Cephaelis Ipecacuanha.

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CEPHAELIS IPECACUANHA.*

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BOTANICAL DESCRIPTION AND SYNONYMS,

The plant which produces this drug belongs to the large natural order of rubiaceae, which includes a number of our medicinal plants. The stem of the plant is simple, short, shrubby, seldom over two feet high, bearing opposite leaves above, and usually naked below. The roots are numerous, branched, and covered with a thick, ringed bark, which is very characteristic of the drug. The leaves are opposite, petioled, entire, smooth, dark-green, and usually crowded near the top of the plant. At the base of each pair of leaf stalks there is a pair of whitish, laciniate, cut stipules, similar to the stipules which we find in several of the rubiaceae of this country. The flowers are small, white, funnel-shape, and collected with a terminal head (whence the generic name of the plant†), which is enclosed in four large ovate bracts. The stamens and pistils are dimorphous, that is, some flowers bear long stamens and short pistils, and conversely, other flowers short stamens and long pistils.

The name cephaelis ipecacuanha, designating the genuine ipecacuanha plant, has by no means the merit of priority. Different authors have successively assigned it to different genera[44], as follows: *Uragoga,* (Linnaeus, 1731); *psychotria,* (Linnaeus, 1759) ; *cephaelis,* (Swartz, 1788); and *callicocca,* (Schreber, 1789.) The following synonyms now exist:

(1) *Uragoga ipecacuanha,* established by Baillon31 quite recently (1879), evidently by right of priority which is claimed for the generic name uragoga.

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(2) *Psychotria ipecacuanha* This is the name now recognized by the Index Kewensis[44], in which Stokes, Bot Mat. Medica (1812), is credited as introducing the name of the species. Recently (in 1881) the name has been authoritatively proposed again by Müller Argoviensis[29].

(3) *Callicocca ipecacuanha* Brotero, 1802[7].

(4) *Cephaelis ipecacuanha* Willdenow, 1804[9].

(5) *Cephaelis ipecacuanha* De Candolle, 1804[9a].

(6) *Cephaelis emetica,* Persoon, 1807[10].

(7) *Cephaelis ipecacuanha,* Tussac, 1813[11].

(8) *Cephaelis ipecacuanha,* A. Richard, 1820[14].

The conferring of the latter names involves certain historical points of interest which we will now consider.

HISTORICAL NOTES,

The beginning of the history of ipecacuanha root and the first study of its virtues is clouded in mystery and fable. It is stated that the South American Indians were acquainted with the medicinal properties of the plant, having gained their experience from observing the habits of animals[15].‡ A vague yet probably the first source of information on the subject of ipecacuanha root is found in a work published in London in 1625, named " The Pilgrimes, " by Samuel Purchas, which in five volumes gives an account of many travels and the natural history of foreign countries[1].

In Vol. IV, page 1311, where Brazilian plants and their uses are considered, the following passage occurs:

"Igpecaya or *pigaya* is profitable for the bloudie fluxe, The stalke is a quarter long and the roots of another or more, it hath only four or five leaves, it smelleth much wheresoever it is, but the smell is strong and terrible." The subsequent description of its medicinal virtues bears further evidence that we have here a plant at least closely related to official ipecacuanha. According to a printed note at the head of that chapter, the author is believed to

†From *Kephale* (Greek), ahead.

‡This fable has a parallel in the quaint description given by Clusius concerning the discovery of the healing virtues of nux vomica bark in cases of snake bite.

be a Jesuit by the name of Manoel Tristaon, who probably wrote the treatise in the year 1601.

The first definite information we have of ipecacuanha dates from the publication of a work by Piso and Marcgraf, called "Historia Naturalis Brasiliae," Amsterdam, 1648, chapter LXIV being entitled "De Ipecacuanha ejusque Facultatibus."[2] Two species are described, a white and a brown species, the latter evidently being the true ipecacuanha plant. An illustration of the plant is added, which Mérat considers quite a creditable reproduction of the true ipecacuanha. The entire chapter was reprinted, with French translation, by Mérat, and inserted in his "Dictionnaire," as a testimony of the extreme exactness of the description given by Piso[17].

