REVIEW ARTICLE

SOME RECENT ADVANCES IN THE KNOWLEDGE OF THE CONSTITUENTS OF VEGETABLE DRUGS

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FUTURE historians may record that the discovery of the chemotherapeutic effects of the sulphonamides, far from sounding the death-knell of interest in medicinal plants, acted rather as a stimulus in this field of investigation. The impression had been growing, since the recent discovery of vitamins and hormones, that future medical treatment would soon become independent of the "bottle of medicine," an expression which can be taken to include such things as injections and tablets as well as the traditional eight ounce mixture. The spectacular results of sulphonamide therapy, however, served to focus attention again on the use of materia medica as a means of treating disease. The branch of materia medica which received the greatest stimulus was naturally concerned with synthetic organical chemicals but slowly the stimulating effect extended to natural products of vegetable and animal origin, especially since the discovery of the antibiotics. I think it is safe to say that there is now a greater scientific interest in the vegetable materia medica than for the last decade or two. This interest falls into three categories; re-investigations of the constituents of well-known crude drugs, investigations of crude drugs comparatively new to Western medicine and an enquiry as to the role of the active principles in the plant or animal from which they are derived. I propose dealing with each section separately, treating one or two examples of each in detail and referring briefly to other examples.

WELL-KNOWN MEDICINAL PLANTS

Podophyllum (the rhizomes and roots of *Podophyllum peltatum* L.)

Podophyllum and its resin have long been known to cause irritation of the mucous membranes and even of the skin of workers handling them[1] and it may have been knowledge of this fact which initiated the attempts to destroy soft warts by means of the resin. The first published account of this treatment was given by Kaplan in 1942[2] though the urologists of New Orleans had been using the treatment for several years previously[3]. Kaplan[2] and later Culp, Magid and Kaplin (1944)[4] and MacGregor (1945)[5] obtained strikingly successful results when soft warts or condylomata acuminata (commonly known as "venereal warts") were treated by topical application of a 25 per cent. suspension of podophyllum resin in mineral oil. The warts were destroyed rapidly and painlessly, whereas the surrounding tissues were scarcely affected. This treatment is now well established and justifies the suggested inclusion of podophyllum resin in the International Pharmacopœia. Naturally, work on the constituents and the biology of the resin was stimulated and has resulted in the isolation of several crystalline compounds (see below) and an evaluation of their activity. The crude resin or its active constituents when applied

to normal skin or condylomata produces marked effects on the nucleus and cytoplasm resulting in characteristic "podophyllum cells" being formed[6]; these effects resemble those of colchicine, and colchicine in oil can be used for destroying the warts; colchicine however is more toxic than podophyllin[7]. As already stated, however, these degenerative effects are more marked in the wart tissue than in normal cells and several workers have investigated whether podophyllin has a like selective effect on cancer cells. Ormshee, Cornman and Berger[8] and Belkin[9] found that the resin selectively destroyed cancer cells both in tissue cultures and in experimental tumours in mice. Brief reports on the screening of about 1200 organic compounds show that podophyllin compares favourably for its tumour damaging properties[10] and shows a differential toxic effect more marked than any other mitotic poison tested[11]. Other workers[12] have shown that podophyllotoxin has a depressing effect on tissue metabolism and enzyme systems.

The following crystalline active constituents have been isolated from the commercial resin; podophyllotoxin, about 10 per cent., α peltatin, about 5 per cent. and β peltatin, about 6 per cent. These crystalline derivatives seem to account for most of the mitotic activity of the resin[13]. Podophyllo-resin, picropodophyllin, podophyllic acid and quercetin are without such activity, though quercetin may possess other interesting biological activities[7]. Hartwell and Detty[14] tentatively suggest that the peltatins are derivatives of 1-phenyl-1:2:3:4-tetrahydronaphthalene.

It should be noted that this recent work has probably been done entirely on the resin from American podophyllum (*P. peltatum* L.), however, it is very probably that the resin from Indian podophyllum (*P. hexandrum*, Royle) will contain the same active constituents, perhaps in greater quantity. A recent analysis of Indian podophyllum,[15] reports the presence of podophyllotoxin but does not mention the peltatins; however these may be discovered on further search.

