Strophanthus Hispidus, D. C.

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REPRINTED FROM

THE WESTERN DRUGGIST,

CHICAGO, SEPTEMBER, 1897.

STROPHANTHUS HISPIDUS, D.C.*[1]

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BOTANICAL DESCRIPTION AND HISTORICAL NOTES.

The genus strophanthus, which produces this drug, is chiefly African, belonging to the apocynaceae and the tribe echitideae of this order, distinguished from the other tribes of the order chiefly from having the anthers united after the manner of the asclepiadaceae. Index Kewensis mentions seventeen species, Bentham and Hooker eighteen species, Pax[29] twenty-five species, and the genus is being rapidly augmented as the flora of Africa becomes better known. Plants of the genus have usually woody stems, emitting a milky juice when wounded, and are generally twining vines. The seed of commerce is probably collected from various species indiscriminately, which have been classified and differentiated by Pax[29], Planchon[31], Hartwich[28], Holmes[24], Blondel[19] and others. Space will permit us to mention only the two species which are acknowledged to be the principal source of the drug.

Strophanthus hispidus, D. C., was one of four species described by De Candolle as early as 1802, and is the species to which the drug was first ascribed. Its habitat is Senegambia and Guinea and other parts of western Africa. The

* The thanks of the writer are extended to Mr. C. G. Lloyd for botanical notes, and to Dr. Sigmond Waldbott, librarian of the Lloyd Library, for invaluable assistance.

stem is a twining, milky shrub, with opposite hirsute leaves. (Hence the name *hispidus*, Latin for bristly, hairy).

The flowers are borne in terminal, many-flowered dense cymes. The calyx consists of five hairy green sepals about the length of the corolla tube. The corolla is white, with a short funnel-shaped tube yellowish within and furnished with ten small nectariferous glands. The segments of the corolla are very long, tapering, slender, hairy without, having a length sometimes of eight inches, and are the conspicuous part of the flower, giving the plant its generic name (from *strophos*, Greek for a twisted chord). The stamens are five, with sagittate anthers and slender filaments. The pistil consists of two distinct carpels, each of which, if fertilized, ripens into a long pod filled with numerous seed. The seed, which bears a slender style terminating in a plumose pappus consisting of long fine hairs*[2] , are the part used in medicine.

Strophanthus kombe, Oliver, is a similar plant, native, however, of eastern Africa. It was at first referred to *S. hispidus*, and is still considered by some writers to be but the oriental form of this species. It has the same hirsute leaves, but they are more coriaceous. The sepals are shorter than the corolla tube, and cymes are fewer flowered than *S. hispidus*.

*[2]Hartwich[21] calls special attention to the fact that the hairs of strophanthus seed are very sensitive to moisture, spread horizontally in dry air, and becoming erect in moist atmosphere. He suggests that the pappus would thus make an hygrometer sufficiently sensitive for practical purposes.

As stated before, the genus strophanthus was established by De Candolle as far back as the year 1802. It was not until the early sixties, however, that the drug came to the general notice of Europeans as being one of the arrow poisons used among the African native tribes. There were two kinds of arrow poisons derived from this source. A poison was prepared on the west coast of Africa (Senegambia, Guinea and Gaboon) called *inee* or *onaye*, which is derived from *Strophanthushispidus*, D. C. This is on the authority of Hendelot, who observed the plant yielding this poison in Senegambia at the river Nunez[6]. A specimen of this arrow poison was sent to Europe and investigated by Pelikan in 1865[4].

On the east coast of Africa the kombe or gombe poison was in use in the Manganjah tribe, located near Lake Nyassa on the banks of the river Shire, a tributary of the Zambesi river. Consul Kirk in Zanzibar, in 1861, established that this poison originated from a strophanthus species, and forwarded specimens to Prof. Sharpey in England for the purpose of investigation[6]. Subsequently, in 1865, Livingstone's famous reports brought the kombe poison to a more general notice among the Europeans[3].

This species of strophanthus was at first considered identical with *S. hispidus*, D. C., but the plant was shown by Oliver in 1885 to be distinct from the latter, and justified the establishing of a new species, *Strophanthus* *kombe*[5].

The physiological features of the drug as a powerful cardiac were recognized by the first investigators (Sharpey, 1862; Pelikan, 1865; Fraser, 1871). Livingstone reports the observation of Consul Kirk that the poison remarkably reduced the pulse, but the drug was not authoritatively recognized by the medical profession until about the year 1885.

As the demand for strophanthus began to increase, substitution by allied though often inert species became common. Those engaged in gathering this drug supposed that all species of strophanthus were alike energetic, whereas the facts are that many of them are inert and that only a few species contain the active principle strophanthin. Substitution until recently was facilitated by the difficulty in accurately distinguishing between the seeds of different species. Thus Christy informs us that from three seeds sown, and supposed to be of the same species (*S. kombe*), two plants were sprouted, one having smooth, the other hairy leaves (11). Authorities therefore now urgently recommend that the seeds should always be purchased in the follicles, and tests for strophanthin applied[28]. (See chemistry of the drug.) This precaution would also exclude the fraudulent substitution of the entirely different plant, *Kickxia africana*, Benth., which was practiced even very recently[14,35]. Seeds of the true species from which the active principle has been partially extracted have also been thrown on the market, according to Blondel's observations[19].