The root first came to Europe in 1672 through the agency of Le Gras, who sought to introduce it into medical practice. Keeping a stock supply in the care of an apothecary by the name of Claquenelle in Paris, he associated himself with J. A. Helvetius, a physician of German descent, who had graduated under the medical faculty at Reims, However, the venture was at first a failure, owing to the employment of too large doses.

In 1680 a merchant by the name of Garnier in Paris, well acquainted with the medicinal virtues of the root, sent for a supply, obtaining 150 pounds from Spain. Through this gentleman, directly or indirectly, Helvetius secured a new lot of the drug, which he skilfully managed to exploit by extensively advertising it as "radix antidysenterica," the origin of which, however, he kept a secret. Finally the fame of the remedy came to the notice of Minister Colbert, who ordered that the remedy be given an official trial in the Paris municipal hospital.

In 1688 Helvetius obtained the sole license for the sale of the drug which proved to be an efficient, or at least popular, remedy among the members of an aristocratic patronage, including no less a personage than the dauphin. King Louis the XIV then bought the secret from Helvetius for 1,000 louis d'or, and made the remedy public property. He was induced to do so by the combined influences of his physician, Ant. d'Aquin, and of Franç.

de Lachaise, confessor to the king. Garnier, the merchant, however, brought suit in order to obtain his share of profit in the transaction, but was unsuccessful in his eff orts.

After the use of the dtug had thus been established in France, the remedy was introduced into other countries+ e.g. by Leibnitz (1696), and Valentini (1698), into Germany, and 1694 by Fried. Dekker into Holland.

During the first part of the eighteenth century the drug was in frequent use in the various pharmacies of Germany, as is evidenced from its being mentioned in several old documents of that age. It is, for example, mentioned in the authoritative drug list of the Silesian town of Strehlen in 1724. For earlier references see note 39.

However, during the increasing employment of the drug, in the latter part of the eighteenth century, much confusion arose as to its botanical origin, inasmuch as it became the habit to designate as ipecacuanha any emetic plant, regardless of its botanical source. A long list of such plants is enumerated, for example, in Martius15. In this manner the characteristics of the plant furnishing true ipecacuanha root became almost forgotten, other plants being substituted for it. Ray, for-example, held it to be a species of *paris,* and no less an authority than Linnaeus himself thought *viola ipecacuanha* now known as *ionidum ipecacuanha* (see allied species to be the plant yielding true ipecacuanha root[6].

in 1764, Mutis, a celebrated botanist in Santa Fe de Bogota, sent the younger Linnaeus a Peruvian emetic plant with description, which he thought was the true ipecacuanha root, Linnaeus fil. accepted the statement of Mutis as correct and, moreover, believing the illustration given by Piso of the true ipecacuanha plant to represent the specimen he received from Mutis, in 1871 gave it the name *psychotria emetica* Mutis[17],

To Dr. Gomez, who in 1800 returned from Brazil, is finally due the credit of having corrected this error. He reestablished the nearly forgotten botanical character of true ipecacuanha in his memoir published at Lisbon in

1801[6], wherein he describes and figures the plant, and especially distinguishes it from psychotria emetica, Mutis.

Having donated some specimens of the plant in his possession to his fellow countryman, F. A. Brotero, professor of botany, Coimbra, the latter published an account of it (1802) in the Trans. Linn. Soc., naming it *callicocca ipecacuanha*[7], but without giving credit to the source of his information, which chagrined Gomez considerably[17]. Twelve years later Brotero left a copy of his article with a botanist by the name of Hectot, of Nantes, who communicated it to M. Tussac, and the latter, in publishing it,[11] gave it the name *cephaelis ipecacuanha* also laying stress upon its distinction from *psychotria emetica*, Mutis, perhaps without having had any knowledge of Gomez's paper written twelve years before.

In 1820 A. Richard again called attention to this distinction[14], but, as it seems, also without giving proper credit to Gomez, with the result that later authorities frequently quote the true ipecacuanha root under the name of cephaelis ipecacuanha, A. Richard.

CULTIVATION AND COLLECTION.

