CROTON TIGLIUM.

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BOTANICAL DESCRIPTION AND HISTORICAL NOTES.

The genus croton, established by Linnaeus in 1737, is extensive, 625 species being recognized in the Index Kewensis. We have a number of herbaceous species in this country, but none of any economic importance. The croton plant is a native of India and is grown all through the East Indies. It is a small tree fifteen to twenty feet high. The leaves are ovate, petiolate, acuminate, alternate, the margins faintly serrate. The flowers are borne in loose terminal spike-like racemes, and are monoicious, the male flowers being at the top of the the raceme, the females below. The male flowers have five sepals, each sepal bearing a yellow gland, five petals, and from ten to twenty stamens with slender filaments. The female flowers have floral envelopes similar to those of the male, and a large sessile, three-celled ovary, thickly covered with stellate hairs and bearing three slender styles, each style dividing into two linear stigmas. The fruit is a three-celled capsule, each cell having a single seed which yields the croton oil of commerce.

Croton tiglium is considered indigenous to Malabar, Ceylon, Amboina (of the Molucca

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islands), the Philippines and Java. Joannes Scott, in his dissertation on the medicinal plants of Ceylon (Edinburg, 1819), states that the seeds of croton tiglium under the name of "gayapala," are a most powerful purgative, and also that the leaves are very acrid, causing an intolerable burning in the mouth and throat.

Dr. Irvine, in 1848, gave a short account of the materia medica of Patna (part of the province of Bengal) mentioning "jamalgoota," which he stated is derived from croton tiglium and several other species of croton. The croton seeds furnish a violent purge and are made into pills with ginger and "kutkaranja or kath karanja seeds," which he explains are known as bonduc nut (the febrifuge seed of *Caesalpiniabonducella*, or nicker tree).

More recently, Mr. 0. Weynton[11] calls attention to the occurrence of *Croton tiglium*, in all parts of the fertile and wealthy province of Assam, especially in the dry districts. He states that the demand for the drug is small and that the plant has a tendency to spread. Hence efforts are being made to restrict the growth and keep it within certain bounds.

The ancient Hindu physicians were not acquainted with the drug, which seems to have originated in China, from whence at an early day the seeds were also introduced into Persia (where they are now called *dand*), by way of the caravan routes of central Asia. Subsequently the Arabs derived their knowledge of the seeds from the Persians, their name, *hab-el-kathai* (Cathay

seeds), being in turn suggestive of the Chinese origin.[13] Some of the vernacular Indian names, according to Dymock, seem to indicate that the plant reached India through the Himalayan province of Nepal.[13]

The drug was imported into Europe by the Dutch during the 16th century. The first account of the *Croton tiglium* plant in European literature, however, must be credited to the Portuguese physician Christoval Acosta, who in 1578 described the wood as lignum pavanae (or L. panavae or L. moluccense), and the seeds as pini nuclei moluccani.[1] The prominent writings of Rheede (1678), who gives the Malayan name cadel avanacu,[15] Ray (1688) and others subsequently, gave the drug due consideration, while C. Bauhinus (1671) differentiated between several synonyms of the seeds and woods that were then in use. To Caspar Commelyn (1667-1731) is attributed the first use of the name cataputiae minores for the seeds, while the well-known synonym grana tiglii is also stated to have been originated in his time. And yet this author's work on the Flora Malabarica (1696) does not record the first term, although the name grana tiglii is therein accredited to Samuel Dale;s Pharmacologia, (the first edition of which appeared in 1693).[3]

As regards the use of the oil derived from the seeds, E. von Hirschheydt, in the exhaustive historical introduction to his dissertation,[12] mentions that Peter Borellus, a French physician (1620-1689), in 1657 lauds the cathartic virtues of the oil which in as small an

amount as two drops caused purging even when merely rubbed into the skin. Similar mention of its virtues is made by Rumphius (Herbarium Amboinense, 1750). Geoffroy[5] in his Materia Medica (1756) reports that the natives of India use this oil to make what they call the royal purging apple (poma cathartica), the mere odor of which is said to purge persons of delicate constitution. The directions for making this potent “apple” are as follows:

Macerate an orange or a lemon in oil of tilli (croton oil) for one month. Remove it, hold to the nostrils and inhale the breath; soon afterwards the bowels will move.