CHEMISTRY OF STROPHANTHUS.

The chemistry of this drug has not been so closely elaborated as the importance of the remedy in medical practice would warrant. This is obviously due to the difficulty heretofore experienced, as already related, in obtaining strophanthus from a reliably uniform source, which fact naturally makes any exact chemical investigation illusory from the start.

The active principle was first isolated from strophanthus kombe by Fraser in 1872, who named it *strophanthin*, but he took it to be an alkaloid, a statement which he amply corrected afterward[6].

In 1877 the name strophanthin was applied by Hardy and Gallois to a crystalline substance obtained from the seed of *S. hispidus*, D. C., by extracting the latter with alcohol acidulated with hydrochloric acid[8]. The resulting substance was found to contain no nitrogen, neither did it prove to be a glucosid. The authors, besides, claim to have obtained from the hairy tufts (awns) of the seeds an alkaloid, which they called *ineine*. Later researches by Elborne,[12] Gerrard[13] and Fraser[10], however, failed to discover an alkaloid in the awns, Fraser having subjected to examination one pound of tufts without success.

Fraser, in the years 1885-90, found his original strophanthin to be a glucosid, capable of splitting under the action of acids into glucose and *strophanthidin*, a bitter nonnitrogenous body, insoluble in water, soluble in alcohol. The failure of Hardy and Gallois to obtain the glucosid Fraser ascribed to their employing acidulated alcohol for extraction, whereby they probably obtained strophanthidin direct. Fraser also succeeded in isolating, a peculiar acid, which he called *kombic acid*. Catillon, in 1880, affirmed the existence of two glucosids in strophanthus seeds (*S. kombe*), one being strophanthin, the other nitrogen-bearing and splitting with acids into sugar and an alkaloid. He stated that when strophanthus seeds, exhausted with alcohol and ether (being thus deprived of their strophanthin and fat), are treated with boiling acidulated water, they give up to this solvent a considerable quantity of a very distinct glucosid associated with a perfectly characterized alkaloid[20].

Strophanthin is freely soluble in water and alcohol, insoluble in pure ether or chloroform.[13] According to Merck, its melting point is about 185 deg. C.[17]; strophanthin obtained by Arnaud from *S. hispidus* melts at 172.5 deg. C.[18]

Arnaud's strophanthin has the formula $C_{31}H_{48}O_{12}$ which, as will be seen, bears a close relation to *ouabain*, the active principle of another African arrow poison.

The most striking test of the seeds for strophanthin is carried out as follows, by using a low magnifying microscope:

Make a cross section of the seed, and touch with concentrated sulfuric acid. The end sperm is at once colored blue, then a beautiful green results. The cotyledons likewise turn green, but with less intensity. Gradually the color changes to red, and after a short while fades out.

In Helbing's test the cross section of the seed is moistened with a trace of solution of ferric chlorid then with a drop of concentrated sulfuric acid. A red-brown precipitate occurs, which is green after a lapse of one or two hours[15].

Employing the first test, Hartwich[28] has demonstrated that only a few species among those found in commercial strophanthus contain strophanthin, and he discovered the apparent rule that calcium oxalate and strophanthin seem to exclude each other in the seeds. However, a positive exception occurs in the strophanthus seeds from the island of Los, where both bodies are present, and a negative exception is seen in *S. Fischeri*, where both are absent.

The yield of strophanthin from *S. kombi* is about 0.95 per cent, from *S. hispidus*, 0.65 per cent and from *S. glaber* 5 per cent[72]. The latter species, in addition to its high yield in alkaloid, is very poisonous, and was for this reason expressly excluded from one of the European pharmacopeias[27]. It contains *ouabain* as its active principle.

Strophanthus seed contains a large percentage (from 20 to 32 per cent) of fatty substance. The bitter principle is claimed to reside in the fatty oil, and is said to be completely abstracted by petroleum ether, without affecting strophanthin[32].

NOTES ON ARROW POISONS.

In our paper on calabar we referred briefly to the ordeal poison of Africa. In the present paper we also find a necessary diversion, and will give some attention to arrow poisons.

Arrow poisons are in common usage in warfare, as well as in hunting among various aboriginal tribes. While we find in Africa strophanthus yielding the inee and kombe poisons, and acokanthera yielding ouabaio, poison, aconitum ferox is used in Nepal (Himalaya mountains), antiaris toxicaria, or upas tree, in Java, and cumane in South America. Neither are these poisons confined to vegetable origin. Livingstone cites a poisonous caterpillar that is employed in south Africa, and suggests that the animal probably derives the poison from the plant it feeds on. Lewin mentions in this connection *Diamphidia simplex*, Peringuey, an underground chrysalis30.