Veratrum

Recent work on the American veratrum, *Veratrum viride* Aiton, (Fam. Liliaceæ) has shown its usefulness for the treatment of hypertension and it is very probable that the European Veratrum or White Hellebore (*V. album* L.) has a similar action; in fact, it is said that much of the American drug is actually imported *V. album*[16].

These plants are quite distinct from the black and green hellebores which are species of *Helleborus* (Fam. Ranunculaceæ), a distinction which even Theophrastus warned his readers to maintain. "The white and blackHellebore appear to have nothing in common except the name[17]." Since the black hellebore, being a cardiac stimulant, has a pharmacological action directly opposite to that of white hellebore, this distinction is more important than it appeared to be in those far off days.

The toxic nature of *V. viride* was known to the North American Indians who used the drug as an ordeal poison. The European settlers used it as an insecticide and purgative[18] and introduced it into Europe. Its effects were compared with those of the European *V. album* and found to be

similar. It is interesting to note that as far back as 1862 its effects in lowering the heart rate and acting as an arterial sedative were reported[19]. In 1868 Bezold and Hirt[20] showed that intravenous injection of crude veratrum preparations causes a fall in blood pressure and heart rate and concluded that these effects were due to reflex action initiated by stimulation of receptors in the heart itself. Recently, Jarisch *et al.*[21,22] and Krayer *et al.*[23,24] have confirmed Bezold and Hirt's work and suggest that the receptors are probably in the area of the distribution of the coronory arteries. Doses in excess of therapeutic ones exert a direct action on the central nervous system. The veratrum alkaloids may act by heightening the response of plain muscle to potassium ions[25], or they may act through a central mechanism[26]. It is generally agreed, however, that peripheral vasodilatation is the immediate cause of the fall in blood pressure, following administration of veratrum preparations.

The pharmacological and clinical evaluation of veratrum preparation have been greatly hindered by the paucity of knowledge of the chemistry of the crude drug. At least 15 alkaloids have been reported[27], some crystalline and some amorphous and differing markedly in their biological action. Some of the alkaloids are esters of an alkamine and an organic acid and those ester alkaloids are more potent pharmacologically than the alkamines which also occur free in the drug. The alkamines are built on a modified sterol structure[28]. The presence of this complex mixture in the crude drug may explain the occasional contradictory reports on the pharmacological effects of veratrum preparations and the unfortunate side effects sometimes reported[29]. The most satisfactory solution of the problem would be to isolate individual alkaloids and evaluate them separately. This policy is being adopted and has already yielded useful information. Thus Cotten and Walton[30] have shown that the alkaloids veratrine, veratridine and cevadine are pronounced heart stimulants but that therapeutic doses produce such unwanted side effects as to render them unsuitable clinically. Similarly Meilman and Krayer[31] using clinical tests found that veratridine, though active, had serious side effects when given in therapeutic doses. On the other hand, however, they found that *protoveratrine* produced a significant fall in blood pressure and decrease in heart rate in doses free from serious side effects.

Another attempt to afford at least an interim solution of the problem is illustrated by the work of Stutzman *et al.*[32] who have prepared a potent, stable extract of veratrum known as "Veriloid." This was the result of carefully screening 75 fractions of the drug, using pharmacological tests, in order to eliminate undesirable alkaloids. The extract is a pale yellow powder, is biologically standardised on dogs and subjected to toxicity tests before use; it contains amorphous alkaloids only so that none of the well-known crystalline alkaloids of veratrum are present.

Among other well-known drugs the following can be briefly mentioned:–

Liquorice (*Glycyrrhiza* spp)

Dutch workers[33,34] have recently reported the beneficial effects of extract of liquorice for gastric ulcers; they also noted that about 20 per cent.

of their patients developed cardiac asthma during treatment. Further investigation showed that the extract exerts an action *by mouth* similar to that of injections of deoxycortone, causing sodium retention and potassium loss and they report beneficial effects of the treatment in Addison's disease[34]. One of the components of liquorice is glycyrrhetic acid which is a polyterpene whose structural formula shows a striking resemblance to the *cyclo*pentanophenanthrene steroids. Japanese workers have recently studied the pharmacology of this compound[35,36] and report that it possesses an anticholinergic action on the heart, but shows no action on the intestine or uterus.

