NEW SUBSTANCES OF PLANT ORIGIN[1]

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New Substances of Plant Origin

Exploration of the plant kingdom for chemical compounds of medicinal value has been an important activity of mankind since the pre-Christian era. Herbalism and native folk medicine, ancient and modern, have been the source of much useful therapy, and most of our present-day knowledge of the active principles of the medicinally useful vegetable drugs began to develop when, during the nineteenth century, organic chemists took up the study of the many plant principles whose conspicuous and demonstrable physiological effects were then recognized. At the present time all of the well-known vegetable drugs—quinine, atropine, morphine, strychnine, cocaine, eserine, and many others—have been relegated to the realm of solved problems; and although such continuing studies as the preparation of analogues, the search for new pharmacological applications, and the further study of mechanisms of physiological action and fate go on, the attention of many organic chemists is turning to a search for new chemical compounds in the many thousands of plants still untouched.

It is a curious and interesting fact that while the backlog of chemical problems based upon folk medicine and empirical practice of demonstrable utility was being worked upon, very few new and useful discoveries of plant drugs were added to the list from ethnobotanical sources. It was as if the centuries of empirical discoveries by primitive man had uncovered the main sources of botanical drugs and as if, by the end of the nineteenth century, organic chemists had brought most of the useful plant drugs under experimental scrutiny.

There are, of course, reasons for the study of plant principles other than conspicuous physiological activity, and the study of naturally occurring compounds from plants has by no means abated. Rather, with improved techniques for the assay of plant materials and for the isolation and separation of complex mixtures, and the powerful modern physical methods for the determination of chemical structure, the field is active and expanding. But much of this work has been devoted to the study of compounds of relatively lesser importance as drugs or medicinals. Pigments, bitter principles, glycosides, terpenes and steroids, alkaloids of no present medicinal usefulness, and compounds of no known physiological activity provide a rich field of study from which come continuing contributions to chemistry and biology. It is safe to say that were close pharmacological scrutiny to be devoted to the many natural compounds now known and available for study, useful new medicinals would be found among them. The aphorism that "drugs are poi-

[1] The survey of literature pertaining to this review was completed June 1, 1963.

sons and *vice versa*" suggests that a rich field of potential rewards lies in the continuing pharmacological investigation of natural products from plant materials, for one of the characteristics that has often incited chemical interest in a plant is its poisonous quality; and many toxic plants are known.

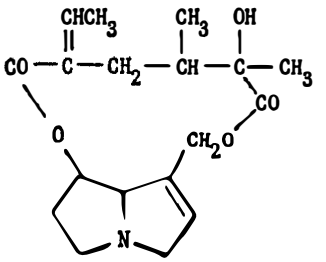
A new impetus was given to the search for medicinal plant principles by the dramatic discovery of the clinical usefulness of the alkaloids of *Rauwolfia* species, and during the past decade this has provided a fresh stimulus for an enlarged and concerted attack upon the still unexploited botanical resources of the world. A number of large scale academic and industrial screening and evaluation programs are now in existence, and many thousands of new plants are being studied in the firm belief that primitive man has not exhausted the potentialities of the vegetable kingdom. The returns on this enormous investment have so far been small, for no new vegetable drug of major therapeutic usefulness has been discovered in recent years. Many new compounds, most of them alkaloids, have been discovered, and many alkaloid-bearing species that remain to be examined in detail have been brought to light. But the gap between the possession of physiological activity—which most alkaloids and many nonnitrogenous compounds have to some degree—and clinical usefulness is so large that few new compounds have successfully run the course of screening, pharmacological study, clinical trial, and acceptance. For this reason, this review would have little to say were it to be confined to new plant drugs of established medical utility; and although some kind of pharmacological response has been observed in a great many naturally occurring compounds, no useful purpose would be served by noting such observations, most of which are still isolated and unexploited.

This review will be confined to a discussion of several classes of plant substances which, while they have pronounced physiological activity, cannot be regarded as important medicinals. Certain features of the nature of their activity are of interest, and certain of them may be of potential usefulness as therapeutic agents. In addition, diverse as they are, some of the compounds to be discussed are bound together by their possession of real or potential activity as antitumor agents.

