THE RECENT CHEMISTRY OF NATURAL PRODUCTS, INCLUDING TOBACCO

Proceedings of the Second Philip Morris Science Symposium, 2nd, Richmond, 1975

Richmond, Virginia
October 30, 1975

Edited by NICHOLAS J. FINA

The Plant Kingdom: A Virgin Field for New Biodynamic Constituents

By Richard Evans Schultes*
and Tony Swain**

---

* Paul C. Mangelsdorf Professor of Natural Sciences, Curator of Economic Botany in and Director of the Botanical Museum, Harvard University

** Director, Biochemical Laboratory, Royal Botanic Gardens, Kew, and Research Associate in Phytochemistry, Botanical Museum, Harvard University

> *. . . Plants of the same Figure or Likeness, have for the generality much the same Vertues and Use: Especially if we consider, that the Organs or Structure of the same Vessels and Ductus's to consummate that Regular formation, and consequently the Juices Circulated and strained thro' them cannot be very Heterogenous; and that as for the most part, the Scent and Tast have great affinity, so of course their Vertue likewise cannot be very dissonant.*
>
> JAMES PETIVER (1699)

A SURVEY OF THE PLANT KINGDOM

In 1753 Carl von Linné, who believed that he had classified all living organisms, stated that the Plant Kingdom* comprised 10,000 or fewer species.[56] Ninety-six years later, in 1847, John Lindley set the figure at nearly 100,000 species in 8900 genera.[54] He assigned 1200 species to the algae, 400 to the fungi, 8400 to the lichens, 1800 to the bryophytes, 2000 to the ferns and their allies, 200 to the gymnosperms, and 80,000 to the angiosperms.

Modern plant taxonomy is only just over 200 years old, yet what changes in concepts has consistent research brought about in this field![20,26] Estimates for the Plant Kingdom now vary between 280,000 and 700,000 species, with those botanists most familiar with the still only partially explored tropical regions overwhelmingly favoring the higher estimates. Until recently, the algae have been thought to comprise approximately 18,000 species; the fungi (including bacteria), about 90,000; the bryophytes, from 14,000 to 20,000; the ferns and their allies, 6000 to 9000; the gymnosperms, 675 in 63 genera; the angiosperms, about 200,000 in some 300 families and 10,500 genera.[91] These are very conservative figures, now rather outdated.

---

* We use the term here in the traditional sense to include algae, including blue-greens, fungi, and all photosynthetic terrestrial organisms.[118]

Contemporary specialists estimate the fungi at between 30,000 and 100,000 species—the discrepancy being due to lack of study and adequate means of discriminating these mostly unicellular organisms. In fact, one modern specialist calculates that the grand total might exceed 200,000. The fungi are currently divided approximately as follows: phycomycetes, about 1000 species in 235 genera; ascomycetes, 12,000 to 40,000 species; basidiomycetes, 13,500 to 14,500 species; fungi imperfecti, 10,500 to 30,000 species.[28,46,91]

There is hardly a need to stress the importance of the fungi as a rich source of biodynamic compounds.[16] Almost all of our antibiotics and many other useful medicines are derived from fungi,[14,115] and they are also widely used in the pharmaceutical industry for carrying out specific transformations in the synthesis of steroids and for other purposes.

The algae—all aquatic, but about 56% marine—make up a most varied group of organisms[15,19,61,118,123] now estimated at from 19,000 to about 32,000 species. The procaryotic blue-green algae are among the earliest known organisms: pre-Cambrian fossils dated variously from one to 3 billion years of age and even including modern families. Although used as foods and as a source of iodine since ancient times, the algae have only recently captured the interest of research workers as sources of new biodynamic compounds. Already, however, an impressive number of new compounds have been isolated.[80]

Until the last few years, the lichens have also been neglected as a source of biodynamic constituents. They number from 16,000 to 20,000 species in some 450 genera.[4,29] Recent research has heightened interest in their potentialities, since they have been found to be rich in bacteria-inhibiting compounds[18,44] and to have many chemovars.[9]

The bryophytes—mosses and liverworts—number from 14,000 to 25,000 species, mainly tropical. They have been neglected by phytochemists, and those that have been studied, although giving results of evolutionary importance,[105] appear to be rather devoid of medicinally useful compounds.

