mice and improved the colon of healthy mice by increasing glutathione, reducing MDA, and reducing NO.	[50]
	Apricots	DMBA-induced liver damaged rats	20% (w/w)/day, 6 weeks	Combined with radiotherapy, reduced NFκB expression and increased Bax and caspase 3 expression.	[51]
	Apricots	Alcohol-induced testicular damaged rats	20% (w/w)/day, 28 weeks	Reduced testicular oxidative stress and histopathological markers of tubule damage.	[52,53]
	Apricots	MTX-induced renal damage rats	10% (w/w)/day, 3 weeks before, and 1 week after MTX administration	Reduced oxidative stress and improved kidney antioxidant function (catalase activity and superoxide dismutase activity).	[54]
Human intervention	Raisins	Randomized, controlled, and crossover interventional trail	90 g/day, 2 weeks	Improved markers of antioxidant function (increased the serum-free ORAC values and reduced the urinary 8-epi $PGF_{2}\alpha$).	[56]
	Raisins	Randomized trial	144 g/day, 0-4 hours	Increased plasma total phenols and resistance to serum oxidation at 4 hours after consumption.	[57]

(*Continued*)

Table 19.1 (Continued) Summary of Studies Utilizing Dried Fruits for Anticarcinogenic Activity

Study	*Dried Fruit/Extract*	*Experimental Model*	*Dose*	*Outcome*	*References*
	Raisins	Randomized trial	160 g/day, 6 weeks	Reduced TNF-α secretion.	[58]
	Prunes	Intervention trial	100 g/day, 6 months	Reduced urinary excretion 16α-hydroxyestrone and bioactive estrogen metabolite.	[59]
	Prunes	Crossover human trial	100 g/day, 4 weeks	Reduced colon cancer risk by attenuation of fecal lithocholic acid.	[61]
	Prunes	Breast cancer survivors	90 g/day, 6 months	No effect on CRP.	[62]
	Dates	Randomized, controlled, and crossover trial	~50 g/day, 21 days	Reduced fecal water genotoxicity and fecal ammonia. Gut microbiota and SCFA production were unchanged.	[63]

Abbreviations: 8-epi $PGF_2\alpha$, 8-isoprostaglandin-$F_2\alpha$; AOM, azoxymethane; COX-2, cyclooxygenase-2; CRP, C-reactive protein; DEN, diethylnitrosamine; DMBA, 7,12-dimethylbenz[a]anthracen; FM3A, mammary carcinoma cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSH, glutathione; IC_{50}, the half maximal inhibitory concentration; ICAM-1, intercellular adhesion molecule-1; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-8, interleukin-8; LPS, lipopolysaccharide; MDA, malondialdehyde; MTX, methotrexate; NFκB, nuclear factor kappa B; NO, nitric oxide; ORAC, oxygen radical absorbance capacity; SCFA, short-chain fatty acids; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α.

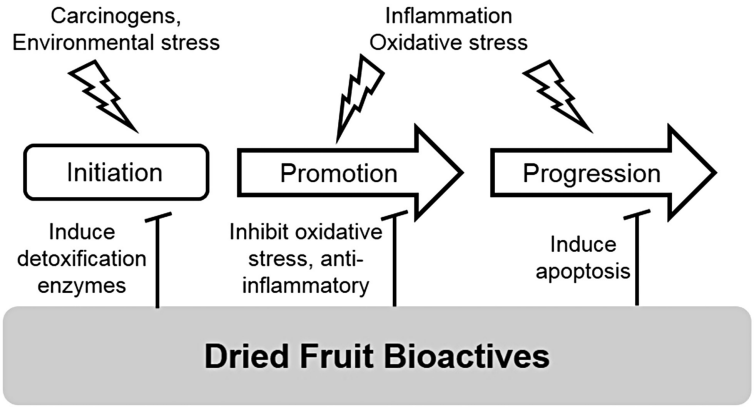


Figure 19.2 Potential anti-carcinogenic mechanisms of bioactives from dried fruits.

interleukin-8 (IL-8) release from AGS cells, having half-maximal inhibitory concentration (IC_{50}) values of 0.49 and 3.34 μg/mL, respectively [25]. Raisin seed extracts contained higher proanthocyanidin and flavonol than the fruit extract [25]. Methanolic extracts of Greek currants and sultanas inhibited proliferation of HT29 human colon cancer cells [26]. These extracts inhibited TNF-α induced IL-8, cyclooxygenase-2 (COX-2), glutathione, and p65 protein levels in HT29 cells [26]. To the best of our knowledge, the anti-carcinogenic activity of raisin consumption has not yet been investigated in animal models. Therefore, the available *in vitro* data suggest that consumption of raisins may protect against gastric and colon cancers.

19.2.2.2 Figs

Similar to other dried fruits, figs are rich in fiber, polyphenols, and nutrients (see details in Chapter 14). The fig skins of some varieties contain anthocyanins, and fig pulp is rich in proanthocyanidins [27]. Figs are also a source of chlorogenic acid and flavonoids (such as kaempferol-rutinoside, quercetin glycosides, and rutinoside) [27]. Ethanolic extract prepared from dried figs inhibited MCF-7 breast-cancer cell proliferation, with an IC_{50} of 31 μg/mL after 72 hours [28]. Figs were successively extracted with hexane, ethyl acetate, and methanol and applied to MCF-7 cells [29]. Ethyl acetate fig extracts exerted the most potent inhibition of viability, having IC_{50} values between 12.5 and 6.25 μg/mL [29]. Tirucallane-type triterpenoids (ficutirucins A-I) isolated and purified from an ethanolic extract of air-dried figs were individually applied to cultured MCF-7, HepG2, and U2OS cell lines, representing breast cancer, hepatocarcinoma, and osteocarcoma cell lines, respectively [30]. Ficutirucins A, B, F, G, and I were cytotoxic to all three cell lines, having IC_{50} values less than 50 μM [30]. Thus, fig polyphenols and triterpenoids may possess anti-carcinogenic activity.

Alcohol is a known carcinogen, and increased consumption is associated with cancer risk [31]. Limited data from an *in vivo* rodent study suggests that fig consumption confers hepatoprotection from ethanol [32]. Dried figs (10% w/w) fed to Wistar albino rats for 50 days with or without 20% ethanol to induce oxidative stress and hepatotoxicity prevented increased lipid oxidation in the liver (e.g.,

malondialdehyde [MDA]), reduced subchronic liver damage (histopathology), and normalized hepatic glutathione peroxidase activity [32].

19.2.2.3 Dates

Dates contain a variety of phenolics and carotenoids, as reviewed by others [33]. Dates have appreciable phenolic acids and flavonoids and provide fiber, vitamins, and minerals (see details in Chapter 14). Methanolic extracts of Ajwa dates inhibited proliferation of MCF-7 breast cancer cells at 5 mg/mL by increasing apoptosis, pro-apoptotic gene expression (p53, Bax, caspase 3), and cell DNA fragmentation [34]. An ethyl acetate extract of defatted Ajwa dates applied to PC-3 prostate cancer cells and normal fibroblast skin cells inhibited cancer cell growth, having an IC_{50} of 0.4 mg/mL, but did not affect the viability of normal fibroblasts [35]. In PC-3 cells, the date extracts increased apoptosis by inducing cell-cycle arrest, increasing oxidative stress, and reducing mitochondrial membrane potential [35]. The active components of these extracts remain undefined, and further studies in animal models of breast and prostate cancer are warranted. Nonetheless, consumption of date extracts exhibited anti-carcinogenic activity in Wistar rats treated with diethylnitrosamine to induce hepatocellular carcinoma [36]. After diethylnitrosamine treatment, rats consumed dried aqueous Ajwa date extracts at 0.5 or 1 g/kg body weight for 10 weeks [36]. Date-extract consumption prevented the histological appearance of hepatic fibrosis and immunocyte infiltration; increased interleukin-2, interleukin-12, and anti-tumor cytokines; and inhibited the proinflammatory cytokines interleukin-1 alpha, interleukin-1 beta, granulocyte-macrophage colony-stimulating factor, and interleukin-6. The highest level of date-extract consumption also reduced hepatic oxidative stress (e.g., MDA), and both levels increased superoxide dismutase activity relative to the control diet [36].

19.2.2.4 Prunes

Prunes have a significant polyphenol content that consists mainly of chlorogenic and neochlorogenic acids (see details in Chapter 14). Prunes are also noted for their nutrient density and fiber content [37]. Inflammation increases the proliferation of precancerous cells and is associated with the progression of tumor formation and malignancy [38]. A polyphenol-rich prune extract at a dose of 1 mg/mL inhibited inflammation in cultured RAW 264.7 macrophages *via* inhibition of lipopolysaccharide (LPS)-stimulated COX-2 and reduced nitric oxide (NO) production. In another study, prune polyphenols inhibited hydrogen peroxide–induced TNF-α excretion in RAW 264.7 macrophages but stimulated TNF-α in LPS-treated cells [40]. Polyphenol treatment increased Toll-like receptor 4 (TLR4) expression in LPS-stimulated macrophages, potentially explaining increased TNF-α.

Ethanolic extracts of prune juice were administered to Caco-2 and KATO-III cancer cell lines and a normal colon fibroblast cell line (CCD-18Co) [41]. The prune extracts inhibited growth of the stomach and cancer cell lines to viability below 20% at 0.25 mg/mL after 24 hours and increased cellular apoptosis, while viability was unaffected in normal fibroblasts [41].

Prunes have been evaluated in a rodent model of colon cancer [42]. Low-moisture prune powder was fortified at 4.75% or 9.5% (w/w) in rodent diets and fed for 10 days prior to azoxymethane injection and for 9 weeks after [42]. Neither level

of prune consumption inhibited the appearance of aberrant crypts or foci relative to the control diet [42]. In contrast, prune consumption improved other markers relevant to colon cancer risk, including decreased fecal bile acids, cecal β-glucuronidase activity, and cecal 7α-dehydroxylase activity [42]. Thus, despite a null effect on precancerous lesions, prune consumption may inhibit risk factors that accelerate colon cancer.

19.2.2.5 Apricots

Fresh apricots contain carotenoids, flavan-3-ols, proanthocyanidins, and hydroxycinnamic acids, among others [43]. Dried apricots also retain carotenoids and polyphenols in addition to their fiber and nutrient content (see details in Chapter 14). Terpenoids from Japanese apricot ('Ume') have received attention for their anti-cancer activity. The extract, MK615 (Misatol), contains apricot terpenoids (e.g., ursolic acid, oleanic acid, and lupeol) and is derived from a diethyl-ether extract of the fresh fruits (Figure 19.1) [44,45]. The apricot extracts inhibit growth of cell lines relevant to stomach cancer (Kato-III), promyelocytic leukemia (HL-60), breast cancer (MCF-7, MDA-MB-468), hepatocellular carcinoma (HuH7, HepG2), and colon cancer (SW48, COLO, WiDr) [44,46–48]. Mice injected with mammary carcinoma cells (FM3A) and treated with 660 μg MK615 per day had improved survival relative to the control [49]. The apricot extracts also improved splenic CD4/CD8 ratios in mice relative to the control [49].

Several studies have utilized dried apricots for inhibition of cancer in rodent models. Sun-dried or sulfur-fumigated apricots were compared in azoxymethane (AOM)-treated rats [50]. Rodent diets were supplemented with 20% (w/w) apricots for 7 weeks. AOM-induced oxidative stress and increased telomerase activity in the colon. Apricot consumption increased colonic glutathione and reduced MDA relative to the AOM-treated control group [50]. Apricot consumption also inhibited AOM-induced NO levels in the colon, inhibited telomerase activity by 59%–78%, and ablated colonic dysplasia [50]. The authors concluded that sun-dried apricots provided a marginally better response to AOM on the basis of telomerase activity. Apricot consumption also improved colonic antioxidant function in healthy rats by increasing glutathione (26.79%) and reducing MDA (6.69%) and NO (31.57%) compared to untreated controls.

Apricot supplementation was evaluated in combination with radiotherapy for inhibiting hepatic carcinogenesis induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) [51]. Consumption of 20% (w/w) apricots for 6 weeks reduced DMBA-induced mitosis and nuclear factor kappa B (NFκB) in liver tissue, and increased Bax and caspase 3 compared to the DMBA-treated group [51]. Apricot consumption further augmented the effect of radiation treatment on liver tissue of DMBA-treated rats by further decreasing hepatic Bcl-2 (~38%) and NFκB (~10%) compared to radiation treatment alone [51].

Dried-apricot consumption improved testicular health concurrent with exposure to alcohol or low-dose X-rays. Alcohol consumption increases cancer risk, in part by increasing cellular damage and oxidative stress [52]. In Sprague-Dawley rats, apricot consumption (20% w/w) reduced the impact of chronic ethanol consumption on Leydig and Sertoli cell counts, seminiferous tubule diameter, as well as markers of histopathological damage to seminiferous tubules in the testis [52]. In a different study, low-dose X-rays were applied to Sprague-Dawley rats to induce testicular damage [53]. Testicular oxidative stress and histopathological markers

of tubule damage were reduced by consumption of 20% apricots (w/w) for different intervals prior, concurrent, or after X-ray treatment, with sustained apricot consumption being most effective at preventing X-ray testicular damage [53].

Apricot consumption also inhibited chemotherapy-induced kidney toxicity in rats [54]. In this model, methotrexate administration increased renal failure and oxidative stress in the kidney tissue of Wistar albino rats [54]. Rats consumed 10% apricots (w/w) for 3 weeks prior to methotrexate treatment and then continued for 1 week after chemotherapy. Apricot consumption reduced oxidative stress by decreasing MDA by 25% and improved antioxidant function by increasing catalase activity by 48% and superoxide dismutase activity by 44% in kidney tissue, while also reducing methotrexate-induced glomerulosclerosis [54].

19.2.3 Human Intervention Studies

No long-term randomized controlled trials utilizing dried fruits for cancer prevention are available. Shorter intervention studies have used dried-fruit interventions to evaluate modulation of biomarkers relevant to cancer risk, such as oxidative stress, inflammation, estrogen metabolites, microbiota, and fecal water genotoxicity, as described below. Although the physiological relevance of total plasma antioxidant capacity has been questioned as a biomarker, some cancer diagnoses are associated with a reduction of this measure [55]. These studies are summarized in Table 19.1 and will be discussed below.

19.2.3.1 Raisins

A randomized, controlled trial with a crossover design evaluated fasting and postprandial markers of oxidative stress and inflammation in overweight men and women (n = 17) after consuming 90 g of raisins for 2 weeks [56]. Raisin consumption modestly increased fasting plasma protein-free oxygen radical absorbance capacity values by 3.5% and reduced urinary 8-isoprostaglandin-$F_{2\alpha}$ by 22% relative to controls, but fasting and postprandial inflammation were not affected [56]. Another study evaluated how the acute consumption of 144 g of raisins affected plasma antioxidant activity and phenolics in healthy adults (n = 15) [57]. At 1 hour after raisin consumption, plasma total phenols and resistance to serum oxidation reached peak capacity, indicating an acute antioxidant benefit [57]. Increased raisin intake also reduced biomarkers of chronic inflammation in healthy older men and post-menopausal women aged 50–70 years [58]. Daily intake of ~160 g raisins reduced plasma TNF-α from 3.5 to 2.1 ng/L (n = 12), although this change was not observed in a group that consumed raisins and also increased walking frequency (n = 12) [58]. Notably, this study lacked a dietary control group.

Although biomarkers of oxidative stress, antioxidant function, and chronic inflammation can be altered by raisin consumption, further long-term clinical studies are required to investigate the effect of raisin consumption on cancer risk.

19.2.3.2 Prunes

Prune consumption modulated biomarkers relevant to breast cancer risk in healthy pre-menopausal women [59]. After a run-in phase of three menstrual cycles, women

consumed 100 g of prunes daily for 6 months. Urinary 16α-hydroxyestrone, a bioactive estrogen metabolite hypothesized to be associated with breast cancer risk, was reduced by prune consumption [59]. While this result is promising, the design of this trial was not randomized and did not include a control food.

Fecal bile acids, such as lithocholic acid, are associated with an increased colon cancer risk because of their tumor-promoting activity [60]. A crossover intervention study in hypercholesterolemic men compared 100 g daily prune consumption to grape juice for 4 weeks and showed that prunes reduced fecal lithocholic acid by ~20% compared to grape juice [61].

The combination of prunes with resistance training for breast cancer survivors was evaluated for strength, body composition, bone turnover biomarkers, and inflammation [62]. No treatment effect was reported for circulating C-reactive protein, a marker of inflammation.

19.2.3.3 Dates

A randomized, controlled, crossover study in healthy adults aged 18–55 years (n = 21) evaluated how Ajwa date consumption affected biomarkers relevant to colon cancer risk [63]. Participants consumed ~50 g Ajwa dates or a control food of maltodextrin/dextrose for 21 days each, having had a 2-week washout. Fecal microbiota was assessed by fluorescence *in situ* hybridization assessing the bacterial groups *Bifidobacterium*, *Lactobacillus*, *Ruminococcus*, and *Clostridium*, among others, but the date intervention did not change microbiota or fecal short-chain fatty acids. Date consumption reduced fecal water genotoxicity, determined by applying fecal water to colonic HT29 cells, and also reduced fecal ammonia [63]. The lower genotoxicity of fecal water suggests a potential modulation of colon cancer risk by date consumption.

19.2.3.4 Apricots

To the best of our knowledge, there is no evidence from human intervention studies for a putative anti-cancer activity of dried apricots.

19.3 Conclusion

The cumulative evidence for the cancer-preventive effects of dried-fruit consumption is promising but limited (Table 19.1). Cell-based and rodent models of cancer suggest that dried-fruit bioactives and fiber contribute to cancer prevention. Epidemiological data imply that increased dried-fruit consumption is inversely associated with risk of prostate, pancreatic, and gastric cancer. Human intervention studies suggest that frequent consumption of some dried fruits (prunes, raisins, and dates) modulates oxidative stress, inflammation, and other biomarkers relevant to cancer risk in some individuals. However, the long-term nature of cancer etiology and prohibitive costs of long-term human intervention studies has left a notable research gap that might hopefully be filled by future trials. At present, increased fruit consumption is recommended for cancer prevention in healthy individuals as well as cancer survivors [5,64]. Dried fruit should continue to help fill this dietary need.

References

1. World Health Organization (WHO), Cancer Fact Sheet. Published online at: http://www.who.int/news-room/fact-sheets/detail/cancer (accessed November 8, 2018).
2. International Agency for Research in Cancer (IARC), All Cancers Fact Sheet. Published online at: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf (accessed November 8, 2018).
3. United States Department of Health and Human Services Food and Drug Administration, 21 CFR 101.76 – Health claims: Fiber-containing grain products, fruits, and vegetables and cancer. *Federal Register*, 1993.
4. United States Department of Health and Human Services Food and Drug Administration, 21 CFR 101.78 – Health claims: Fruits and vegetables and cancer. *Federal Register*, 1993.
5. World Health Organiziation (WHO), Healthy Diet Fact Sheet. Published online at: http://www.who.int/news-room/fact-sheets/detail/healthy-diet (accessed November 8, 2018).
6. International Nut and Dried Fruit Council (INC), *Nuts and Dried Fruits, Statistical Yearbook 2017/2018 and Nutfruit Magazine July 2018*, INC, Reus, Spain, 2018.
7. Kula, M., and Krauze-Baranowska, M., *Rubus occidentalis*: The black raspberry – its potential in the prevention of cancer. *Nutr. Cancer*, 68, 18–28, 2016.
8. Wang, X., Ouyang, Y., Liu, J., Zhu, M., Zhao, G., Bao, W., and Hu, F.B., Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: Systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ*, 349, g4490, 2014.
9. Oyebode, O., Gordon-Dseagu, V., Walker, A., and Mindell, J.S., Fruit and vegetable consumption and all-cause, cancer and CVD mortality: Analysis of health survey for England data. *J. Epidemiol. Community Health*, 68, 856–862, 2014.
10. World Cancer Research Fund and American Institute for Cancer Research, Diet, Nutrient, Physical Activity and Cancer: A Global Perspective, Third Expert Report. Published online at: https://www.wcrf.org/dietandcancer/resources-and-toolkit (accessed November 8, 2018).
11. Aune, D., Giovannucci, E., Boffetta, P., Fadnes, L.T., Keum, N., Norat, T., Greenwood, D.C. et al., Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality – A systematic review and dose–response meta-analysis of prospective studies. *Int. J. Epidemiol.*, 46, 1029–1056, 2017.
12. Appleby, P.N., Key, T.J., Burr, M.L., and Thorogood, M., Mortality and fresh fruit consumption. *IARC Sci. Pub.*, 156, 131–133, 2002.
13. Colditz, G.A., Branch, L.G., Lipnick, R.J., Willett, W.C., Rosner, B., Posner, B.M., and Hennekens, C.H., Increased green and yellow vegetable intake and lowered cancer deaths in an elderly population. *Am. J. Clin. Nutr.*, 41, 32–36, 1985.
14. Key, T.J., Thorogood, M., Appleby, P.N., and Burr, M.L., Dietary habits and mortality in 11,000 vegetarians and health conscious people: Results of a 17 year follow up. *BMJ*, 313, 775–779, 1996.
15. Gonzalez, C.A., Sanz, J.M., Marcos, G., Pita, S., Brullet, E., Saigi, E., Badia, A. et al., Dietary factors and stomach cancer in Spain: A multi-centre case-control study. *Int. J. Cancer*, 49, 513–519, 1991.

16. Mills, P.K., Beeson, W.L., Abbey, D.E., Fraser, G.E., and Phillips, R.L., Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer*, 61, 2578–2585, 1988.
17. Mills, P.K., Beeson, W.L., Phillips, R.L., and Fraser, G.E., Cohort study of diet, lifestyle, and prostate cancer in Adventist men. *Cancer*, 64, 598–604, 1989.
18. Schuurman, A.G., Goldbohm, R.A., Dorant, E., and van den Brandt, P.A., Vegetable and fruit consumption and prostate cancer risk: A cohort study in the Netherlands. *Cancer Epidemiol. Biomarkers Prev.*, 7, 673–680, 1998.
19. Agudo, A., Slimani, N., Ocke, M.C., Naska, A., Miller, A.B., Kroke, A., Bamia, C. et al., Consumption of vegetables, fruit and other plant foods in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts from 10 European countries. *Public Health Nutr.*, 5, 1179–1196, 2002.
20. Perez-Cornago, A., Travis, R.C., Appleby, P.N., Tsilidis, K.K., Tjonneland, A., Olsen, A., Overvad, K. et al., Fruit and vegetable intake and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int. J. Cancer*, 141, 287–297, 2017.
21. Food and Agriculture Organization of the United Nations and the International Organisation of Vine and Wine, Dried Grapes, FAO-OIV Focus 2016. Published online at: www.fao.org/3/a-i7042e.pdf (accessed November 8, 2018).
22. Williamson, G., and Carughi, A., Polyphenol content and health benefits of raisins. *Nutr. Res.*, 30, 511–519, 2010.
23. Wu, X., Beecher, G.R., Holden, J.M., Haytowitz, D.B., Gebhardt, S.E., and Prior, R.L., Lipophilic and hydrophilic antioxidant capacities of common foods in the United States. *J. Agric. Food Chem.*, 52, 4026–4037, 2004.
24. Kaliora, A.C., Kountouri, A.M., Karathanos, V.T., Koumbi, L., Papadopoulos, N.G., and Andrikopoulos, N.K., Effect of Greek raisins (*Vitis vinifera* L.) from different origins on gastric cancer cell growth. *Nutr. Cancer*, 60, 792–799, 2008.
25. Di Lorenzo, C., Sangiovanni, E., Fumagalli, M., Colombo, E., Frigerio, G., Colombo, F., Peres de Sousa, L. et al., Evaluation of the anti-inflammatory activity of raisins (*Vitis vinifera* L.) in human gastric epithelial cells: A comparative study. *Int. J. Mol. Sci.*, 17, E1156, 2016.
26. Kountouri, A.M., Gioxari, A., Karvela, E., Kaliora, A.C., Karvelas, M., and Karathanos, V.T., Chemopreventive properties of raisins originating from Greece in colon cancer cells. *Food Funct.*, 4, 366–372, 2013.
27. Vallejo, F., Marín, J.G., and Tomás-Barberán, F.A., Phenolic compound content of fresh and dried figs (*Ficus carica* L.). *Food Chem.*, 130, 485–492, 2012.
28. Jasmine, R., Manikandan, K., and Karthikeyan, K., Evaluating the antioxidant and anticancer property of *Ficus carica* fruits. *Afr. J. Biotechnol.*, 14, 634–641, 2015.
29. Uz, R.I., Bakar, N.H.A., Swethadri, G.K., Baig, A., Idris, M.A., and Maryam, I.U., Non-toxic antiproliferative effect of *Ficus carica* fruit extracts on estrogen receptor positive breast cancer cell (MCF-7). *J. Chem. Pharm. Res.*, 7, 815–821, 2015.
30. Jing, L., Zhang, Y., Luo, J., and Kong, L., Tirucallane-type triterpenoids from the fruit of *Ficus carica* and their cytotoxic activity. *Chem. Pharm. Bull.*, 63, 237–243, 2015.
31. Vingeliene, S., Chan, D.S.M., Vieira, A.R., Polemiti, E., Stevens, C., Abar, L., Rosenblatt, D.N. et al., An update of the WCFR/AICR systematic literature review and meta-analysis on dietary and anthropometric factors and esophageal cancer risk. *Ann. Oncol.*, 28, 2409–2419, 2017.