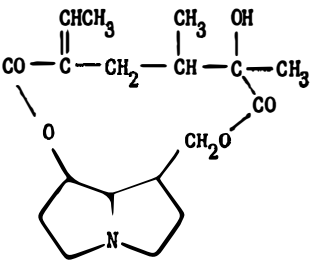
To be mentioned only in passing are the many plant substances of pharmacological interest that have occupied attention for so long that they either need no extensive review at this time or cannot be justly treated in the confines of this chapter. Among these are the hypotensive and tranquilizing alkaloids of *Rauwolfia* species; the use of plant steroids as starting materials for the synthesis of steroidal hormones; colchicine and its derivatives in cancer chemotherapy; the hypoglycemic amino acids of *Blighia sapida;* the psychotropic drugs derived from ergot and various species of mushrooms (1, 2), and other related indole alkaloids of plant origin. Recent discoveries of the antitumor effects of the alkaloids of *Vinca rosea* (*Lochnera rosea*) have been reviewed (3), and form the subject of recent comprehensive articles (4, 5). Finally, this review is confined largely to substances from higher

plants; hence, the many antibiotic substances of microbiological origin are not dealt with.

Pyrrolizidine alkaloids.—The toxic character of many plants of the genera *Senecio* and *Crotalaria* and the family Boraginaceae has long been recognized as a major cause of stock losses throughout the world, and in more recent times has been implicated in human disease (6, 7, 8). Extensive chemical studies over some twenty-five years have led to the establishment of the structures of most of the pyrrolizidine alkaloids, nearly all of which are esters of bicyclic amino alcohols (necines) with aliphatic acids (necic acids) of five to ten carbon atoms. Two typical *Senecio* alkaloids are senecionine (I) and platyphylline (II):



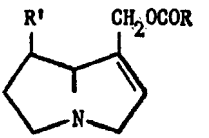
I



II

These two are selected from the more than seventy known alkaloids of the group because they show an important structural difference: the saturated necine in II and the corresponding unsaturated necine in I.

Poisoning of cattle, horses and sheep by pyrrolizidine alkaloids involves severe liver damage and necrosis by acute action, and progressive hepatic degeneration on chronic exposure to the alkaloids. Extensive physiological studies by several investigators (1, 9) led by 1962 to the conclusion that the minimum structural requirements for toxicity were (*a*) the presence of the double-bond in the necine (as in I), and (*b*) esterification of the primary alcohol grouping (III):



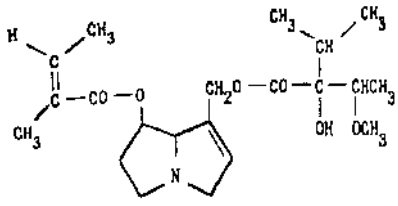
III

R′ = H, OH, OAcyl.

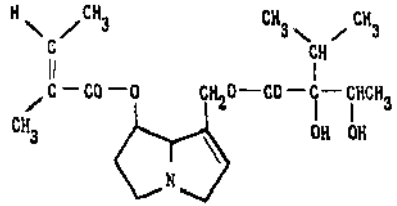
Alkaloids derived from a saturated necine base, such as II, rosmarinine, angularine and sarracine, have shown no hepatotoxicity.

No satisfactory explanation for the toxicity of these compounds was found until the recent discovery (9) that these allylic esters can act as alkylating agents *in vitro*, a finding which led to the suggestion that their toxic effects *in vivo* are due to their ability to act in the same way. This proposal is supported by the recognized structural requirements for toxicity and the fact that the natural alkaloids possess highly α-branched acid residues (R in III). Attack upon the hindered carbonyl group of esters of this kind would be expected to be slow, and nucleophilic attack at the allylic $-CH_2-$ group, leading to alkylation, would be favored. The observations that the hepatotoxic pyrrolizidine alkaloids cause mutations (10) and chromosome breakage (11, 12), and lead to liver tumors (13, 14) in animals indicate that the compounds act upon a variety of cell nuclei. While these actions are not uniquely diagnostic of nuclear alkylation, they are reminiscent of the actions of alkylating radiomimetic compounds, and there is the strong possibility that this is the mechanism by which the alkaloids produce their toxic effects (9).

The few studies of the antitumor activity of pyrrolizidine alkaloids that have been carried out have shown them to be only moderately effective anticancer agents (15, 16). Lasiocarpine (IV) showed a moderate activity (21 per cent weight reduction of tumor *vs.* controls) against hepatoma in rats and mice; lasiocarpine and heliosupine (V) inhibited rat sarcoma 45 to the extent of 17 per cent and 28 per cent, and heliosupine and seneciphylline inhibited Ehrlich ascites tumor 54 per cent and 19 per cent. A most significant observation is that there exists a parallelism between antitumor activity and hepatotoxicity (15).