The pteridophytes—the ferns and their allies—appear generally to lack biodynamic constituents, in spite of the fact that some (*e.g.*, *Dryopteris felixmas)* are still used as drugs. But again, phytochemical investigation has been far from intense.[107] Recent research has shown that a whole host of compounds which are of potential medicinal interest occurs, including sesquiterpenoid lactones, ecdysones, alkaloids, and cyanogenic glycosides. Further investigation is likely to uncover equally interesting constituents in the 12,000-15,000 species in 250 genera of this very ancient group of plants.[114] One hint may be derived from the results of a recent survey for antibacterial activity in methanol extracts of ferns from Trinidad:[59] crude extracts of 34 of 44

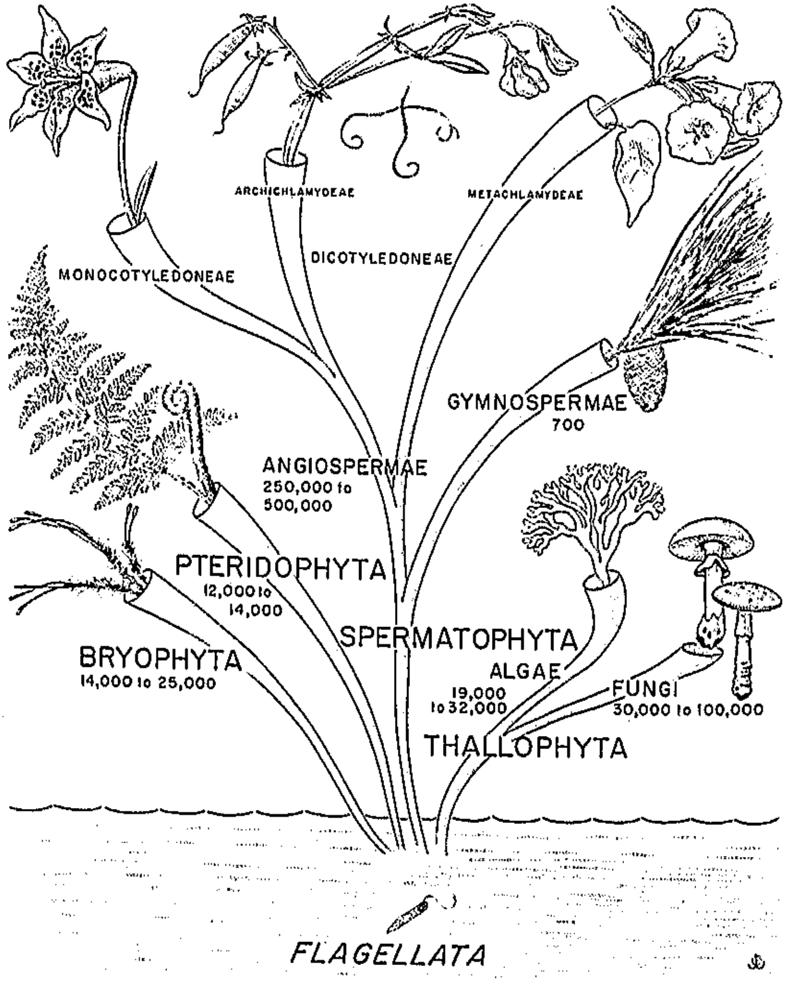


Fig. 1. Phylogenetic representation of the Plant Kingdon showing estimated size of groups in number of species.

(77%) were positive. Although these results may have been due in part to the presence of procyanidins, there are likely to be other components which require investigation. Another hint of the potentialities of this group lies in the recent isolation from the comparatively small family Lycopodiaceae of nearly 100 extraordinarily interesting alkaloids, some of a wholly new type.[10]

In the spermatophytes, the gymnosperms—a group of plants going back in the geological record to the Carboniferous—are of economic importance mainly as a source of timber and resins. The 675 species of this group[91] are known in medicine principally because of *Ephedra*, source of the sympathomimetic alkaloid ephedrine, and *Taxus*, which contains the highly toxic alkaloid taxine. However, there are many other physiologically important constituents, such as the stilbenes and C-methylflavones which act as protective agents against heartwood decay.

The major group of spermatophytes is the angiosperms. Dominant today in most of the world's floras and the major basis of human social and material evolution, the angiosperms are the plants known best to man. Estimates of the extent of the angiosperms vary. Most botanists hold that there are 200,000 to 250,000 species in 300 families. The monocotyledons are usually credited with a quarter of the total. It is now clear from our increased knowledge of the tropical species that this figure is far from reality, and that some estimate nearer 500,000 must be allowed.[91] But even though the angiosperms are phytochemically the best studied group of plants and have been the source of most of our medicinal, toxic, and narcotic species,[104,113] the potentialities in many fields that lie hidden in this group of plants have really been but superficially explored.

It can truthfully be said that chemical examination of the whole Plant Kingdom has only just begun.

THE VAST ARRAY OF PLANT-DERIVED NATURAL PRODUCTS

There are now well over 12,000 secondary organic compounds of known structure, excluding oligo- and poly-saccharides, peptides, and proteins, and the vast majority of these have been isolated from plants. This census includes 5500 alkaloids, 2500 terpenoids (including 400 carotenoids), 1500 flavonoids and related phenolic compounds, 700 acetylenes, 500 polyketides, 250 nonprotein amino acids, 200 fatty acids, and up to 1000 other compounds such as glucosinolates, cyanogenic glycosides, quinones, purines, and others.[22,24,25,27,37,67,72–74,76,77,79,102] Most of these latter groups are certain to be increased in number, complexity, and novelty when modern sophisticated chemical techniques are intensely applied to an examination of the Plant Kingdom as a whole.