32. Turan, A., and Celik, I., Antioxidant and hepatoprotective properties of dried fig against oxidative stress and hepatotoxicity in rats. *Int. J. Biol. Macromol.*, 91, 554–559, 2016.
33. Yasin, B.R., El-Fawal, H.A., and Mousa, S.A., Date (*Phoenix dactylifera*) polyphenolics and other bioactive compounds: A traditional Islamic remedy's potential in prevention of cell damage, cancer therapeutics and beyond. *Int. J. Mol. Sci.*, 16, 30075–30090, 2015.
34. Khan, F., Ahmed, F., Pushparaj, P.N., Abuzenadah, A., Kumosani, T., Barbour, E., AlQahtani, M. et al., Ajwa date (*Phoenix dactylifera* L.) extract inhibits human breast adenocarcinoma (MCF7) cells *in vitro* by inducing apoptosis and cell cycle arrest. *PLoS One*, 11, e0158963, 2016.
35. Mirza, M.B., Elkady, A.I., Al-Attar, A.M., Syed, F.Q., Mohammed, F.A., and Hakeem, K.R., Induction of apoptosis and cell cycle arrest by ethyl acetate fraction of *Phoenix dactylifera* L. (Ajwa dates) in prostate cancer cells. *J. Ethnopharmacol.*, 218, 35–44, 2018.
36. Khan, F., Khan, T.J., Kalamegam, G., Pushparaj, P.N., Chaudhary, A., Abuzenadah, A., Kumosani, T. et al., Anti-cancer effects of Ajwa dates (*Phoenix dactylifera* L.) in diethylnitrosamine induced hepatocellular carcinoma in Wistar rats. *BMC Comp. Alt. Med.*, 17, 418, 2017.
37. Stacewicz-Sapuntzakis, M., Dried plums and their products: Composition and health effects – An updated review. *Crit. Rev. Food Sci. Nutr.*, 53, 1277–1302, 2013.
38. Todoric, J., Antonucci, L., and Karin, M., Targeting inflammation in cancer prevention and therapy. *Cancer Prev. Res. (Phila.)*, 9, 895–905, 2016.
39. Hooshmand, S., Kumar, A., Zhang, J.Y., Johnson, S.A., Chai, S.C., and Arjmandi, B.H., Evidence for anti-inflammatory and antioxidative properties of dried plum polyphenols in macrophage RAW 264.7 cells. *Food Funct.*, 6, 1719–1725, 2015.
40. Bu, S.Y., Lerner, M., Stoecker, B.J., Boldrin, E., Brackett, D.J., Lucas, E.A., and Smith, B.J., Dried plum polyphenols inhibit osteoclastogenesis by downregulating NFATc1 and inflammatory mediators. *Calcif. Tissue Int.*, 82, 475–488, 2008.
41. Fujii, T., Ikami, T., Xu, J.-W., and Ikeda, K., Prune extract (*Prunus domestica* L.) suppresses the proliferation and induces the apoptosis of human colon carcinoma Caco-2. *J. Nutr. Sci. Vit.*, 52, 389–391, 2006.
42. Yang, Y., and Gallaher, D.D., Effect of dried plums on colon cancer risk factors in rats. *Nutr. Cancer*, 53, 117–125, 2005.
43. Le Bourvellec, C., Gouble, B., Bureau, S., Reling, P., Bott, R., Ribas-Agusti, A., Audergon, J. et al., Impact of canning and storage on apricot carotenoids and polyphenols. *Food Chem.*, 240, 615–625, 2018.
44. Adachi, M., Suzuki, Y., Mizuta, T., Osawa, T., Adachi, T., Osaka, K., Suzuki, K. et al., The "*Prunus mume* Sieb. Et zucc" (Ume) is a rich natural source of novel anti-cancer substance. *Int. J. Food Prop.*, 10, 375–384, 2007.
45. Yamai, H., Sawada, N., Yoshida, T., Seike, J., Takizawa, H., Kenzaki, K., Miyoshi, T. et al., Triterpenes augment the inhibitory effects of anticancer drugs on growth of human esophageal carcinoma cells *in vitro* and suppress experimental metastasis *in vivo*. *Int. J. Cancer*, 125, 952–960, 2009
46. Mori, S., Sawada, T., Okada, T., Ohsawa, T., Adachi, M., and Keiichi, K., New anti-proliferative agent, MK615, from Japanese apricot "*Prunus mume*" induces striking autophagy in colon cancer cells *in vitro*. *World J. Gastroenterol.*, 13, 6512–6517, 2007.

47. Nakagawa, A., Sawada, T., Okada, T., Ohsawa, T., Adachi, M., and Kubota, K., New antineoplastic agent, MK615, from Ume (a variety of) Japanese apricot inhibits growth of breast cancer cells *in vitro*. *Breast J.*, 13, 44–49, 2007.
48. Sakuraoka, Y., Sawada, T., Okada, T., Shiraki, T., Miura, Y., Hiraishi, K., Ohsawa, T. et al., MK615 decreases rage expression and inhibits TAGE-induced proliferation in hepatocellular carcinoma cells. *World J. Gastroenterol.*, 16, 5334–5341, 2010.
49. Al-Jahdari, W.S., Sakurai, H., Yoshida, Y., Mobaraki, A., Suzuki, Y., and Nakano, T., MK615, a prospective anti-proliferative agent, enhances CD4/CD8 ratio after exposure to irradiation. *Int. J. Radiat. Biol.*, 87, 81–90, 2011.
50. Karabulut, A.B., Ozgor, D., Gurocak, S., Karadag, N., Otlu, O., and Colak, C., Comparison between the effects of dietary supplements of sun dried or sulfur fumigated apricots on the telomerase activity and oxidative stress parameters in azoxymethane administered rats. *Int. J. Nutr. Metab.*, 6, 50–55, 2014.
51. Karabulut, A.B., Karadag, N., Gurocak, S., Kiran, T., Tuzcu, M., and Sahin, K., Apricot attenuates oxidative stress and modulates of Bax, Bcl-2, caspases, NFkappa-B, AP-1, CREB expression of rats bearing DMBA-induced liver damage and treated with a combination of radiotherapy. *Food Chem. Toxicol.*, 70, 128–133, 2014.
52. Kurus, M., Ugras, M., Ates, B., and Otlu, A., Apricot ameliorates alcohol induced testicular damage in rat model. *Food Chem. Toxicol.*, 47, 2666–2672, 2009.
53. Ugras, M.Y., Kurus, M., Ates, B., Soylemez, H., Otlu, A., and Yilmaz, I., *Prunus armeniaca* L (apricot) protects rat testes from detrimental effects of low-dose X-rays. *Nutr. Res.*, 30, 200–208, 2010.
54. Vardi, N., Parlakpinar, H., Ates, B., Cetin, A., and Otlu, A., The protective effects of *Prunus armeniaca* L (apricot) against methotrexate-induced oxidative damage and apoptosis in rat kidney. *J. Physiol. Biochem.*, 69, 371–381, 2013.
55. Rashad, Y.A., Elkhodary, T.R., El-Gayar, A.M., and Eissa, L.A., Evaluation of serum levels of HER2, MMP-9, nitric oxide, and total antioxidant capacity in Egyptian breast cancer patients: Correlation with clinico-pathological parameters. *Sci. Pharm.*, 82, 129–145, 2014.
56. Rankin, J.W., Andreae, M.C., Chen, C.Y.O., and O'Keefe, S.F., Effect of raisin consumption on oxidative stress and inflammation in obesity. *Diab. Obesity Metabol.*, 10, 1086–1096, 2008.
57. Kanellos, P.T., Kaliora, A.C., Gioxari, A., Christopoulou, G.O., Kalogeropoulos, N., and Karathanos, V.T., Absorption and bioavailability of antioxidant phytochemicals and increase of serum oxidation resistance in healthy subjects following supplementation with raisins. *Plant Foods Hum. Nutr.*, 68, 411–415, 2013.
58. Puglisi, M.J., Vaishnav, U., Shrestha, S., Torres-Gonzalez, M., Wood, R.J., Volek, J.S., and Fernandez, M.L., Raisins and additional walking have distinct effects on plasma lipids and inflammatory cytokines. *Lipids Health Dis.*, 7, 14, 2008.
59. Kasim-Karakas, S.E., Almario, R.U., Gregory, L., Todd, H., Wong, R., and Lasley, B.L., Effects of prune consumption on the ratio of 2-hydroxyestrone to 16alpha-hydroxyestrone. *Am. J. Clin. Nutr.*, 76, 1422–1427, 2002.
60. Reddy, B.S., Role of bile metabolites in colon carcinogenesis animal models. *Cancer*, 36, 2401–2406, 1975.
61. Tinker, L.F., Schneeman, B.O., Davis, P.A., Gallaher, D.D., and Waggoner, C.R., Consumption of prunes as a source of dietary fiber in men with mild hypercholesterolemia. *Am. J. Clin. Nutr.*, 53, 1259–1265, 1991.

62. Simonavice, E., Liu, P.Y., Ilich, J.Z., Kim, J.S., Arjmandi, B., and Panton, L.B., The effects of a 6-month resistance training and dried plum consumption intervention on strength, body composition, blood markers of bone turnover, and inflammation in breast cancer survivors. *App. Phys. Nutr. Metabol.*, 39, 730–739, 2014.
63. Eid, N., Osmanova, H., Natchez, C., Walton, G., Costabile, A., Gibson, G., Rowland, I. et al., Impact of palm date consumption on microbiota growth and large intestinal health: A randomised, controlled, cross-over, human intervention study. *Br. J. Nutr.*, 114, 1226–1236, 2015.
64. Mourouti, N., Panagiotakos, D.B., Kotteas, E.A., and Syrigos, K.N., Optimizing diet and nutrition for cancer survivors: A review. *Maturitas*, 105, 33–36, 2017.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 20

Dried Fruits

Bone Health and Osteoprotection

Bahram H. Arjmandi and Kelli S. George

20.1 Introduction 469
20.2 Bone Health and Osteoprotection of Dried Fruits 470
20.2.1 Pomegranates 471
20.2.2 Figs 471
20.2.3 Apples 474
20.2.4 Apricots 474
20.2.5 Dates 475
20.2.6 Mangoes 476
20.2.7 Raisins 477
20.2.8 Prunes 477
20.3 Conclusion 480
References 481

20.1 Introduction

As the population continues to age, the prevalence of chronic diseases increases in parallel. Osteoporosis is a highly prevalent chronic disease, most likely due to the rate of bone resorption exceeding the rate of bone formation. This condition begins to appear in most individuals over the age of 50, particularly in postmenopausal women. The sudden cessation of estrogen production at the onset of menopause has numerous negative health effects, including being associated with significant bone loss. This loss of bone mass and the deterioration of the bone microstructure dramatically increase the risk of fractures. These events are associated with increases in markers of inflammation and oxidative stress [1]. Normal levels of

estrogen work to inhibit osteoclastogenesis directly and through upregulation of bone biomarkers that are secreted by osteoblasts. Besides the decline in estrogen production associated with menopause, the regulation of bone formation and resorption is hindered by numerous factors [2]. There are a number of options for prevention and treatment to help slow the decline in further bone loss, and in some cases, even reversal is possible. There are pharmaceutical treatment options available such as hormone replacement therapy, anti-resorptive medications, and bone forming agents; however, these drugs are not free from side effects, they can be costly, and compliance with these medications is usually low [3]. One alternative to pharmacological agents is diet modification with nutrient-rich foods. Among all foods, fruits are especially rich in polyphenolic compounds, which are often found in even more concentrated amounts in their dried counterparts. Polyphenols have been shown to be anti-inflammatory and to affect bone metabolism [4]. Among all dried fruits, prunes have been the most extensively studied in regards to osteoprotection, with promising results [5]. Research suggests that the beneficial effects of prunes on bone are exclusive to the dried version of the plum fruits. That then begs the question of which other dried fruits may have similar beneficial effects on bone. The key modes by which bone loss may be prevented or reversed through dietary intervention include direct effects on bone cells, estrogen receptors, and inflammation. This chapter highlights selected dried fruits and their potential for osteoprotection.

20.2 Bone Health and Osteoprotection of Dried Fruits

Fruits naturally contain a number of phytochemicals with potential osteoprotective effects. Many of these bioactives, including but not limited to resveratrol, kaempferol, proanthocyanidins, quercetin, and catechins, have been shown to directly affect bone cells, as well as estrogen receptors in *in vitro* studies. Many phytochemicals are also potent antioxidants that help reduce inflammation, which is a risk factor for bone loss [6]. Another important factor which influences bone homeostasis is the acid/base balance. Overall, consumption of fruits and vegetables has been shown to positively influence the alkalinity of blood, and hence the benefits of fruits and vegetables on bone might be explained in part by their effects on the acid/base balance [7].

With reference to phytochemicals found in fruits, anthocyanin intake alone has also been positively associated with hip bone mineral density (BMD) [8]. A number of animal studies have similarly demonstrated a positive relationship between polyphenols and bone health. In ovariectomized rats, kaempferol [9], quercetin [10], catechins [11], and resveratrol [12] supplementation were all able to prevent ovariectomy (Ovx)-induced bone loss. Additionally, resveratrol alone was able to improve calcium retention in bone [13].

Many animal and epidemiological studies have demonstrated the beneficial effects of fruits, both fresh and dried, on a number of chronic diseases. However, to our knowledge, there are very few clinical studies that have examined the effects of fresh and dried fruits on bone health. Common dried fruits that have been studied with regard to bone health, mostly in cell culture and animal studies, include dried pomegranates, figs, apples, apricots, dates, mangoes, and grapes, and prunes. There have been several clinical studies demonstrating short and long-term effects

of prunes on bone [14–16]. The following sections summarize the evidence for the osteoprotective effects of certain dried fruits. We start this chapter with dried fruits that have less evidence of their efficacy on bone, and will end with prunes, for which more clinical studies are available.

20.2.1 Pomegranates

As the popularity of pomegranates (*Punica granatum L.*) increases, so does research on their potential health benefits. Though not typically consumed in dried form, pomegranates contain fatty acids, sterols, alkaloids, vitamin C, vitamin K, and a number of polyphenolic compounds, namely tannins (ellagic acid), ellagitannins (punicalagin), and flavonoids (anthocyanins, quercetin, and kaempferol) [17]. Dried pomegranates alone and in combination with red clover extract were shown to have an inhibitory effect on estrogen deficiency-related osteoporosis in Ovx rats [18]. Pomegranates have also been shown to possess antioxidant activity through their nutritive and nonnutritive components including punicalagin, a large ellagatannin that is important for osteoprotection [19]. The nutritive content of dried pomegranates, namely vitamin C and vitamin K, may also play a role in its ability to promote bone health (Table 20.1). Nonetheless, there is a need for conducting clinical studies using pomegranates to explore outcomes on post-menopausal bone health, since pomegranates are known to contain estrogenic compounds and even estrone itself (17 mg/kg dried seed) [20].

20.2.2 Figs

Figs (*Ficus carica L.*), which are often consumed in their dried form, are particularly rich in vitamin K, manganese, copper, and phenolic acids (gallic acid) [21]. These nutrients are likely the source of dried fig's role in osteoprotection (Table 20.1 and Figure 20.1). Though the potential health benefits of figs have not been extensively studied, they are seen as a possible hepatoprotective functional food, and there is some limited research available about their potential effects on bone health. Several *in vitro* and *in vivo* studies have shown the antioxidative actions of figs and their polyphenols [22,23]. In a study done by our research team, Sprague-Dawley rats were fed a diet containing 2% fructo-oligosaccharides (FOS) and 7.5% figs for 60 days, after 45 days on a maintenance diet to establish bone loss after Ovx. We found that the diet supplemented with figs and FOS effectively reversed the Ovx-induced loss of calcium content in the fourth lumbar vertebrae of the rats [24]. FOS are known to play a role in calcium and magnesium absorption in the colon and to increase the bioavailability of select polyphenols, thus playing a possible role in promoting bone health [25]. It is likely that the combination of FOS and figs created an additive effect, leading to the beneficial results on bone calcium content. Additionally, since many risk factors for osteoporosis such as smoking, hypertension, and diabetes are also associated with high levels of oxidative stress, the antioxidant activity of the polyphenols found in figs may be another important factor for osteoprotection [26]. Estrogen deficiency is shown to decrease antioxidant levels in a model for Ovx-induced loss of bone [27], and dried figs have been able to increase antioxidant activity and eventually overcome the oxidative stress

Table 20.1 Evidence Supporting a Role of Nutritive Compounds Found in Dried Fruits in Osteoprotection

Nutrient of Interest	*Sources (per 100 g Serving)*	*Suggested Role of Selected Nutrient in Bone*	*References*
Vitamin K (% AI)	Prunes (15.6%) Figs (15.6%) Pomegranates (14.3%)	Promotes calcium balance; required for γ-carboxylation of osteocalcin.	[65]
Vitamin C (% RDA)	Pomegranates (14.8%)	Influences expression of bone matrix genes in osteoblasts; influences genes involved in skeletal development and maintenance; and plays a role in mediating bone matrix deposition.	[79,80]
Vitamin E (% RDA)	Apricots (35.8%)	Tocotrienols can protect osteoblasts against oxidative damage and suppress osteoclastogenesis.	[81]
Potassium (%AI)	Apricots (25.1%) Raisins (15.9%) Prunes (15.6%) Dates (14.8%)	Contributes to the maintenance of BMD; may reduce bone resorption.	[82]
Boron (% ADI)	Prunes (200%)	Stimulates bone growth and metabolism; may play a role in preserving BMD, bone microarchitecture, and bone strength.	[61]
Manganese (% AI)	Figs (25%) Dates (15%) Raisins (15%) Apricots (10%)	Component of superoxide dismutase; necessary for bone matrix formation and is a cofactor for several enzymes in bone tissue.	[58–60]
Copper (% RDA)	Dates (44.4%) Apricots (33.3%) Raisins (33.3%) Prunes (28.9) Figs (23.1%) Apples (22.2%)	Required for the cross linking of collagen and elastin.	[57]

Abbreviations: ADI, average daily intake; AI, adequate intake; BMD, bone mineral density; RDA, recommended dietary allowances.

Note: Fruits listed contain 10% or more of the U.S. RDA or AI when RDA is not available.

associated with high sugar-sweetened soda consumption [21]. Based on our rat study, we suggest that future clinical trials are warranted to evaluate the efficacy of dried figs in preventing or reversing bone loss. A rat model is an appropriate model for bone studies [28], as we have always observed that what happens in rats in terms of bone can almost be duplicated in humans. However, research in humans is needed in the future.

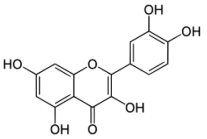
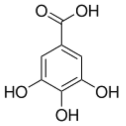
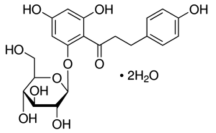
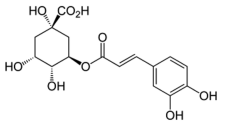
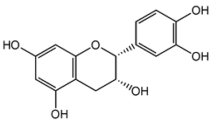
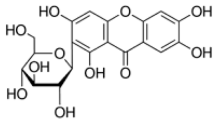
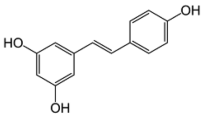
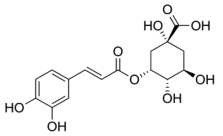
Dried fruit and major polyphenol	Chemical structure	Pictures
Pomegranates (Quercetin)		
Figs (Gallic acid)		
Apples (Phlorizin)		
Apricots (Chlorogenic acid)		
Dates (Epicatechin)		
Mangoes (Mangiferin)		
Raisins (Resveratrol)		
Prunes (Neochlorogenic acid)		

Figure 20.1 **(See color insert.)** A diagram depicting the major polyphenol in selected fruits, with images of their fresh and dried forms.

20.2.3 Apples

Aside from their nutritive value and cholesterol lowering properties, as shown by our research group in a 1-year clinical study [29], dried apples (*Malus pumila*) may have osteoprotective potential due to their polyphenol content, which includes mainly hydroxycinnamic acids (chlorogenic acid), flavan-3-ols (catechin), and flavonols (quercetin). Apples are also good sources of copper (Table 20.1) and phloridzin, which is a flavonoid specific to the apple fruit (Figure 20.1). Some of these individual compounds have demonstrated bone-protective effects in both cell culture and animal studies. Quercetin was able to partially preserve the development of an osteoblast phenotype in fetal rat calvaria cells exposed to oxidative stress [30]. The presence of quercetin in the hydroxyapatite environment enhanced proliferation and differentiation of osteoblast-like MG63 cells and downregulated osteoclastogenesis from osteoclast precursors 2T-110 [31]. In osteoblast-like MC3T3-E1 cells damaged by hydrogen peroxide, quercetin preserved the structural integrity of the cells and protected against peroxide damage when added in tandem with hydrogen peroxide [32]. In rabbits given intramuscular injections of quercetin three times per week over 3 months, cortical bone thickness increased in those animals given doses of 10 μg/kg and 100 μg/kg [33]. Additionally, in all three doses of quercetin (10, 100, and 1000 μg/kg), there was a lower density of secondary osteons (irregular Haversian bone tissue). Though dried apples are increasing in popularity, research on the dried version of the fruit is scarce in general, and especially in regard to bone. A dried apple–supplemented diet has been shown to down-regulate osteoclast activity after inhibition of the osteoclastogenesis regulator *Nfatc-1* in Ovx mice and up-regulate Bcl-2 homologous antagonist/ killer 1 (*Bak1*), which promotes apoptosis of osteoclasts [34]; however, in the same study, dried apples had no effect on osteoblast activity. Clinical studies on the regular consumption of dried apples remains warranted to observe whether results from these studies are applicable to the human population.

20.2.4 Apricots

The polyphenolic compounds contained in apricots (*Prunus armeniaca*) are largely hydroxycinnamic acids (neochlorogenic and chlorogenic acid), which also make up a large portion of the polyphenols in prunes, which numerous clinical studies have shown to be effective in preventing bone loss in postmenopausal women. Dried apricots are also a good source of vitamin E, potassium, copper, and manganese. Research on dried apricots with regard to bone health is limited. One 2011 study demonstrated the potential of an apricot extract to promote osteoblastic differentiation in cell culture [35]. Though this study used an extract from fresh apricots, an animal study found that mice given a dried apricot–supplemented diet were able to prevent the Ovx-induced loss in the whole body and the spine BMD (Figure 20.2) after 8 weeks when compared to the Ovx control mice [34]. These improvements in BMD were due to an increase in whole-body bone mineral content (BMC). This same group of mice had greater vertebral trabecular bone volume per unit of total volume (BV/TV) and trabecular number (Tb.N.) compared to the Ovx control animals. Dried apricots also effectively restored the compromise in trabecular bone connectivity density, structural model index, and density seen after Ovx [34]. Finite element analysis found that dried apricots reversed Ovx-induced decreases

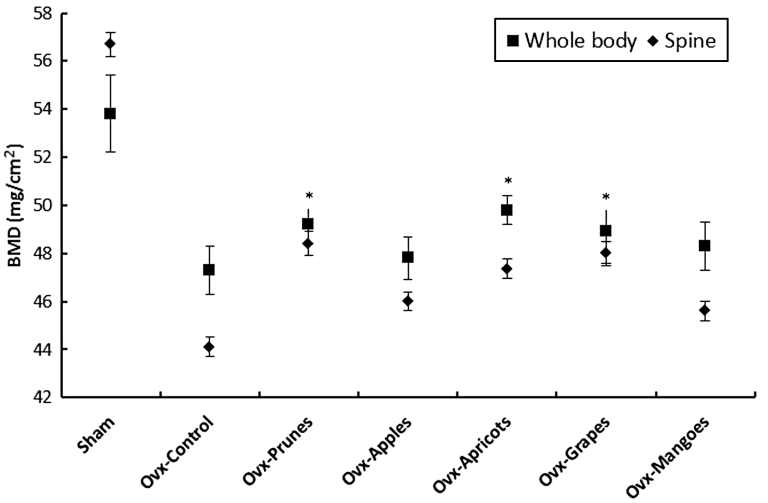


Figure 20.2 Whole body (■) and spine (◆) BMD. Dual energy X-ray absorptiometry scans after 8 weeks of sham-operated (Sham) and Ovx mice fed control diet or Ovx receiving control diet supplemented with either 25% (w/w) prunes, apples, apricots, grapes, or mangoes. Values are expressed as mean ± SE (n = 8) mice in each group. *Indicates significance ($P < 0.05$). *Abbreviations*: BMD, bone mineral density; Ovx, ovariectomy. (Adapted with modification from Rendina, E. et al., *PLoS One*, 8, e60569, 2013, Open access journal.)

in biomechanical parameters of vertebral body trabecular bone (total force, stiffness, and size-independent stiffness) to the level of the sham control group. Dried apricots also up-regulated *Bak1*, which may be one mechanism by which they protect against bone loss. Based on these initial findings, it is suggested that dried apricots are second to plums in their bone-protective effects. A feasibility study is warranted to observe short-term and long-term effects of dried apricots on bone health in humans.

20.2.5 Dates

Dates, which are most commonly eaten in their dried form, are a good source of copper, potassium, and manganese, which may contribute potential bone-protective effects (Table 20.1). The polyphenols hydroxybenzoates, hydroxycinnamates, and flavanols (procyanidins, catechins, and tannins) are also found in dates [36,37]. In 2010, Arjmandi et al. [24] demonstrated that a combination of 7.5% dried dates and 2% FOS added to the diet of Sprague-Dawley rats was able to reverse Ovx-induced loss of BMD in the right femur (Figure 20.3). We also found that the same combination of dried dates and FOS also reversed the Ovx-induced loss of calcium content in the fourth lumbar vertebra [24]. These results were comparable to the effects of prunes plus FOS given in this study. To our knowledge, there are no proposed mechanisms by which dried dates may potentiate these effects on BMD; however, it is possible that the quercetin content of dates may be one contributing factor to its possible osteoprotective capabilities (see previously referenced studies). Again,

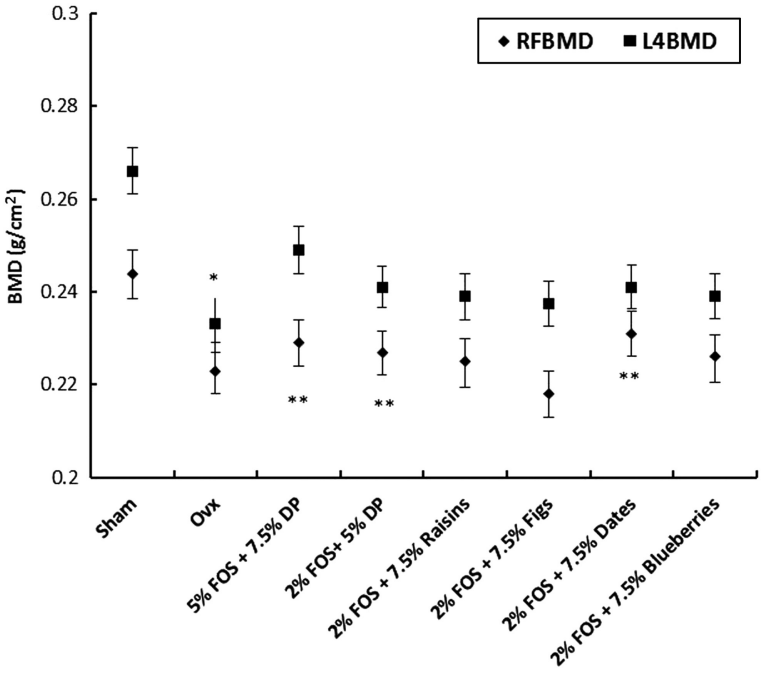


Figure 20.3 Right femur (◆) and fourth lumbar (■) BMD. *$P < 0.05$, treatment that has a significantly improved BMD at the right femur compared to Ovx. ** $P < 0.05$, treatment that had a significant effect on improving fourth lumbar BMD compared to Ovx. *Abbreviations*: BMD, bone mineral density; DP, dried plums; FOS, fructo-oligosaccharides; L4BMD, bone mineral density of fourth lumbar vertebra; Ovx, ovariectomy; RFBMD, bone mineral density of the right femur. (Adapted with modification from Arjmandi, B.H. et al., *J. M. Food,* 13, 312, 2010. With permission.)

initial findings warrant replication and new clinical studies to investigate the bone-protective effects of dates in humans.