IV



V

In view of the importance of alkylating agents in cancer chemotherapy it would be desirable to extend the search for effective antitumor drugs into the area of allylic amino alcohols of which I, III, IV and V are natural prototypes. Synthetically modified or wholly synthetic analogues of these hepatotoxic agents would be expected to be suitable candidate compounds for further study as potential anticancer drugs.

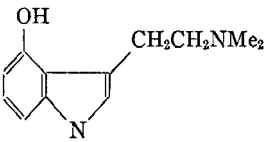
Other actions of pyrrolizidine alkaloids.—The only one of the pyrrolizidine alkaloids that has received extensive pharmacological and clinical study is platyphylline (II), a nonhepatotoxic compound (17). Platyphylline has, as might be anticipated from its structure, an atropine-like activity, and it has been recommended as an effective mydriatic (18). Its central actions and effects on blood pressure (19, 20) are unexceptional. For obvious reasons, the

hepatotoxic alkaloids (III) have not been extensively tested with a view to therapeutic applications, but studies of their activity as central depressants and anticholinergic agents have been reported (21, 22, 23). The latter activity, which is similar to but weaker than that of atropine, is not related to the hepatotoxic properties of the alkaloids.

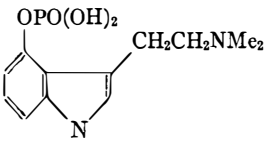
Indole derivatives.—The prevalence of the indole nucleus in physiologically active compounds of the most diverse function is noteworthy (1). Many of these substances are by now so well documented that they need not be considered here. Among the familiar compounds of the class are reserpine and reserpic acid derivatives; the fungal ergot alkaloids; serotonin (5-hydroxytryptamine) and related tryptamine derivatives; yohimbine; eserine; harmine and its derivatives; and the iboga alkaloids (24).

Certain more recent developments in the field of indole-derived compounds from plant sources deserve review.

Psychotropic compounds from mushrooms.—The discovery of the hallucinogenic principles of mushrooms used in ritualistic practices in Mexico was first accomplished by Hofmann and his collaborators (25), following the early studies of the Wassons. The active compounds, psilocin (VI) and psilocybin (VII), are present in mushrooms of several genera, including *Psilocybes*, *Paneolus*, *Stropharia* and *Conocybe* (26).



VI

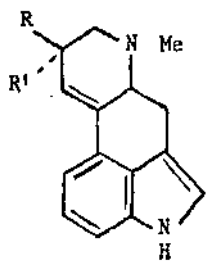


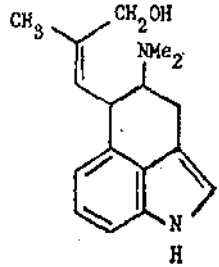
VII

Psilocin and psilocybin produce psychotomimetic effects when taken orally, the hallucinogenic reactions resembling those of mescaline and lysergic acid diethylamide (LSD). The physiological effects of psilocybin and psilocin are qualitatively similar, and it has been found (27) that psilocybin is readily dephosphorylated in the intact mouse. Peak liver and kidney concentrations occurred 10 to 20 minutes after intraperitoneal administration of psilocybin, and behavioral effects followed the increase of brain levels of the dephosphorylated compound. The role of serum alkaline phosphatase, the activity of which is shown by *in vitro* experiments, is indicated by the effect of sodium β-glycerophosphate in reducing the tissue concentrations of psilocin. Psilocin is excreted partly unchanged, partly as the glucuronide and partly as 5-hydroxyindole-3-acetic acid (2). Two recent reviews describe the chemistry and pharmacology of other indole-derived compounds related to psilocin (1, 24).

Ololiuqui.—The Mexican hallucinogen known since the 17th century as "ololiuqui" has been the subject of interest to ethnobotanists for many years (28, 29). Attempts to identify the drug with a specific plant led to conflicting

conclusions: some botanists identified it as the convolvulaceous plant *Rivea corymbosa*; others decided that it was a member of the Solanaceae, perhaps a species of *Datura*. Recently, the former claim has been substantiated, and *R. corymbosa* is now recognized as the narcotic "ololiuqui." Attempts to identify the active principle in *R. corymbosa* led at first to numerous inconclusive results. Indeed, several investigators in recent years were unable to demonstrate the presence of alkaloids in the seeds of this plant; but in 1960, Hofmann & Tscherter isolated several alkaloids of the ergot group from the seeds of *R. corymbosa* and from *Ipomoea tricolor*. Among them were isolysergamide (VIII), lysergamide (IX), and chanoclavine (X) (30, 31).





