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CUCURBITACEOUS PLANTS

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THE CONSTITUENTS OF SOME CUCURBITACEOUS PLANTS.*

By Frederick B. Power.

A Contribution from the Wellcome Chemical Research Laboratories, London.

In response to a request to contribute a paper to the Pharmaceutical Conference at Sydney, it has been considered that a somewhat comprehensive survey of the results of some recent investigations pertaining to the constituents of a number of tropical or semi-tropical plants which are used medicinally would not be without some features of interest to those who are engaged in the practice of pharmacy under the Southern Cross.

The particular plants which have been chosen for present consideration are representatives of the natural order of *Cucurbitaceæ*—the so-called Gourd or Cucumber Family. This natural order has been stated to contain nearly 100 genera, comprising about 500 species, which appear to be pretty equally distributed between the eastern and western hemispheres. Although these plants are chiefly natives of hot countries, such as India and South America, a few are found in North America and the north of Europe, while some are also met with at the Cape of Good Hope and in Australia.

The plants belonging to the family of *Cucurbitaceæ* are particularly characterized by the occurrence in them of acrid or purgative principles, and it is for this reason that a considerable number have been employed to a greater or less extent as medicinal agents. On the other hand, many of the species, when cultivated, yield edible

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and nutritious fruits, such, for example, as the pumpkin and squash, the cucumber, the many varieties of melon, etc.

In considering those plants, or the parts or products of them, which are known or reputed to possess certain physiological properties, attention may specially be devoted to such as have recently been made the subjects of complete chemical investigation in the Wellcome Chemical Research Laboratories, London. In this connection it would appear of interest to note that of the drugs under present consideration, elaterium, pumpkin seed, watermelon seed, and bryony root were recorded in the inventory of a pharmacy at Frankfort-on-Main, Germany, dating from about the year 1450. All of the above, together with colocynth pulp (*Colocynthidis pulpa*), were likewise noticed in the *Dispensatory* of Valerius Cordus, first published in 1546, which affords further evidence that these simple drugs were kept by the apothecaries and used medicinally at a very remote period (compare Tschirch, *Handbuch der Pharmakognosie*, 1910, Bd. I, pp. 576, 798).

Elaterium.

The product known as *Elaterium* is at present recognized by but few of the national pharmacopœias. It is, however, still retained in the British Pharmacopœia, where it is defined as "a sediment from the juice of the fruit of *Ecballium Elaterium*, A. Richard."

The history of this drug indicates it to have been employed in ancient times, for it is recorded (*Pharmacographia*, 2d edit., p. 292) that "Dioscorides explicitly describes (about A.D. 77 or 78) the singular process for making elaterium, which was almost exactly like that followed at the present day." It is also noted in the *Pharmacographia Indica*, Vol. II., p. 96, that "the Mahometan writers attach considerable importance to elaterium as a purgative of the diseased humours which they suppose to be the cause of a great number of diseases."

Although the administration of a drug possessing such drastic purgative properties as elaterium is seldom indicated, its comparatively rare employment in modern medicine is probably also attributable in part to its variable character and consequent uncertainty of action. This difficulty was supposed to have been overcome by the use of the chief crystalline constituent of the drug, the so-called elaterin, which was regarded as its active principle, and has therefore

been officially recognized by both the British and United States Pharmacopœias.

In the course of a recent chemical examination of elaterium [1] some quite unexpected and interesting results were obtained. The material employed for this purpose consisted of the best English elaterium, which conformed in its general characters to the requirements of the British Pharmacopœia. After having isolated the crystalline product known as elaterin, it was subjected to a prolonged process of fractional crystallization, when it was observed not to be homogeneous, but to consist, to the extent of 60–80 per cent., of a substance which is completely devoid of purgative action. This substance which, in its optical behavior, is laevorotatory, is accompanied in the crude elaterin by a substance of apparently the same percentage composition, but which possesses strongly purgative properties and is dextrorotatory. An examination of the crystalline elaterin of commerce, both of English and German manufacture, showed that this likewise was not of uniform composition, but that it varied considerably in its physical characters and consequently in its physiological action, for the latter, as already indicated, depends upon the proportion of dextrorotatory substance present.

With consideration of the results above described, it was subsequently deemed desirable to make a complete examination of the fresh fruits of *Ecballium Elaterium*,[2] especially as a previous investigator [3] had affirmed that elaterin does not exist in the fruit as such but in the form of a glucoside. In the course of this research it was found, however, that the elaterin is present in a free state, and, furthermore, that various other products which had heretofore been regarded as definite constituents of the fruit, such as the so-called prophetin, ecbalin or elateric acid, hydro-elaterin, and elateride, which were mostly amorphous, must have consisted of complex mixtures (compare Gmelin's *Handbook of Chemistry*, vol. xvii (1866), pp. 364–367).