20.2.6 Mangoes

Dried mangoes are a good source of proanthocyanidins, flavan-3-ols (catechin), flavonols (quercetin), hydroxycinnamic acids (chlorogenic, ferulic, and caffeic acids), and hydroxybenzoic acids (gallic and vanillic acid) [37]. Mangoes also contain mangiferin, a xanthone that is unique to them. Previously mentioned research explored the potential bone-protective benefits of quercetin, a proanthocyanidin, to which the possible bone-protective benefits of dried mangoes may be attributed. Mangoes contain cholorogenic acid, which is also found in prunes, dried fruits that have been well studied in regard to their bone-protective effects. Most studies focus on the bark, leaves, and peel of mangoes due to their greater concentration of compounds with health promoting effects, so research on the flesh of the fruit in relation to bone health is limited. One study found that a dried mango–supplemented diet likely down-regulated osteoclast activity in Ovx mice after an observed increase

in glutathione (GPx) activity; however, no skeletal response was observed with its supplementation [34]. Consumption of mangoes may be of overall benefit, but this primary study does not suggest that it has any tangible effects on bone.

20.2.7 Raisins

Raisins, which are dried grapes, may have potential health benefits in osteoprotection due again to their polyphenol content. Grapes are significant sources of polyphenols such as stilbenes (resveratrol), anthocyanidins, tannins (proanthocyanidins), and catechins [38,39]. Epidemiological studies have shown a positive relationship between grape polyphenols and bone health. In a study conducted in Australia, red wine consumption in men was shown to be positively associated with lumbar BMD [40], and flavonoid intake in women has been positively associated with spine and femoral neck BMD [8,41]. Grape seed proanthocyanidin extract was able to restore depleted calcium stores in bone to a greater extent than calcium alone [42] and was shown to decrease levels of N-terminal telopeptide (NTX), a marker of bone resorption [13]. Aside from their phytochemical profiles, raisins are also a good source of other vitamins and minerals, including potassium, magnesium, and copper, all of which are positively associated with bone health (Table 20.1).

Given that raisins are derived from grapes, they have the potential to exhibit similar osteoprotective benefits as observed with red wine, flavonoids, or grape seed proanthocyanidin extracts. The dehydration of fruits leaves the dried version with a more concentrated nutrient profile and therefore higher amounts of polyphenols compared to the original fruit on a weight-by-weight basis [43], thus further suggesting the osteoprotective potential of raisins. We showed that a 2% FOS and 7.5% raisin diet prevented the Ovx-induced loss of calcium content in the fourth lumbar vertebra of female rats [24]. A raisin supplemented diet was also able to prevent the Ovx-induced loss of whole-body and spine BMD in mice [34], improve the total force mechanical parameter of trabecular bone compared to the Ovx control group [34], increase bone calcium retention [44], and increase cortical bone structure and strength [44]. It is likely that the raisin-supplemented diet improved bone calcium deposits through both improving renal calcium retention and reducing bone turnover, and improved cortical bone by protecting against endocortical bone resorption, which is elevated in postmenopausal women [45]. Raisins were also able to down-regulate osteoclast activity through an increase in GPx activity and an up-regulation of *Bak1* [34]. These promising results provide evidence for the osteoprotective potential of raisins, though research on the topic is even more limited than the research on grapes; therefore, the full potential of raisins in osteoprotection is undetermined at present and it is unknown if these demonstrated effects differ between grapes and raisins, warranting further clarification and research.

20.2.8 Prunes

Prunes are particularly rich in nutrients including vitamin K, potassium, magnesium, boron, and polyphenols including chlorogenic acid, neochlorogenic acid, and proanythocyanins, all of which are known to be important for bone health (Table 20.1). Prunes have also been ranked with one of the highest oxygen radical

absorbance capacities among common fruits and vegetables [4,46]. The observed antioxidant activity of prunes is likely attributed to their polyphenol content.

The findings from numerous studies looking at the osteoprotective effects of prunes compared to other fresh and dried fruits largely suggest that prunes are the most effective. Arjmandi et al. [47] were among the first to observe the bone-protective effects of prunes, both in general and in established osteoporosis. A prune-supplemented diet effectively prevented the Ovx-induced loss of BMD in the spine and whole body of mice, which was believed to be due to the increase in whole-body BMC, compared to the Ovx control animals [34,48]. Other studies [49,50] confirmed that a prune diet prevented Ovx-induced decline in whole-body, fourth lumbar, femur, and tibial BMD in rats. Multiple doses of prunes also effectively restored established bone loss in the femur and tibia to the same extent as estrogen supplementation in Ovx rats [51]. Ovx mice fed a prune-supplemented diet had greater vertebral trabecular BV/TV, Tb.N., and trabecular thickness, and demonstrated an anabolic effect on their vertebral trabecular bone [34]. Prunes also prevented the Ovx-induced loss of bone at the proximal tibia where BV/TV and Tb.N. were comparable to the sham control group [34] and restored the compromise in trabecular bone connectivity density, structural model index, and density after Ovx.

Similarly, Smith et al. [50] found that 15% and 25% wt/wt prune diet improved trabecular bone and cortical thickness in Ovx rats, which was likely partially due to decreased bone turnover hypothesized after a reduction in the biomarkers of bone metabolism, N-terminal procollagen type 1 (PINP), and deoxypyridoline (Dpd). Finite element analysis found that prunes effectively reversed Ovx-induced decreases in total force, stiffness, and size-independent stiffness of vertebral body trabecular bone to the level of the sham control group, and increased size-independent stiffness in the tibia. These improvements in microarchitectural properties of bone indicate greater bone strength. Prunes have also been shown to down-regulate osteoclast activity due to an increase in GPx activity, an up-regulation of *Bak1*, and an inhibition of the osteoclastogenesis regulator *Nfatc 1*, bringing them to the level of the sham control group, perhaps suppressing Ovx-induced apoptosis; there was, however, no effect on osteoblast activity. On the other hand, there is evidence from Ovx rat models that prunes increase circulating insulin-like growth factor-I (IGF-I) levels, which stimulates osteoblast proliferation and differentiation [47,50]. In 2003, Mühlbauer et al. [52] were the first to report the ability of prunes to inhibit bone resorption in male rats, as assessed by urinary excretion of tritium-labeled tetracycline released from the bones of rats pre-labelled with tritiated tetracycline. Prunes were the only fruit shown to demonstrate similar bone resorptive effects compared to onions, which had been previously identified for their bone-protective properties. In a male rat model of gonadal hormone deficiency, a 15% and 25% prune diet prevented orchidectomy (Orx)-induced loss of BMD in the whole body, femur, and lumbar spine [53]. Both diets prevented Orx-induced decrease in biomechanical properties, including cortical bone ultimate load and compressive force, and stiffness of the trabecular bone within the vertebrae. Deterioration of trabecular bone microarchitectural properties in the distal femur and vertebral body was also prevented with both doses of prunes. Serum levels of IGF-I were increased, while urinary excretion of Dpd and bone mRNA levels of RANKL and osteoprotogerin (OPG) were reduced by all doses of prunes, suggesting a suppression of bone turnover. In 2007, Bu et al. [54] reported that prunes reversed Orx-induced bone loss in terms of increased density and enhanced microarchitectural properties. The effects of prunes on increasing

BV/TV and number and decreasing trabecular separation in this study were comparable to parathyroid hormone (PTH). Prunes also led to significant improvements in vertebral and femoral BMD and cortical thickness; however, the extent was not as great as with PTH. To determine whether prune supplementation could reverse aged-related bone loss in a male model, Halloran et al. [55] fortified the diets of 6-month-old (adult) and 18-month-old (old) male mice with 0%, 15%, and 25% prunes by weight for 6 months. A 25% prune diet led to a gain in cancellous bone volume, which exceeded baseline by approximately 50% in adult mice and 40% in old mice. This study demonstrated that supplementation with prunes can restore bone that has been lost as a result of aging.

When combined with FOS in Ovx rats, prunes showed enhanced efficacy in reversing Ovx-induced BMD loss in the right femur and fourth lumbar, calcium loss in the fourth lumbar, and trabecular separation [24]. A combination of FOS, prunes, and a soy-based diet had the greatest effect on improving lumbar BMD and also improved the biomechanical properties of bone [56]. These results may be due to enhanced bone formation and suppressed bone resorption, as evidenced by an increase in alkaline phosphatase (ALP) and a decrease in urinary Dpd.

In osteopenic postmenopausal women, daily consumption of 100 g of prunes for 3 months significantly increased biomarkers of bone formation, namely total ALP, bone-specific ALP (BALP), and IGF-I, by 12%, 6%, and 17%, respectively [16]. The following 1-year study in osteopenic postmenopausal women comparing dried apples (control diet) and prunes demonstrated that 100 g daily prune consumption improved BMD of the ulna and lumbar spine [14]. In the same study, prune consumption was also associated with significantly decreased tartrate-resistant acid phosphatase 5b (TRAP-5b) and BALP levels, suggesting an increase in bone resorption. Osteocalcin and C-reactive protein (CRP) levels were significantly lower than that of the group receiving dried apples, suggesting increased osteoblast activity. Additionally, prune consumption increased levels of receptor activator of nuclear factor kappa-B ligand (RANKL) to a lesser extent than the control group (+1.99% and +18.33%, respectively), increased OPG levels to a greater extent than the control group (+4.87% and –2.15%, respectively), and decreased sclerostin levels compared the control group (–1.12% and +3.78%, respectively). Though these percent changes did not reach statistical significance, they do suggest that prunes may prevent bone loss in postmenopausal women by suppressing bone turnover. Six months of supplementation with either 50 or 100 g of prunes daily also demonstrated a reduction in TRAP-5b levels, and suggests that a dose of 50 g of prunes is just as effective as 100 g of prunes in prevention of bone loss in postmenopausal women [15]. Recent data from a follow-up study, 5 years after 1 year of regular prune consumption, suggests that even without continued regular consumption of prunes, participants in the prune group retained BMD of the ulna and lumbar spine to a greater extent than the original control group of dried apples [5].

Though the exact components of prunes that contribute to their osteoprotective effects are not certain, it is likely that many of their components, for example, polyphenols, dietary fiber, vitamin K, boron, copper, magnesium, and potassium, contribute to an additive effect, rather than only one responsible nutrient. Boron is a trace element that is critical for bone health, as a deficiency or excess in consumption of boron can be harmful to bone. Boron has been shown to stimulate bone growth and bone metabolism [57] and to play an important role in preserving BMD, bone microarchitecture, and bone strength [58–60]. Epidemiological studies

suggest that potassium contributes to the maintenance of BMD in men and women [61], and higher intakes of potassium have been shown to reduce bone resorption, particularly alongside high protein intake [62]. Copper is a cofactor for lysyl oxidase, which is involved in the cross-linking of collagen and elastin [63,64]. Vitamin K promotes a calcium balance and is a cofactor for the γ-carboxylation of osteocalcin, a bone-matrix protein secreted by osteoblasts that promotes normal bone mineralization by regulating the growth of hydroxyapatite crystals [65]. Previous research has also demonstrated that chlorogenic acid is bone protective. Zhou et al. [66] demonstrated that supplementing Ovx rats with chlorogenic acid led to improved BMD and bone microarchitecture, and an increased proliferation of osteoblast precursors and osteoblast differentiation, as well as increases in bone-formation biomarkers. Despite this, Léotoing et al. [67] demonstrated that the bone-protective effect of prunes is not dependent on the content of chlorogenic acid. However it is important to consider that other polyphenols in prunes, such as quercetin, rutin, and proanthocyanidins, as well as dietary fiber including pectin, fructans, hemicelluloses, and cellulose [63,67], may also be responsible for the effects of prunes on bone. Polyphenols and their metabolites are known to act as antioxidants themselves [68–70] and also activate endogenous antioxidants and inhibit inflammatory signaling pathways [71,72]. Since bone loss has also been linked to free radicals, an imbalance in antioxidant defenses, oxidative stress [73,74], and a pro-inflammatory state [6], it is possible that the polyphenols in prunes work through this mechanism. Lastly, prunes are rich in soluble and insoluble fibers including pectin, fructans, hemicelluloses, and cellulose [63,67], which are known to increase mineral absorption (e.g., calcium) [75], likely through the production of short-chain fatty acids (SCFA) in the intestine, where they, in turn, enhance calcium absorption. Both dietary fiber and polyphenolic compounds have been shown to alter the microbial composition in the gut [75–77]; therefore it is possible that chronic prune consumption stimulates changes in the gut microbiome, increasing SCFA production.

Since prunes have been shown to increase serum ALP, decrease serum sclerostin, and favorably tilt the ratio of OPG to RANKL, it is possible that the positive effect of prunes on bone is mediated through epigenetic regulation of bone metabolism. This notion is speculative, and direct evidence is not available; however, it can be indirectly supported, as all of the aforementioned molecules seem to exert epigenetic influences on osteoblast and osteoclast cells [78]. Figure 20.4 depicts the possible mechanisms of action by which prunes or their bioactive components exert their effects on bone.

20.3 Conclusion

Overall, the research in Ovx rats indicates a possible relationship between consumption of dried mangoes, dates, apples, apricots, raisins, and even pomegranates; however, this evidence has not yet been reproduced in a clinical setting. Though this evidence for the possible osteoprotective effects of these fruits exists, the best evidence suggests that prunes have the ability to both prevent and reverse bone loss in postmenopausal women and potentially in men. These dried fruits may have osteoprotective effects through the action of their phenolic composition, including quercetin and chlorogenic acid; however, the exact mechanism by which these effects may occur remains unknown. It is important to note that for most dried fruits, there

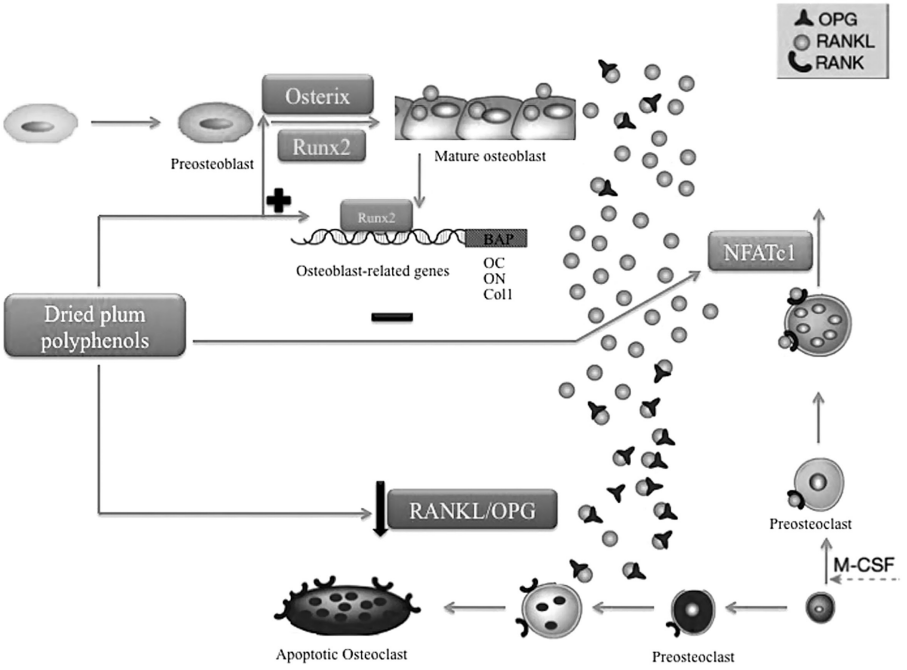


Figure 20.4 **(See color insert.)** Proposed mechanisms of action of prune polyphenols on bone. *Abbreviations*: BAP, bone-specific alkaline phosphatase; M-CSF, macrophage colony stimulating factor; NFATc1, nuclear factor of activated T-cells 1; OPG, osteoprotogerin; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand.

are hundreds of different cultivars, whose nutritive and phenolic composition may differ. There is a possibility that any putative health benefits of each dried fruit could differ based on the type and cultivar of the fruit that is available. On the other hand, the overall additive effect of the nutritive and nonnutritive components of these fruits may be enough to counteract this possibility, since the exact proportions of nutrients may not matter so much as the existence of the nutrients themselves within the matrices of each of these dry fruits. In conclusion, scientific evidence showing that dried fruits have beneficial effects on bone is limited; therefore, further research and more randomized clinical trials are warranted to make future recommendations based on evidence.

References

1. Office of the Surgeon General (US). *Bone Health and Osteoporosis: A Report of the Surgeon General*, Office of the Surgeon General (US), Rockville, MD, 2004.
2. Raisz, L.G., Pathogenesis of osteoporosis: Concepts, conflicts, and prospects. *J. Clin. Invest.*, 2005, 115, 3318–3325.
3. Warriner, A.H., and Curtis, J.R., Adherence to osteoporosis treatments: Room for improvement. *Curr. Opin. Rheumatol.*, 21, 356–362, 2009.

4. Hooshmand, S., and Arjmandi, B.H., Viewpoint: Dried plum, an emerging functional food that may effectively improve bone health. *Ageing Res. Rev.*, 8, 122–127, 2009.
5. Arjmandi, B.H., Johnson, S.A., Pourafshar, S., Navaei, N., George, K.S., Hooshmand, S., Chai, S.C. et al., Bone-protective effects of dried plum in postmenopausal women: Efficacy and possible mechanisms. *Nutrients*, 9, 2017.
6. Mundy, G.R., Osteoporosis and inflammation. *Nutr. Rev.*, 65(Suppl.), S147–S151, 2007.
7. Wynn, E., Krieg, M.A., Lanham-New, S.A., and Burckhardt, P., Postgraduate symposium: Positive influence of nutritional alkalinity on bone health. *Proc. Nutr. Soc.*, 69, 166–173, 2010.
8. Welch, A., MacGregor, A., Jennings, A., Fairweather-Tait, S., Spector, T., and Cassidy, A., Habitual flavonoid intakes are positively associated with bone mineral density in women. *J. Bone Miner. Res.*, 27, 1872–1878, 2012.
9. Trivedi, R., Kumar, S., Kumar, A., Siddiqui, J.A., Swarnkar, G., Gupta, V., Kendurker, A. et al., Kaempferol has osteogenic effect in ovariectomized adult sprague-dawley rats. *Mol. Cell. Endocrinol.*, 289, 85–93, 2008.
10. Siddiqui, J.A., Sharan, K., Swarnkar, G., Rawat, P., Kumar, M., Manickavasagam, L., Maurya, R. et al., Quercetin-6-c-β-D-glucopyranoside isolated from Ulmus wallichiana planchon is more potent than quercetin in inhibiting osteoclastogenesis and mitigating ovariectomy-induced bone loss in rats. *Menopause*, 18, 198–207, 2011.
11. Shen, C.L., Wang, P., Guerrieri, J., Yeh, J.K., and Wang, J.S, Protective effect of green tea polyphenols on bone loss in middle-aged female rats. *Osteoporos. Int.*, 19, 979–990, 2008.
12. Liu, Z.P., Li, W.X., Yu, B., Huang, J., Sun, J., Huo, J.S., and Liu, C.X., Effects of trans-resveratrol from *Polygonum cuspidatum* on bone loss using the ovariectomized rat model. *J. Med. Food*., 8, 14–19, 2005.
13. Pawlowski, J.W., Martin, B.R., McCabe, G.P., Ferruzzi, M.G., and Weaver, C.M., Plum and soy aglycon extracts superior at increasing bone calcium retention in ovariectomized Sprague Dawley rats. *J. Agric. Food Chem.*, 62, 6108–6117, 2014.
14. Hooshmand, S., Chai, S.C., Saadat, R.L., Payton, M.E., Brummel-Smith, K., and Arjmandi, B.H., Comparative effects of dried plum and dried apple on bone in postmenopausal women. *Br. J. Nutr.*, 106, 923–930, 2011.
15. Hooshmand, S., Kern, M., Metti, D., Shamloufard, P., Chai, S.C., Johnson, S.A., Payton, M.E. et al., The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: A randomized, controlled trial. *Osteoporos. Int.*, 27, 2271–2279, 2016.
16. Arjmandi, B.H., Khalil, D.A., Lucas, E.A., Georgis, A., Stoecker, B.J., Hardin, C., Payton, M.E. et al., Dried plums improve indices of bone formation in postmenopausal women. *J. Womens Health Gend. Based. Med.*, 11, 61–68, 2002.
17. Amri, Z., Zaouay, F., Lazreg-Aref, H., Soltana, H., Mneri, A., Mars, M., and Hammami, M., Phytochemical content, fatty acids composition and antioxidant potential of different pomegranate parts: Comparison between edible and non edible varieties grown in Tunisia. *Int. J. Biol. Macromol.*, 104, 274–280, 2017.
18. Kang, S.J., Choi, B.R., Kim, S.H., Yi, H.Y., Park, H.R., Kim, D.C., Choi, S.H. et al., Dried pomegranate potentiates anti-osteoporotic and anti-obesity activities of red clover dry extracts in ovariectomized rats. *Nutrients*, 7, 2622–2647, 2015.
19. Wang, Y., Zhang, H., Liang, H., and Yuan, Q, Purification, antioxidant activity and protein-precipitating capacity of punicalin from pomegranate husk. *Food Chem.*, 138, 437–443, 2013.

20. van Elswijk, D.A., Schobel, U.P., Lansky, E.P., Irth, H., and van der Greef, J., Rapid dereplication of estrogenic compounds in pomegranate (*Punica granatum*) using on-line biochemical detection coupled to mass spectrometry. *Phytochemistry*, 65, 233–241, 2004.
21. Vinson, J.A., Zubik, L., Bose, P., Samman, N., and Proch, J., Dried fruits: Excellent *in vitro* and *in vivo* antioxidants. *J. Am. Coll. Nutr.*, 24, 44–50, 2005.
22. Cheng, J., Yi, X., Chen, H., Wang, Y., and He, X., Anti-inflammatory phenylpropanoids and phenolics from *Ficus hirta* vahl. *Fitoterapia*, 121, 229–234, 2017.
23. Ammar, S., del Mar Contreras, M., Belguith-Hadrich, O., Segura-Carretero, A., and Bouaziz, M., Assessment of the distribution of phenolic compounds and contribution to the antioxidant activity in Tunisian fig leaves, fruits, skins and pulps using mass spectrometry-based analysis. *Food Funct.*, 6, 3663–3677, 2015.
24. Arjmandi, B.H., Johnson, C.D., Campbell, S.C., Hooshmand, S., Chai, S.C., and Akhter, M.P., Combining fructooligosaccharide and dried plum has the greatest effect on restoring bone mineral density among select functional foods and bioactive compounds. *J. Med. Food.*, 13, 312–319, 2010.
25. Tokunaga, T., Novel physiological function of fructooligosaccharides. *Biofactors*, 21, 89–94, 2004.
26. Warnholtz, A., Wendt, M., August, M., and Münzel, T., Clinical aspects of reactive oxygen and nitrogen species. *Biochem. Soc. Symp.*, 71, 121–133, 2004.
27. Weitzmann, M.N., and Pacifici, R., Estrogen deficiency and bone loss: An inflammatory tale. *J. Clin. Invest.*, 116, 1186–1194, 2006.
28. Kalu, D.N., The ovariectomized rat model of postmenopausal bone loss. *Bone Miner.*, 15, 175–191, 1991.
29. Chai, S.C., Hooshmand, S., Saadat, R.L., Payton, M.E., Brummel-Smith, K., and Arjmandi, B.H., Daily apple *versus* dried plum: Impact on cardiovascular disease risk factors in postmenopausal women. *J. Acad. Nutr. Diet.*, 112, 1158–1168, 2012.
30. Messer, J.G., La, S., Hopkins, R.G., and Kipp, D.E., Quercetin partially preserves development of osteoblast phenotype in fetal rat calvaria cells in an oxidative stress environment. *J. Cell. Physiol.*, 231, 2779–2788, 2016.
31. Forte, L., Torricelli, P., Boanini, E., Gazzano, M., Rubini, K., Fini, M., and Bigi, A., Antioxidant and bone repair properties of quercetin-functionalized hydroxyapatite: An *in vitro* osteoblast-osteoclast-endothelial cell co-culture study. *Acta. Biomater.*, 32, 298–308, 2016.
32. Fatokun, A.A., Tome, M., Smith, R.A., Darlington, L.G., and Stone, T.W., Protection by the flavonoids quercetin and luteolin against peroxide- or menadione-induced oxidative stress in mc3t3-e1 osteoblast cells. *Nat. Prod. Res.*, 29, 1127–1132, 2015.
33. Babosova, R., Duranova, H., Omelka, R., Kovacova, V., Adamkovicova, M., Grosskopf, B., Capcarova, M. et al., Structural changes in femoral bone microstructure of female rabbits after intramuscular administration of quercetin. *Acta. Vet. Scand.*, 58, 43, 2016.
34. Rendina, E., Hembree, K.D., Davis, M.R., Marlow, D., Clarke, S.L., Halloran, B.P., Lucas, E.A. et al., Dried plum's unique capacity to reverse bone loss and alter bone metabolism in postmenopausal osteoporosis model. *PLoS One*, 8, e60569, 2013.
35. Kono, R., Okuno, Y., Inada, K., Tokuda, A., Hashizume, H., Yoshida, M., Nakamura, M. et al., A prunus mume extract stimulated the proliferation and differentiation of osteoblastic mc3t3-e1 cells. *Biosci. Biotechnol. Biochem.*, 75, 1907–1911, 2011.