VIII, $R = CONH_2$, $R' = H$.

IX, $R = H$, $R' = CONH_2$.

X

More recently, the seeds of sixteen commercial varieties of morning glory (*Ipomoea* and *Convolvulus* spp.) have been examined, and clavine and lysergic acid alkaloids were found in thirteen of the varieties studied (32). It is of great interest that alkaloids of these groups have been found in higher plants since these compounds have heretofore been encountered only in certain fungi, notably ergot (*Claviceps* spp.). It has been established that these convolvulaceous alkaloids are true metabolic products of the plants, and not the adventitious consequence of microbial contamination.

Salvia divinorum, *Epling and Jativa*.—Wasson has recently described the psychotropic properties of a new hallucinogenic plant used by the Mazatecs of Oaxaca in Southern Mexico (33). This plant, a new species (34), is a member of the *Labiate*, and is used by the Mazatecs as a substitute for the psychotropic mushrooms. This is the first member of the mint family to be added to the group of *phantastica* brought to light in recent years by the Wassons and others. The physiological effect of the plant (the fresh leaves) is reported to be similar to the first phase of that produced by the psychotropic mushrooms. Elaborate color vision, which came sooner and was of shorter duration than that caused by the mushroom hallucinogens, was the principal result of the ingestion of the freshly expressed leaf juices. No further information is yet available, and the chemistry of the active principle has not yet been elucidated.

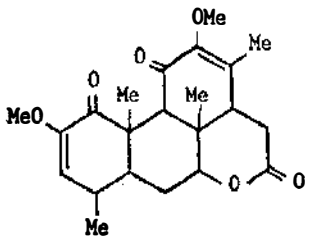
Antiamebic principles of simaroubaceous plants.—Certain plants of the

family Simaroubaceae have been long and widely used as native remedies for amebic dysentery. These remedies are infusions of the plant or seeds of several genera of the family, and are characterized by extreme bitterness. In at least some of the known cases, the bitter principles are diterpenoid lactones, usually highly oxygenated. While physiological (amebacidal) studies of the pure, crystalline compounds that have been isolated have not yet been extensive, chemical investigation of their structures has recently been advanced to the stage at which the structures of two of them have been established. Work is actively proceeding on others of the class.

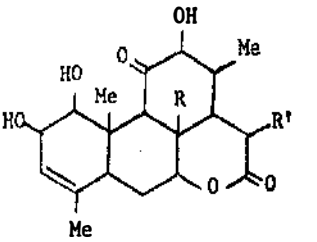
The oldest known bitter principle of the Simaroubaceae is quassin (XI), a compound found in *Quassia amara* L. and *Picrasma excelsa* Planch. (*Picraena excelsa* Planch.; *Aeschrion excelsa*). Quassia (the plant contains at least two closely related compounds, quassin (35), a lactone, and neoquassin, the corresponding lactol; the drug would, of course, provide both in an extract) has been used for over a century as a bitter tonic and as a remedy for intestinal parasites. Quassia is not used as an antiamebic drug.

The first of the quassin congeners to be intensively studied was the bitter principle of *Simarouba glauca* Dc., glaucarubin, the α-hydroxy-α-methylbutyric acid ester of glaucarubol ($C_{20}H_{28}O_8$) (36). The structure of glaucarubol (XII) was shown to be closely related to that of chaparrin (XIII), the bitter lactone from the antiamebic plant *Castela nicholsoni* Hook (37, 38).

Castela nicholsoni was first examined in detail in 1922 by Bosman (39), who isolated from it a crystalline bitter principle, called castelamarin, and a glucoside, castelin. The structures proposed for these compounds by Bosman were not correct, and it now seems probable that castelamarin was incompletely purified chaparrin, later isolated in a pure state (40), and characterized as a lactone, $C_{20}H_{28}O_7$. The close chemical relationship between glaucarubol and chaparrin was recognized during the course of studies on the latter compound, and it is now known that glaucarubol is a hydroxychaparrin (41):



XI



XII, R = CH_2OH, R′ = OH.

XIII, R = CH_2OH, R′ = H.

The structural similarity between quassin, chaparrin and glaucarubol is striking, as is the extremely bitter taste that characterizes all of these compounds.