There are many compounds in each of the major classes known to be pharmacologically active or highly toxic to man and his domestic animals. Others are used by man, often in crude decoctions, to kill insects, fungi, other mammals, birds, reptiles, amphibia, or fish. Yet the whole number of compounds investigated as potential curative agents represents probably less than 10% of those so far known. This is surprising when we realize that chemical signals, together with their biochemical control mechanisms, are the basis of the inherent coherence of all ecosystems[61] and that plants, by the very catholicity of their biosynthetic pathways, contribute much more than animals to the overall complexity of the interactions involved.[31,101,106,118]

The chemical defences which plants possess against animal herbivores, phytopathogens, and the vagaries of the physical universe must obviously demand our attention in any search for biodynamic agents. For example, plants synthesize many potent insect-feeding deterrents like azadiriachtin[64] and so called third-generation insecticides[20] which are far more effective than DDT. They produce, on being challenged, effective fungicides, such as pisatin and other coumestans, and many compounds that grossly reduce the germination and seedling development of other competing species.[78] All of these compounds are worthy of further study, either for direct use or as models for substances with possibly even more potent activities.

EXAMPLES OF ANGIOSPERM COMPOUNDS

Let us examine the distribution of a few classes of compounds in the angiosperms. This will show not only how widespread are certain groups, but which families or orders of the flowering plants might reward further examination. We will take as examples the alkaloids, the cyanogenic glycosides, and the steroidal sapogenins.

Alkaloids

All chemists recognize that the alkaloids encompass a very diverse assortment of different chemical structures of very different biogenetic origins.[67] The widely employed definition has characterized alkaloids as basic, nitrogen-containing, pharmacologically active compounds which are found both in plants and animals. Specialists have distinguished "alkaloids proper" as those compounds with heterocyclic nitrogen, thus excluding the alkaloidal amines. The term "alkaloid proper" coincides, by and large, with the currently employed definition of "true alkaloids" by Hegnauer, who added a further criterion: that the heterocyclic systems in this group should be derived from amines arising by decarboxylation of amino acid (phenylalanine, tryptophan, ornithine, lysine, histidine, or anthranilic acid);[36] the biological amines and their derivatives which do not contain a heterocyclic ring were grouped as "proto-alkaloids." A third class is recognized: the "pseudo-alkaloids," which, although containing nitrogen, are derived from terpenoids (including sterols) or polyketides. Purines and peptides are usually included in this latter class as well. Fig. 2 gives examples of these 3 types of alkaloids.

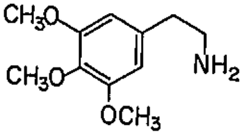
The concept of considering alkaloids or other compounds in relation to their biogenetic origins and pathways has become basic to their use in modern chemotaxonomic research.[27] Phylogenetic relationships between plant groups can often be established, substantiated, or clarified through the use of such biogenetic relationships, whereas consideration of "alkaloids" *per se* throws little light on the problem.[36,74] It is, however, sufficient for our purposes here, in examining their distribution in the Plant Kingdom, to accept a rather loose and inclusive definition of alkaloids, and to include the "proto-" and "pseudo-" alkaloids together with the rest.

Before 1805, when Sertürner discovered a new kind of nitrogenous (alkaline) chemical compound in the opium poppy, *Papaver somniferum*, no alkaloids were known.[43] Sertürner named the new compound morphine for the Greek god of sleep Morpheus, and, because it was basic, he termed this class of compound "alkaloids." Chemists very quickly discovered more such compounds. By 1949, approximately 1000 were recognized. Ten years later, this figure was increased to 2000. By 1969, the total stood at 4350, and the current figure undoubtedly passes the 5500 mentioned above.[73]

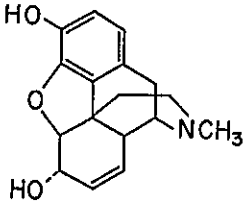
Of the 1969 total,* only 270 were found in nonangiosperms: fungi, 130; algae, 5; horsetails, 5; lycopods, 100; gymnosperms, 30. (Note: there are no alkaloids known in the ferns.) The remaining

---

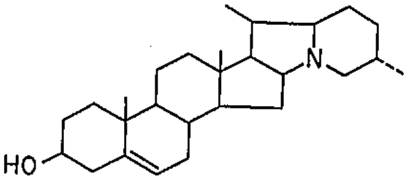
* It should be noted that much of our knowledge about the distribution of alkaloids relies on the application of color or precipitation tests. These are not always reliable, as many nonalkaloidal compounds may give similar reactions.[22]



Mescaline
A proto-alkaloid



Morphine
A true alkaloid



Solanidine
A pseudo-alkaloid

Fig. 2. Some examples of alkaloids.

figure of over 4000 alkaloids are found in the angiosperms, which means that over 90% of known alkaloidal compounds occur in this class.