36. Hammouda, H., Chérif, J.K., Trabelsi-Ayadi, M., Baron, A., and Guyot, S., Detailed polyphenol and tannin composition and its variability in Tunisian dates (*Phoenix dactylifera* L.) at different maturity stages. *J. Agric. Food Chem.*, 61, 3252–3263, 2013.
37. Borochov-Neori, H., Judeinstein, S., Greenberg, A., Volkova, N., Rosenblat, M., and Aviram, M., Date (*Phoenix dactylifera* L.) fruit soluble phenolics composition and anti-atherogenic properties in nine Israeli varieties. *J. Agric. Food Chem.*, 61, 4278–4286, 2013.
38. Xu, Y., Simon, J.E., Welch, C., Wightman, J.D., Ferruzzi, M.G., Ho, L., Pasinetti, G.M. et al., Survey of polyphenol constituents in grapes and grape-derived products. *J. Agric. Food Chem.*, 59, 10586–10593, 2011.
39. Cantos, E., Espín, J.C., and Tomás-Barberán, F.A., Varietal differences among the polyphenol profiles of seven table grape cultivars studied by LC-DAD-MS-MS. *J. Agric. Food Chem.*, 50, 5691–5696, 2002.
40. Yin, J., Winzenberg, T., Quinn, S., Giles, G., and Jones, G., Beverage-specific alcohol intake and bone loss in older men and women: A longitudinal study. *Eur. J. Clin. Nutr.*, 65, 526–532, 2011.
41. Hardcastle, A.C., Aucott, L., Reid, D.M., and Macdonald, H.M., Associations between dietary flavonoid intakes and bone health in a Scottish population. *J. Bone Miner. Res.*, 26, 941–947, 2011.
42. Yahara, N., Tofani, I., Maki, K., Kojima, K., Kojima, Y., and Kimura, M., Mechanical assessment of effects of grape seed proanthocyanidins extract on tibial bone diaphysis in rats. *J. Musculoskelet. Neuronal Interact.*, 5, 162–169, 2005.
43. Williamson, G., and Carughi, A., Polyphenol content and health benefits of raisins. *Nutr. Res.*, 30, 511–519, 2010.
44. Hohman, E.E., and Weaver, C.M., A grape-enriched diet increases bone calcium retention and cortical bone properties in ovariectomized rats. *J. Nutr.*, 145, 253–259, 2015.
45. Szulc, P., Seeman, E., Duboeuf, F., Sornay-Rendu, E., and Delmas, P.D., Bone fragility: Failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. *J. Bone Miner. Res.*, 21, 1856–1863, 2006.
46. Stacewicz-Sapuntzakis, M., Dried plums and their products: Composition and health effects—an updated review. *Crit. Rev. Food Sci. Nutr.*, 53, 1277–1302, 2013.
47. Arjmandi B.H., Lucas E.A., Juma S., Soliman A., Stoecker B.J., Khalil D.A., Smith B.J. et al., Prune prevents ovariectomy-induced bone loss in rats. *JANA*, 4, 50–56, 2001.
48. Rendina, E., Lim, Y.F., Marlow, D., Wang, Y., Clarke, S.L., Kuvibidila, S., Lucas, E.A. et al., Dietary supplementation with dried plum prevents ovariectomy-induced bone loss while modulating the immune response in c57bl/6j mice. *J. Nutr. Biochem.*, 23, 60–68, 2012.
49. Arjmandi B.H., Lucas E.A., Juma S., Soliman A., Stoecker B.J., Khalil D.A., Smith B.J. et al., Prune prevents ovariectomy-induced bone loss in rats. *JANA*, 4, 50–56, 2001.
50. Smith, B.J., Bu, S.Y., Wang, Y., Rendina, E., Lim, Y.F., Marlow, D., Clarke, S.L. et al., A comparative study of the bone metabolic response to dried plum supplementation and PTH treatment in adult, osteopenic ovariectomized rat. *Bone*, 58, 151–159, 2014.

51. Deyhim, F., Stoecker, B.J., Brusewitz, G.H., Devareddy, L., and Arjmandi, B.H., Dried plum reverses bone loss in an osteopenic rat model of osteoporosis. *Menopause*, 12, 755–762, 2005.
52. Mühlbauer, R.C., Lozano, A., Reinli, A., and Wetli, H., Various selected vegetables, fruits, mushrooms and red wine residue inhibit bone resorption in rats. *J. Nutr.*, 133, 3592–3597, 2003.
53. Franklin, M., Bu, S.Y., Lerner, M.R., Lancaster, E.A., Bellmer, D., Marlow, D., Lightfoot, S.A. et al., Dried plum prevents bone loss in a male osteoporosis model *via* IGF-I and the rank pathway. *Bone*, 39, 1331–1342, 2006.
54. Bu, S.Y., Lucas, E.A., Franklin, M., Marlow, D., Brackett, D.J., Boldrin, E.A., Devareddy, L. et al., Comparison of dried plum supplementation and intermittent PTH in restoring bone in osteopenic orchidectomized rats. *Osteoporos. Int.*, 18, 931–942, 2007.
55. Halloran, B.P., Wronski, T.J., VonHerzen, D.C., Chu, V., Xia, X., Pingel, J.E., Williams, A.A. et al., Dietary dried plum increases bone mass in adult and aged male mice. *J. Nutr.*, 140, 1781–1787, 2010.
56. Johnson, C.D., Lucas, E.A., Hooshmand, S., Campbell, S., Akhter, M.P., and Arjmandi, B.H., Addition of fructooligosaccharides and dried plum to soy-based diets reverses bone loss in the ovariectomized rat. *Evid. Based Complement. Alternat. Med.*, 1–7, 2011.
57. Nielsen, F.H., Hunt, C.D., Mullen, L.M., and Hunt, J.R., Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women. *FASEB J.*, 1, 394–397, 1987.
58. Nielsen, F.H., Biochemical and physiologic consequences of boron deprivation in humans. *Environ. Health Perspect.*, 102(Suppl. 7), 59S–63S, 1994.
59. Nielsen, F.H., Is boron nutritionally relevant? *Nutr. Rev.*, 66, 183–191, 2008.
60. Zofkova, I., Davis, M., and Blahos, J., Trace elements have beneficial, as well as detrimental effects on bone homeostasis. *Physiol. Res.*, 66, 391–402, 2017.
61. Tucker, K.L., Hannan, M.T., Chen, H., Cupples, L.A., Wilson, P.W., and Kiel, D.P., Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *Am. J. Clin. Nutr.*, 69, 727–736, 1999.
62. Zwart, S.R., Hargens, A.R., and Smith, S.M., The ratio of animal protein intake to potassium intake is a predictor of bone resorption in space flight analogues and in ambulatory subjects. *Am. J. Clin. Nutr.*, 80, 1058–1065, 2004.
63. Bowen, P.E., Role of commodity boards in advancing the understanding of the health benefits of whole foods: California dried plums. *Nutr. Today*, 52, 19–25, 2017.
64. Yee, C.D., Kubena, K.S., Walker, M., Champney, T.H., and Sampson, H.W., The relationship of nutritional copper to the development of postmenopausal osteoporosis in rats. *Biol. Trace Elem. Res.*, 48, 1–11, 1995.
65. Iwamoto, J., Takeda, T., and Sato, Y., Effects of vitamin K2 on osteoporosis. *Curr. Pharm. Des.*, 10, 2557–2576, 2004.
66. Zhou, R.P., Lin, S.J., Wan, W.B., Zuo, H.L., Yao, F.F., Ruan, H.B., Xu, J. et al., Chlorogenic acid prevents osteoporosis by shp2/pi3k/akt pathway in ovariectomized rats. *PLoS One*, 11, e0166751, 2016.
67. Léotoing, L., Wauquier, F., Davicco, M.J., Lebecque, P., Gaudout, D., Rey, S., Vitrac, X. et al., The phenolic acids of Agen prunes (dried plums) or Agen prune juice concentrates do not account for the protective action on bone in a rat model of postmenopausal osteoporosis. *Nutr. Res.*, 36, 161–173, 2016.

68. Dismore, M.L., Haytowitz, D.B., Gebhardt, S.E., Peterson, J.W., and Booth, S.L., Vitamin K content of nuts and fruits in the US diet. *J. Am. Diet. Assoc.*, 103, 1650–1652, 2003.
69. Kayano, S., Kikuzaki, H., Fukutsuka, N., Mitani, T., and Nakatani, N., Antioxidant activity of prune (*Prunus domestica* L.) constituents and a new synergist. *J. Agric. Food Chem.*, 50, 3708–3712, 2002.
70. Nakatani, N., Kayano, S., Kikuzaki, H., Sumino, K., Katagiri, K., and Mitani, T., Identification, quantitative determination, and antioxidative activities of chlorogenic acid isomers in prune (*Prunus domestica* L.). *J. Agric. Food Chem.*, 48, 5512–5516, 2000.
71. Rahman, I., Biswas, S.K., and Kirkham, P.A., Regulation of inflammation and redox signaling by dietary polyphenols. *Biochem. Pharmacol.*, 72, 1439–1452, 2006.
72. Stevenson, D.E., and Hurst, R.D., Polyphenolic phytochemicals—just antioxidants or much more? *Cell. Mol. Life Sci.*, 64, 2900–2916, 2007.
73. Garrett, I.R., Boyce, B.F., Oreffo, R.O., Bonewald, L., Poser, J., and Mundy, G.R., Oxygen-derived free radicals stimulate osteoclastic bone resorption in rodent bone *in vitro* and *in vivo*. *J. Clin. Invest.*, 85, 632–639, 1990.
74. Callaway, D.A., and Jiang, J.X., Reactive oxygen species and oxidative stress in osteoclastogenesis, skeletal aging and bone diseases. *J. Bone Miner. Metab.*, 33, 359–370, 2015.
75. McCabe, L., Britton, R.A., and Parameswaran, N., Prebiotic and probiotic regulation of bone health: Role of the intestine and its microbiome. *Curr. Osteoporos. Rep.*, 13, 363–371, 2015.
76. Duda-Chodak, A., Tarko, T., Satora, P., and Sroka, P., Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: A review. *Eur. J. Nutr.*, 54, 325–341, 2015.
77. Tuohy, K.M., Conterno, L., Gasperotti, M., and Viola, R., Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. *J. Agric. Food Chem.*, 60, 8776–8782, 2012.
78. Marini, F., Cianferotti, L., and Brandi, M.L., Epigenetic mechanisms in bone biology and osteoporosis: Can they drive therapeutic choices? *Int. J. Mol. Sci.*, 17, 1329, 2016.
79. Aghajanian, P., Hall, S., Wongworawat, M.D., and Mohan, S., The roles and mechanisms of actions of vitamin C in bone: New developments. *J. Bone Miner. Res.*, 30, 1945–1955, 2015.
80. Finck, H., Hart, A.R., Jennings, A., and Welch, A.A., Is there a role for vitamin C in preventing osteoporosis and fractures? A review of the potential underlying mechanisms and current epidemiological evidence. *Nutr. Res. Rev.*, 27, 268–283, 2014.
81. Shen, C.L., Klein, A., Chin, K.Y., Mo, H., Tsai, P., Yang, R.S., Chyu, M.C. et al., Tocotrienols for bone health: A translational approach. *Ann. N. Y. Acad. Sci.*, 1401, 150–165, 2017.
82. Palacios, C., The role of nutrients in bone health, from A to Z. *Crit. Rev. Food Sci. Nutr.*, 46, 621–628, 2006.

Chapter 21

Dried Fruits

Gut Health and Microbiota

María Marhuenda Muñoz and
Rosa M. Lamuela Raventós

21.1 Introduction 487
21.2 Benefits of Dried Fruits on Gut Health and Microbiota 488
21.2.1 Epidemiologic Studies 490
21.2.2 *In Vitro* and *In Vivo* Animal Studies 491
21.2.3 Human Intervention Studies 492
21.3 Conclusion 492
References 492

21.1 Introduction

Dried fruits are a form of fresh fruits that have been concentrated by means of drying techniques, and hence they have a lower moisture content and water activity [1]. There are two classes of dried fruits, depending on whether the fruits have been treated or not before drying. Apples, apricots, currants, dates, figs, peaches, pears, prunes, and raisins are called *conventional* or *traditional* dried fruits because they are not treated, whereas fruits such as mangoes and the different berries are commonly infused with sugar solutions or fruit juice before drying. Regardless, the drying of both types can be either natural, by exposition to the sun; or artificial, through the use of specialized dryers or dehydrators [2]. The drying of the fruits allows easy storage and distribution and has the advantage of being available throughout the year [1].

The consumption of dried fruits was discouraged more than 30 years ago because of their high sugar content [3]. However, consumption has increased in

recent times since studies in the 1990s demonstrated the potential beneficial effects of some of their components, such as resveratrol and other polyphenols, on cardiovascular disease (CVD) [4].

Regarding incorporation of dried fruits in the habitual diet, few studies have evaluated possible links between their consumption and diet quality. A prospective study performed within the 1999–2004 National Health and Nutrition Examination Survey (NHANES) demonstrated an association between dried-fruit consumption and diet quality, relating dried-fruit consumption to improved nutrient intake, a higher overall diet quality score, and lower body weight/adiposity measures [5]. In addition, a cross-sectional study described an inverse association between dried fruit intake, among other foods, and the prevalence of metabolic disorders [6].

As with every food, the first contact that dried fruits have in our organism is with the gut lining; therefore their components could, to some extent, exert health benefits there as well. The human gastrointestinal tract is home to millions of microorganisms, representing the largest community in the body. The current knowledge of gut microbiota is quite wide, and it has been suggested that intestinal permeability may play a role in intestinal inflammatory status and gut-barrier integrity [7]. Furthermore, deleterious changes in the microbiota, known as *dysbiosis*, or changes in the intestine due to dysbiosis, have been shown to be involved in the development of chronic diseases such as obesity and diabetes [8]. Several studies have shown that germ-free animals have higher susceptibility to infections and reduced nutrient uptake. Nevertheless, these animals restore their normal function when colonized by normal microbiota [9]. While some of these illnesses are caused by physical changes in the gut, most of them are due to changes in bacteria and other organisms or in the products generated by them. In fact, a significant part of the molecules that are absorbed by the enterocytes are not those that have been eaten but, instead, their metabolites [10]. Figure 21.1 shows an example of this: 2*R*, 3*S*-dihydromyricetin, and quercetin are modified by the gut microbiota into products such as phloroglucinol, 5-(3,4,5-trihydroxybenzyl)dihydro-2(3H)-furanone, 3,4-dihydroxyhydrocinnamic acid, and 3,4-dihydroxyphenylacetic acid. These are the molecules that enter the cells after reaching the bloodstream [11]. The human microbiota has been reported to have a greater metabolic capacity than our own cells [12,13]; therefore, when the balance is broken, there is a risk of malfunction.

Diet is an important modulator of the microbiota and its products. For this reason, it is of interest to know the composition of the different dried fruits and their effect on the gut microbiota and their metabolites. The relationship between gut health and microbiota and the consumption of dried fruits has not been investigated thoroughly. A few studies, though, have described to some extent the effect that dried fruits, their extracts, or their fresh counterparts have on the composition of the microbial community of the gastrointestinal tract and the status of the gut lining. This chapter highlights the effect that the components of dried fruits exert on gut health and microbiota.

21.2 Benefits of Dried Fruits on Gut Health and Microbiota

Since the composition of dried fruits does not vary much after dehydration, apart from in the concentration of nutrients and phytochemicals, regular intake of these fruits can exert various health benefits. Although there are different drying

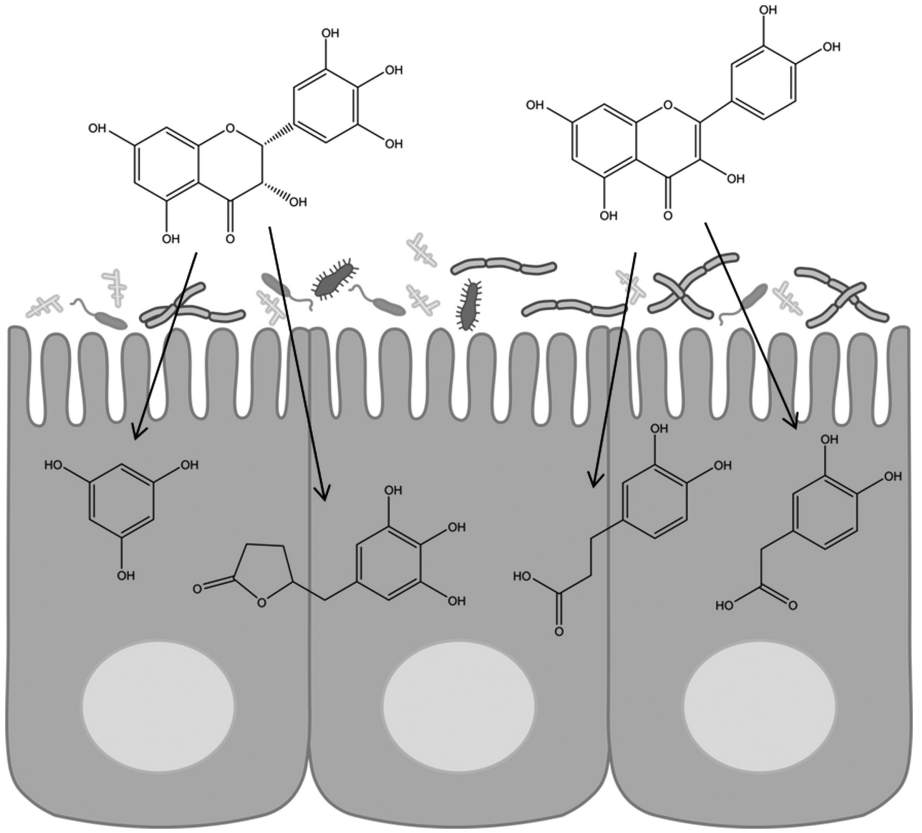


Figure 21.1 **(See color insert.)** 2*R*, 3*S*-dihydromyricetin, and quercetin are modified by the microbiota, and different products [1,3,5-benzenetriol, dihydro-5-(3,4,5-trihydroxyphenyl)methyl-2(3H)-furanone, 3,4-dihydroxyhydrocinnamic acid, and 3,4-dihydroxyphenylacetic acid] enter the cells.

methods, the most commonly known and used to date are related to heat, which clearly reduces the amount of the micronutrient ascorbic acid because of its thermolability [14].

Dried fruits are remarkable sources of carbohydrates and simple sugars but, despite their sweetness, they have low to moderate glycemic and insulin indices comparable to those of their fresh counterparts [15–17]. The fact that they do not mediate a major spike in blood sugar or insulin might be due to their high content of fiber, fructose, and phenolic compounds that are able to moderate the glycemic response [18]. For this reason, dried fruits with a low glycemic index could be useful in the treatment of hyperglycemic conditions. Moreover, their effects may be even more beneficial in subjects with a high body weight because of their low fat content and also because they seem to reduce food intake to a greater extent than their fresh analogues [19].

Dried fruits are also relevant sources of dietary fiber, which is why they are included in high fiber diets recommended to reduce the risk factors of several non-communicable diseases such as type-2 diabetes, obesity, and CVD [20,21]. Some of these dried fruits are also well recognized as an effective treatment for constipation [22,23].

Carbohydrates are the main sources of carbon and energy for the microbiota and, as mentioned, are abundant in dried fruits. The microbiota has a great capacity to hydrolyze complex polysaccharides, of which xylan-, pectin-, and arabinose-containing structures are common in the plant-origin foods that we consume [24]. This capacity of hydrolysis is very important to humans, as our genome lacks most of the enzymes needed for the degradation of these glycans, non-starch polysaccharides. They stimulate fermentation leading to bacterial proliferation and increased biomass [25]. Polysaccharides are fermented by the microbiota to short chain fatty acids (SCFA), organic acids that serve as an energy source for other bacteria, the epithelium, and other tissues. The main SCFA are acetate, propionate, and butyrate, the latter serving not only as a source of energy but also for maintaining mucosal integrity, modulating intestinal inflammation, and promoting genomic stability, thereby protecting against colon cancer [26]. These weak acids also contribute to lowering the colonic pH, which contributes to the inhibition of growth and activity of pathogenic bacteria.

In addition, when fiber is not completely fermented, it increases digesta mass due to its physical presence and ability to adsorb water, resulting in the dilution of toxins and shortening of transit time, which, in turn, reduces the exposure to potential harmful molecules [27]. In view of their low levels of protein and fat, dried fruits do not increase the risk of colorectal cancer or intestinal permeability, which are unwanted consequences of the digestion or fermentation products derived from these macronutrients [27].

Regarding micronutrients, as with vegetables, dried fruits are particularly rich in potassium and can, therefore, help in reducing blood pressure [28]. There is no information available about the possible relationship between potassium and microbiota.

Phenolic compounds integrated in the food matrix are non-nutrients that have recently been related to the modulation of metabolism. In the case of dried fruits, it has been shown that phytoestrogens (isoflavones and lignans) might modulate the secretion of insulin from the pancreas (1), and genistein and daidzein could regulate glucose homeostasis [29].

The effect of dietary polyphenols on overall health is very dependent on their metabolism by the microbiota, but in the case of gut health, these phytochemicals may exert a direct effect thanks to their interaction with the epithelium and the microbiota. In this way, a two-way interaction between phenolic compounds and microbiota has been described [30]. Regarding the effects on the microbiota, it has been reported that polyphenols are able to modulate intestinal ecology not only because of their prebiotic capacity but also due to selective antimicrobial activity [31]. The phenolic composition of dried fruits is still under investigation, with different study groups evaluating different drying methods and determinations that may not be comparable [32].

Very few studies have focused on the relationship between dried fruits and gut health and the microbiota, but in the following sections, we will review the evidence that has arisen in this area.

21.2.1 Epidemiologic Studies

A recent study associated a higher body mass index and body fat with higher acetate fecal concentrations and lower levels of the *Bacteroides* species [33]. It was also

found that obese individuals had a lower consumption of fish, fruits, and dried fruits, as well as a lower fiber intake and antioxidant capacity from the diet. These results can likely be explained by the low consumption of fruits and dried fruits, which are good sources of fiber and rich in antioxidant phytochemicals.

21.2.2 In Vitro *and* In Vivo *Animal Studies*

Dates are the second most commonly consumed dried fruit. One study assessed their effect on the microbiota using pH-controlled, mixed fecal batch cultures, and also their potential to inhibit colon cancer cell growth using Caco-2 cells [34]. The aim of this study was not only to assess the role of whole dates but also that of their polyphenols; therefore, polyphenol-rich extracts as well as whole date extracts were applied to the cell cultures. Both extracts significantly increased the growth of bacteria such as bifidobacteria. These bacteria are beneficial in that their growth may inhibit the progression of pathogens and promote the production of SCFA. Nonetheless, the bifidogenic activity was weaker than that induced by cereals. The growth of other bacteria from the *Atopobium* species that are thought to modulate caspases, leading to apoptosis and the inhibition of Caco-2 cancer cell growth *in vitro*, was promoted by the whole date extract, as were some species of the *Coccoides-Eubacterium* group, which relate to the production of butyrate, have anticancer properties, and protect against ulcerative colitis. Whole date extracts also exerted a direct antiproliferative action [34].

Another study demonstrated a similar effect of raisins on the growth of beneficial bacteria. In this study, a full dynamic gastric model was used instead of cultures in order to provide a more accurate approach to the human gastrointestinal tract. On comparison with fructooligosaccharides (FOS), it was observed that the promotion of *Bifidobacterium* proliferation was again related to the polyphenol content of the raisins. In addition, FOS was found to promote the growth of *Lactobacillus* species. A decrease in *Bacteroidetes* and an increase in *Proteobacteria* and *Actinobacteria* was also found after exposure to both raisins and FOS, whereas only raisins promoted an increase in *Roseburia* species and butyrate-producing strains and a decrease in *Ruminococcaceae* and *Faecalibacterium prausnitzii* [35].

Other studies have been performed with fruit extracts that may have the same effect as their dried-fruit counterparts. Pigs fed grape seed and grape marc meal extract showed a decrease of *Streptococcus* and *Clostridium* species and downregulation of several pro-inflammatory genes in the intestinal mucosa [36]. Broiler chicks fed similar extracts (grape pomace and grape seed extracts) showed a higher biodiversity in beneficial bacteria and an increase in the ratio of villus height to crypt depth at the jejunum, both of which may influence gut physiology and biochemistry [37]. Both studies associated the modulation of the microbiota with the polyphenol content of the extracts.

Another study found that intake of grape antioxidant dietary fiber induced an increase of beneficial *Lactobacillus* in rat cecum, which was found to be not only due to polyphenols but also to the high dietary fiber content [38]. A similar approach to the previous studies was taken using *Ume*, a Japanese apricot. The fiber of this fruit was fed to mice, which showed an increase in the amount of feces and *Bacteroides* and *Clostridium* occupation ratios after the intervention [39].

Two studies on different fish species showed that when they were fed a diet enriched with a mix of dates and probiotics, there was a change in the expression of

several genes related to mucosal immunity, such as a down-regulation of *rbl* and *hep* and up-regulation of *fbl* [40,41].

21.2.3 Human Intervention Studies

A pilot study performed in San Diego showed a modest, albeit positive, effect of prunes in women. The intervention compared two 100-kcal snacks: low-fat cookies and prunes. These snacks were incorporated twice a day in a crossover design for two 2-week periods, separated by a 2-week wash-out period. After the prune period, the volunteers' bowel habits were slightly improved compared with the cookie period: stools were softer and had increased bulk, and their motion was facilitated. These results were attributed to the combination of fiber and sorbitol present in prunes [42].

A more recent randomized, controlled, and crossover study investigated the effect of palm-date consumption on microbiota growth and large intestinal health. Volunteers followed a 3-week intervention period in which they incorporated 50 g of dates daily into their diet. There was no significant change in the growth of bacteria, but fecal water disclosed inhibition of cancer cell proliferation, and its genotoxicity was significantly reduced. However, date consumption led to a significant increase in stool frequency, which was between 3 and 4 on the Bristol chart (normal status) [43].

There are few studies on general analyses of dried fruits as well as a lack of studies on individual fruits or comparative studies of different dried fruits, making it difficult to determine whether the few effects described above are related to one fruit or are general for all dried fruits. Apart from their content in micronutrients, the composition of the different dried fruits does not vary greatly, and therefore the effects derived from their carbohydrate or fiber content could be very similar.