As a rule, the African arrow poisons do not consist of single substances, but compounds made up of various roots and leaves which are difficult to identify botanically and chemically.

The natives are very reluctant about disclosing the origin or the manner of preparation of their arrow poisons, only the initiated few among them being acquainted with the art. For the purpose of concocting the arrow poison one man betakes himself into the forest's depths, far away from human habitations. He frees the seeds of strophanthus from their hairy appendages (which, by the way, are an article of commerce, serving in the making of vegetable silk[29]), and pounds them to a pulp in a mortar; he then adds water and the expressed juice of the rind of a tiliaceae species yielding a gum that serves to make the poison stick to the arrow. The poison thus prepared is then smeared upon the shaft to a length of about six inches. It is said that game wounded by an arrow poisoned by strophanthus dies at once, seldom being able to move a hundred yards. The flesh of animals killed in this way is eaten without any evil effect, the precaution alone being taken either to cut out and exclude the flesh surrounding the wound, or to squeeze into it the sap from a branch of the baobab tree (adansonia digitata). Elephants and hippopotami cannot be destroyed in this manner, as they do not respond to the amount of poison an arrow can carry[3,33].

The pigmies use five ingredients in compounding their arrow poisons, and three to make their antidote to this poison. Surgeon Parke was so fortunate as to secure detailed information with regard to the source of these ingredients. An exceedingly interesting account thereof is given in reference 22. The poison, however, is not connected with strophanthus; it has as its basis some species of strychnos and the bark of *Erythrophlaeum guineense*, Don, the tree that yields the “red-water ordeal” of the African native tribes.

The *ouabaio* poison of the Somali deserves special mention because its active principle, ouabain, is believed to stand in close connection with strophanthin. The ouabaio poison, liberally referred to by Burton, according to our present state of knowledge, is derived from either of the following species of apocynaceae: *Acokanthera Schimperi* (D. C.), Benth. and H., A. Deflersii, Schweinf., or *A. ouabaio.* Cathelineau[23,33].

The making of this poison among the Somali is attended with the mystery that is thrown about that of the strophanthus arrow poison already related. The wood is chipped and then boiled with water in an earthenware pot for hours or even days until a pitch-like extract is obtained, which is smeared upon the iron arrow point. To prevent the poison from rubbing off, the barb is surrounded with parchment-like prepared goat-skins or plant fibers, which are removed immediately before use. To test this poison the Somali scratches his arm until the blood flows; he then applies the poison to the lower end of the bloody pool and watches the blood coagulating from below upward, estimating therefrom its virulency[33].

In 1882 some roots, stems and leaves of the plant yielding ouabaio poison were sent to France by Revoil, and investigated by Arnaud. In 1888 Arnaud obtained from similar specimens an active principle, an amorphous glucosid, which he called ouabain. For this substance he arrived at the formula $C_{30}H_{46}O_{12}$. This differs by the group CH. from the formula for strophanthin, $C_{31}H_{48}O_{12}$, which he obtained from *S. hispidus*, D. C. He therefore concluded that strophanthin represents the higher homologue of ouabain. Besides, both substances have identical physiological action which differs in degree only. Arnaud finally discovered that ouabain is identical with the active principle obtainable from *Strophanthus glaber*, to the amount of 4.7 per cent[18].

PHARMACOPEIAL RECORD OF STROPHANTHUS.

Consequent upon the recent introduction of strophanthus into medicine, only the latest issues of the different pharmacopeias carry the drug. The tincture of strophanthus is the only preparation as yet officially recognized, but the tinctures of the various pharmacopeias are not uniform in strength nor in the mode of their preparation.

The German pharmacopeia of 1890, for example, directs a strength of 1:10, while the British pharmacopeia (additions of 1890), the Austrian pharmacopeia, 1889, and the United States pliarmacopeia, 1890, direct a strength of 1:20. According to the British and Austrian pharmacopeias the fatty oil is to be previously removed by ether. The German pharmacopeia directs the fatty oil to be removed by cold pressure, while the United States pharmacopeia gives no special direction for the removal of the oil. According to the latter authority, 50 grams of the seeds in No. 30 powder are extracted with a mixture of 650 Cc of alcohol and 350 Cc of water.

In 1889 Mr. Beringer pointed out that the tincture of strophanthus should not be prescribed in aqueous solution, because, as Larmuth has observed, the bitter principle undergoes some change in aqueous solution by standing for a few days, thereby becoming far more toxic than when recently prepared[25].

Of late some physiological experiments have been carried on with favorable results by H. C. Wood and W. S. Carter in order to test the advisability of introducing an alcoholic extract of definite strength, or the active principle strophanthin, into the next edition of the United States pharmacopeia[34].

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