Having ascertained that elaterin as found in commerce, and as recognized by the British and United States Pharmacopœias, is a mixture of two substances, possessing widely different properties,

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[1] Power and Moore, *Pharm. Journ.*, 1909, **83**, pp. 501–504.

[2] Power and Moore, *Journ. Chem. Soc.*, 1909, **95**, pp. 1985–1993. Compare also Moore, *Ibid.*, 1910, **97**, pp. 1797–1805.

[3] Berg, *Bull. Soc. Chim.*, 1897 [iii], **17**, p. 85.

it was evidently important that these substances should receive distinctive names. It was therefore proposed to designate the predominating constituent of crude elaterin, which is laevorotatory, as α-elaterin, and the physiologically active, dextrorotatory constituent as β-elaterin.

On account of the very small proportion of β-elaterin contained in crude elaterin, it has not, as yet, been found practicable to obtain it in a pure state, and, in an undiluted form, it would doubtless be too potent a remedy for medicinal use. On the other hand, it would appear to be possible to standardize elaterin in such a manner as to secure uniformity with respect to the proportion of its physiologically active constituent, and consequent certainty of action when administered in definite doses. This could doubtless be most easily and satisfactorily accomplished by the adoption of such a standard for its specific optical rotation as would insure the presence of a sufficient proportion of the physiologically active β-elaterin.

Colocynth.

Colocynth, or "Bitter Apple," as it occurs in commerce, consists of the dried, peeled fruit, or the pulp of the fruit, of *Citrullus Colocynthis,* Schrader. This fruit has been known and used medicinally from the earliest times, being mentioned in the writings of Theophrast, Dioscorides, and Pliny (compare *Pharmacographia Indica,* Vol. II., p. 61), and its value would appear to be attested by the fact that it is still recognized by all the national pharmacopœias. Under these circumstances it may be considered somewhat remarkable that, until quite recently, so little of a definite nature has been known respecting the constituents of colocynth. It was stated, for example, many years ago by Walz [4] that this fruit contains a bitter glucoside, designated "colocynthin," which, on boiling with dilute acids, became resolved in another amorphous compound, termed "colocynthein," and dextrose. A crystalline, tasteless substance, named "colocynthitin," has likewise been stated to occur in the fruit, but it was not further characterized.

Although in the intervening years colocynth has attracted the attention of several investigators, their results were more or less conflicting, and could not be considered as having satisfactorily elucidated the nature of its active constituents. Thus Henke [5] could

[4] *N. Jahrb. Pharm.,* 1858, **9**, pp. 16, 225; 1861, **16**, p. 10.

[5] *Arch. d. Pharm.,* 1883, **221**, p. 200.

obtain a product corresponding to the so-called colocynthin only in the form of an amorphous powder, and was unable to confirm the statement of Walz respecting its glucosidic character. Johannson,[6] on the other hand, has stated that "colocynthin," when heated with dilute sulphuric acid, yields colocynthein, elaterin, and bryonin, and some color reactions were recorded which were supposed to differentiate these products. More recently, Naylor and Chappel,[7] in an examination of the fruit of *Cucumis trigonus,* Roxb.[8] (*C. Pseudocolocynthis,* Royle), have taken consideration of the characters of the so-called colocynthin. They were led to conclude that colocynthin is capable of crystallizing, and that it is glucosidic, yielding on hydrolysis, amongst other products, colocynthein, elaterin, and dextrose. Their conclusions were, however, chiefly based on certain color reactions, which are by no means characteristic of the substances they were assumed to identify.

The various discrepancies in the results obtained by the above-mentioned investigators may readily be explained, for it is quite obvious that the products described by them did not represent pure compounds, but consisted of more or less indefinite mixtures. With consideration, therefore, of the unsatisfactory state of knowledge respecting the constituents of so important a drug, it was deemed desirable to subject colocynth to a complete examination. The results of the investigation conducted in these laboratories,[9] for which purpose a good quality of Turkish colocynth was employed, may in this connection briefly be noted.

The pulp of the fruit, which, when deprived of the seeds, amounted to 24.5 per cent. of the whole, was completely extracted with hot alcohol, and the resulting extract distilled in a current of steam, when a very small amount of an essential oil was obtained. From the portion of the extract which was soluble in water, the following substances were isolated: (1) a new, crystalline, dihydric alcohol, $C_{22}H_{36}O_2(OH)_2$ (m.p. 285–290°), which has been designated citrullol; (2) an amorphous, alkaloidal principle, which pos-

[6] *Zeitschr. Analyt. Chem.,* 1885, **24**, p. 154.