21.3 Conclusion

There are very few studies on gut microbiota of dried fruits. The health effects related to gut health and microbiota of the macronutrients, the main components of dried fruits, have been established, but there is a need for further investigation regarding micronutrient and non-nutrient composition. Apart from the prebiotic effect of fiber, the modulation of the microbiota and gut health is very dependent on the micronutrient composition of the diet. There is a lack of studies related to dried fruit consumption and gut microbiota. Studies of dried fruits are of great interest, taking into account that dried fruits are often recommended as a "healthy" snack choice and that recent studies have shown that modulation of the microbiota has a profound influence on health status.

References

1. Chang, S.K., Alasalvar, C., and Shahidi, F., Review of dried fruits: Phytochemicals, antioxidant efficacies, and health benefits. *J. Funct. Foods*, 21, 113–132, 2016.
2. Alasalvar, C., and Shahidi, F., Composition, phytochemicals, and beneficial health effects of dried fruits: An overview, in *Dried Fruits: Phytochemicals and Health Effects*. Alasalvar, C. and Shahidi, F., Eds., John Wiley & Sons, Inc., Oxford, UK, 2013, pp. 1–18.

3. Hernández-Alonso, P., Camacho-Barcia, L., Bulló, M., and Salas-Salvadó, J., Nuts and dried fruits: An update of their beneficial effects on type 2 diabetes. *Nutrients*, 9, 673, 2017.
4. Pace-Asciak, C.R., Hahn, S., Diamandis, E.P., Soleas, G., and Goldberg, D.M., The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: Implications for protection against coronary heart disease. *Clin. Chim. Acta*, 235, 207–219, 1995.
5. Keast, D.R., O'Neil, C.E., and Jones, J.M., Dried fruit consumption is associated with improved diet quality and reduced obesity in US adults: National Health and Nutrition Examination Survey, 1999–2004. *Nutr. Res.*, 31, 460–467, 2011.
6. Chan, R., Wong, V.W.-S., Chu, W.C.-W., Wong, G.L.-H., Li, L.S., Leung, J., Chim, A.M.-L. et al., Diet-quality scores and prevalence of nonalcoholic fatty liver disease: A population study using proton-magnetic resonance spectroscopy, *PLoS One*, 10, e0139310, 2015.
7. Teixeira, T.F., Collado, M.C., Ferreira, C.L., Bressan, J., and Peluzio, Mdo, C., Potential mechanisms for the emerging link between obesity and increased intestinal permeability. *Nutr. Res.*, 9, 637–647, 2012.
8. Tai, N., Wong, F.S., and Wen, L., The role of gut microbiota in the development of type 1, type 2 diabetes mellitus and obesity. *Rev. Endocr. Metab. Disord.*, 16, 55–65, 2015.
9. O'Hara, A.M., and Shanahan, F., The gut flora as a forgotten organ. *EMBO Rep.*, 7, 688–693, 2006.
10. Yadav, M., Verma, M.K., and Chauhan, N.S., A review of metabolic potential of human gut microbiome in human nutrition. *Arch. Microbiol.*, 200, 203–217, 2018.
11. Kawabata, K., Mukai, R., and Ishisaka, A., Quercetin and related polyphenols: New insights and implications for their bioactivity and bioavailability. *Food Funct.*, 6, 1399–1417, 2015.
12. Gill, S.R., Pop, M., DeBoy, R.T., Eckburg, P.B., Turnbaugh, P.J., Samuel, B.S., Gordon, J.I. et al., Metagenomic analysis of the human distal gut microbiome. *Science*, 312, 1355–1359, 2006.
13. Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., Nielsen, T. et al., A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*, 464, 59–65, 2010.
14. Bennett, L.E., Singh, D.P., and Clingeleffer, P.R., Micronutrient mineral and folate content of Australian and imported dried fruit products. *Crit. Rev. Food Sci. Nutr.*, 51, 38–49, 2011.
15. Kim, Y., Hertzler, S.R., Byrne, H.K., and Mattern, C.O., Raisins are a low to moderate glycemic index food with a correspondingly low insulin index. *Nutr. Res.*, 28, 304–308, 2008.
16. Esfahani, A., Lam, J., and Kendall, C.W.C., Acute effects of raisin consumption on glucose and insulin reponses in healthy individuals. *J. Nutr. Sci.*, 3, e1, 2014.
17. Miller, C.J., Dunno, E.V., and Hashim, I.B., The glycaemic index of dates and date/yoghurt mixed meals: Are dates the candy that grows on trees? *Eur. J. Clin. Nutr.*, 57, 427–430, 2003.
18. Stacewicz-Sapuntzakis, M., Bowen, P.E., Hussain, E.A., Damayanti-Wood, B.I., and Farnsworth, N.R., Chemical composition and potential health effects of prunes: A functional food? *Crit. Rev. Food Sci. Nutr.*, 41, 251–286, 2001.
19. Patel, B.P., Luhovyy, B., Mollard, R., Painter, J.E., and Anderson, G.H., A premeal snack of raisins decreases mealtime food intake more than grapes in young children. *Appl. Physiol. Nutr. Metab.*, 38, 382–389, 2013.

20. Council on Scientific Affairs, Dietary fiber and health. *JAMA*, 262, 542–546, 1989.
21. Anderson, J.W., Baird, P., Davis, R.H., Ferreri, S., Knudtson, M., Koraym, A., Waters, V. et al., Health benefits of dietary fiber. *Nutr. Rev.*, 67, 188–205, 2009.
22. Bell, S.J., A review of dietary fiber and health: Focus on raisins. *J. Med. Food*, 14, 877–883 2011.
23. Lever, E., Cole, J., Scott, S.M., Emery, P.W., and Whela, K., Systematic review: The effect of prunes on gastrointestinal function. *Aliment. Pharm. Ther.*, 40, 750–758, 2014.
24. Gill, S.R., Pop, M., Deboy, R.T., Eckburg, P.B., Turnbaugh, P.J., Samuel, B.S., Gordon, J.I. et al., Metagenomic analysis of the human distal gut microbiome. *Science*, 312, 1355–1359, 2006.
25. Stephen, A.M., and Cummings, J.H., Mechanism of action of dietary fiber in the human colon. *Nature*, 284, 283–284, 1980.
26. Fung, K.Y.C., Cosgrove, L., Lockett, T., Head, R., and Topping, D.L., A review of the potential mechanisms for the lowering of colorectal oncogenesis by butyrate. *Br. J. Nutr.*, 108, 820–831, 2012.
27. Conlon, M.A., and Bird, A.R., The impact of diet and lifestyle on gut microbiota and human health. *Nutrients*, 7, 17–44, 2015.
28. Lichtenstein, A.H., Appel, L.J., Brands, M., Carnethon, M., Daniels, S., Franch, H.A., Franklin, B. et al., Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. *Circulation*, 114, 82–96, 2006.
29. Choi, M.S., Jung, U.J., Yeo, J., Kim, M.J., and Lee, M.K., Genistein and daidzein prevent diabetes onset by elevating insulin level and altering hepatic gluconeogenic and lipogenic enzyme activities in non-obese diabetic (NOD) mice. *Diabetes Metab. Res. Rev.*, 24, 74–81, 2008.
30. Dueñas, M., Muñoz-González, I., Cueva, C., Jiménez-Girón, A., Sánchez-Patán, F., Santos-Buelga, C., Moreno-Arribas, M.V. et al., A survey of modulation of gut microbiota by dietary polyphenols. *Biomed. Res. Int.*, 850902, 2015.
31. Cardona, F., Andrés-Lacueva, C., Tulipani, S., Tinahones, F.J., and Queipo-Ortuño, M.I., Benefits of polyphenols on gut microbiota and implications in human health. *J. Nutr. Biochem.*, 24, 1415–1422, 2013.
32. Kamiloglu, S., Toydemir, G., Boyacioglu, D., Beekwilder, J., Hall, R.D., and Capanoglu, E., A review on the effect of drying on antioxidant potential of fruits and vegetables. *Crit. Rev. Food Sci. Nutr.*, 56(Suppl.), S110–S129, 2016.
33. Fernández-Navarro, T., Salazar, N., Gutiérrez-Díaz, I., de Los Reyes-Gavilán, C.G., Gueimonde, M., and González, S., Different intestinal microbial profile in over-weight and obese subjects consuming a diet with low content of fiber and antioxidants. *Nutrients*, 9, e551, 2017.
34. Eid, N., Enani, S., Walton, G., Corona, G., Costabile, A., Gibson, G., Rowland, I. et al., The impact of date palm fruits and their component polyphenols, on gut microbial ecology, bacterial metabolites and colon cancer cell proliferation. *J. Nutr. Sci.*, 3, e46, 2014.
35. Mandalari, G., Chessa, S., Bisignano, C., Chand, L., and Carughie, A., The effect of sun-dried raisins (*Vitis vinifera* L.) on the *in vitro* composition of the gut microbiota. *Food Funct.*, 7, 4048, 2016.
36. Fiesel, A., Gessner, D.K., Most, E., and Eder, K., Effects of dietary polyphenol-rich plant products from grape or hop on pro-inflammatory gene expression in the intestine, nutrient digestibility and faecal microbiota of weaned pigs. *BMC Vet. Res.*, 10, 196, 2014.

37. Viveros, A., Chamorro, S., Pizarro, M., Arija, I., Centeno, C., and Brenes, A., Effects of dietary polyphenol-rich grape products on intestinal microflora and gut morphology in broiler chicks. *Poult. Sci.*, 90, 566–578, 2011.
38. Pozuelo, M.J., Agis-Torres, A., Hervert-Hernandez, D., Lopez-Oliva, M.E., Muñoz-Martínez, E., Rotger, R., and Goni, I., Grape antioxidant dietary fiber stimulates Lactobacillus growth in rat cecum. *J. Food Sci.*, 77, H59–H62, 2012.
39. Tamura, M., Ohnishi, Y., Kotani, T., and Gato, N., Grape antioxidant dietary fiber stimulates Lactobacillus growth in rat cecum. *Int. J. Mol. Sci.*, 12, 2088–2099, 2011.
40. Esteban, M.A., Cordero, H., Martínez-Tomé, M., Jiménez-Monreal, A.M., Bakhrouf, A., and Mahdhi, A., Effect of dietary supplementation of probiotics and palm fruits extracts on the antioxidant enzyme gene expression in the mucosae of gilthead seabream (*Sparus aurata* L.). *Fish Shellfish Immunol.*, 39, 532–540, 2014.
41. Guardiola, F.A., Porcino, C., Cerezuela, R., Cuesta, A., Faggio, C., and Esteban, M.A., Impact of date palm fruits extracts and probiotic enriched diet on antioxidant status, innate immune response and immune-related gene expression of European seabass (*Dicentrarchus labrax*). *Fish Shellfish Immunol.*, 52, 298–308, 2016.
42. Howarth, L., Petrisko, Y., Furchner-Evanson, A., Nemoseck, T., and Kern, M., Snack selection influences nutrient intake, triglycerides, and bowel habits of adult women: A pilot study. *J. Am. Diet Assoc.*, 110, 1322–1327, 2010.
43. Eid, N., Osmanova, H., Natchez, C., Walton, G., Costabile, A., Gibson, G., Rowland, I. et al., Impact of palm date consumption on microbiota growth and large intestinal health: A randomised, controlled, cross-over, human intervention study. *Br. J. Nutr.*, 114, 1226–1236, 2015.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 22

Other Health Benefits of Dried Fruits

Cognitive Function, Appetite, Satiety Control, Intestinal Health, and Hepatoprotection

Jie Liu, Ziyuan Wang, and Mingsi Xie

22.1 Introduction 497
22.2 Other Health Benefits of Dried Fruits 498
22.2.1 Cognitive Function 498
22.2.2 Appetite and Satiety Control 499
22.2.3 Intestinal Health 500
22.2.4 Hepatoprotection 501
22.3 Conclusion 502
References 508

22.1 Introduction

It is commonly accepted that regular consumption of an appropriate amount of fruit has multiple health benefits, including antioxidative, anti-inflammation, lipid lowering, improved glycemic control, cardioprotective, and anticancer effects [1–3]. The contents of nutrients or phytonutrients in traditional dried fruits remain similar to those in the fresh equivalents that contribute to human health. Dried fruits have also been shown to contribute to various other health benefits, such as cognitive function, appetite and satiety control, intestinal health, and hepatoprotection due to their high content of dietary fibers and polyphenols with prebiotic effects. It has also been reported that addition to the diet of easily achievable quantities of dried fruits

could improve some aspects of cognitive function, not only in elderlies but also in young individuals [4,5]. Dietary fiber sourced from dried fruits can slow absorption of some nutrients and improve appetite regulation, which is beneficial for weight control, prevention of overconsumption, and obesity. In addition, dried fruits have been reported to help reduce oxidative damage, prevent inflammation, and bowel disease, along with enhancing hepatoprotection [6–9].

In this chapter, the physiological functions of dried fruits on outcomes such as cognitive function, appetite and satiety control, and intestinal health improvement as well as hepatoprotection are discussed. Furthermore, the underlying mechanisms behind their bioactivities are also reviewed to aid better understanding of the nutritive values of dried fruits. The experimental animal studies and human randomized clinical trials on above health benefits of dried fruits are summarized in Table 22.1 and Table 22.2, respectively.

22.2 Other Health Benefits of Dried Fruits

22.2.1 Cognitive Function

A growing body of research suggests that nutritional factors can preserve brain function from age-related decline. Recent research has highlighted the potential cognitive health benefits of dried fruits. For example, in experimental studies, dietary supplementation with dried blueberries, strawberries, or spinach could reverse age-related decline in neuronal signal transduction, cognitive, and motor behavioral deficits in rats [10,11]. Moreover, there are also clinical data pointing to the positive effect of dried berries on cognition. Thus, a randomized, double-blind, placebo-controlled trial conducted by Miller et al. [4] indicated that participants (between 60 and 75 years old) consuming 24 g/day of freeze-dried blueberries (equivalent to 1 cup of fresh blueberries) for 90 days had significantly fewer repetition errors in the California Verbal Learning test ($P = 0.031$, $\eta p2 = 0.126$) and reduced switch cost on a task-switching test ($P = 0.033$, $\eta p2 = 0.09$) relative to the placebo control group. Positive effects of dried blueberries on cognition were also found in children. The research reported by Whyte et al. [5] showed that in an acute study, 7–10-year-old children consuming blueberry drinks containing 15 or 30 g freeze-dried wild blueberries (WBB) powder could improve cognitive function, including immediate recall, word recognition, and capable of learning new skills. Further analysis revealed that WBB-related cognitive improvements took place in a dose–response manner, with the best performance following 30 g WBB. These effects seem to be particularly sensitive to the cognitive demand of the task.

Many bioactive components, including polyphenols, polysaccharides, vitamins, and minerals, may play an important role in the cognitive-enhancing effects of dried fruits. Polyphenols have many biological properties, such as enhancing antioxidant activity, modulating endothelial function, promoting gastrointestinal digestion, and reducing blood lipid levels. There is also evidence that polyphenols have the ability to prevent neurodegenerative diseases [2]. Numerous studies have also shown that polyphenolic compounds are able to attenuate cognitive impairment and reduce brain lesions in experimental Alzheimer's Diseases (AD) animal models. These effects are associated with an improvement in brain antioxidant status and the prevention of free radical–induced neuronal damage. For example, grape

powder intake could reverse social defeat–induced behavioral and cognitive deficits in rats by increasing the antioxidant pool and preventing cell damage and death in rats [11]. Quercetin and resveratrol are the major contributors towards the beneficial effects of grape powder [11]. Berries, including blueberries, cherries, strawberries, and blackcurrants, which are regular fruits in our daily life, are rich in various types of anthocyanins and flavonoids (see detail in Chapter 14). Flavonoids are the key components supporting the beneficial effects of improving antioxidant capacity and reducing blood pressure [12]. Other common polyphenols found in dried fruits are catechins, which have been reported to improve perception and recognition through reducing the protein expression of Aβ1-42 and increasing superoxide dismutase (SOD) activity [13,14].

Dried fruits, which contain many polysaccharides with antioxidant capacity, could improve learning and memory ability. For example, *Lycium barbarum* polysaccharides extracted from dried wolfberries have been reported to reduce the lipofuscin content in myocardial tissue while increasing SOD activity in the brain and liver, which plays an important role in delaying senility. Another experimental study in mice also suggested that administration of dried aqueous extract of *Euphoria longan* can enhance learning and memory, and its beneficial effects appear to be mediated in part by brain-derived neurotrophic factor expression and immature neuronal survival [15].

Beyond that, dried fruits contain various vitamins and minerals that cannot be autosynthesized in adequate amounts and are necessary for human physiological processes. Minerals, especially calcium and iron, are also important nutrients involved in regulating several brain physiological functions. Vitamins and their metabolites are involved in many cellular processes, including neuronal differentiation and neurotransmitter release. Vitamin C is suggested to play a major role in the pathogenesis of AD by direct neuroprotection against oxidative stress [16]. Dried pineapples are rich in vitamin C and manganese, which can enhance memory. Juice and ethanolic extract of pineapples significantly restored object-recognition ability in mice with scopolamine-induced amnesia, indicating its potential effect in the management of cognitive disorders [16]. Because few studies have evaluated the effect of dry fruits on cognitive function, large randomized clinical trials are warranted in the future to increase the evidence level.

22.2.2 Appetite and Satiety Control

On a global scale, obesity represents one of the most important public health issues. Hence, there is a great need to find preventive strategies for weight gain [17,18]. Appetite and satiety reflect the motivation to eat and the behavior that is directed towards consumption of food and energy supply [6,19]. Therefore, suppressing appetite and enhancing satiety would be a plausible method to control food intake and weight gain. Dried-fruit consumption (at least 1 ounce/day) could reduce abdominal obesity and reduced the risk of being overweight or obese (body mass index [BMI] > 25 kg/m^2) in adults [20].

In general, daily food consumption consists of three meals and possible snacks, and the time gap between meals is a measure of satiety. In this view, satiety and appetite regulation in part control the daily amount of food consumption [21,22]. The relationship between dried-fruit consumption and appetite and satiety regulation

has been assessed in several studies in recent years. A clinical study examined the effects of ad libitum consumption of an after-school snack on appetite and energy intake in 26 children (8–11 year-old normal weight) examined over 4 separate weekdays. The results showed that an after-school ad-libitum snack of raisins could lead to a lower cumulative food intake ($P < 0.001$) and lower appetite ($P < 0.001$) than after snacks of potato chips or cookies [23]. Similar results were observed in another clinical study showing that an afternoon snack with mixed berries could decrease subsequent energy intake at dinner in adult women [24], and dried plum snacks were proven to increase satiety compared to an isoenergetic amount of bread, which could reduce food intake at a meal after the consumption of the snack [25]. Mechanistic studies showed that dried fruits could promote satiety by changing the levels of some hormones such as leptin, which regulates appetite [7]. That was also evidenced by another report that consuming dried plums suppressed hunger by lowering plasma glucose and/or satiety-regulating hormone concentrations [26].

Many bioactive components in dried fruits could play an important role in satiety and appetite regulation. The peel of *Citrus aurantium* (also known as bitter orange) has a high content of volatile oils that give a strong bitter flavor and would suppress appetite in the recipes of certain areas [6]. Moreover, *C. aurantium* contains a kind of alkaloid named *synephrine*, an adrenergic agonist that is typically incorporated into supplements to help weight loss [27]. An experimental *in vivo* study demonstrated that synephrine alkaloid significantly reduce food intake and body weight in rodents [28]. Another appetite-suppressing component derived from the dried fruit rind of *Garcinia cambogia*, hydroxycitric acid, could induce hepatic glycogen accumulation, which may result in a feeling of satiety or reduced appetite, especially in rodents [29].

Dietary fiber, another important component of dried fruits, induces satiation by increasing chewing time, secretion of saliva, gastric juice, and satiety hormones, while decreasing absorption rates in the small intestine [21]. Therefore, consuming dried fruits could influence weight control by impacting satiation and satiety through their fiber contents [30–32]. Dried fruits are usually preferred in situations where convenience is a priority, such as outdoors, which makes dried fruits a preferred snack between meals to lower appetite and control satiety [33].

Dried fruits are good for human health as they provide a great source of nourishment, including essential nutrients, fiber, and various phytochemicals. Further research should be carried out to analyze their complete profiles of phytochemicals, such as phenolic acids, flavonoids, phytoestrogens, and carotenoids, and to illustrate the relation between their appetite regulation and satiety control activity. Nutritionists should continue to encourage the consumption of dried fruits as part of a healthy diet and overall healthy lifestyle and to help weight control. In addition, more human intervention studies or clinical trials are needed to validate the effect of dried fruits on appetite and satiety control.

22.2.3 Intestinal Health

Dried fruits have been reported to be beneficial for intestinal health, a topic that has been drawing attention recently [26]. Dietary fiber is one of the factors that might be responsible for the protection offered by dried fruits against bowel diseases [34,35]. Dried fruits retain dietary fiber which is not affected by drying and can be completely preserved, thereby playing a major role in the gut through accelerating

gastrointestinal transit. A meta-analysis of randomized controlled trials (RCTs) investigating the impact of prunes on stool output found a statistically significant increase in stool frequency of 1 stool/week [34]. Dried fruits, such as apricots, contain high levels of sorbitol, which has laxative properties and could increase stool weight [26]. A meta-analysis of RCT in 21 healthy human volunteers found that consuming 50 g dates (3.9 g fiber, 1 g sorbitol)/day for 3 weeks compared with a maltodextrin and dextrose control had a statistically significant benefit on stool frequency with no evidence of gastrointestinal side-effects [36]. Dried apples, which are rich in dietary fiber and pectin, could play a two-way regulation on stool output. The pectin in apples can absorb 2.5 times of its own volume of water, making the stool soft and easy to expel, thus relieving constipation. When the problem is diarrhea, the pectin of dried fruits can absorb fecal water, thicken the stool, and alleviate diarrhea [37]. Furthermore, dietary dried *Citrus unshiu* peels have been used as a traditional folk medicine for the treatment of gastrointestinal motility disorders in Korea, and the aqueous extracts of dried mature *C. unshiu* peels have shown the potential to be developed as a prokinetic agent that may prevent or alleviate gastrointestinal motility dysfunction in humans [31]. Tannins, molecules that stimulate gastric and gut mucosa, can induce diarrhea. This would make dried fruits more suitable for people with altered gastrointestinal function [38]. Moreover, dried fruits are an excellent source of vitamins and minerals (e.g., vitamin C, vitamin E, potassium, magnesium, and iron) (see detail in Chapter 14). Vitamin E could help to repair intestinal mucosal damage and promote wound healing. Cadir et al. [39] found that oral administration of vitamin E to rats could reduce intestinal morphological damage caused by hypoxia. As a new functional factor, intestinal flora also play an important role in regulating the intestinal health of host. Generally, high-molecular weight dietary fiber cannot be digested by gastric and pancreatic enzymes; it thus enters the large intestine intact and is used by the intestinal flora. Desai et al. [8] reported that when there is a chronic or intermittent deficiency of dietary fiber, the gut microbiota use the host mucin glycoprotein as a source of nutrients, reducing the width of the mucus barrier and increasing the opportunity for pathogen invasion. In addition, in an experimental mouse model of ulcerative colitis, a diet containing freeze-dried black raspberries (5%–10%) for 1 week significantly reduced dextran sulfate sodium (DSS)-induced acute injury to the colonic epithelium by suppressing tissue levels of several key pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin 1β [40]. In another experimental study in mice by Piberger et al. [41], oral administration of dried bilberries during acute DSS-induced acute colitis ameliorated disease severity and reduced the secretion of interferon-γ and TNF-α from mesenteric lymph node cells. Given the limited number of clinical studies with dried fruits and the present insight into their molecular mechanisms of action for prevention of intestinal diseases, more studies are warranted to investigate the relative contribution of phytochemicals to these effects.

22.2.4 Hepatoprotection

Oxidative stress plays an important role in the pathogenesis of liver disease. At present, certain antioxidative ingredients in fruits such as polyphenols, flavonoids, and vitamins have been reported to reduce oxidative stress with ensuing hepatoprotection [42]. In fact, there are many reports indicating that fruit consumption is

associated with a reduced risk of liver disease [43], and the antioxidants contained in fruits have been suggested as possible mediators of the beneficial effects [44].

Natural antioxidant compounds such as polyphenols, organic acids, vitamin E, and carotenoids are common in different fruits. These molecules can inhibit free-radical formation by reducing or donating hydrogen to other compounds. Dried figs are rich sources of phenolic acids, flavonoids, and carotenoids [45–47] and have shown hepatoprotective effects. Turan et al. [9] incorporated fig powder into rats' chow to study the hepatoprotective and antioxidant effects of dried figs on ethanol-induced oxidative stress. They demonstrated that treatment with fig powder effectively protected the rats against ethanol-induced hepatotoxicity, as evidenced by a decrease in levels of aspartate aminotransferase, alanine aminotransferase, gamma glutamyltranspeptidase, and lactate dehydrogenase serum enzyme. Debib et al. [48] studied the hepatoprotective effects of dried figs (*Ficus carica*) combined with extra virgin olive oil and its phenolic components on CCl_4-induced oxidative stress and hepatotoxicity in rats. Results indicate that extra virgin olive oil and dried fig extract are effective in preventing CCl_4-induced liver damage in rats and that the hepatoprotective effects are attributable to the antioxidant properties of these foods. Freeze-dried mango pulp is also a rich source of phenolic compounds and dietary fiber. Domínguez-Avila et al. [49] showed that mango bioactive substances beneficially altered lipoprotein metabolism and attenuated nonalcoholic steatohepatitis in Wistar rats. Yurt and Celik [50] studied the hepatoprotective and antioxidant effect of sun, sulphited dried apricots and their kernels against ethanol-induced oxidative stress in the rat. They concluded that dried apricots have an hepatoprotective effect, probably through promotion of a systemic antioxidant milieu. Reports by Raju et al. [51] also showed that dried fruits of *Solanum nigrum* Linn could counteract CCl_4-induced hepatic damage in rats. Dried fruits also retain most functional oils and glycosides. For example, dried fruit of *Sophora japonica* L. is rich in polyphenol sophoricoside, an isoflavone glycoside. Li et al. [52] studied the hepatic protective effect of oral sophoricoside infusion in mice fed a high fructose diet, well-known to cause liver injury, and showed that it could decrease liver damage by regulating lipid metabolism, enhancing antioxidant activity, and inhibiting the release of inflammatory cytokines. All these results provide a scientific basis for the development and application of sophoricoside as a new natural therapeutic agent for alleviating chronic liver injury.