Digitalis

One possibly interesting development in the study of this much studied drug is the emphasis on its cardiotonic rather than its cardiotoxic properties[37,38] (as measured by present methods of bioassay) and the reported discovery of a new glycoside digicorin[37,39,40]. This glycoside which has low toxicity is claimed to possess the curative action of digitalis as distinct from that of the better known glycosides which are largely cardiotoxic. It can be extracted from the leaves of *D. purpurea* L. and *D. lanata* Ehrh. The aglycone is similar to gitoxigenin but has an acetyl group at C_3. The sugar is unusual, being a monobasic acid $C_6H_{12}O_6$ (possibly a desoxyuronic acid) linked to the C_{16} of the aglycone[40]; these facts about the sugar may be responsible for the distinctive pharmacological properties of this glycoside; digitoxose appears to be absent as the glycoside does not give the Keller-Kiliani reaction.

Anthraquinone drugs

Recent work on this group of purgative drugs has drawn attention to the importance of the form in which the anthraquinones occur in the crude drug. Fairbairn *et al.*[41,42] and Lou[43,44,45] have devised satisfactory chemical and biological methods of assay and by applying these methods to a number of these drugs and their constituents Fairbairn[46] concluded that the anthracene derivatives are highly active as "anthranol" glycosides, less active as free anthranols and much less active as free anthraquinones. For example, work on one of the active glycosides of senna showed that breaking off the sugar moiety led to a loss of about two-thirds of the activity and subsequent oxidation of the liberated "anthranol" aglycone to the anthraquinone form led to the loss of the remaining activity. The importance of the glycosidal fraction of these drugs was therefore emphasised; and further work on this fraction was carried out. For senna (*Cassia* spp.) it was shown[47] that the activity of the sennosides A and B isolated by Stoll *et al.*[48,49] did not account for more than 40 to 60 per cent. of the activity of the crude drug; furthermore, though the leaf contains less sennosides A and B than the pod, it is much more active. The activity of a third glycoside present in senna was investigated and it was shown that if the amount present represented 10 to 14 per cent. of the total glycosidal fraction it exerted a synergistic effect of $\times$ 1·7. The pod

contains very little of this glycoside but the leaf contains about 10 to 14 per cent. so that its synergistic effect accounts for the greater activity of the leaf. Work on rhubarb (*Rheum* spp.) indicated that the activity was proportional to the amount of "combined rhein" present and Bellaart[50] has recently isolated from Dutch-grown rhubarb an ochre-coloured substance which is highly active; on hydrolysis it yields *inter alia* rhein, chrysophanol and an active resinous material. A recent American patent[51] claims to have discovered the active principle of cascara (*Rhamnus purshiana*); this is said to be glycoside of aloe emodin anthranol having a hexital and a lactone group attached to the anthracene nucleus. The galenical preparations of these drugs have been examined and it has been shown[52] that for senna, the B.P. 1948 galenicals are unsatisfactory as they only contain a small portion of the activity due to poor extraction and poor keeping qualities. We have also found a somewhat similar situation for cascara. We hope to publish shortly, methods for the preparation of potent and stable galenicals of senna and cascara. I have been unsuccessful in applying our biological method of assay to *Aloes* or aloin so that we have been unable to carry out work on this drug; however recently, Latven, Sloane and Munch[53] have published a biological method of assay for aloes, which may enable a further study of this drug to be made. A review of our work on anthraquinone drugs has recently been published[54].