About 1750, Cohausen, according to several authorties, employed the oil with success in cases of tenia.

Although during the 17th and 18th centuries the remedy had been frequently used, it seems that towards the end of the 18th century it fell into oblivion, probably on account of the dangers attending its administration. However, its use was revived when in 1812, several English physicians, among them Drs. White and Marshall, observed the action of the seed in medical practice in India, and brought the drug again to the notice of the profession in Europe.[13] Ainslie in 1813, and Conwell in 1819, by their publications gave it further prominence. In connection with its reintroduction we note the interesting fact that a Mr. Short then brought the drug to Europe and was so fortunate as to secure the right (license) to its

exclusive sale in England. That it at once became an important drug is shown by the attention then given it in medical literature. An extensive list of references to the literature on croton tiglium. covering the period from 1820 to 1835 alone, may be found in Hirschheydt's dissertation.[12] According to the latter authority (1890) the seeds and the oil are seldom used in Europe other than in veterinary practice, as he states, on account of the uncontrollable influence exerted by the presence of the powerfully toxic ricin (an albuminoid body) in the oil.

As already stated, the genus croton was established by Linnaeus in 1737,[4] the name being adopted from the Greek synonym for *Ricinus communis*, the seeds of which, as also those of *Croton tiglium*, have a resemblance to a tick (dog-tick, kroton in Greek). As to the origin of the term tiglium, some authorities ascribe it to the Moluccan island of Tilho, while others[6] believe it to be derived (by Dale?) from the Greek word *tilos*, meaning diarrhea. The botanical and vernacular synonyms antedating the name given by Linnaeus are numerous and are generally carried by the older botanico-medical works, e. g. by Dale,[3] Bauhinus,[2] and others. The post-Linnaean synonyms recorded in the Index Kewensis are rarely if ever seen in pharmaceutical print and may well be reproduced. They are as follows:

(1) C. acutus, Thunberg, 1784.

(2) C. jamalgota, Hamilton,[15] 1825.

(3) C. pavana, Hamilton,[15] 1826.

(4) Kurkas tiglium, Rafinesque, (Sylva Tellur.) 1838.

(5) Halecus verus (?) Raf. 1838.

(6) Tiglium officinale, Klotzsch, 1843.

(7) Croton muricatus, Blanco, 1845.

(8) Anisophyllum acutifolium, Bouv. 1860-61.

CHEMICAL CONSTITUENTS & PROPERTIES:

While it has long been known that all parts of the *Croton tiglium* plant (root, bark, leaves and seeds) produce the drastic effects of the oil, only the seeds and the oil resulting therefrom have merited extensive investigation.

The oil is usually abstracted by pressure but is also obtained by extraction with carbon disulfid. Two varieties are distinguished in trade, the India and the English oil; and at present the larger amount is expressed in England (it is said by only one firm) from seeds imported from India. The kernels contain from 50 to 60 per cent of oil, the testa were observed by Zinnel (Amer. Jour. Pharm. 1890, p. 122) to contain about 1.65 per cent.

The chemical investigations of croton oil have been directed towards the isolation of both the vesicant and the purgative principles.

Nimmo of Glasgow, in 1823, was probably the first to observe that alcohol dissolves the vesicant part, leaving behind a comparatively inert oil. Buchheim and Krich in 1857[12] obtained an alcohol-soluble vesicant and an alcohol-insoluble purgative. From the latter, by saponification, these investigators isolated a principle that was both vesicating and purgative, closely related to ricinoleic acid (its lead salt being soluble in ether) to which they gave the name crotonoleic acid. This early work of Buchheim is given detailed consideration by E. von Hirschheydt.[12] Schlippe,[7] in 1858, again observed that the alcohol-soluble part of the oil was by far the most active vesicant. His analysis revealed the presence of glycerids of stearic, palmitic, lauric, myristic and oleic acids, and what he believed to be angelic acid, as well as *crotonol*, the strongly-vesicating, resinous principle, ($C_9H_{14}O_2$) which he considered to be a polyvalent alcohol, and for the isolation of which he gave explicit directions. Crotonol when boiled with alkalies or even with water or dilute sulfuric acid is easily decomposed, a resinous, inert substance resulting.