Crystalline principles of several other simaroubaceous plants are currently under study in several laboratories, but complete structures are not yet known. The seeds of *Simaba cedron*, a total extract of which has been reported to contain a relatively toxic, anti-inflammatory substance of weak and nonspecific activity (42), contains the compounds cedronylin ($C_{22}H_{30}O_8$) and cedronin (43). Cedronyline is a glycerol ether of a C_{19} tetrahydroxy lactone. Early studies of *Simarouba amara* (44, 45) resulted in the isolation of two compounds, simaroubidin ($C_{22}H_{32}O_9$) and simaroubin ($C_{22}H_{30}O_9$), and a later examination of the same plant (46) yielded a third compound, simarolide ($C_{22}H_{32}O_7$). Simarolide is an acetate, and thus represents a C_{20} compound, as are glaucarubol and chaparrin (quassin is a dimethyl ether of a C_{20} compound). Recent additions to the list of crystalline compounds of this group are the samaderines (A: $C_{18}H_{18}O_6$; B: $C_{19}H_{22}O_7$; C: $C_{19}H_{24}O_7$). Little is known about these compounds, but a significant observation is that samaderene C is converted by treatment with acid to a dehydration product that contains a 1,4-dimethylbenzene ring in its structure (47). Both chaparrin and glaucarubol are aromatized by similar treatment with the formation of a 1,4-dimethyl aromatic A-ring (40, 48, 49).

The seeds of several species of *Brucea*, a simaroubaceous plant native to Southeast Asia, have long been used there as a remedy for diarrhea and dysentery. The drug, known as ko-sam, ya-tan-tzu and koo-sheng-tse, has been studied in Asia, with preliminary results that can only be regarded as inconclusive (50 to 58). A number of crystalline substances have been described, and from the descriptions that are available it appears likely that at least two, and perhaps three, individual compounds have been obtained, but in doubtful purity. Two components, a phenol and a "glucoside," have been described. The so-called glucoside appears to be the active amebacidal principle. It has an extremely bitter taste and is reported to give the striking blue-purple color with concentrated sulfuric acid that is given by chaparrin and glaucarubin. Preliminary studies in the reviewer's laboratory have shown that the seeds of *Brucea sumatrana* contain a crystalline "phenol" (probably a diosphenol) and at least three compounds giving the blue sulfuric acid color reaction.

Physiological action.—There is a substantial body of evidence that several of these simaroubaceous drugs are effective in the treatment of human enteric amebiasis. It is of interest to quote Martinez' detailed comparison of emetine, a well-known antiamebic drug, and *Castela nicholsoni*, the latter as the propietary preparation "Castamargina" (59):

	CASTAMARGINA*	EMETINE
use:	amebacide	amebacide
toxicity:	1	25
emesis:	none	emetic

* A 5 percent solution "de glucósidos (sic) de *Castela nicholsoni*."

toxic manifestations: prolonged use in refractory amebiasis produced no toxic manifestations	toxic manifestations in prolonged use
irritant action: none	irritates superficial mucosa; produces conjunctivitis, bronchitis, skin eruptions, asthma, diarrhea, rectal irritation
gastric hyperemia: does not produce	produces gastric hyperemia
max. dilution for toxicity to E. histolytica: 10,000	2,000
secondary effects: rarely causes constipation	high doses cause vomiting, depression
diarrhea: none, orally or parenterally	can produce bloody diarrhea
cumulative action: none	has cumulative effects
action on smooth muscle: practically none	increases tonus; high doses paralyze
form of administration: oral, rectal, hypodermic	oral, rectal, hypodermic

"Chaparro amargoso," the name by which *Castela nicholsoni* is known in Mexico, has been found to have some activity against Sarcoma-37 in mice (60), but its antitumor properties have not yet been extensively explored.

It should be noted that the effectiveness of chaparro amargoso has been questioned (61). Anderson & Hansen report that it is effective in human amebiasis but has some undesirable side effects (62). A medicinal preparation of *C. nicholsoni* is found in the Mexican market; this is "Castamargina," referred to above.

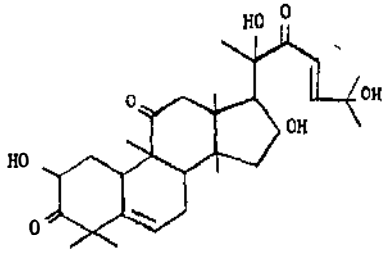
Simarouba glauca, grown in Central America, is of potential value as a vegetable oil crop (63). The bitter seed press cake contains the compound glaucarubin (p. 311). Glaucarubin has received careful pharmacological study, and has been shown to be an effective amebacide (64), less potent than emetine *in vitro* but considerably more effective than carbarsone in experimental amebiasis in animals. Glaucarubin (at the time of its study erroneously called simaroubidin) was reported to be an effective tumor necrotizing agent in mice (60).