22.3 Conclusion

Beneficial biological effects of dried fruits on diverse outcomes such as cognitive function, appetite and satiety control, intestinal health, and hepatoprotection are discussed. The underlying mechanisms behind the bioactivity of dried fruits and their main constituents, based mostly in experimental studies, are also reviewed to help better understand their nutritive values. However, with limited human studies on the effects of traditional dried fruits on the above outcomes, further research is needed to extend our knowledge of the potential beneficial impact of dried fruits on public health. In addition, there remains a challenge for public health advice to discern whether the beneficial health effects of dried fruits in individuals may differ depending upon genetics, lifestyle, and typical dietary intake.

Table 22.1 Summary of Experimental Animal Studies on Other Health Benefits of Dried Fruits

Natural Source	*Active Component*	*Animal Model*	*Results*	*Conclusion*	*References*
Cognitive Function					
Strawberries Blueberries	Dried aqueous extracts	Fischer 344 rats	Reversal of age-related deficits in motor behavioral performance on the rod walking and accelerate tasks and Morris water maze performance.	Phytochemicals present in berries may be beneficial in reversing the course of neuronal and behavioral aging.	[10]
Euphoria longan	Aqueous extract of dried fruits	ICR mice	Enhanced cognitive performances in the passive avoidance task. BDNF, pCREB, or pERK 1/2 was significantly increased in the hippocampal dentate gyrus and CA1 regions after treatment.	Enhancement of learning and memory, with beneficial effects mediated in part by BDNF expression and immature neuronal survival.	[15]
Kiwi fruits	Dried extracts	Sprague-Dawley rats	Repair of Pb-induced learning and memory deficits and dendritic spine loss; reversal of enzymatic activity SOD and GSH-Px; and decreased microglial activation by reversing the increased expression of Ibal marker in Pb-exposed rats.	Alleviation of Pb-induced cognitive deficits, possibly through antioxidant stress and microglia inactivation.	[13]
Appetite and Satiety Control					
Citrus aurantium	Synephrine from peel	Sprague–Dawley rats	Body weight of rats treated with metaraminol (5 mg/kg) and phenylephrine (10 mg/kg) decreased significantly from days 1 to 9.	Synephrine could reduce food intake and body weight.	[28]

(Continued)

Table 22.1 (Continued) Summary of Experimental Animal Studies on Other Health Benefits of Dried Fruits

Natural Source	*Active Component*	*Animal Model*	*Results*	*Conclusion*	*References*
Intestinal Health					
Black raspberries	Freeze-dried berries	C57BL/6J mice	Reduced DSS-induced acute injury to colonic epithelium through suppressing tissue levels of key pro-inflammatory cytokines.	Potent anti-inflammatory effect on DSS-induced colonic injury.	[40]
Bilberries	Anthocyanins from dried berries	Balb/c mice	Anthocyanins ameliorated DSS-induced acute colitis and reduced secretion of IFN-γ and TNF-α from mesenteric lymph node cells.	Amelioration of acute and chronic experimental colitis.	[41]
Hepatoprotection					
Figs	Dried fig powders	Wistar rat	Restoration of ethanol-induced MDA and ADS; reduction of AST, ALT, GGT, and LDH serum enzyme levels.	Diet-derived antioxidants and antihepatotoxic agents from dried figs useful to prevent oxidative damage from ethanol-induced free radicals and hepatotoxicity in rats.	[9]
Apricots	Sun, sulphited-dried apricot and their kernels	Wistar rat	Supplementation restored the ethanol-induced imbalance between liver damage level and antioxidant system by increasing antioxidant enzyme activity such as SOD and decreased serum levels of liver damage markers such as MDA.	Hepatoprotection in rats mediated by promotion of antioxidant enzyme activities.	[50]

(Continued)

Table 22.1 (Continued) Summary of Experimental Animal Studies on Other Health Benefits of Dried Fruits

Natural Source	*Active Component*	*Animal Model*	*Results*	*Conclusion*	*References*
Solanum nigrum	Ethanol extracts of dried fruits of *Solanum nigrum*	Wistar rat	The ethanol extract decreased serum levels of AST, ALT, ALP, and total bilirubin.	Dried fruit of *Solanum nigrum* has remarkable hepatoprotective effect in CCl4-induced liver damage in rats.	[51]
Sophora japonica L.	Sophoricoside (isoflavone glycoside)	Kunming mice	Oral infusion in mice with liver damage induced by a high-fructose diet decreased hepatic cholesterol, TAG, serum LDL cholesterol, and ApoB and raised serum HDL cholesterol and ApoA1. It also reduced elevations of hepatic MDA, IL-1, and TNF-α levels and increased hepatic SOD and GSH-Px activities.	Amelioration of liver injury in fructose-fed mice through regulation of lipid metabolism, enhanced antioxidant activity, and inhibition of inflammatory cytokine release.	[52]

Abbreviations: ADS, antioxidant defense system; ALP, alkaline phosphatase; ALT, alanine transaminase; ApoA1, apolipoprotein-A1; ApoB, apolipoprotein-B; AST, aspartate aminotransferase; BDNF, brain-derived neurotrophic factor; CA1, first region of cornu Ammonis; DSS, dextran sulfate sodium; GGT, γ-glutamyl transpeptadase; GSH-Px, glutathione peroxidase; HDL, high-density lipoprotein, IFN-γ, interferon-γ; IL-1, interleukin-1; LDH, lactic dehydrogenase; LDL, low-density lipoprotein; MDA, malonaldehyde; Pb, lead; pCREB, phosphorylated CAMP-response element binding protein; pERK, phosphorylated extracellular regulated protein kinases; SOD, superoxide dismutase; TAG, triacylglycerols; TNF-α, tumor necrosis factor-alpha.

Table 22.2 Summary of Human Randomized Clinical Trials on Other Health Benefits of Dried Fruits

Natural Source	*Active Component*	*Study Model (Participants)*	*Results*	*Conclusion*	*References*
Cognitive Function					
Blueberries	Dried blueberry powder	Cross-over study (n = 21 children)	Significant improvements in final immediate recall at 1.15 hours, delayed word recognition, and accuracy on cognitively demanding incongruent trials.	Blueberries could cause significant cognitive improvements in 7–10-year-old children.	[5]
Appetite and Satiety Control					
Dried fruits	Dried fruit consumption	Cross-sectional study (n = 13292 adults)	Covariate-adjusted mean weight at the end of the intervention (78.2 ± 0.6 *versus* 80.7 ± 0.3 kg), BMI (27.1 ± 0.2 *versus* 28.1 ± 0.2 kg/m^2), and WC (94.0 ± 0.5 *versus* 96.5 ± 0.2 cm).	Dried fruit consumption was associated with improved nutrient intakes, a higher overall diet quality score, and lower body weight/ adiposity measures.	[31]
Plums	Dried plums snack	Cross-over study (n = 19 adult women)	The satiety index, AUC, was greater those participants in the dried plum group *versus* the low-fat cookie group (P < or = 0.05). The dried plums elicited lower plasma glucose and insulin AUC than the low-fat cookie (P < or = 0.05) and tended to promote a greater plasma ghrelin AOC (P = 0.056).	Compared to low-fat cookie snacks, plum snacks could increase satiety after ingestion in adult women.	[26]

(Continued)

Table 22.2 (Continued) Summary of Human Randomized Clinical Trials on Other Health Benefits of Dried Fruits

Natural Source	*Active Component*	*Study Model (Participants)*	*Results*	*Conclusion*	*References*
Raisins	Dried raisin snack	Cross-over study (n = 26 children between 8 and 11 years)	Children consuming raisins and grapes consumed less calories that those consuming cookies ($P < 0.001$). Raisins and grapes led to lower cumulative food intake ($P < 0.001$). Grapes lowered appetite compared to all other snacks ($P < 0.001$)	Ad libitum consumption of raisins has potential as an after-school snack to achieve low-energy snack intake prior to dinner, similar to grapes, compared to potato chips and cookies in children.	[23]
Dried berries	Dried berry snack	Cross-over study (n = 12 women)	Energy intake was lower ($P < 0.001$) after consumption of a berry snack than after a confectionary snack.	Afternoon confectionary snack with mixed berries decreased subsequent energy intake at dinner, but did not affect subjective appetite.	[24]
Intestinal Health					
Prunes	Dried prunes	Meta-analysis of RCTs	Prunes significant increase stool frequency of 1 stool/week, with no impact on stool consistency.	Prunes appear superior to psyllium for improving stool frequency and consistency.	[34]

Abbreviations: AUC, area under curve; BMI, body mass index; RCTs, randomized controlled trials; WC, waist circumference.

References

1. Olivas-Aguirre, F.J., González-Aguilar, G.A., Velderrain-Rodríguez, G.R., Torres-Moreno, H., Robles-Zepeda, R.E., Vázquez-Flores, A.A., de la Rosa, L.A. et al., Radical scavenging and anti-proliferative capacity of three freeze-dried tropical fruits. *Int. J. Food Sci Tech.*, 52, 1699–1709, 2017.
2. Chang, S.K., Alasalvar, C., and Shahidi, F., Review of dried fruits: Phytochemicals, antioxidant efficacies, and health effects. *J. Funct. Foods*, 21, 113–132, 2016.
3. Jeszka-Skowron, M., Zgoła-Grześkowiak, A., Stanisz, E., and Waśkiewicz, A., Potential health benefits and quality of dried fruits: Goji fruits, cranberries and raisins. *Food Chem.*, 221, 228–236, 2017.
4. Miller, M.G., Hamilton, D.A., Joseph, J.A., and Shukitt-Hale, B., Dietary blueberry improves cognition among older adults in a randomized, double-blind, placebo-controlled trial. *Eur. J. Nutr.*, 57, 1169–1180, 2018.
5. Whyte, A.R., Schafer, G., and Williams, C.M., Cognitive effects following acute wild blueberry supplementation in 7- to 10-year-old children. *Eur. J. Nutr.*, 55, 2151–2162, 2016.
6. Astell, K.J., Mathai, M.L., and Su, X.Q., A review on botanical species and chemical compounds with appetite suppressing properties for body weight control. *Plant Foods Hum. Nutr.*, 68, 213–221, 2013.
7. Alasalvar, C., and Shahidi, F., Composition, phytochemicals, and beneficial health effects of dried fruits: An overview, in *Dried Fruits: Phytochemicals and Health Effects*, Alasalvar, C. and Shahidi, F., Eds., John Wiley & Sons, Oxford, UK, 2013, pp.1–18.
8. Desai, M.S., Seekatz, A.M., Koropatkin, N.M., Kamada, N., Hickey, C.A., Wolter, M., Pudlo, N.A. et al., A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell*, 167, 1339–1353, 2016.
9. Turan, A., and Celik, I., Antioxidant and hepatoprotective properties of dried fig against oxidative stress and hepatotoxicity in rats. *Int. J. Biol. Macromol.*, 91, 554–559, 2016.
10. Joseph, J.A., Shukitt-Hale, B., Denisova, N.A., Bielinski, D., Martin, A., McEwen, J.J., and Bickford, P.C., Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. *J. Neurosci.*, 19, 8114–8121, 1999.
11. Solanki, N., Salvi, A., Patki, G., and Salim, S., Modulating oxidative stress relieves stress-induced behavioral and cognitive impairments in rats. *Int. J. Neuropsychopharmacol.*, 20, 550–561, 2017.
12. Carey, A.N., Gomes, S.M., and Shukitt-Hale, B., Blueberry supplementation improves memory in middle-aged mice fed a high-fat diet. *J. Agric. Food Chem.*, 62, 3972–3978, 2014.
13. Xue, W.Z., Yang, Q.Q., Chen, Y.W., Zou, R.X., Xing, D., Xu, Y., Liu, Y.S. et al., Kiwifruit alleviates learning and memory deficits induced by Pb through anti-oxidation and inhibition of microglia activation *in vitro* and *in vivo*. *Oxid. Med. Cell Longev.*, 5645324, 2017.
14. Guo, Y., Zhao, Y., Nan, Y., Wang, X., Chen, Y., and Wang, S., (-)-Epigallocatechin-3-gallate ameliorates memory impairment and rescues the abnormal synaptic protein levels in the frontal cortex and hippocampus in a mouse model of Alzheimer's disease. *Neuroreport*, 28, 590–597, 2017.

15. Park, S.J., Park, D.H., Kim, D.H., Lee, S., Yoon, B.H., Jung, W.Y., Lee, K.T. et al., The memory-enhancing effects of *Euphoria longan* fruit extract in mice. *J. Ethnopharmacol.*, 128, 160–165, 2010.
16. Momtazi-Borojeni, A.A., Sadeghi-Aliabadi, H., Rabbani, M., Ghannadi, A., and Abdollahi, E., Cognitive enhancing of pineapple extract and juice in scopolamine-induced amnesia in mice. *Res. Pharm. Sci.*, 12, 257–264, 2017.
17. Gonzalez-Anton, C., Lopez-Millan, B., Rico, M.C., Sanchez-Rodriguez, E., Ruiz-Lopez, M.D., Gil, A., and Mesa, M.D., An enriched, cereal-based bread affects appetite ratings and glycemic, insulinemic, and gastrointestinal hormone responses in healthy adults in a randomized, controlled trial. *J. Nutr.*, 145, 231–238, 2015.
18. Haslam, D.W., and James, W.P.T., Obesity. *Lancet*, 366, 1197–1209, 2005.
19. Van der Meij, B.S., Wijnhoven, H.A.H., Lee, J.S., Houston, D.K., Hue, T., Harris, T.B., Kritchevsky, S.B. et al., Poor appetite and dietary intake in community-dwelling older adults. *J. Am. Geriatr. Soc.*, 65, 2190–2197, 2017.
20. Keast, D.R., and Jones, J.M., Dried fruit consumption associated with reduced overweight or obesity in adults: NHANES, 1999–2004. *FASEB J.*, 23, LB511–LB511, 2009.
21. Campbell, C.L., Wagoner, T.B., and Foegeding, E.A., Designing foods for satiety: The roles of food structure and oral processing in satiation and satiety. *Food Struct.*, 13, 1–12, 2017.
22. Cummings, D.E., Weigle, D.S., Frayo, R.S., Breen, P.A., Ma, M.K., Dellinger, E.P., and Purnell, J.Q., Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N. Engl. J. Med.*, 346, 1623–1630, 2002.
23. Patel, B.P., Bellissimo, N., Luhovyy, B., Bennett, L.J., Hurton, E., Painter, J.E., and Anderson, G.H., An after-school snack of raisins lowers cumulative food intake in young children. *J. Food Sci.*, 78(Suppl. 1), 5S–10S, 2013.
24. James, L.J., Funnell, M.P., and Milner, S., An afternoon snack of berries reduces subsequent energy intake compared to an isoenergetic confectionary snack. *Appetite*, 95, 132–137, 2015.
25. Farajian, P., Katsagani, M., and Zampelas, A., Short-term effects of a snack including dried prunes on energy intake and satiety in normal-weight individuals. *Eat. Behav.*, 11, 201–203, 2010.
26. Furchner-Evanson, A., Petrisko, Y., Howarth, L., Nemoseck, T., and Kern, M., Type of snack influences satiety responses in adult women. *Appetite*, 54, 564–569, 2010.
27. Haaz, S., Fontaine, K.R., Cutter, G., Limdi, N., Perumean-Chaney, S., and Allison, D.B., *Citrus aurantium* and synephrine alkaloids in the treatment of overweight and obesity: An update. *Obesity Rev.*, 7, 79–88, 2006.
28. Yeh, S.Y., Comparative anorectic effects of metaraminol and phenylephrine in rats. *Physiol. Behav.*, 68, 227–234, 1999.
29. Triscari, J., and Sullivan, A.C., Anti-obesity activity of a novel lipid synthesis inhibitor. *Int. J. Obes.*, 8(Suppl. 1), 227S–239S, 1984.
30. Flood-Obbagy, J.E., and Rolls, B.J., The effect of fruit in different forms on energy intake and satiety at a meal. *Appetite*, 52, 416–422, 2009.
31. Keast, D.R., O'Neil, C.E., and Jones, J.M., Dried fruit consumption is associated with improved diet quality and reduced obesity in US adults: National Health and Nutrition Examination Survey, 1999–2004. *Nutr. Res.*, 31, 460–467, 2011.
32. Sadler, M.J., Gibson, S., Whelan, K., Ha, M.A., Lovegrove, J., and Higgs, J., Dried fruit and public health—What does the evidence tell us? *Int. J. Food Sci. Nutr.*, 70, 675–687, 2019.

33. Sijtsema, S.J., Jesionkowska, K., Symoneaux, R., Konopacka, D., and Snoek, H., Perceptions of the health and convenience characteristics of fresh and dried fruits. *LWT-Food Sci. Technol.*, 49, 275–281, 2012.
34. Lever, E., Cole, J., Scott, S.M., Emery, P.W., and Whelan, K., Systematic review: The effect of prunes on gastrointestinal function. *Aliment. Pharmacol. Ther.*, 40, 750–758, 2014.
35. Andersen, V., Chan, S., Luben, R., Khaw, K.T., Olsen, A., Tjonneland, A., Kaaks, R. et al., Fibre intake and the development of inflammatory bowel disease: A European prospective multi-centre cohort study (EPIC-IBD). *J. Crohns. Colitis*, 12, 129–136, 2018.
36. Eid, N., Osmanova, H., Natchez, C., Walton, G., Costabile, A., Gibson, G., Rowland, I. et al., Impact of palm date consumption on microbiota growth and large intestinal health: A randomised, controlled, cross-over, human intervention study. *Br. J. Nutr.*, 114, 1226–1236, 2015.
37. Becker, B., Kuhn, U., and Hardewig-Budny, B., Double-blind, randomized evaluation of clinical efficacy and tolerability of an apple pectin-chamomile extract in children with unspecific diarrhea. *Arzneimittelforschung*, 56, 387–393, 2006.
38. Xiao, H.T., Wen, B., Shen, X.C., and Bian, Z.X., Potential of plant-sourced phenols for inflammatory bowel disease. *Curr. Med. Chem.*, 25, 5191–5217, 2018.
39. Cadir, F.O., Bicakci, U., Tander, B., Kilicoglu-Aydin, B., Rizalar, R., Ariturk, E., Aydin, O. et al., Protective effects of vitamin E and omeprazole on the hypoxia/reoxygenation induced intestinal injury in newborn rats. *Pediatr. Surg. Int.*, 24, 809–813, 2008.
40. Montrose, D.C., Horelik, N.A., Madigan, J.P., Stoner, G.D., Wang, L.S., Bruno, R.S., Park, H.J. et al., Anti-inflammatory effects of freeze-dried black raspberry powder in ulcerative colitis. *Carcinogenesis*, 32, 343–350, 2011.
41. Piberger, H., Oehme, A., Hofmann, C., Dreiseitel, A., Sand, P.G., Obermeier, F., Schoelmerich, J. et al., Bilberries and their anthocyanins ameliorate experimental colitis. *Mol. Nutr. Food Res.*, 55, 1724–1729, 2011.
42. Xia, T., Yao, J., Jin, Z., Yu, Z., Jia, S., and Min, W., Protective effects of Shanxi aged vinegar against hydrogen peroxide-induced oxidative damage in LO2 cells through Nrf2-mediated antioxidant responses. *Rsc. Advances*, 7, 17377–17386, 2017.
43. Brandt, K., Christensen, L.P., Hansen-Møller, J., Hansen, S.L., Haraldsdottir, J., Jespersen, L., Purup, S. et al., Health promoting compounds in vegetables and fruits : A systematic approach for identifying plant components with impact on human health. *Trend Food Sci. Tech.*, 15, 384–393, 2004.
44. Nicolle, C., Cardinault, N., Gueux, E., Jaffrelo, L., Rock, E., Mazur, A., Amouroux, P. et al., Health effect of vegetable-based diet: Lettuce consumption improves cholesterol metabolism and antioxidant status in the rat. *Clin. Nutr.*, 23, 605–614, 2004.
45. Konak, R., Kosoglu, I., and Yemenicioglu, A., Effects of different drying methods on phenolic content, antioxidant capacity and general characteristics of selected dark colored Turkish fig cultivars. *Acta Hortic.*, 335–340, 2017.
46. Nakİlcİoğlu, E., and Hışıl, Y., Research on the phenolic compounds in sarilop (*Ficus carica* L.) fig variety. *Gıda*, 38, 267–274, 2013.
47. Slatnar, A., Klancar, U., Stampar, F., and Veberic, R., Effect of drying of figs (*Ficus carica* L.) on the contents of sugars, organic acids, and phenolic compounds. *J. Agr. Food Chem.*, 59, 11696–11702, 2011.

48. Debib, A., Dueñas, M., Boumediene, M., Mothana, R.A., Latifa, A., and Tir-Touil, M.A., Synergetic hepatoprotective effect of phenolic fractions obtained from *Ficus carica* dried fruit and extra virgin olive oil on CCL_4-induced oxidative stress and hepatotoxicity in rats. *J. Food Biochem.*, 40, 507–516, 2016.
49. Domínguez-Avila, J.A., Astiazaran-Garcia, H., Wall-Medrano, A., de la Rosa, L.A., Alvarez-Parrilla, E., and Gonzalez-Aguilar, G.A., Mango phenolics increase the serum apolipoprotein A1/B ratio in rats fed high cholesterol and sodium cholate diets. *J. Sci. Food Agric.*, 99, 1604–1612, 2019.
50. Yurt, B., and Celik, I., Hepatoprotective effect and antioxidant role of sun, sulphited-dried apricot (*Prunus armeniaca* L.) and its kernel against ethanol-induced oxidative stress in rats. *Food Chem. Toxicol.*, 49, 508–513, 2011.
51. Raju, K., Anbuganapathi, G., Gokulakrishnan, V., Rajkapoor, B., Jayakar, B., and Manian, S., Effect of dried fruits of *Solanum nigrum* LINN against CCl4-induced hepatic damage in rats. *Biol. Pharm. Bull.*, 26, 1618–1619, 2003.
52. Li, W., and Lu, Y., Hepatoprotective effects of sophoricoside against fructose-induced liver injury *via* regulating lipid metabolism, oxidation, and inflammation in mice. *J. Food Sci.*, 83, 552–558, 2018.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Chapter 23

Dried Fruits as Components of Health Dietary Patterns

Ana Paula Silva Caldas and Josefina Bressan

23.1 Introduction 513
23.2 Dried Fruits as Components of Healthy Dietary Patterns 514
23.2.1 Vegetarian Dietary Patterns 515
23.2.2 Mediterranean Dietary Patterns 515
23.3 Descriptive Consumption of Dried Fruits 516
23.4 The Inclusion of Dried Fruits in Dietary Guidelines 517
23.4.1 Dietary Guidelines in Asia and the Pacific 520
23.4.2 Dietary Guidelines in Europe 521
23.4.3 Dietary Guidelines in Latin America 521
23.4.4 Dietary Guidelines in the Near East 522
23.4.5 Dietary Guidelines in North America 522
23.5 Conclusion 523
References 523

23.1 Introduction

Fruits are essential foods for maintaining optimum health. In the context of nutritional risk, a recent systematic review has shown that fruit consumption is a key food factor with a beneficial impact on cardiovascular disease (CVD), type-2 diabetes mellitus (T2DM), and cancer [1]. Several studies have shown that eating between three and five servings of fruits and vegetables per day can prevent the development of chronic non-communicable diseases (NCDs). The 2010 Dietary Guidelines for

Americans recommended that half of the food consumed in a meal should be fruits and vegetables [2]. In addition to proven health benefits, fruit consumption is present in different cultures around the world, regardless of religious dietary practices, nutritional therapies, and dietary patterns, which makes fruits even more important from a nutritional point of view [3,4].

The most common fruits are available subject to the seasonality of their production, making them unavailable in fresh form all year round [5,6]. For this reason, fresh fruits are submitted to various methods of processing, resulting in dried fruits, which are presented as concentrated forms of the fresh fruits; they contain less moisture when compared with their fresh counterparts, which provides greater durability [5]. Dried fruits can be processed whole (such as grapes, berries, apricots, and plums) or sliced (mangoes, papayas, and kiwis). Today, these foods represent important healthy snack options and can be consumed as substitutes for fresh fruits. Moreover, dried fruits have the advantage of being easily stored and distributed, constituting themselves as easily accessible commodities, used as healthy alternatives to the consumption of processed snacks that contain high sodium and sugars [5].

Recently, several studies have highlighted the health benefits of dried fruit consumption; however, there is no consensus in the literature about the portion size of this food that should be consumed. The impact of dried fruit intake on diet quality has also been poorly studied [5]. In addition, despite the fact that there are no specific recommendations, the consumption of dried fruits has been encouraged as a strategy to reach the recommendation of the daily intake of fruits and of several nutrients frequently consumed in low quantities [7].

In this chapter, the benefits of dried fruit consumption and the importance of including these types of food in the habitual diet as a strategy to make the food pattern healthier are discussed. In addition, the total amount of dried fruits recommended in the current food guidelines of some countries around the world is highlighted.

23.2 Dried Fruits as Components of Healthy Dietary Patterns

It is well established that a nutritionally healthy diet is crucial to good health and wellbeing throughout the various stages of life development [8]. An unhealthy diet contributes to poor health and is traditionally recognized as a modifiable risk factor for the development of NCDs [8]. Currently, the Mediterranean dietary pattern and the vegetarian dietary pattern are among the healthiest recognized eating patterns in the world closely associated with the reduction of CVD and increased life expectancy [9–11]. In these two dietary patterns, fruit consumption plays a prominent role since, fundamentally, fruits are the main micronutrient and antioxidant carriers of the diet [9,12,13]. Fruit consumption is associated with a beneficial effect on cardiometabolic risk factors, oxidative stress, and cancer independently of the background diet [14,15]. The consumption of fruits in their dehydrated form is included in the eating habits of different cultures around the world, thus highlighting fruits as critical components of diverse food patterns [5]. When prepared without added sugar, dried fruits have a nutritional composition similar to that of their fresh counterparts and are also consistently associated with health benefits [5,16].