Within the angiosperms there is great disparity in the distribution of alkaloids among the various families. We have taken here the results of a random survey of over 4000 species of plants for alkaloids.[99] Although this survey is based on color and precipitation tests, we have noted only the chloroform-soluble bases. We have also based our analysis on the distribution in genera rather than species, since there is a tendency to examine many related species which biases the data. On this basis, we find that 30.5% of the angiosperm genera examined show a positive reaction for alkaloids, with the monocots having only 26% and the dicots 31% of alkaloid-containing genera.

Within the superorders of the dicotyledons,[109] the Ranunculanae (81%), Magnolianae (53%), and the Lamianae (42%) are all alkaloid-rich, while the Ericanae (7%), Myrtanae (7.5%), and Hamamelidanae (8%) are almost devoid of alkaloidal families and genera. In the monocotyledons, the Lilianae (32%), Arecanae (24%), and Commelinanae (22%) have the highest percentage of alkaloidal genera, with the remaining superorders, Juncanae (10%) and Alismanae (6%) being much lower. These figures are approximately the same as those obtained when one examines the distribution of known alkaloids in the various lower taxonomic concepts.

It should be noted, however, that the overall picture given by this survey may be only approximately correct, since there are many families which have not been examined in depth for alkaloids. This cannot be better illustrated than by studies on the Orchidaceae. This group is the largest of all plant families, with 25,000-35,000 species in about 600 genera. Earlier surveys of alkaloids showed only 11 genera as being positive, although only 2 alkaloids—dendrobine and nobiline from the horticulturally important *Dendrobium nobile*—were isolated. The family, then, stood out as one of the least important from the point of view of alkaloids. As Lindley, orchidologist of the last century, wrote: "It often happens that those productions of nature which charm the eye with their beauty . . . have the least relation to the wants of mankind, while the most powerful virtues or most deadly poisons are hidden beneath a mean exterior . . ."[54] In view of the relationship of the orchids to the lily group, a spot test was carried out for alkaloids on 1500 herbarium specimens randomly sampled throughout the family in the Orchid Herbarium of Oakes Ames in the Botanical Museum of Harvard University. The results indicated 8% positive.[91] More recent phytochemical studies on fresh orchids,[56-58] however, showed that 32% of the 1000 or so species examined were alkaloidal. What is even more significant is the uniqueness of many of the orchid alkaloids, some of which will undoubtedly turn out to be of extreme biodynamic interest.[93]

Cyanogenic Glycosides

Let us now turn to cyanogenesis. Most plants which yield hydrocyanic acid on crushing contain cyanogenic glycosides.[98] These compounds (an example of which is illustrated in Fig. 3) occur in at least 800 species in over 70 (22% of) angiosperm families. They are especially important in the Araceae, Euphorbiaceae, Flacourtiaceae, Gramineae,

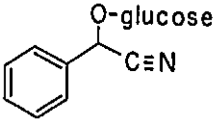


Fig. 3. Prunasin, a cyanogenic glycoside.

Leguminosae, Malesherbiaceae, Passifloraceae, Proteaceae, Rosaceae, and Turneraceae. Many families are devoid of such compounds (*e.g.*, Orchidaceae). Their distribution in lower plants is not so well known, but a recent survey of over 300 ferns showed only 3% to be cyanogenic.[33] It is of interest, however, that cyanogenesis has been shown to be genetically polymorphic in *Lotus corniculatus* and several other legumes,[49] as well as in bracken (*Pteridium aquilinum*);[33] this polymorphism is reflected in the selection of the plant by herbivores. Obviously, this factor is of importance here and in the search for many other types of new drugs, as shown in the case of the steroidal lactones in *Withania.*[53]

Steroidal Sapogenins

Finally, let us consider the steroidal sapogenins. Species containing these compounds have been valued by primitive societies for ages in the preparation of arrow poisons. These principles are extremely active in altering membrane permeability and, hence, show hemolytic and other important effects.[3] Their distribution is chemotaxonomically interesting, since they are much less common than the corresponding triterpenoid sapogenins.[27] They are found only in the

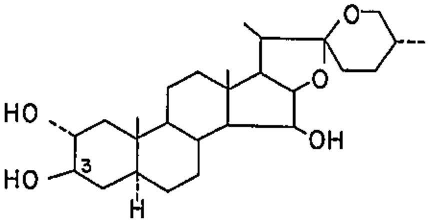


Fig. 4. Digitogenin, a steroidal sapogenin (aglycone). In the saponin complex sugar residue is attached to the -OH group at C-3.