[7] *Pharm. Journ.,* 1907, **79**, p. 117.

[8] *Cucumis trigonus,* Roxb., which is indigenous to India (compare *Pharmacographia Indica,* Vol. II, p. 65) has been noted by Mr. J. H. Maiden, F.L.S., Director of the Botanic Gardens, Sydney, as being also a native of New South Wales, Queensland, and Northern and Western Australia (*Pharm. Journ.,* 1899, **63**, p. 16).

[9] Power and Moore, *Journ. Chem. Soc.,* 1910, **97**, p. 99.

sesses an extremely bitter taste, and represents one of the purgative principles of the fruit. The aqueous liquid contained, furthermore, a quantity of inorganic salts, a little sugar, and a very small amount of an amorphous, glucosidic substance.

The substance designated citrullol is of special interest, inasmuch as it is a member of a group of dihydric alcohols which form an homologous series, represented by the general formula $C_nH_{2n-6}O_4$. The other known members of this group, which were likewise isolated in these laboratories, are: ipuranol, $C_{23}H_{38}O_2(OH)_2$, which was first obtained from the stems of *Ipomœa purpurea,* Roth,[10] but has since been found to be a constituent of numerous other plants, and trifolianol, $C_{21}H_{34}O_2(OH)_2$, which was first isolated from red clover flowers,[11] subsequently from the flowers of the carnation clover,[12] and quite recently from Calabar beans.[13]

The portion of the above-mentioned alcoholic extract which was insoluble in water consisted chiefly of resinous material, but from it a quantity of α-elaterin,[14] $C_{28}H_{38}O_7$ (m.p. 232°; $[\alpha]_D$–68.9°) was isolated. On subsequently extracting the resin with various solvents, it yielded, furthermore, a small amount of hentriacontane, $C_{31}H_{64}$; a phytosterol, $C_{27}H_{46}O$ (m.p. 160–162°); a mixture of fatty acids, and an additional amount of α-elaterin, together with a little of the above-described alkaloidal principle. The ether and chloroform extracts of the resin possessed marked purgative properties.

The seeds of the colocynth, which amounted to 75.5 per cent. of the entire peeled fruit, were extracted with light petroleum, when they yielded 12.7 per cent. of their weight of a fatty oil. The latter was found to agree very closely in character with the oils from some other cucurbitaceous seeds, such as those of the pumpkin and watermelon, which will subsequently be described. The colocynth seeds also contain a small amount of an enzyme which hydrolyses β-glucosides, and traces of an alkaloidal principle, which is probably identical with that contained in the pulp of the fruit.

The results of the recent research on the constituents of colocynth have, on the one hand, afforded conclusive evidence that the so-called "colocynthin" and "colocynthitin" of previous investigators were

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[10] Power and Rogerson, this Journal, 1908, **80**, p. 264.
[11] Power and Salway, *Journ. Chem. Soc.*, 1910, **97**, p. 249.
[12] Rogerson, *Ibid.*, 1910, **97**, p. 1014.
[13] Salway, *Ibid.*, 1911, **99**, p. 2154.
[14] Power and Moore, *Ibid.*, 1909, **95**, p. 1989.

not homogeneous, but consisted of mixtures of a very indefinite character, and that the amount of glucosidic substance contained in the fruit is extremely small. On the other hand, it has been shown that the purgative action of colocynth is due to at least two compounds, one of which is alkaloidal, although a very weak base and apparently incapable of crystallizing or forming crystalline salts, whilst the other source of activity is represented by some principle or principles contained in both the ether and chloroform extracts of the resin. The attempts to obtain the last-mentioned active principles in a more definite state were unsuccessful.

Pumpkin Seed.

The seeds of the common pumpkin (*Cucurbita Pepo,* Linné) are chiefly of interest on account of their reputed value as a tænifuge, and it is evidently for this reason that they have long been officially recognized by the United States Pharmacopœia. Although the seeds are usually administered in the form of the bruised kernels, in doses, for an adult, of 100 to 200 grammes, their action has been variously attributed to both the fatty oil and the resin which they contain. In order to ascertain whether any definite active principle is present in the seeds, they were subjected to a complete chemical examination,[15] and the products, so far as practicable, submitted to physiological or clinical tests.