23.2.1 Vegetarian Dietary Patterns

The vegetarian diet mainly consists of consuming foods of vegetable origin, including fruits, vegetables, nuts, seeds, and grains. However, some vegetarians also consume eggs and dairy products as part of the diet [9]. When well planned, a vegetarian diet can be nutritionally adequate and healthy. This dietary pattern has been associated with lower risk of heart disease, T2DM, obesity, and certain types of cancer, and helps to reduce blood cholesterol concentrations. Nonetheless, when unbalanced, a vegetarian diet can lead to nutritional deficiencies, especially in situations of high metabolic demand [17].

The Adventist Health Study 2, a cohort with a relatively high proportion of vegetarians, has long examined the relationship between vegetarian eating patterns, health benefits, and disease risk [4]. According to this cohort study, the vegetarian dietary pattern is associated with lower body mass index (BMI) [18], lower prevalence and incidence of T2DM [18,19], and lower prevalence of metabolic syndrome [20] and hypertension [21], as well as reduced all-cause mortality [22] and, in some cases, a lower risk of cancer [23].

As discussed earlier, dried fruits represent concentrated forms of their fresh counterparts, which, together with vegetables, make up the basis of the vegetarian diet. Among strict vegetarians, fruit consumption is fundamental for adequate intake of vitamins [24]. In this sense, within the vegetarian dietary pattern, dried fruits are an important alternative to help in the adequate intake of micronutrients, considering their higher content of vitamins and minerals in relation to fresh fruits. In addition, they also contribute to adequate fiber intake and increase the diet quality index [5]. Nevertheless, there are no studies that have directly investigated the role of dried fruit consumption within the vegetarian dietary pattern.

23.2.2 Mediterranean Dietary Patterns

The most relevant food pattern known for its positive impact on life expectancy and reducing CVD is the Mediterranean dietary pattern [10]. The traditional Mediterranean diet is characterized by high consumption of fruits, vegetables, nuts, legumes, and whole grains; moderate consumption of fish; and low consumption of meat and dairy products. Alcohol is often consumed, but in moderation and in the form of wine, usually accompanying meals. The total intake of lipids usually is high (40% of energy intake), in which monounsaturated fatty acids are the most prevalent [13,10]. The great growth in the quantity and quality of scientific evidence available over the last 25 years shows that the traditional Mediterranean diet is one of the healthiest food patterns in the world [10].

Like nuts, traditional dried fruits are also components of the Mediterranean diet valued for their sweetness and long-term stability [25]. Several studies have highlighted the benefits of fruit consumption in the context of the Mediterranean diet [25–28]. The prospective SUN cohort study showed that fruit and vegetable consumption was inversely associated with hypertension in a Mediterranean population with high vegetable-fat intake [26,27]. Buil-Cosiales et al. [28], when evaluating an elderly Mediterranean population with a high cardiovascular risk, found that those who consumed nine or more portions per day of fruit plus vegetables had a CVD risk

hazard ratio of 0.60 (95% CI 0.40, 0.96), as compared with those who consumed less than five servings of fruit per day.

Although several studies highlight the role of fresh fruit consumption in the benefits associated with the Mediterranean dietary pattern, there are no studies in the literature that have evaluated the effect and/or contribution of dried fruit consumption on the benefits attributed to this dietary pattern. Despite this, scientific evidence has shown that dried fruits promote the same health benefits attributed to fresh fruits, given their similar nutritional composition.

23.3 Descriptive Consumption of Dried Fruits

It is estimated that in the 2000s, about 2.7 (4.9%) million of the world's deaths were directly attributed to the low consumption of fruits and vegetables [29]. In the United States, institutions such as The National Cancer Institute, The American Heart Association, and The Produce for Better Health Foundation's More Matters program stimulate fruit intake as recommended by My Pyramid (2 cups per day), which can be consumed in various forms, that is, fresh, frozen, natural juice, or dried, with the aim of reaching the recommended portion of daily fruit consumption [7]. However, among Americans, fruit consumption has historically been below recommended levels, and little has changed over the years. Data from the Centers for Disease Control and Prevention indicate that 39% of American adults consume less than one serving of fruit per day [30]. Even in other developed nations such as Australia, Canada, and the United Kingdom, research has shown that there is a gap between recommendations for fruit and vegetable intake and what is actually consumed [31]. A study of 52 middle-income countries showed that 78.4% of men and 77.6% of women partook of fruit and vegetable consumption below the recommended minimum quantities, despite decades of concern and publicity about the importance of consuming these foods [32].

In this scenario, traditional dried fruits have been considered as key food items in some healthy food patterns because of their nutritional value, ease of access, and long-term stability [16]. Besides having a similar nutrient profile to their fresh counterparts, dried fruits are excellent sources of fibers [33]. Currently, dried fruits are consumed in lower quantities than fresh and canned fruits. An epidemiological study showed that only 6.9% of the adult American population consumed dried fruits [7]. Another study showed that 2.6% of the total calories of the whole fruit group came from the consumption of dried fruits [34]. The analysis of data from the National Health and Nutrition Examination Survey (NHANES) study (1999-2004) showed that raisins are the most consumed dried fruits, often about six times more than other dried fruits [7]. This is due to their diversified form of consumption and use in different food products such as breads, muffins, cakes, cereal bars, and chocolates [16].

In the NHANES study (1999–2004), the dried fruit portion corresponded to one-eighth of the fresh fruit portion and could be consumed one or more times per day. From this definition, it was verified that the individuals who consumed dried fruits in greater quantity had significantly lower intakes of solid fats, alcohol, and added sugar, plus a greater intake of vegetables, meats, and products derived from soy in comparison to the non-consumers [7]. Besides, the non-consumers had a significantly greater waist circumference and BMI than the consumers. In view of the

nutritional value of these foods, consumers of dried fruits also had higher intakes of fiber, vitamins (A, C, E, thiamine, riboflavin, niacin, and folate), minerals (calcium, phosphorus, magnesium, iron, zinc, copper, and potassium), and significantly lower sodium intake [7]. As an additional evaluation, the association between dried fruit consumption and diet quality was verified according to the Healthy Eating Index 2005, and it was observed that the consumption of dried fruits contributed to an improvement of 8% in the total Healthy Eating Index 2005 scores among consumers of dried fruits compared to non-consumers [7].

Although evaluations of dried fruit consumption are still scarce in the scientific literature, the nutritional value of these foods has been consistently reported, along with their potential to improve diet quality and prevent disease. Thus, these foods are increasingly highlighted as viable alternatives to fruit consumption and unhealthy snacks [16]. Lloyd-Williams et al. [35] estimated the potential impact of replacing unhealthy snacks (fried potatoes, sweets, and cakes) with healthy snacks (fruits, dried fruits, and unsalted nuts) on CVD mortality, and observed that at least one daily substitution of an unhealthy snack for a healthy snack may prevent about 6,000 cases of CVD per year in the United Kingdom.

The 2010 Dietary Guidelines Advisory Committee identified the 10 nutrients (vitamins A, C, D, E, and K, choline, calcium, magnesium, potassium, and dietary fiber) that are often ingested in smaller amounts than recommended by men and women, and verified that adequate intake of fruits, including dried fruits, contributes to the reversal of this scenario [36]. In addition, adequate fruit consumption, which can be achieved with dried fruits, was also associated with a lower frequency of dyslipidemia, arterial hypertension, acute myocardial infarction, T2DM, and some types of cancer [7]. Thus, the regular consumption of dried fruits contributes to an adequate intake of nutrients, making the habitual diet healthier and reducing the risk of NCDs.

23.4 The Inclusion of Dried Fruits in Dietary Guidelines

Considering the evidence presented here about the benefits of dried fruits consumption for human health, as well as their popularity in the food culture of different populations around the world, some food-based dietary guidelines have begun to recommend their consumption (Table 23.1). Food-based dietary guidelines are brief nutritional recommendations used to guide consumers adequately as to the choice of foods and beverages that constitute a proper dietary intake of nutrients and reduce the risk of NCDs [37]. In addition, dietary guidelines are based on the best available scientific evidence regarding diet–health interaction and are influenced by the current dietary pattern and public health problems in the country for which it is intended.

Dietary guidelines in some countries now provide recommendations for the ingestion of dried fruits that reflect the consumption of these foods in the local culture and are aimed at promoting health. We reviewed the dietary guidelines available in English on the website of the Food and Agriculture Organization of the United Nations, and 12 of them had recommendations for dried fruits consumption (2 from Europe, 3 from the Near East, 4 from the Asia and the Pacific regions, 1 from Latin America and the Caribbean, and 2 from North America), which are presented below and summarized in Table 23.1.

Table 23.1 Summary of Dried Fruit Consumption Recommendations in Selected Food-Based Dietary Guidelines

Country and Publication Year	*Food Group Used to Classify Dried Fruits*	*Qualitative Guidelines Relating to Dried Fruits*	*Quantitative Guidelines Relating to Dried Fruits*	*Serving Size*	*References*
Albania, 2008	Fruits group	"General nutrition recommendations for children: Daily intake recommended to young children"	Food portion for children 2–6 years: • Fruits every meal and after lunch	¼ Cup dried fruits	[43]
Australia, 2013	Fruits and vegetables	"Enjoy a wide variety of nutritious foods from these five groups every day"	For total food group: • Males aged 19–50 years: 2 Serves per day • Females aged 19–50 years: 2 Serves per day	30 g	[40]
Brazil, 2014	Natural or minimally processed foods	"Make natural or minimally processed foods the basis of your diet" "Fruits"	–	–	[46]
Canada, 2011	Fruits and vegetables	"A healthy eating pattern for Canadians: eat the recommended amount and type of food each day: Fruits and vegetables"	For total food group: • Males aged 19–50 years: 8–10 Servings per day • Females aged 19–50 years: 7–8 Servings per day	¼ Cup	[50]
Fiji, 2013	–	"Give children healthy meals and snacks"	–	–	[38]
Lebanon, 2013	Fruits	"Eat a variety of nutritious foods every day for a balanced diet" "Enjoy more fruits and vegetables daily"	• 2 Servings per day	½ Cup dried fruits	[47]

(*Continued*)

Table 23.1 (Continued) Summary of Dried Fruit Consumption Recommendations in Selected Food-Based Dietary Guidelines

Country and Publication Year	*Food Group Used to Classify Dried Fruits*	*Qualitative Guidelines Relating to Dried Fruits*	*Quantitative Guidelines Relating to Dried Fruits*	*Serving Size*	*References*
Malta, 2015	Fruits and vegetables	"Healthy plate guidelines"	• 2 Servings (160 g) of fruit each day	One portion	[44]
New Zealand, 2015	Fruits and vegetables	"Choose and/or prepare foods and drinks"	• At least 2 servings of fruit each day	It is recommended to limit the amount of dried fruits included in the diet	[42]
Oman, 2009	Fruits	"Consume 2-4 servings of fruits daily"	For total food group: • Males aged 19–70 years: 4 cups per day • Females aged 19–70 years: 3.5 cups per day	–	[49]
Qatar, 2015	Fruits	"Eat a variety of healthy choices from the six food groups"	• 2–4 Servings of a variety of fruit every day	1 Serving = ¼ cup	[48]
Sri Lanka, 2011	Fruits	"Eat a variety of food every day"	• One-two medium size fruits	2 tbsp = 20-30 g	[39]
The United Kingdom, 2016	Fruits and vegetables	"A closer look at: Fruits and vegetables"	• Five portions of a variety of fruits and vegetables each day (one portion = 80 g)	30 g	[45]
The United States, 2015	Fruits	"Food groups: Fruits'' "Healthy U.S.-style eating pattern: Recommended amounts of food from each food group at 12 calorie levels"	• Two cup-equivalents per day	½ Cup dried fruits	[2]

23.4.1 Dietary Guidelines in Asia and the Pacific

The Dietary Guidelines for the Fijian population were published in 2013 and are based in 10 sections about food and health that highlight three food groups and lifestyle patterns to promote good nutrition and health. Each section refers to an important health problem that affects wellbeing and, if followed, helps to achieve a balanced and healthy life. Within the Dietary Guidelines for Fijians, the consumption of dried fruits is recommended in the seventh section "Give children healthy meals and snacks" as a healthy snack option to be used occasionally. However, the recommendations for dried fruits consumption are brief, and no portion sizes are defined for these foods [38].

The first version of the Food Based Dietary Guidelines for Sri Lankans was published in 2002. This guideline has been revised taking into account the latest evidence and scientific principles and the constant changes in eating patterns and lifestyle that occur over time [39]. In these Dietary Guidelines, dried fruits are included within the recommendations for fruit consumption (1–2 medium-size fresh fruits or 4–6 tablespoons of dried fruits/day). In addition, some dried fruits are indicated as sources of fiber (dates, prunes, and raisins) and antioxidants (prunes and dates). The Food Based Dietary Guidelines for Sri Lankans also recommends eating at least five fruits and vegetables daily to meet micronutrient needs.

The Australian Dietary Guidelines [40] were updated in 2013 after extensive review of the scientific evidence. The consumption of dried fruits is specified in the second section of the Dietary Guideline entitled "Enjoy a wide variety of nutritious foods from these five groups every day," which highlights that eating patterns with high intake of vegetables/beans and fruits helps to protect against NCDs, including heart disease, stroke, and some types of cancer, as well as avoid excessive weight gain. In this dietary guideline, dried fruits are indicated as a suitable option for fruit consumption; however, it is recommended that they may be consumed with moderation and occasionally due to the high sugar content and risk of promoting tooth decay. For men and women between the ages of 19 and 50 years, two daily servings of fruits (1 serving = 150 g) are recommended, and these may be occasionally substituted and/or supplemented with dried fruit (1 serving of the fruit group = 30 g of dried fruit).

In 2015, the New Zealand Ministry of Health released the Eating and Activity Guidelines for New Zealand Adults to replace the Food and Nutrition Guidelines for Adults [41]. The Eating and Activity Guidelines for New Zealand Adults is the first in a new series of guidelines providing comprehensive advice on nutrition, physical activity, and obesity prevention for all New Zealanders over time [42]. Theses dietary guidelines have been developed from the review dietary guidelines of other countries and renowned institutions around the world. As in the Australian Dietary Guidelines, consumption of dried fruits is also cautiously recommended in the New Zealand Dietary Guidelines. In Eating Statement 2, titled "Choose and/or prepare foods and drinks with little or no added sugar," dried fruits are discussed as snacks containing high amounts of sugar. It should be noted that because they are dehydrated, and therefore have reduced volume, a large quantity of dried fruits may be easier to consume at a single time, providing a high sugar intake and favoring the development of dental caries. For this reason, the New Zealand Ministry of Health's recommendation is to limit the amount of dried fruits included in the diet. However, there is no recommendation in relation to the size of a portion of dried fruits that should be consumed.

23.4.2 Dietary Guidelines in Europe

The Recommendations on Healthy Nutrition in Albania was published in 2013 and drawn up by experts from various institutions (Ministry of Health, Ministry of Agriculture, Food and Consumer Protection, Ministry of Education and Science, Economic Center for Education and Child Growth in the Municipality of Tirana, The Public Health Institute, and the Tirana Regional Public Health Directorate), who participated in the process of implementing the Stability Pact Project "Strengthening Food Safety and Nutrition Services in the South Eastern European Countries" [43]. In the dietary guidelines for Albanians, the consumption of dried fruits is recommended for children aged 2–6 years as an alternative to their fresh counterparts. Both types of fruits, in fresh and dehydrated forms, are part of the fruit group, of which two servings per day should be consumed (1 portion of the fruit group = 1 portion of fresh fruit, or approximately ¾ of a cup of 100% juice fruit or ¼ cup of dried fruits).

The Dietary Guideline for Adult Maltese, titled "Healthy Eating: the Mediterranean Way!" follows the Mediterranean dietary patterns in its recommendations and was published in November 2015 by the Ministry of Health of Malta [44]. In this dietary guideline, dried fruits are part of the fruit and vegetable group. At least two daily servings of fruit are recommended (1 portion of fruit = 160 g of fresh fruits). Regarding the consumption of dried fruits, it is recommended that only one of the daily portions of fruits may be consumed in the form of dried fruits because of the high sugar content of these foods, but the amount in grams representing a portion of dried fruits is not established. In addition, as in the dietary guidelines of other countries [40,42], the dietary guideline for the Maltese population also raises the concern that the excessive consumption of this type of food may favor the development of caries, impairing dental health.

"The Eatwell Guide Helping You Eat a Healthy, Balanced Diet" was published in 2016 by Public Health England to serve most people regardless of weight, dietary restrictions, and/or ethnic preference [45]. In this dietary guideline, dried fruits are part of the fruit and vegetable group, of which it is recommended to consume at least five daily servings of various fruits and vegetables, whether fresh, frozen, canned, dehydrated, or in the form of juice. In these guidelines, one serving of fruit is equal to 80 g of fresh fruit and can be replaced with one serving of dried fruit (1 portion of dried fruit = 30 g).

23.4.3 Dietary Guidelines in Latin America

The dietary guidelines for the Brazilian population were published in 2014 by the Ministry of Health of Brazil and were designed to promote the health and wellbeing of Brazilians [46]. In this dietary guideline, consumption of dried fruits is recommended within the group of natural or minimally processed foods as an alternative to healthy foods to be consumed in small meals. However, there is no established recommendation for the size of the dried fruit portion, since Brazilian Dietary Guidelines do not establish portions for the food groups but rather focus on encouraging the consumption of a variety of natural or minimally processed foods, with special emphasis on plant foods.

23.4.4 Dietary Guidelines in the Near East

The Food Based Dietary Guideline Manual for Promoting Healthy Eating in the Lebanese Adult Population was published in 2013 by the Faculty of Agricultural and Food Sciences and the American University of Beirut, in collaboration with the Lebanese National Council for Scientific Research [47]. Lebanese dietary guidelines are based on simple and easily achievable recommendations based on locally available and affordable foods for the promotion of healthy eating and lifestyle practices. In the third section of this dietary guideline, "Eat a Variety of Nutritious Foods Every Day for a Balanced Diet," dried fruits are recommended in the fruit group, which should be consumed daily (1 serving = 1 small apple or 1 large banana, orange, or peach, or ½ cup of dried fruits such as dates, prunes, raisins, and apricots). In order to increase fruit consumption, it is also recommended that dried fruits may be added to yogurts and eaten in snacks. Moreover, a recommendation to consume traditional dried fruits without the addition of sugar and without chocolate coverage is emphasized.

The Qatar Dietary Guideline was published in 2015 and developed by The Supreme Council of Health, Health Promotion, and Noncommunicable Diseases/ Public Health Department [48]. These dietary guidelines mainly recommend consumption of plant foods (vegetables, fruits, whole grains, nuts, and seeds), based on decades of research demonstrating their health benefits. A serving of dried fruits is defined as ¼ cup and appears as part of the fruit group, of which it is recommended to consume 2–4 servings per day. In addition, dried fruits are also suggested as healthy snack options because they are easy to pack and carry; however, the proviso is made that these foods should be consumed in moderation and that preference should be given to those without added sugar.

In a process that took more than 4 years and involved many experts, the Department of Nutrition developed the Omani Food Based Dietary Guidelines consisting of 10 guidelines, plus a visual presentation to guide the Omanis to a healthy lifestyle [49]. In the fourth section of this guideline, titled "Consume 2–4 servings of fruits daily," dried fruits are described as part of the fruit group, of which a consumption of four servings is recommended for men and 3.5 servings for women aged 19–50 years. However, there is no definition of the amount in grams representing a portion of dried fruits.

23.4.5 Dietary Guidelines in North America

The first American Dietary Guideline was published in 1980 and has been updated every 5 years. Each issue reflects the essence of nutrition science and brings with it the scientific advances in the field. The American Dietary Guideline, entitled "The 2015–2020 Dietary Guidelines for Americans," brings recommendations on the components of a healthy and nutritionally adequate diet to help promote health and prevent NCDs in current and future generations [2]. In these dietary guidelines, two daily servings of fruit are recommended, which can be achieved by ingestion of fresh, cooked, canned, frozen, or dehydrated fruits (1 serving of the fruit group = ½ cup of dried fruits), with the proviso that at least half of the recommendation should be achieved with the intake of whole fresh fruits. Although recommended in the fruit group as an equivalent of fresh fruits, it is recommended that the consumption of dried fruits be done carefully, considering the caloric density of these foods.

Canada's Food Guide defines and promotes healthy eating for Canadians, translating the science of nutrition and health into a healthy eating pattern [50]. The Canadian Dietary Guideline emphasizes the importance of combining healthy eating with physical activity. By following the recommendations of Canada's Food Guide, Canadians will be able to meet their nutrition needs and reduce the risk of obesity and NCDs such as T2DM, heart disease, certain cancers, and osteoporosis. In the third session of the Canadian Dietary Guideline, entitled "The Healthy Eating Pattern for Canadians Eat the Recommended Amount and Type of Food Each Day: Vegetables and Fruits," dried fruits are recommended as part of the fruit and vegetable group. The recommendation is that men consume 8–10 and women 7–8 servings of the fruit and vegetable group per day. The dried fruit portion is defined as ¼ cup.

23.5 Conclusion

Like fresh fruits, dried fruits are rich in various nutrients beneficial to health, and their incorporation in the habitual diet may support improving its quality. The consumption of these foods as part of a healthy dietary pattern potentially promotes the same benefits attributed to fresh fruit consumption, such as reducing the risk of CVD and other NCDs. Furthermore, dried fruit consumption is widely disseminated due to their durability, accessibility, sweetness, and culinary use in various preparations and food products. Nevertheless, little has been investigated regarding the role of these foods in the food cultures in different regions around the world.

Understanding key food patterns and how some foods contribute to healthier eating patterns is critical to the development and implementation of dietary guidelines to reduce diet-related diseases. Thus, based on the recognition of the nutritional value of dried fruits and their potential to help in the optimum intake of fruits and micronutrients, further studies should be carried out to correctly guide the population regarding the consumption of these foods. Besides, it should be highlighted that dried fruits consumption, as part of the food culture, may make different food patterns healthier.

References

1. Lim, S.S., Vos, T., Flaxman, A.D., Danaei, G., Shibuya, K., Adair-Rohani, H., Al Mazroa, M.A. et al., A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380, 2224–2260, 2012.
2. U.S. Department of Health and Human Services (HHS) and U.S. Department of Agriculture (USDA), *2015–2020 Dietary Guidelines for Americans*, U.S. Department of Health and Human Services, U.S. Department of Agriculture, Washington, DC, 2015.
3. Vayalil, P.K., Date fruits (*Phoenix dactylifera* Linn): An emerging medicinal food. *Crit. Rev. Food Sci. Nutr.*, 52, 249–271, 2012.
4. Orlich, M.J., and Fraser, G.E., Vegetarian diets in the Adventist Health Study 2: A review of initial published findings. *Am. J. Clin. Nutr.*, 100, 353S–358S, 2014.

5. Chang, S.K., Alasalvar, C., and Shahidi, F., Review of dried fruits: Phytochemicals, antioxidant efficacies, and health benefits. *J. Funct. Foods*, 21, 113–132, 2016.
6. Slavin, J.L., and Lloyd, B., Health benefits of fruits and vegetables. *Adv. Nutr.*, 3, 506–516, 2012.
7. Keast, D.R., O'Neil, C.E., and Jones, J.M., Dried fruit consumption is associated with improved diet quality and reduced obesity in US adults: National Health and Nutrition Examination Survey, 1999–2004. *Nutr. Res.*, 31, 460–467, 2011.
8. Leech, R.M., Worsley, A., Timperio, A., and McNaughton, S.A., Understanding meal patterns: Definitions, methodology and impact on nutrient intake and diet quality. *Nutr. Res. Rev.*, 28, 1–21, 2015.
9. Marsh, K., Zeuschner, C., and Saunders, A., Health implications of a vegetarian diet. *Am. J. Lifestyle Med.*, 6, 250–267, 2012.
10. Martinez-Gonzalez, M.A., and Bes-Rastrollo, M., Dietary patterns, Mediterranean diet, and cardiovascular disease. *Curr. Opin. Lipidol.*, 25, 20–26, 2014.
11. Martinez-Gonzalez, M.A., Salas-Salvadó, J., Estruch, R., Corella, D., Fitó, M., and Ros, E., Benefits of the Mediterranean diet: Insights from the PREDIMED study. *Prog. Cardiovasc. Dis.*, 58, 50–60, 2015.
12. Salas-Salvadó, J., Garcia-Arellano, A., Estruch, R., Marquez-Sandoval, F., Corella, D., Fiol, M., Gómez-Gracia, E. et al., Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur. J. Clin. Nutr.*, 62, 651–659, 2008.
13. Trichopoulou, A., Martínez-González, M.A., Tong, T.Y., Forouhi, N.G., Khandelwal, S., Prabhakaran, D., Mozaffarian, D. et al., Definitions and potential health benefits of the Mediterranean diet: Views from experts around the world. *BMC Med.*, 12, 112–128, 2014.
14. Folchetti, L., Monfort-Pires, M., de Barros, C.R., Martini, L., and Ferreira, S.R., Association of fruits and vegetables consumption and related-vitamins with inflammatory and oxidative stress markers in prediabetic individuals. *Diabetol. Metab. Syndr.*, 6, 22–30, 2014.
15. Cavallo, D.N., Horino, M., and McCarthy, W.J., Adult intake of minimally processed fruits and vegetables: Associations with cardiometabolic disease risk factors. *J. Acad. Nutr. Diet.*, 116, 1387–1394, 2016.
16. Carughi, A., Feeney, M.J., Kris-Etherton, P., Fulgoni, V., Kendall, C.W.C., Bulló, M., and Webb, D., Pairing nuts and dried fruit for cardiometabolic health. *Nutr. J.*, 15, 23–36, 2015.
17. Craig, W.J., Nutrition concerns and health effects of vegetarian diets. *Nutr. Clin. Pract.*, 25, 613–620, 2010.
18. Tonstad, S., Butler, T., Yan, R., and Fraser, G.E., Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. *Diabetes Care.*, 32, 791–796, 2009.
19. Tonstad, S., Stewart, K., Oda, K., Batech, M., Herring, R.P., and Fraser, G.E., Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. *Nutr. Metab. Cardiovasc. Dis.*, 23, 292–299, 2013.
20. Rizzo, N.S., Sabaté, J., Jaceldo-Siegl, K., and Fraser, G.E., Vegetarian dietary patterns are associated with a lower risk of metabolic syndrome: The Adventist Health Study 2. *Diabetes Care*, 34, 1225–1227, 2011.
21. Fraser, G., Katuli, S., Anousheh, R., Knutsen, S., Herring, P., and Fan, J., Vegetarian diets and cardiovascular risk factors in black members of the Adventist Health Study 2. *Public Health Nutr.*, 18, 537–545, 2015.