Fouquieriaceae, Leguminosae, Scrophulariaceae, Solanaceae, and Zygophyllaceae in the dicotyledons but are particularly prominent in the Agavaceae, Dioscoriaceae, Liliaceae, and Amaryllidaceae in the monocotyledons. Except for one report of their occurrence in the Palmae and one in the Bromeliaceae, they have not been identified in any other plant family. This is surprising in view of the known wide distribution of plant sterols which occur in almost all plant species. It appears also that this class of sapogenins is almost mutually exclusive with their triterpenoid congeners.[27]

INFORMATION SOURCES

Unless one were forewarned, one might assume that the great advances in phytochemistry have resulted from a carefully organized search on the part of botanists and chemists alone. This picture is far from true. The progress that has characterized recent phytochemical research has been, in great part, the result of the cooperative interplay of many other diverse and often seemingly unrelated disciplines; and in few other fields has the interdisciplinary approach been so essential and so effective. Naturally, the basic disciplines involved are botany, chemistry, and pharmacology. But anthropology, archaeology, linguistics, history, sociology, comparative religion, and other specialties have likewise contributed to our search for new biodynamic constituents. This intertwining of data and points of view from diverse fields has been called ethnopharmacology.[83–86,90]

Random Screening

Clearly, a number of different avenues are open in the search for new plant constituents. The most obvious is probably a random or semirandom screening of plants. This method is direct, but it is expensive in time and money. It has been employed in several recent surveys. Some have concentrated on a search for specific constituents—alkaloids,[72,99] flavonoids,[11] etc.[17] Other surveys have been geographically limited and concerned with a larger number of constituents, such as those which have been carried out on the floras of Australia,[8] New Guinea,[34] West Africa,[108] India,[50] and many other countries, including parts of the United States.[103]

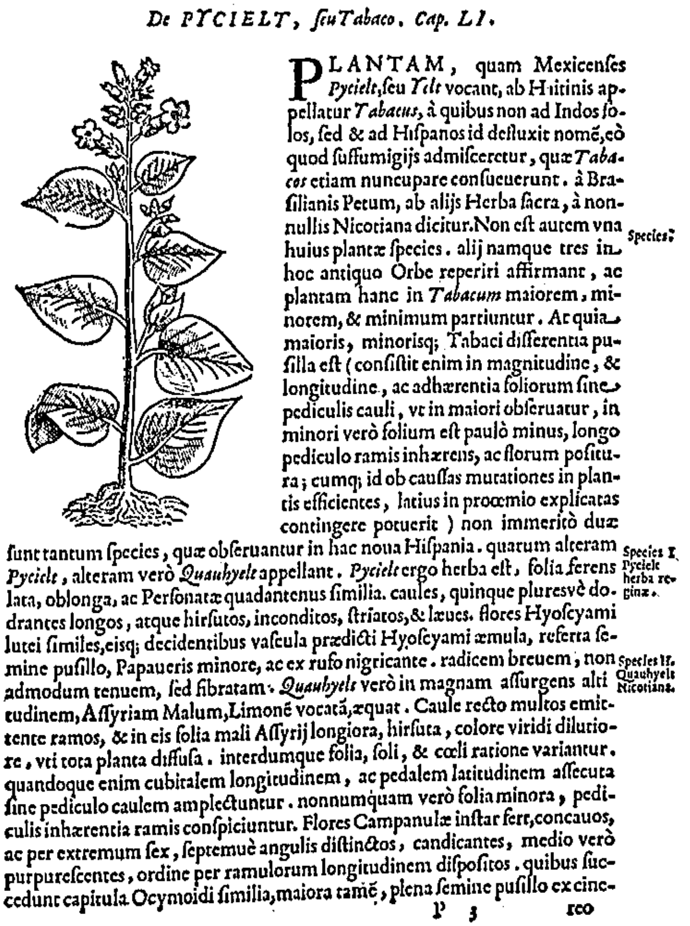
Other random surveys have concentrated upon a search for plant constituents active for specific diseases or for very definite biological properties. Thus, there have been surveys for antiviral or antibacterial activity, for cytotoxic effects, and for a broad spectrum of other properties. About 50% of temperate-zone lichens, for example, have been shown to possess lichen acids capable of inhibiting gram-positive bacteria and even tuberculosis bacilli and some fungi.[18,44] Undoubtedly, one of the most ambitious random searches has been the National Institutes of Health's screening of plants for possible antineoplastic activity.[35] More than 26,000 plant extracts representing some 6500 species have been tested. It has been suggested that "... in the light of present knowledge and experience ... a random selection and testing of plants selected from a broad cross section of families and genera will prove of greatest value in attempts to discover new entities for the treatment of clinical malignancies."[23] Faced with the enormous size of the Plant Kingdom—even of only the higher plants—this type of random sampling requires the investment of great sums of money, the availability of many kinds of specialists, and relatively long periods of time. It can be carried out today only with governmental or international support.

Literature

Another common approach is to concentrate research on plants which have been, or still are, used in folk medicine as described in both ancient and contemporary literature.[83,84,86] Unfortunately, this literature has many drawbacks. It is often diffuse, uncritical, of hearsay nature, and is scattered throughout many fields: anthropology, ethnology, history, a variety of chronicles, reports of explorers, travelers and missionaries, and the writings of others whose direct contact has been with primitive societies.