The kernels of the seed yielded, on expression, an amount of fatty oil equivalent to 19.3 per cent. of the weight of the entire seed. When, however, the entire seed were ground, and extracted with light petroleum, the yield of oil amounted to 34.3 per cent. of their weight. This fatty oil, which, when viewed in layers of moderate thickness, had a cherry-red color with a marked fluorescence, was found to consist of the glycerides of linolic, oleic, palmitic, and stearic acids, together with a very small amount of a phytosterol, $C_{27}H_{46}O$. The resinous material, as extracted from the press-cake, amounted to only about 0.5 per cent. of the weight of the entire seed. Neither the fatty oil, in amounts of 15 to 60 c.c (about half a fluidounce to two fluidounces), nor the resin, in amounts of 1 gramme (representing about 200 grammes of the seed), were found to effect the complete removal of tape-worm, when administered to different individuals under the usual conditions of fasting and followed by a dose of castor oil.

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[15] Power and Salway, *Journ. Amer. Chem. Soc.*, 1910, **32**, pp. 346–360.

In view of the above-mentioned results, and the fact that pumpkin seed contain no principle which exhibits marked physiological activity,[16] it could only be concluded that any value which they may actually possess as a tænifuge, when administered in substance, must be attributable to a mechanical action. In any case, the remedial value of pumpkin seed cannot be considered such as to justify their recognition by a national pharmacopœia.

Watermelon Seed.

The seeds of the common pumpkin having been subjected to a complete chemical examination, as already noted, it was deemed desirable also to examine those of the watermelon (*Cucurbita Citrullus,* Linné),[17] since the latter have been employed to some extent medicinally on account of the diuretic properties attributed to them, although chiefly as a domestic remedy.

Nothing, hitherto, appears to have been known respecting the constituents of watermelon seeds beyond the fact that they contain a fatty oil, of which the physical and chemical constants have been recorded, as also those of the mixed fatty acids obtained therefrom (compare Lewkowitsch, *Chemical Technology and Analysis of Oils, Fats, and Waxes,* 3d edit., Vol. II., p. 511).

The kernels of the seed yielded, on expression, an amount of fatty oil equivalent to 7.4 per cent. of the weight of the entire seed. When, however, the entire seed were ground, and extracted with light petroleum, they yielded 19 per cent. of oil. The expressed oil, unlike that from pumpkin seed, possessed a yellow color, and was completely devoid of fluorescence. On the other hand, the physical and chemical constants of watermelon seed oil approximate very closely to those of pumpkin seed oil. As might, therefore, be expected, the two oils are very similar in composition, consisting, as noted in connection with pumpkin seed oil, of the glycerides of linolic, oleic, palmitic, and stearic acids.

From the press-cake an amount of resinous material was obtained corresponding to about 0.3 per cent. of the weight of the entire seed. This resin was found to exhibit no physiological activity

[16] The expressed oil of pumpkin seed is largely used for culinary purposes in Austria, Hungary, and Russia (compare *Journ. Soc. Chem. Ind.*, 1898, **17**, p. 1054, and Lewkowitsch, *loc. cit.*, p. 509), whilst the press-cake has been recommended as a food for cattle (Hager's *Handbuch*, 1900, Bd. I, p. 978).

[17] Power and Salway, *Journ. Amer. Chem. Soc.*, 1910, **32**, pp. 360–374.

when administered to a dog in doses of 1 gramme. A chemical examination of the resin led, however, to some results of interest, inasmuch as it yielded, besides a little phytosterol, a new crystalline alcohol, $C_{24}H_{40}O_4$ (m.p. 260°), which has been designated cucurbitol. This compound will be further noticed in connection with the constituents of bryony root.

Bryony Root.

Bryony root has been used medicinally from a very remote period on account of its purgative properties (compare Tschirch, *Handbuch der Pharmakognosie,* 1910, Bd. I, pp. 576, 798). It was formerly recognized by several of the national pharmacopœias, including that of the United States, but was omitted from the latter in the eighth revision (1900), and is now rarely employed. The plants yielding this root are *Bryonia alba,* Linné, and *Bryonia dioica,* Linné, both of which are indigenous to the greater part of Europe, but the last-named species is the only one commonly found in England, and, therefore, is frequently designated English bryony.

Bryony root has previously been the subject of several investigations, chiefly for the purpose of determining the nature of its active constituent (compare Husemann, *Die Pflanzenstoffe,* 2d edit., p. 1349, and van Rijn, *Die Glykoside,* p. 463), but until quite recently [18] no complete examination had been made of it. According to the earlier investigators, the root contains an amorphous, bitter glucoside, designated as bryonin. As obtained by Masson,[19] this product was stated to possess the formula $C_{34}H_{48}O_9$, and, on heating with dilute sulphuric acid, to become resolved into dextrose and an amorphous, yellow resin, termed bryogenin, $C_{20}H_{38}O_4$. Another product obtained by Masson, which was of a purely resinous nature, was named bryoresin, and to this the formula $C_{37}H_{68}O_{18}$ was assigned. A consideration of the method of preparation and characters of the above-mentioned products, as described in the literature, renders it evident, however, that they could not have represented pure or homogeneous substances.