22. Orlich, M.J., Singh, P.N., Sabaté, J., Jaceldo-Siegl, K., Fan, J., Knutsen, S., Beeson, W.L. et al., Vegetarian dietary patterns and mortality in Adventist Health Study 2. *JAMA Intern. Med.*, 173, 1230–1238, 2013.
23. Tantamango-Bartley, Y., Jaceldo-Siegl, K., Fan, J., and Fraser, G., Vegetarian diets and the incidence of cancer in a low-risk population. *Cancer Epidemiol. Biomarkers Prev.*, 22, 286–294, 2013.
24. Rizzo, N.S., Jaceldo-Siegl, K., Sabaté, J., and Fraser, G.E., Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *J. Acad. Nutr. Diet.*, 113, 1610–1619, 2013.
25. Hernández-Alonso, P., Camacho-Barcia, L., Bulló, M., and Salas-Salvadó, J., Nuts and dried fruits: An update of their beneficial effects on type 2 diabetes. *Nutrients*, 9, 673–707, 2017.
26. Alonso, A., de la Fuente, C., Martín-Arnau, A.M., de Irala, J., Alfredo Martínez, J., and Martínez-González, M.A., Fruit and vegetable consumption is inversely associated with blood pressure in a Mediterranean population with a high vegetable-fat intake: The Seguimiento Universidad de Navarra (SUN) Study. *Br. J. Nutr.*, 92, 311–319, 2004.
27. Martínez-González, M.A., Fernández-Jarne, E., Martínez-Losa, E., Prado-Santamaría, M., Brugarolas-Brufau, C., and Serrano-Martinez, M., Role of fibre and fruit in the Mediterranean diet to protect against myocardial infarction: A case–control study in Spain. *Eur. J. Clin. Nutr.*, 56, 715–722, 2002.
28. Buil-Cosiales, P., Toledo, E., Salas-Salvadó, J., Zazpe, I., Farràs, M., Basterra-Gortari, F.J., Diez-Espino, J. et al., Association between dietary fibre intake and fruit, vegetable or whole-grain consumption and the risk of CVD: Results from the PREvención con DIeta MEDiterránea (PREDIMED) trial. *Br. J. Nutr.*, 116, 534–546, 2016.
29. World Health Organization (WHO), *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*, WHO, Geneva, Switzerland, 2004.
30. Centers for Disease Control and Prevention (CDC), State-specific trends in fruit and vegetable consumption among adults – United States, 2000–2009. *MMWR Morb. Mortal. Wkly. Rep.*, 59, 1125–1130, 2010.
31. Sachdeva, S., Sachdev, T., and Sachdeva, R., Increasing fruit and vegetable consumption: Challenges and opportunities. *Indian J. Community Med.*, 38, 192–197, 2013.
32. Hall, J.N., Moore, S., Harper, S.B., and Lynch, J.W., Global variability in fruit and vegetable consumption. *Am. J. Prev. Med.*, 36, 402–409, 2009.
33. U.S. Department of Agriculture (USDA), National Nutrition Database for Standard Reference, Release 28, 2016. Published online at: https://ndb.nal.usda.gov/ndb/search/list (accessed October 22, 2017).
34. Bachman, J.L., Reedy, J., Subar, A.F., and Krebs-Smith, S.M., Sources of food group intakes among the US Population, 2001–2002. *J. Am. Diet. Assoc.*, 108, 804–814, 2008.
35. Lloyd-Williams, F., Mwatsama, M., Ireland, R., and Capewell, S., Small changes in snacking behaviour: The potential impact on CVD mortality. *Public Health Nutr.*, 12, 871–876, 2009.
36. U.S. Department of Agriculture (USDA), *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010*, U.S. Department of Agriculture, Department of Health and Human Services, Washington, DC, 2010.

37. World Health Organization (WHO), *Preparation and Use of Food-Based Dietary Guidelines*, World Health Organization – Technical Report Series, Nicosia, Cyprus, 1998.
38. National Food and Nutrition Centre, *Food & Health Guidelines for Fiji*, National Food and Nutrition Centre, Suva, Fiji Islands, 2013.
39. Nutrition Division Ministry of Health, *Food Based Dietary Guidelines for Sri Lankans*, Nutrition Division Ministry of Health, Colombo, Sri Lanka, 2011.
40. Department of Health and Ageing and National Health and Medical Research Council, *Australian Dietary Guidelines*, Department of Health and Ageing, National Health and Medical Research Council, Canberra, Australia, 2013.
41. Ministry of Health, *Food and Nutrition Guidelines for Adults*, Ministry of Health, Wellington, New Zealand, 2003.
42. Ministry of Health, *Eating and Activity Guidelines for New Zealand Adults*, Ministry of Health, Wellington, New Zealand, 2015.
43. Department of Public Health, *Recommendations on Healthy Nutrition in Albania*, Department of Public Health, Tirana, Albania, 2008.
44. Ministry of Health, *Dietary Guidelines for Maltese Adults*, Ministry of Health, Valletta, Malta, 2016.
45. Public Health England, *From Plate to Guide: What, Why and How for the Eatwell Model*, Public Health England, London, UK, 2016.
46. Ministry of Health of Brazil, *Dietary Guidelines for the Brazilian Population*, Ministry of Health of Brazil, Brasilia, Brazil, 2014.
47. American University of Beirut, *The Food-Based Dietary Guideline Manual for Promoting Healthy Eating in the Lebanese Adult Population*, The Faculty of Agricultural and Food Sciences, American University of Beirut, Beirut, Lebanon, 2013.
48. The Supreme Council of Health Qatar, *Qatar Dietary Guidelines*, Public Health Department, The Supreme Council of Health, Doha, Qatar, 2015.
49. Ministry of Health Sultanate of Oman, *The Omani Guide to Healthy Eating*, Ministry of Health Oman, Department of Nutrition, Muscat, Oman, 2009.
50. Health Canada, *Eating Well with Canada's Food Guide*, Health Canada, Ottawa, ON, Canada, 2007.

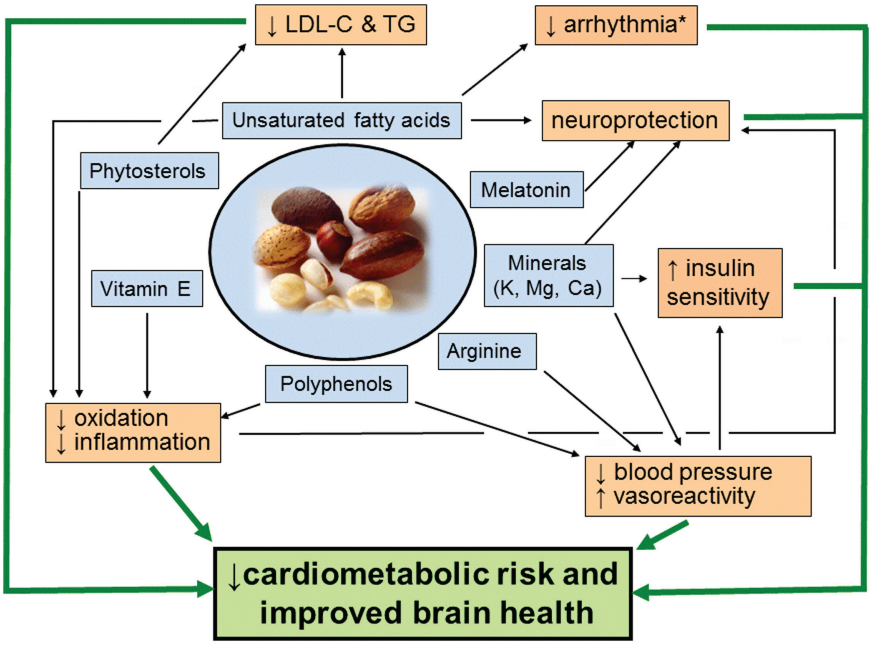


Figure 11.1 Summary of mechanisms whereby nut consumption benefits cardiometabolic risk and brain health. *Note*: *Only α-linolenic acid may have an antiarrhythmic effect. *Abbreviations*: LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerols; K, potassium; Mg, magnesium; Ca, calcium.

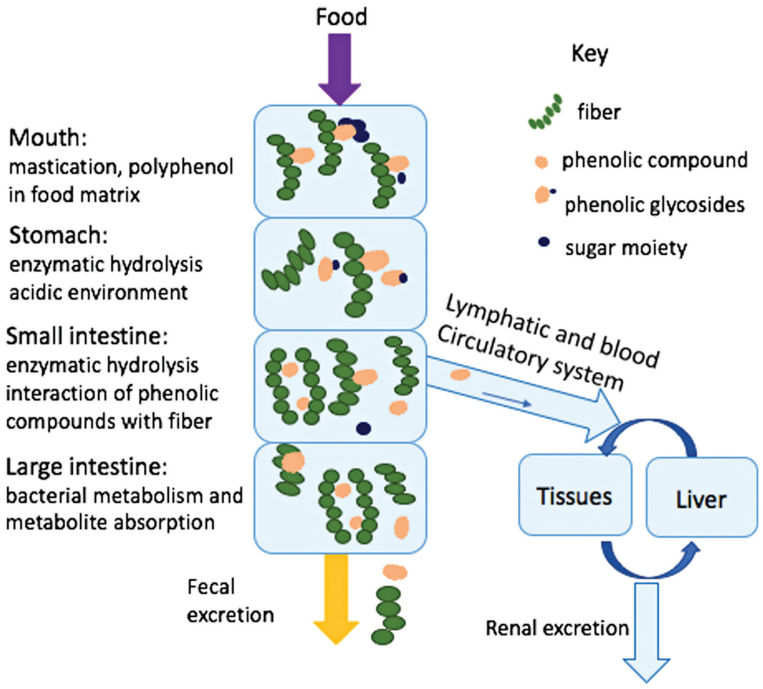


Figure 15.3 General pathway of absorption of phenolic compounds contained in foods rich in dietary fiber, such as fruits and vegetables. *Source*: Adapted from Palafox-Carlos, H. et al., *J. Food Sci.*, 76, R6, 2011. Open access journal.

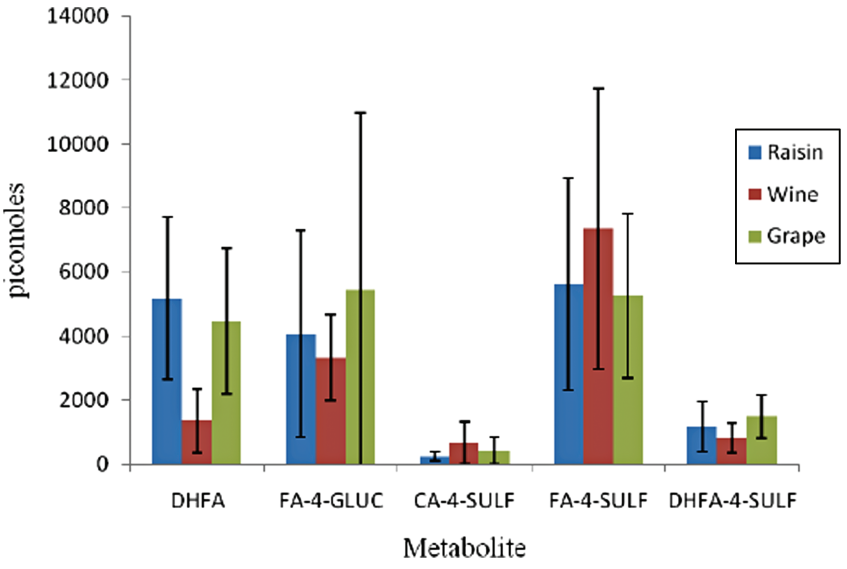


Figure 15.4 Total urinary excretion of phenolic acid metabolites from raisins, white wine, and grapes per 24 hours. *Source*: Adapted from Carughi, A., *Ann. Nutr. Metab.*, 62, 14, 2013. With permission.

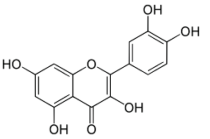
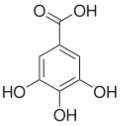
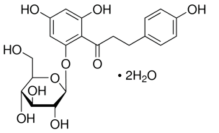
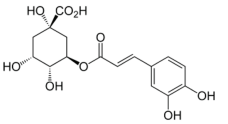
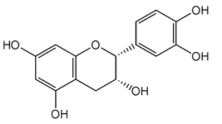
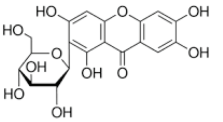
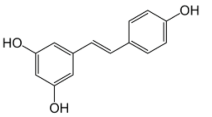
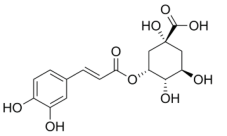
Dried fruit and major polyphenol	Chemical structure	Pictures
Pomegranates (Quercetin)		
Figs (Gallic acid)		
Apples (Phlorizin)		
Apricots (Chlorogenic acid)		
Dates (Epicatechin)		
Mangoes (Mangiferin)		
Raisins (Resveratrol)		
Prunes (Neochlorogenic acid)		

Figure 20.1 A diagram depicting the major polyphenol in selected fruits, with images of their fresh and dried forms.

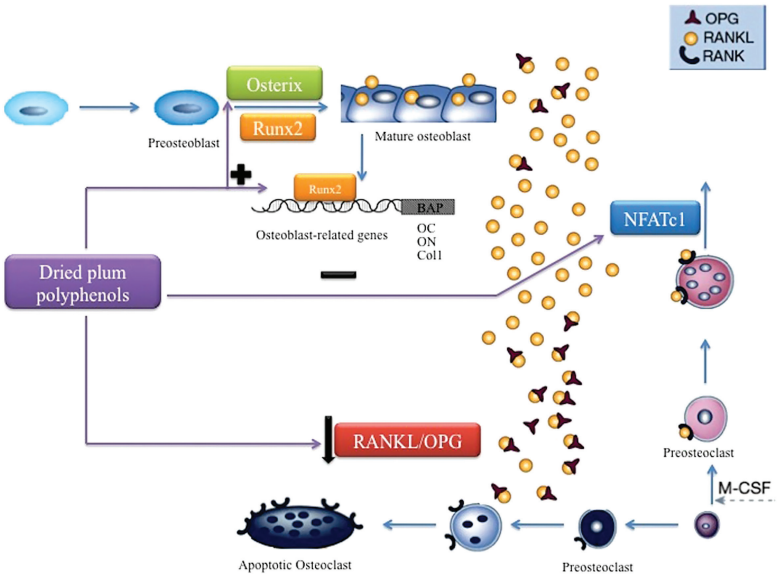


Figure 20.4 Proposed mechanisms of action of prune polyphenols on bone. *Abbreviations*: BAP, bone-specific alkaline phosphatase; M-CSF, macrophage colony stimulating factor; NFATc1, nuclear factor of activated T-cells 1; OPG, osteoprotogerin; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand.

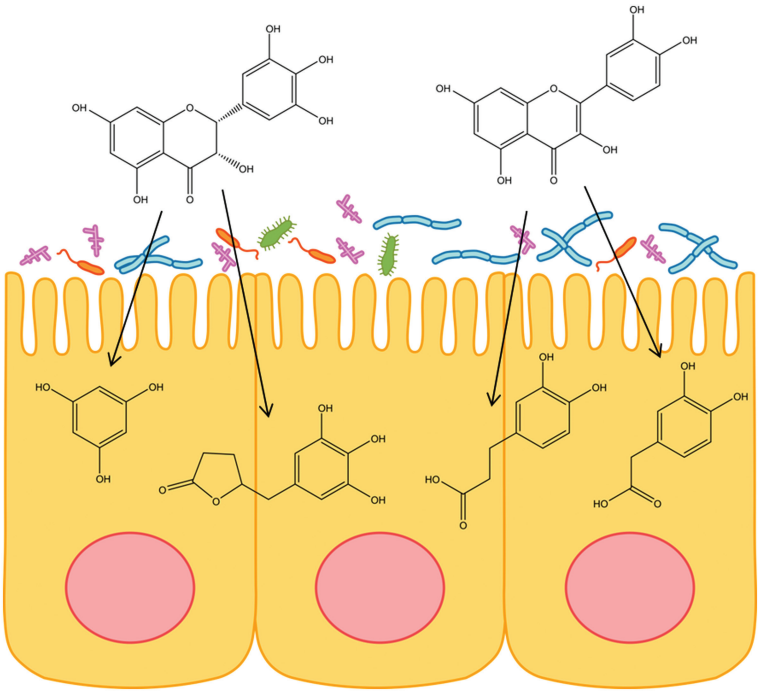


Figure 21.1 2*R*, 3*S*-dihydromyricetin, and quercetin are modified by the microbiota, and different products [1,3,5-benzenetriol, dihydro-5-(3,4,5-trihydroxyphenyl)methyl -2(3H)-furanone, 3,4-dihydroxyhydrocinnamic acid, and 3,4-dihydroxyphenylacetic acid] enter the cells.

Index

A

Adequate intake (AI), 16, 23–27, 336, 345–349
Adiposity, 167, 168, 176
All-cause mortality, 247–252, 255, 256
Alzheimer disease (AD), 262, 263, 272, 274–278
Angiogenesis, 231–233, 241
Antioxidant capacity, 380
Antioxidants, 437, 441, 443
Apolipoproteins, 59, 64–66, 74–78
Apoptosis, 231–233, 241, 452–454, 459
Appetite, 125, 126, 130, 136–139, 147, 497–500, 502, 503, 506, 507
Atherosclerosis, 397, 398, 403, 409
Atrial fibrillation, 155, 160, 163, 166

B

Bioaccessibility, 130–132, 147
Bioactive compounds, 369, 370, 385, 389
Bioactives, 2, 3, 5, 13, 14, 16, 31–34, 50, 351, 450, 452, 458, 462, 470
Bioavailability, 369–383, 386, 388
Biological plausibility, 167, 176
Blood lipids, 59–62, 65–78
Blood pressure, 418, 420, 422–424, 426, 428, 437, 438, 440
Body mass index (BMI), 168–171, 174–176
Body weight, 168, 172, 175, 177, 437, 438, 441, 443
Bone health, 469–471, 474–477, 479

C

Cancer chemopreventive, 449, 451
Cancer mortality, 247, 251, 254, 255
Cancer, 3, 4, 224–241, 247, 248, 251, 254–256, 449–462
Cardiovascular disease (CVD), 2–4, 156–161, 164, 165, 167, 168, 175, 177, 182, 183, 195, 198, 204, 212, 290, 292, 300, 305, 314, 324, 438, 440–443, 488, 489, 513–515, 517, 523
Carotenoids, 13, 14, 29–34, 36, 335, 351, 352, 364, 369, 370, 375–379
Cause-specific mortality, 247, 248, 252, 256
CHD mortality, 247, 251–253
Chemoprevention, 224, 233, 241
Cognition, 262–265, 267–271, 273, 276–279
Cognitive function, 4, 497–499, 502, 503, 506
Compensation, 125, 126, 138–145, 147
Consumers, 292, 293, 295, 301, 303–306, 516, 517
Consumption, 125–130, 136–140, 145–147
Coronary heart disease (CHD), 2, 3, 155–158, 161, 164, 165, 290, 303, 397, 398, 407,
C-reactive protein (CRP), 416, 417, 422–425, 427, 428
CVD mortality, 247, 251–253, 255
Cyclooxygenase-2 (COX-2), 453, 454, 457–459

D

Dementia, 262, 263, 266, 274, 275, 277–280
Depression, 262, 263, 265, 266, 270, 277, 278

Diabetes risk, 181, 194, 211
Diabetes, 182–212, 247, 251, 254–257, 437–441
Dietary guidelines, 293–305, 513, 517–522
Dietary patterns, 290–293, 513–515, 521
Digestion, 376–382, 388
Diversity, 316, 318, 321, 323
Dysbiosis, 488

E

Endothelial dysfunction (ED), 92, 97–100
Endothelial function, 414–421, 426
Energy balance, 125, 126, 130, 132, 140, 147
Energy intake, 126–130, 135, 136
Epidemiological studies (prospective), 263–266, 273–279
European Food Safety Authority (EFSA), 3, 4, 22, 35, 344

F

Fasting glucose, 191, 194–206, 208–210, 437, 439
Fasting insulin, 194–204, 206, 208–210
Fat-soluble bioactives, 13, 14, 16, 31–34, 50, 351
Fatty acids, 13, 14, 19, 20, 31–34, 61, 66, 71, 73, 168, 177, 343
Fermentation (intestinal fermentation), 369, 378–380, 383–387
Fiber, 20, 37, 59, 71–74, 78, 169, 171, 176, 177, 313–315, 317, 318, 324, 336, 338, 339, 364
Flow-mediated dilatation (FMD), 92, 93, 101–107, 109, 111, 112, 114–116, 422, 425, 426
Food and Drug Administration (FDA), 3, 4, 22, 23
Fructo-oligosaccharides (FOS), 471, 475–477, 479

G

Glycemic control, 182, 183, 194–212, 438, 442
Glycemic index (GI), 369, 371, 373, 437–439, 489
Gut hormone, 125, 126
Gut microbiome, 59, 73, 224, 232, 233, 241, 313–326, 369, 383–388

H

Health claims, 3, 4, 13, 22, 35, 335, 344
Healthy eating, 517, 518, 521–523
Healthy snack, 514, 517, 520, 522
Heart failure, 155, 160, 163, 166, 247, 255
Hemoglobin A1c (HbA_{1c}), 194–205, 207–212, 438
Hepatic lipid, 398, 399, 403, 408
Hepatoprotection, 497, 498, 501, 502, 504
High-density lipoprotein cholesterol (HDL-C), 59, 61, 63, 67–70, 73–78, 398, 400–408
HOMA-IR, 194–204, 206, 208–210
Human intervention, 449, 456, 461, 462
Hypertension, 289, 290, 292, 515, 517

I

Infections, 247, 254–256
Inflammation, 233–235, 241, 416, 427, 437, 438, 440–442, 452, 459–462
Insulin resistance (IR), 92, 110, 113, 114
Insulin-like growth factor-1 (IGF-1), 232, 234, 241
Inter-cellular adhesion molecule-1 (ICAM-1), 92–95, 98, 105–108, 110–116, 452, 453, 457
Intestinal health, 497, 498, 500–502, 504, 507
Intestinal permeability, 488, 490

K

Kidney disease, 247, 254

L

α-Linolenic acid (ALA), 271, 273–276
Lipid profiles, 398, 399, 403, 407–409
Lipoproteins, 59–61, 64–66, 73–78, 398–400, 402, 403, 406–408
Longevity, 247–249
Low-density lipoprotein cholesterol (LDL-C), 59–63, 66–78, 398–408, 419, 439–442

M

Mastication, 125, 126, 130–132, 136, 137, 177
Mediterranean diet (MedDiet), 172, 173, 175, 177, 290, 291, 314, 315, 515
Melatonin, 271, 273, 276, 279
Meta-analyses, 167, 175
Metabolic syndrome (MetS), 3, 92, 100, 102–105, 107–115, 182, 183–190, 205, 207, 439, 441
Metagenomics, 325, 326
Microbiota, 488, 490–492
Minerals, 13, 14, 16, 17, 21, 23–25, 335, 336, 339, 343–347, 369, 370, 376, 477

N

National nutrition surveys, 305, 306
Natural antioxidants, 13, 29, 335
Neurodegenerative disease, 247, 251, 254
Nitric oxide synthase (NOS), 418–423

Nut consumption, 59–78, 167–177
Nutrients, 13, 14, 16, 22, 59, 71, 77, 78, 335, 336, 338, 364
Nutritive compounds, 472

O

Obesity, 3, 4, 168–175, 177, 488, 489
Oral processing, 125, 126, 130, 136, 137
Osteoprotection, 469–472, 477

P

Peripheral arterial disease (PAD), 155, 161, 163, 166
Peripheral arterial tonometry (PAT), 92, 93, 102, 103, 105, 108, 112–114, 116
Phenolic compounds, 369, 370, 376, 378–383, 386
Phenolics, 13, 14, 16, 23, 28, 29, 37–50, 335, 350–359, 363
Phytochemicals, 3–5, 16, 23, 29, 37, 50, 335, 336, 350–352
Phytoestrogens, 335, 350–352, 362
Phytosterols, 13, 14, 31, 32, 35, 59, 62, 72
Plant-based diet, 313–315
Polyphenols, 59, 72, 73, 75, 78, 262, 271–273, 275, 276, 279, 470, 471, 474, 475, 477, 479–481, 488, 490, 491
Prebiotic effect, 318, 319, 324, 325
Prebiotic, 490, 492
Prospective Cohort Studies, 167, 169–171
Proximate composition, 13, 16, 17, 335, 338, 339
Pulse wave velocity (PWV), 415, 425, 426

R

Randomized controlled trials (RCTs), 168, 172, 175, 176, 182, 192, 194, 205–212, 225, 234, 235, 237, 262, 263, 267–270, 275–280
Reactive oxygen species (ROS), 418–420, 426
Recommended dietary allowances (RDA), 16, 23–27, 35, 336, 345–349
Respiratory disease, 247, 251, 254–256

S

Satiety control, 497–499, 502, 503, 506
Serum lipids, 398–409
Short chain fatty acids (SCFA), 490, 491
Sorbitol, 369–375
Sphingolipids, 13, 14, 31–35
Stroke mortality, 247, 251–253, 256
Stroke, 155–159, 162, 164–166
Sudden cardiac death, 155, 163, 164, 166

T

Tocols, 13, 31, 32, 34, 35
Total cholesterol (TC), 59, 61, 70, 74, 77, 398–408
Triacylglycerols (TAG), 59, 63–70, 74–78, 398–408, 441–443
Tumor necrosis factor-α (TNF-α), 92, 97, 98, 101, 103, 104, 108, 110–115, 416–418, 423–425, 428, 452, 453, 457–459, 461
Tumor, 225, 231–234, 241, 452, 457, 459, 462
Type-2 diabetes (T2D), 3, 4, 247, 255, 314, 324, 438–443, 489

V

Vegan, 289, 291, 292
Vegetarian, 289–292, 295, 304, 513–515, 523
Vitamins, 13, 14, 16, 18, 21, 23, 26, 27, 29, 335, 336, 340, 344, 345, 348, 349, 369, 370, 375, 379, 477

W

Waist circumference (WC), 172–176
Weight gain, 168–177