Ethnobotanical literature goes back some 3700 years to the Code of Hammurabi. Many might think it folly to spend time on such ancient literature. Yet, had data in the Egyptian papyri been critically evaluated earlier, we might not have had to wait until the 1940's for our knowledge of the antibiotic properties of the products of certain fungi.[14] There may well be much still to be learned from a discerning search for hints in the medieval herbals, especially those from outside Europe and the Near East, even though it is generally assumed that they have been wholly exhausted.

There are 2 other sources that must not be neglected. One is the writing of naturalists, physicians, and herbalists of the sixteenth and seventeenth centuries—intrepid, enquiring, insatiable chroniclers of things and events in the new lands fast opening in that exciting period. In many cases it is possible to winnow the grain from the chaff; yet this



De PYCIELT, ſeu Tabaco. Cap. LI.

PLANTAM, quam Mexicenſes *Pycielt*, ſeu *Yelt* vocant, ab Haitinis appellatur *Tabacus*, à quibus non ad Indos ſolos, ſed & ad Hiſpanos id defluxit nomē, eò quod ſuffumigijs admiſceretur, quæ *Tabacos* etiam nuncupare conſueuerunt. à Braſilianis Petum, ab alijs Herba ſacra, à nonnullis Nicotiana dicitur. Non eſt autem vna huius plantæ ſpecies. alij namque tres in hoc antiquo Orbe reperiri affirmant, ac plantam hanc in *Tabacum* maiorem, minorem, & minimum partiuntur. At quia maioris, minoriſq; Tabaci differentia puſilla eſt (conſiſtit enim in magnitudine, & longitudine, ac adhærentia foliorum ſine pediculis cauli, vt in maiori obſeruatur, in minori verò folium eſt paulò minus, longo pediculo ramis inhærens, ac florum poſitura; cumq; id ob cauſſas mutationes in plantis efficientes, latius in proœmio explicatas contingere potuerit) non immeritò duæ ſunt tantum ſpecies, quæ obſeruantur in hac noua Hiſpania. quarum alteram *Pycielt*, alteram verò *Quauhyelt* appellant. *Pycielt* ergo herba eſt, folia ferens lata, oblonga, ac Perſonatæ quadantenus ſimilia. caules, quinque pluresvè dodrantes longos, atque hirſutos, inconditos, ſtriatos, & læues. flores Hyoſcyami lutei ſimiles, eiſq; decidentibus vaſcula prædicti Hyoſcyami æmula, referta ſemine puſillo, Papaueris minore, ac ex rufo nigricante. radicem breuem, non admodum tenuem, ſed fibratam. *Quauhyelt* verò in magnam aſſurgens altitudinem, Aſſyriam Malum, Limonē vocatā, æquat. Caule recto multos emittente ramos, & in eis folia mali Aſſyrij longiora, hirſuta, colore viridi dilutiore, vti tota planta diffuſa. interdumque folia, ſoli, & cœli ratione variantur. quandoque enim cubitalem longitudinem, ac pedalem latitudinem aſſecuta ſine pediculo caulem amplectuntur. nonnumquam verò folia minora, pediculis inhærentia ramis conſpiciuntur. Flores Campanulæ inſtar fert, concauos, ac per extremum ſex, ſeptemuè angulis diſtinctos, candicantes, medio verò purpureſcentes, ordine per ramulorum longitudinem diſpoſitos. quibus ſuccedunt capitula Ocymoidi ſimilia, maiora tamē, plena ſemine puſillo ex cine-

Species.

Species I. Pycielt herba reginæ.

Species II. Quauhyelt Nicotiana.

P 3 reo

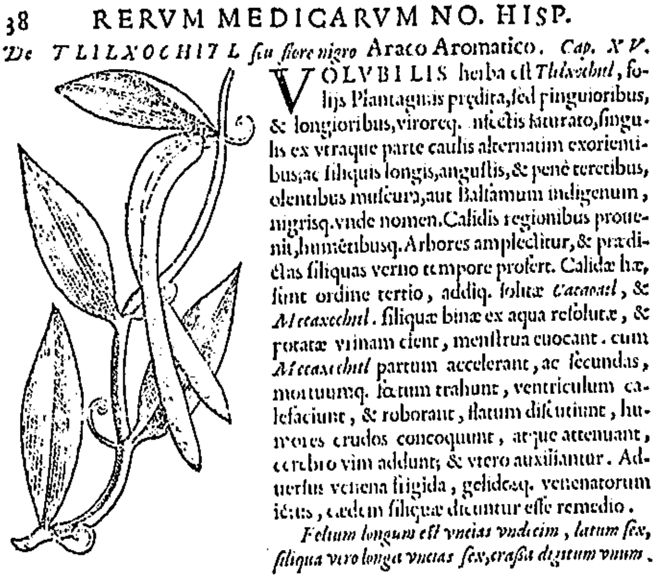
Fig. 5. Reproduction of the illustration of *Nicotiana rustica* (picietl) and part of the discussion of tobacco from Francisco Hernández' *Rerum Medicarum Novae Hispaniae Thesaurus, seu Plantarum, Animalium, Mineralium Historia* (Rome, 1651). Hernández, a medical doctor, carried out ethnopharmacological studies among the Aztecs during the sixteenth century.