The peculiar structure of the flower requires the intervention of insects for the purpose of fertilization; when cultivated in hot-houses it is therefore necessary to transfer mechanically some pollen to the stigma, if the plant is expected to bear fruit[32].

In 1849 Weddell[11] called attention to the fact that a fragment of the plant will strike root if allowed to lie on the ground for any length of time. The corners of the leaf stalks are especially prone to issue such adventitious roots, and the stem will also bud when in contact with the ground. This property of the ipecac plant was rediscovered in 1870 by McNab[24]. Probably this reproductive power accounts for the plant resisting extermination, notwithstanding the rapacious method employed in collecting it.

The root is dug all the year round, but especially in the months of January and February, when it is in bloom. It is perhaps to be regretted that the collection is not post-

poned until May, when the fruit ripens, for then the scattered seeds would insure a new growth. It is stated that, owing to the vicious system of collection, the plant has become scarce in the vicinity of large cities, as Kio de Janeiro. Professor Rusby states that the scarcity in trade of the root during a recent period is also due to the fact that the attention of the natives has shifted towards the rubber industry[36].

The most abundant growth of the drug, on the authority of Weddel[19], is to be found in the interior of the Brazilian province of Matto Grosso, The "poayeros," as the collectors of the plant are called, skillfully cut off the root, taking care to leave part of it in the ground, afterwards they carefully fill the hole again with earth. By taking this precaution, it is stated that after three or four years a new crop may be gathered at the same spot. A skilled poayero collects thirty pounds a day, but the average is not more than six to ten pounds a day[26].

Since 1866 attempts have been made by the British to transfer the cultivation of ipecacuanha to India, but these efforts seem not to have been successful. From one specimen sent to India by Hooker in 1866, an increase of but eleven plants resulted to the date of 1872. Upon McNab's discovery of the propagation by root, 300 specimens obtained in this manner were sent to India and planted in dark woods of the hot and moist valleys of British Sikim in the Himalaya mountains. Although they multiplied in one season to an aggregate of 6,000 specimens, the cultivation seems from some cause to have been impractical. Arthur Meyer concludes from a study of the anatomy of the leaf that the plant, while preferring dark locations, requires at least a certain amount of light, and suggests that cultivation may succeed better in moist woodlands in the direct shade of single trees[32].

CHEMICAL CONSTITUENTS.

While the root of the ipecacuanha plant is the only official part, its active emetic principle has recently been shown to exist also in other parts of the plant, e. g., the stems and the leaves[40], but not in the seeds[39].

In 1817 *Pelletier and Magendie*[12] isolated from true ipecac root an alkaloid which they called emetine but the fact that they obtained 16 per cent of this principle demonstrates their product to have been merely a concentrated extract. Upon further experimentation, however, Pelletier succeeded in obtaining a pure alkaloidal product in the amount of sixty grains to the pound, which corresponds to somewhat less than 1 per cent[17].

Subsequently, the chemistry of ipecacuanha root was elaborated by Reich[21], Lefort[22] and others. H. Kunz[28] in 1887 established for emetine the formula $C_{20}H_{30}N_2O_5$, which is now generally adopted as correct.

Kunz also discovered the presence of cholin in ipecac root and established the dyad nature of the alkaloid emetine in its saturation power with acids, which in 1890 was confirmed by Blunt[37] and W. Simonson[38]; hence the statement in Flückiger[39], that emetine is a monad basis, requires correction. In 1894[43] and 1895[46] Paul and Cownley discovered another alkaloid in ipecac root which they called cephaeline. This they distinguished from emetine principally by its solubility in caustic alkalies, and by its melting point, this being 10.2 deg. C, while for emetine they found 68 deg. C.

Pelletier[12] also discovered that emetine was naturally combined with what he took to be gallic acid, but which was recognized later by Willigk[20] as a new substance and by him called ipecacuanhic acid. Reich" subsequently found it to be a glucosid.

Starch is present in large amounts, and a trace of a nauseating ethereal oil is also present. In some allied species sugar abounds[39].