The material employed for the investigation conducted in these laboratories consisted of the roots of *Bryonia dioica,* Linné, which had been specially collected in districts near London, under the

[18] Power and Moore, *Journ. Chem. Soc.,* 1911, **99**, pp. 937–946.

[19] *Journ. Pharm. Chim.,* 1893 [v], **27**, 300.

supervision of a competent botanist. The details of this investigation have already been recorded (*loc. cit.*), and therefore only a brief summary of the results obtained need here be given.

The amount of fresh root collected was 107.5 kilogrammes, and this, after being sliced and dried, weighed 25.5 kilogrammes, the loss on drying having thus been equivalent to 76.3 per cent. of the original weight.

The root was found to contain an enzyme, which was obtained in the form of a light brown powder. This product slowly hydrolysed the glucosidic constituent of the root, and also effected the hydrolysis of amygdalin and salicin.

For a complete examination of the constituents of the root, 23.9 kilogrammes of the dried and ground material were extracted with hot alcohol. The resulting extract, when distilled in a current of steam, yielded a small amount of a pale yellow essential oil. From the portion of the extract which was soluble in water there were isolated: (1) a small amount of a colorless, crystalline, neutral substance (m.p. 220–222°), which appears to possess the formula $C_{20}H_{30}O_5$; (2) an amorphous, glucosidic product, having a brown color and a bitter taste; (3) an amorphous, alkaloidal principle, possessing a brownish-yellow color and an intensely bitter taste. The aqueous liquid contained, furthermore, a quantity of sugar, which yielded *d*-phenylglucosazone (m.p. 208–210°).

The portion of extract which was insoluble in water consisted of a dark brown, viscid resin, amounting to about 2 per cent. of the weight of dried root employed. From this resin the following compounds were isolated: (1) a phytosterol, $C_{27}H_{46}O$ (m.p. 137°), which was optically inactive; (2) a new dihydric alcohol, bryonol, $C_{22}H_{34}O_2(OH)_2$ melting at 210–212°; (3) a mixture of fatty acids, consisting of oleic, linolic, palmitic, and stearic acids.

The compound designated as bryonol is of particular interest, inasmuch as it belongs to a group of dihydric alcohols which form an homologous series, represented by the general formula $C_nH_{2n-8}O_4$. The other known members of this group, all of which were isolated in these laboratories, are as follows: ipurganol, $C_{21}H_{32}O_2(OH)_2$, from jalap resin;[20] grindelol, $C_{23}H_{36}O_2(OH)_2$, from the resin of *Grindelia camporum*, Greene;[21] and cucurbitol, $C_{24}H_{38}O_2$

[20] *Journ. Amer. Chem. Soc.*, 1910, **32**, p. 89.

[21] *Proc. Amer. Pharm. Assoc.*, 1907, **55**, p. 342.

$(OH)_2$, which, as already noted, was obtained from the resin of watermelon seed.[22]

In the course of the recent investigation of bryony root it was ascertained that both the above-mentioned glucosidic product and the alkaloidal principle, as well as the aqueous liquid from which they had been removed, were abundantly precipitated by tannic acid. It follows, therefore, that the preparations obtained by previous investigators by means of this reagent, which were regarded as a glucoside, and designated "bryonin," must have consisted of complex mixtures, the constituents of which, moreover, were not entirely glucosidic. The various chemical formulæ that have been assigned to these amorphous compounds are accordingly quite fallacious.

Physiological tests conducted with the above-mentioned products have rendered it evident that the activity of bryony root cannot be attributed to a single definite principle. Its purgative property appears to reside chiefly in the resinous and alkaloidal constituents; the crystalline principle, $C_{20}H_{30}O_5$, and the glucosidic product having been found to be quite inactive when administered to dogs in doses of 0.1 gramme. The assumption of previous investigators that the active principle of bryony root is a glucoside, has thus been shown to be incorrect.

In conclusion it may be noted that there are a number of other cucurbitaceous plants besides those here considered which, on careful chemical examination, would doubtless be found to possess constituents of interest. On the other hand, it is apparent that the plants of this family represent but a very small part of the field of organic *materia medica* which still remains to be explored.

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[22] *Journ. Amer. Chem. Soc.*, 1910, **32**, p. 367.