important task has rarely been attempted. Modern research workers might well learn from Rumphius, whose work in the seventeenth century[121] is basic to the natural history of the East Indies and whose writings include notes on folk uses of more than 700 species of plants. Insisting on personally verifying everything whenever possible, he nevertheless wrote down what he considered fact as well as hearsay, or, as he said,

> *. . . fables, superstitions, and old women's babblings. . . certainly not, as it were, that I put a firm trust in them [but because] in those faery tales always some grain of Truth, some unseen natural virtue lies hidden, and to excite amateurs to diligent search, I assure them that in these lands many secrets of nature are revealed daily, erstwhile unknown to Europeans and seemingly unworthy of belief.*

The serious writings of the early explorer-naturalists and missionary-doctors of the New World are especially rich in still uninvestigated ethnopharmacological reports. In many cases these writings are well illustrated, and the identity of the plant is not in question. One of the greatest of these sources is *Nova Plantarum, Animalium et Mineralium Mexicanorum Historia,* written between 1570 and 1575 by Dr. Francisco Hernández, physician to the King of Spain, who sent him to live with and study Aztec medicine.[39]

Use of these older literature sources, though often frustrating because of their casualness and incompleteness, has been spectacularly successful in a number of instances in leading modern specialists to new avenues. Several examples will suffice. The rediscovery of the use in Mexico of several potent hallucinogens—especially of some 24 species of fungi in 4 genera and several morning glories—has led to important, novel, and, in both cases, totally unexpected chemotaxonomic and biochemical discoveries.[38,41,82,87,94,97] An example from the Old World is the rediscovery of the tranquilizing use of the Indian snake root *Rauwolfia,* clearly set forth in the Vedas as early as 1500 B.C., which has led to significant phytochemical discoveries that have revolutionized treatment of hypertension and psychotic disorders and has had a tremendous impact on treatment of many mental instabilities.[122]



38 RERVM MEDICARVM NO. HISP.

De TLILXOCHITL *ſeu flore nigro* Araco Aromatico. *Cap. XV.*

VOLVBILIS herba eſt *Tlilxochitl*, folijs Plantaginis prędita, ſed pinguioribus, & longioribus, viroreq. infectis ſaturato, ſingulis ex vtraque parte caulis alternatim exorientibus; ac ſiliquis longis, anguſtis, & penè teretibus, olentibus muſcum, aut Balſamum indigenum, nigriſq. vnde nomen. Calidis regionibus prouenit, humentibuſq. Arbores amplectitur, & prædictas ſiliquas verno tempore profert. Calidæ hæ, ſunt ordine tertio, addiq. ſolutæ *Cacaoatl*, & *Mecaxochitl*. ſiliquæ binæ ex aqua reſolutæ, & potatæ vrinam cient, menſtrua euocant. cum *Mecaxochitl* partum accelerant, ac ſecundas, mortuumq. fœtum trahunt, ventriculum calefaciunt, & roborant, flatum diſcutiunt, humores crudos concoquunt, atque attenuant, cerebro vim addunt; & vtero auxiliantur. Aduerſus venena frigida, gelidæq. venenatorum ictus, eædem ſiliquæ dicuntur eſſe remedio.

Folium longum eſt vncias vndecim, latum ſex, ſiliqua vero longa vncias ſex, craſſa digitum vnum.

Fig. 6. The earliest illustration of tlilxochitl, the vanilla plant *(Vanilla planifolia)*, from Francisco Hernández' work, *Rerum Medicarum Novae Hispaniae Thesaurus, seu Plantarum, Animalium, Mineralium Historia* (Rome, 1651).

Recent analytical studies of Aztec medicine have indicated that "although magic and religion were quite important in the Aztec treatment of disease, there was a strong empirical underpinning which has not received the attention it merits."[48,60] Of 25 plants studied, 16 would produce most of the effects claimed by the natives; 4 possibly would be active; and 5 do not seem, from what is known of their chemical constitution, to possess the effects claimed. This implies that 80% might be effective.

The second source is undoubtedly more promising: modern ethnobotanical writings. This source is much more prolific and reliable than we suspect. Many projects, especially in recent years, have concentrated on studies of the intricacies of plant uses and interpretation of plant properties in still viable primitive societies. They range from complete studies of the uses of and beliefs about plants among natives[116,117] to incidental but usually significant remarks on one or several species.

Fig. 7. A page from *The Badianus Manuscript (Codex Barberini)*, edited by E. W. Emmart (1940), showing 2 medicinal plants. The plant on the left is tolohuaxihuitl *(Datura inoxia)*, one of the most important of the Aztec medicinal plants. The Badianus manuscript is an Aztec document of 1552 discovered recently in the Vatican Library.