Geuther and Froehlich[8] in 1870 demonstrated the melting point of Schlippe's angelic acid to be 64° C., thus showing that it could not be true angelic acid, which melts at 45° C. They named it tiglinic acid, a substance afterward found by Schmitt and Berendes[9] (1878) to be Frankland and Duppa's methyl-crotonic acid, $C_6H_8O_2$, or CH_3 CH: C (CH_3) COOH). Schlippe's crotonic

acid was declared by Geuther and Froehlich to be a mixture of acetic, butyric and valeric acids; Schmidt and Berendes found isobutyric (not butyric) and a valeric (isobutyl-formic) acid.

Harold Senier[10] in two series of investigations, 1878 and 1883, observed that croton oil became more soluble as it aged, and with seeming disregard of former investigations concerning this point, concluded that croton oil may be conveniently differentiated by alcohol into a vesicating, alcohol-soluble part and a purgative alcohol-insoluble part; the conclusion being that the oil improved with age as far as the vesicating principle was concerned. The correctness of this separation theory, however, inasmuch as it implied the existence of a fundamental difference between the alcohol-soluble and the alcohol-insoluble part, was invalidated by the exact experiments of Kobert and v. Hirschheydt as well as by Buchheim's and Krich's observation of the fact that a vesicant principle may be isolated from the purgative portion. However, to Senier belongs the credit of having ascertained, in his second series of investigations, that the vesicating principle is to be found in that part of the alcohol-soluble oil represented by a nonvolatile fatty acid the barium salt of which is soluble in alcohol. Buchheim having resumed in 1873 the study of this subject failed to isolate the true vesicant principle on account of having sought it in less soluble barium salts.

Kobert and v. Hirschheydt[12] in 1890 finally decided that the efficacy of the alcohol-soluble

part of croton oil as a vesicant is due to the presence of free *crolonoleic acid*, which also composes as a glycerid the alcohol-insoluble part of croton oil. L. Reuter has recently (1890) shown that free crotonoleic acid increases the solubility of the neutral glycerid in alcohol. This acid is liable to decomposition, and may be destroyed on saponification of the glycerid with even weak bases. Kobert prepared this vesicant compound by treating the alcohol-soluble part of an oil containing as much as possible of the *free* acid, with baryta water; removing the barium salts of the inert acids by treatment with water; abstracting the barium oleate and crotonoleate with ether and finally separating the croton-oleate from the evaporated solution by means of cold absolute alcohol. The free crotonoleic acid is then obtained as an oily mass by adding the calculated amount of sulfuric acid, extracting with ether and evaporating the solvent.

Kobert and v. Hirschheydt also demonstrated that the neutral oil (insoluble in alcohol) maybe decomposed by the pancreatic ferment, the acrid crotonoleic acid being thereby liberated.

Finally, Prof. W. R. Dunstan and Miss L. E. Boole[14] investigated crotonoleic acid. After fractionally differentiating it into some inert oily acids, the last fraction contained a powerfully vesicating resin which the authors called croton resin, a hard, light-yellow, brittle substance, chemically of no pronounced character, nearly insoluble in water, readily soluble in alcohol, ether and chloroform. Prolonged boiling with caustic alkalies destroys its vesicating power;

splitting it thereby into acids of the acetic acid series. Whether this croton-resin exists as such in the oil, or whether it is a modification product of crotonoleic acid, we may still consider to be an open question.

PHARMACOPEIAL RECORD.

Croton oil is now official in all modern pharmacopeias, yet we are unable to find it in any pharmacopeia of the last or previous centuries. It was introduced into the London pharmacopeia, in 1824, as Oleum Tiglii, while in the U. S. pharmacopeia it has been official since 1830.

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(2) Casp. Bauhinus, Pinax Theatrici Botanici; Basileae, 1671, pp. 393 and 492.

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