Literature concerning the assay of ipecacuanha has been abundant and often discordant during the last ten years, but we seem now to have approached a satisfactory solution of the problem, which, however, we cannot consider in detail herein. The proportions of total alkaloids observed by different authors generally ranged from 1 to 3 per cent. Keller thinks that 2 1/2 per cent may not be too excessive a standard of alkaloidal strength".

Dohme[45] has found that the part of the root where it merges into the stem is at least as rich in alkaloid as the rest of the root. The woody core of the root was at one time supposed to be inert, and was therefore rejected in the German pharmacopeias of 1867 and 1872.

ALLIED SPECIES AND ADULTERATIONS.

The species allied to true ipecacuanha, as they sometimes occur in commerce, have various trade names and may he referred on the whole to the following (three) species:

1. *Psychotria emetica,* Mutis. (See history.) This root is much thicker than the genuine, is not annulated, but indentated at long intervals, and marked by longitudinal striæ. The fracture is dark-violet, and the root contains much sugar, on account of which it has been termed ipecacuanha glycyphloea by Vogl[23]. According to Flückiger[39] and Tschirch[35], no emetine is to be found in this root.

2. *Richardsonia scabra,* L., undulated or white, farinaceous ipecacuanha; is not annulated.

3. *Ionidium ipecacuanha* St. Hilaire, also called poaya blanca, white ipecacuanha, belongs to the natural order of violaceæ It is distinguished by containing inulin and salicylic acid, but no emetine[39]. For excellent illustrations of false as well as the genuine species, see among the older works, Esenbeck[16], also Goebel and Kunze[18].

Tschirch and Ludtke[35] have laid down explicit characteristics of true ipecacuanha root and allied species, based on microscopic and chemical examination. Similar examinations have been conducted very recently in order to establish data to exclude Carthagena ipecac *(cephaelis acuminata* Karsten) and other species from the powdered drug[47].

Ipecac root, when whole, presents such distinctive features that it is almost impossible that an adulterant should not at once be recognized; only in powdered form is the door open to falsification. Stephen and Churchill record an instance where for "powdered ipecacuanha

root" alant (elecampane) root was mixed with tartar emetic[18]. More recently Mercer reports the adulteration of powdered ipecacuanha root with almond meal[27]. However, no difficulty whatever need be experienced in obtaining pure powdered ipecac in the United States. Pharmacists willing to pay its value can procure this drug of unquestionable purity.

PHYSIOLOGICAL NOTES AND PHARMACOPEIAL MENTION.

Ipecacuanha root, from its first appearance in our materia medica, has been prized as an antidysentericum and emeticum. In small doses it acts as a tonic and is believed to promote the peristaltic motion of the intestines[6]; in larger doses it is antiperistaltic, causing nausea and vomiting.

In recent years a preparation of ipecacuanha has appeared on the market, which is free from emetine, and is commended in cases of acute dysentery, whereby the symptoms of nausea produced by emetine are claimed to be obviated[42]. We have no authoritative evidence, however, to support the claims that have been made for this de-emetinized ipecac.

The peculiar effect that the dust of ipecacuanha powder exerts upon the respiratory organs of some persons has been noted by early observers. Lewis, in 1761[4], makes the following statement: "Geoffroy observed that in pulverizing considerable quantities, the finer powder that flies off, unless great care be taken to avoid it, is apt to afflict the operator with difficulty of breathing, spitting of blood, and bleeding at the nose, or swelling and inflammation of the eyes and face, and sometimes of the throat, adding that these symptoms disappear in a few days, either spontaneously or by the assistance of venæsection." Kunze[18] (1830) reports a case of poisoning in this manner which was treated by blood-letting and the taking of a decoction of uva ursi and extract of rhatany; in another more recent instance, relief was afforded by a dose of extract of quebracho[34].

Ipecacuanha has been recognized by nearly all pharmacopeias and dispensatories since about 1750. The botan-

ical names affixed to the plant reflect the changes in the nomenclature of the drug as recorded in the preceding historical notes. In American pharmacy the drug was also in earliest use. From 1840 to 1870 its botanical name has been cephaelis ipecacuanha, De Candolle. The Pharmacopeia Portugueza of 1876 gives credit to Dr. Gomez for his part in reestablishing the botanical source of the drug,

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