Chlorophyll

It is difficult to form an unprejudiced opinion of the favourable reports on the de-odorising properties of chlorophyll derivatives because of the din of commercial advertisements calling attention to this new miracle material from Nature's own storeroom. However, there is a remarkable unanimity in the conclusions reached by reliable research workers on the deodorising value of chlorophyll derivatives[55,56] and also on their healing effects in the treatment of war wounds. Further details can be obtained by consulting the reviews by Mitchell[57], Speriando[58] and Zirm and Hams[59]. A leading article in a recent number of the *Lancet*[60] reviews the subject from the medical angle. The chemistry of the pure enzyme has been taken a step further by the reported isolation of a crystalline chlorophyll lipoprotein[61], thus emphasising further the relationship with the closely similar compound hæm which also occurs in nature combined with protein as hæmoglobin. The chlorophyll complex has a molecular weight of about 19,000 and contains 2 molecules of chlorophyll to 1 of lipoprotein. It is important to remember, however, that commercial "chlorophyll" on which all the above-mentioned claims are based is not this pure enzyme; probably not more than 15 per cent. is present. Furthermore, the original chlorophyll molecule (a magnesium phæophytin) has usually been either converted into copper phæophytin or saponified to form sodium chlorophyllins. Hence it is not certain whether the results claimed are due to these modifications of the chlorophyll molecule or to some other constituents present in the 85 per cent. of "ballast."

Lesser Known Crude Drugs

This group of drugs includes those which are probably well known in certain localities and which have been long used as a result of local tradition. Through such local knowledge the attention of scientific workers may be drawn to these "cures" and if subsequent investigation justifies claims made, the drug may be introduced into Western medicine.

Ammi visnaga

A decoction of the dried fruits of *Ammi visnaga* L. (Fam. Umbelliferæ) has been used for centuries by the natives of the Middle East as a diuretic and an antispasmodic for ureteral stones[62] and was included in the Egyptian Pharmacopœia 1934. As far back as 1929–1930 clinical observation by Ibrahim[63,64] and pharmacological experiments by Samaan[65] showed that a tincture of the drug possessed spasmolytic effects on the ureter and intestines and dilator effects on the coronary vessels; the usefulness of this latter observation was not then realised, the chief interest being in its diuretic effect and its beneficial effect on spasm of the ureter. More recently, interest in the coronary action of this drug was aroused by an accidental observation of Anrep *et al.*[66] A member of the laboratory staff who suffered from coronary disease and had frequent anginal attacks took a tincture of *Ammi visnaga* to relieve severe renal colic from which he also suffered. Besides passing a renal calculus the man also showed great improvement in his cardiac condition and this improvement was maintained while he continued taking the preparation of *Ammi visnaga*. Anrep *et al.* investigated the cardiac properties of the drug and found that it was an effective vasodilator with a selective action on the coronary vessels[67]. Later work indicated that the most active constituent of the drug was khellin (after "Khella" the Arabic name for the plant) and numerous pharmacological investigations[68,69] have confirmed its effect on the coronary vessels. Rosenman *et al.*[70] summarise this work by stating that khellin "has been found to be a powerful coronary vasodilator in animals, causing definite increase in coronary blood flow without demonstrable ill effect on the myocardium. It is further characterised by the absence of development of tolerance, by a wide margin of therapeutic safety and by prolonged activity, since its gradual disappearance from blood and tissues results in cumulative effects." Anrep *et al.*[62,67,71] also reported on its relaxing effect on the bronchi, ureter, bile duct and intestines. Clinical trials have shown that khellin is particularly useful in angina pectoris. It is not so effective as nitroglycerine but its action is more prolonged[72] so that it can be used as a continuous treatment for the prevention of attacks[67]. It has also been used effectively in the treatment of bronchial asthma[71,73]. Favourable results have also been reported for the treatment of whooping cough[74].

A useful review of the work on the chemistry of the constituents of *Ammi visnaga* is given by Huttrar and Dale[75]. The most interesting constituents are three crystalline chromones, *khellin* (m.pt. corr. 154° to 155° C.) *khellol glycoside* (m.pt. corr. 174° to 176° C.) and *visnagin* (m.pt.