The drug ya-tan-tzu (*Brucea* spp.) appears to have an antiamebic activity comparable to that of chaparro amargoso and glaucarubin, but little detailed pharmacology is available. It is not clear which of the substances that have been isolated from the drug is the amebacidal principle.

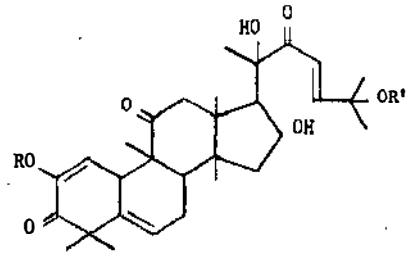
The most interesting aspect of the chemistry of the Simaroubaceae is that this family (most of the genera of which are characterized by intense bitterness) contains a group of chemically allied compounds, most of which appear to be lactones of the diterpenoid class. It is evident from the review of their chemistry that much remains to be done before the structural relationships of these compounds will be known with certainty. Further examination of the pharmacological properties of the pure compounds would be very desirable. There are conflicting reports as to the clinical efficacy of the drugs, although there appears to be no doubt as to their amebacidal activity. The tumor-

damaging properties of chaparro amargoso and glaucarubin deserve further exploration, particularly in view of the recently discovered antitumor activity of the triterpenoid compounds, the curcurbitacins, found in certain bitter species of the curcurbitaceae.

The curcurbitacins.—Belkin & Fitzgerald, in their surveys of plants with putative medicinal properties, found that two cathartic plants, *Ecballium elaterium* and *Citrullus colocynthis*, were effective tumor-damaging agents toward Sarcoma-37 in mice (65). Investigations of these and other cucurbits by Lavie in Israel, Enslin in Pretoria, and, more recently, by several other investigators, have led to the isolation and structural characterization of a group of triterpenoid compounds (modified lanostane derivatives) known as "cucurbitacins" (66–69). Cucurbitacins A, B and C were first described by Enslin in 1956, and to the present time a total of seven compounds of the group have been isolated: cucurbitacins A, B, C, D (=elatericin A), E (=elaterin), I (=elatericin B) and 2-epicucurbitacin B (70). Excellent sources of cucurbitacin B are *Luffa echinata* var. *longistyla* and *L. graveolens* (71).



Elatericin A



Elatericin B(R = R′ = H)

Elaterin (R = H, R′ = CH_3CO)

Elaterin methyl ether (R = CH_3, R′ = CH_3CO)

(dihydro compound lacks side-chain double bond).

Studies on the antitumor effects of the pure crystalline compounds have been carried out with elatericins A and B, elaterin, elaterin methyl ether, and 4-hydroxy-4-methyl-pent-2-enoic acid, which represents the side-chain portion of the parent compounds (67, 72 to 74). Elatericins A and B and elaterin produced inhibition of growth of Sarcoma-180, Sarcoma Black and Ehrlich ascites tumor cells. Elatericins A and B, elaterin, and elaterin methyl ether inhibited the respiration of Ehrlich ascites tumor cells and caused marked morphological changes in the cells. Other cucurbitacin derivatives were found to have little or no antitumor activity. It is of interest to note that elatericins A and B were absorbed by Ehrlich ascites tumor cells in suspension but not by rat leukocytes or by slices of normal or neoplastic tissue. Excretion of methyl-C^{14}-labeled elaterin methyl ether was delayed in Ehrlich ascites tumor-bearing mice as compared with normal mice of the same strain. There

appears to be a special affinity of these tumor cells for the active cucurbitacins.

When injected into mice, the cucurbitacins produce a number of profound physiological effects. There are pronounced effects upon circulation and respiration, with aortic and pulmonary-artery hypotension; increased bronchomotor tone; and strong intestinal peristalsis and diarrhea. The effects upon tumor cells differ from those of such agents as the azapurines, the nitrogen mustards, and azaserine, since these agents, as well as 6-mercaptopurine, did not damage the cell membrane. The cucurbitacins caused a pinocytotic blistering of the Ehrlich ascites cells which, however, was reversible and not inevitably associated with loss of malignancy. No clinical studies of these compounds in human neoplastic disease have been reported at the present time.

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