corr. 144° to 145° C.). These three compounds are closely related; thus if R represents visnagin, then khellin is R–OCH_3 and khellol glycoside R–$OC_6H_{11}O_5$. Anrep *et al.*[62] state that khellin is the most active compound, visnagin has about two-thirds of its activity and khellol glycoside is inactive. If, however, the glycoside is hydrolysed, the resulting khellol is fairly active (about one-fourth that of khellin). This is a remarkable observation as the reverse holds true for the cardiac glycosides and the anthraquinone glycosides, where hydrolysis to the genin leads to great loss of activity. Samaan *et al.*[76], however, report that this glycoside (which they call khellinin) does definitely increase cardiac output and coronary flow. The fruits contain about 1 per cent. of khellin, 0·1 per cent. of visnagin and 0·3 per cent. of khellol glycoside[77]. Fahmy *et al.*[77] give details of how khellin may be characterised by physical and chemical means. They also describe a photoelectric method of assay based on the formation of khellin sulphate, a yellow oxonium compound of khellin with sulphuric acid[78].

Numerous analogues of khellin and visnagin have been prepared but in all cases where details are published their activity was less than that of the parent substances[79]. Recently the total synthesis of khellin has been described[80] but the authors conclude that the commercial production of khellin by synthesis is not practicable.

Ammi majus L.

The fruits of this closely related plant have long been used by the natives of Egypt for the treatment of leucoderma (or vitiligo). Research work carried out by Mofty and others[81,82] have confirmed that the condition can be cured by oral administration of an extract of the drug and subsequent exposure to sunlight of the white patches on the skin. Fahmy and Shady[83] have isolated a crystalline product ammoidin which seems to be the main active principle; they have also shown how the fruits may be distinguished macroscopically and microscopically from those of *A. visnaga*[84].

Rutin

This compound seems to have a vitamin-like activity in restoring to normal, persons with abnormally high capillary permeability and fragility. Szent-Györgyi and Rusznyak[85], first showed that the beneficial effect of such remedies as citrus fruits and paprika in the treatment of scurvy was not entirely due to their content of vitamin C; a second factor, which cured the capillary permeability and fragility sometimes associated with scurvy, occurred in the fruits. They were able to demonstrate that this factor, which they called vitamin P because of its action on vascular permeability, was associated with the flavone glycosides such as hesperidin and eriodictyol. However, neither of these compounds showed any vitamin P activity, and to this day the chemical nature of vitamin P remains unknown.

Griffith, Couch and Lindauer[86], however, noticed that the comparatively well-known glycoside rutin had a structure similar to these flavone

glycosides and accordingly carried out clinical trials with this substance in the treatment of capillary fragility. These experiments were successful and later work has confirmed the usefulness of rutin in the treatment of this and similar conditions[87]. Rutin was first isolated from rue (*Ruta graveolens*) in 1842 and has since been reported in about 40 different species of plants, including buckwheat (the usual source for commercial production), tobacco, elder and forsythia; until 1942 however, it was only a laboratory curiosity. Further details on this compound can be obtained by consulting published reviews[88,89,90].

Recently, an accidental discovery by a group of pharmacologists[90] has led to what may be an important use of rutin in the treatment of the after effects of exposure to atomic radiation. These workers were searching for a method of producing capillary permeability "artificially" in animals and ultimately found that exposure to α radiation had the desired effect; subsequent treatment with rutin brought about recovery. Later, Knowlton *et al.*[91] utilised this information by including rutin in the treatment of β burns arising in sailors taking part in recent atomic bomb tests.

Fundamental Research

Considerations of space necessitate only a brief reference to work on the place of active principles in the biology of the plant producing them. Moreover, it is only comparatively recently that attention has been paid to this aspect of the study of medicinal plants, so that little is yet known on the subject. I shall mention only two groups, viz. alkaloids, and glycosides; a fairly comprehsive account of another large group is given in the book, "*Plants and Vitamins*[92]."

The *alkaloids* have been more studied in this connection than almost any other group; James[93] has recently reviewed our present knowledge and concludes that at least for some plants, the alkaloids are formed from the "soluble nitrogen" pool, which normally consists of amino-acids and amines. These intermediate compounds are removed from the pool to build up proteins and in like manner, the breakdown of proteins results in the return of them to the pool. In alkaloid-producing plants this two-way traffic is partly diverted to alkaloid production and breakdown. Such a theory explains why alkaloids are frequently found in actively growing tissues, where protein metabolism is specially active, and why those fertilisers which increase the growth of the plant also produce a corresponding increase in alkaloidal content.

The *glycosides* form a heterogeneous group of plant constituents whose only distinctive feature is the presence of "glycosidally-linked" sugars; it is not a closely-knit group, and it is not surprising therefore, that few generalisations can be made. However, it is to be noted that the importance to the plant of the glycosides discussed below lies in the properties of the *aglycone*. Quite possibly the glycosidally linked sugar acts rather like a container which can be easily discarded and whose main function is the transport of the active aglycone to the seat of action. Daglish[94] has produced evidence to show that the hydrojuglone glycoside or "apparent

vitamin C" of walnuts (*Juglans regia* L.) is of particular use in the oxidation-reduction systems of the tissues, especially during rapid growth; it may also be utilised in building up new tissues, and may exert a protective function because of its toxic effect on moulds and bacteria. The role of the cyanide group, which occurs in several drugs containing cyanogenetic glycosides, has also received attention lately, because of its possible effect on enzyme systems or in nitrogen metabolism[95,96]; this interest has been heightened by the discovery that vitamin B_{12} is distinguished from B_{12a} by the presence of a cyano group[97]. More recently the first naturally occurring plant growth hormone to be isolated from actively growing plant material is reported[98]; it is 3-indolylacetonitrile and therefore contains the cyanide group and appears to be more active as a hormone than the well-known 3-indolylacetic acid (heteroauxin). This greater activity may be due to its synergistic effect on the free acid, which may be formed from it or which may pre-exist in the cell[99]. Rutin, the quercitin glycoside already discussed, appears to be concerned with ensuring the cross pollination mechanism in forsythia flowers[100].

Conclusion

This survey has indicated that research in the vegetable materia medica is yielding and may yet yield much information useful to medicine. It is well to remember that, as far as materia medica is concerned, the revolution in medicine from empiricism to rationalism has so far affected the methods of *evaluating* the worth of a remedy rather than the methods of discovering them. The discovery of effective remedies is still largely empirical and depends on the accumulated experience of centuries of trial and error, the chance observation of a trained worker or the lucky emergence of an active compound from a large series of analogues. The examples quoted in this article afford some illustration of this statement. Modern methods of analysis and synthesis have resulted in a greatly extended range of compounds which can be tried, but the most important advance is due to modern pharmacological, clinical and statistical methods which have enormously increased our ability to separate the useful from the useless. Advances are being made in correlating therapeutic effect and physicochemical structure but the time still seems remote when the physician can ask for a specific remedy and the scientist can then devise a molecule which would fulfil his requirements or indicate a plant species in which such a compound would be likely to occur. Thus in a recent discussion on cancer research[101] the theory is suggested that cancerous growths occur because certain cells have lost a growth-controlling mechanism. A thorough knowledge of cell metabolism and metabolites might soon indicate what compound or enzyme could replace this mechanism, but who can doubt that at the present state of our knowledge the quickest answer can be obtained by intelligent trial and error? However, the real aim of research work should be to travel the road of advancement which has to be taken by all Natural Sciences, namely, *via* the cataloguing of numerous, apparently unrelated, facts to the formulation of temporary hypotheses, broad principles and ultimately to the discovery of natural

laws. Synge[102] has recently stressed the importance of this route by emphasising the need for more fundamental research on the function of cellular constituents in their native organisms; only by this means can we hope to arrive with certainty at real cures.

Meanwhile it would be foolish to ignore the vegetable materia medica because the principles of investigation involved still savour of "empiricism." These investigations, however, should avoid, on the one hand, hasty conclusions such as has occurred in the past with ergot, senna and possibly digitalis, where the discovery of a well defined chemical or pharmacological entity has led to the hasty assumption that the rest of the crude drug was merely "ballast." Such hastiness may make us guilty of throwing out the baby with the bath! On the other hand, it is unwise to make such *a priori* assumptions as that a galenical containing all the non-cellular part of a crude drug will be the most effective remedy; this may be often true but it can never be assumed till proved. The examples of veratrum and *Ammi visnaga* show that harmful side effects can occur because of the presence in the crude drug of active constituents other than the "therapeutic ones."

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