A first step in evaluating and utilizing this vast fund of scattered modern information would be to gather it together in one large bibliography and possibly to computerize it—a seemingly colossal task, but actually not incommensurate with the wealth of new information that conservatively could be expected to accrue therefrom. An interesting example of the value of this method of handling ethnopharmacological information is the recent computerization of literature references to the use of plants in ethnomedicine as antifertility agents.[100]

Exploration

But ethnobotanical data derived entirely from the literature often have distinct limitations. They may be botanically uncritical or anthropologically unsophisticated—or deficient from both points of view. Voucher specimens for exact identification of the plants in question may not be available. When the data refer to the medicinal uses of plants, diagnosis of diseases may be open to question. Fre-

Fig. 8. Medicine man of the Kamsá Indian tribe in Sibundoy, Colombia, preparing to diagnose an illness after having taken an hallucinogenic drink prepared from *Datura*. (Photograph by R. E. Schultes)

quently, when the information is found in floras, no specific tribes or groups of people or few geographical or ethnographical facts may be mentioned. All in all, it would seem not to be wise to base a whole program of natural-products research on the literature alone, yet there have been pharmaceutical searches organized exclusively on this basis. They have not led to spectacular successes.

And here we come to the great challenge that faces us today: the need for modern, sustained, and well organized field work among people still living in primitive societies. While there is certainly no reason to presume that peoples in primitive cultures possess any particular insight into the discovery of biodynamic plants, it is true

Fig. 9. Medicine man of the Barasana tribe on the Rio Piraparaná in Amazonian Colombia preparing a ritualistic curing ceremony during which the hallucinogenic caapi drink (made from *Banisteriopsis caapi*) is employed as an aid in diagnosis. (Photograph by R. E. Schultes)

that they do live in a much more intimate relationship with their ambient vegetation than do those of urbanized, advanced civilizations. Trial and error and the experience of centuries have built up a rich store of folklore. It is, therefore, a shortcut, as it were, for us today to use to our advantage.

There are not available at the present time enough well trained ethnobotanists, and the immediate future does not promise enough to cope with the rapid disappearance of primitive cultures. Civilization is closing in on many, if not most, parts of the world still sacred to aboriginal peoples. Our great concern lies in the progressive divorcement of man in the less advanced societies from dependence upon his immediate environment. A prime example is the Amazon Valley—an area with an indigenous flora of at least 60,000 species, still only partially known, and with peoples characterized by an exceedingly penetrating perspicacity concerning the uses of unusual biodynamic properties of their plants. Yet, one after another aboriginal cultures in this vast area are rapidly being lost. We must, for both academic and practical purposes, salvage some of the medico-botanical lore of this part of the world, before it shall have been forever entombed with the culture that gave it birth.

Herbaria

There is still another area where research has languished—an area rich in information on folk uses and the properties of plants which, in many cases, might orient the natural products chemist toward profitable goals. This area has been sorely neglected. It is the wealth represented in the herbarium collections of the world.[75]

Taxonomic botanists rely on the archival material filed away in large collections called herbaria—material collected over many years in all parts of the world, usually by trained botanists and prepared in the form of dried and pressed specimens firmly attached to a heavy sheet of paper and provided with a label on which all pertinent information concerning the plant is available. There are approximately 1800 herbaria in the world.[42] Many are small or limited to a certain group of plants or to some specialty. But a large number have very extensive holdings and have been established for more than a century.

The size of several of the larger herbaria of the world will illustrate how vast the potentiality for ethnobotanical notes on the collections may be:[42] Paris (Muséum d'Histoire Naturelle) 7,200,000 speci-

Fig. 10. An herbarium specimen of *Brunfelsia grandiflora* D. Don supsp. *schultesii* Plowman, collected as a phytochemical voucher by James L. Zarucchi, March 4, 1975 in Amazonian Colombia. The specimen is preserved in the Economic Herbarium of Oakes Ames, Botanical Museum, Harvard University.

mens; 5,000,000 specimens each at Leningrad (Komarov Botanical Institute), Geneva (Conservatoire et Jardin Botanique), and Kew (Royal Botanic Gardens); 4,000,000 each in Stockholm (Naturhistoriska Riksmuseet), Cambridge (Harvard University's combined herbaria), New York (New York Botanical Garden), and Washington (United States National Herbarium); and 2,500,000 each in Chicago (Field Museum), Leiden (Rijksherbarium), and St. Louis (Missouri Botanical Garden).

In these major herbaria—together totalling nearly 50,000,000 specimens—many of the sheets of plants contain the collector's annotation of a local use. This information is not only firsthand, but the data concerning locality, people, and time are precise. Furthermore, unlike most literature citations, there can be no doubt about the identity of the plant specimen; there exists the actual voucher specimen for authentication. No matter how many years have elapsed since collection of the specimen, it is always possible to return to the exact locality for more information, for authentication of information, or for bulk samples for chemical study.

Several interesting "herbarium searches" have been done, but there still lie uninvestigated many fertile collections. Dr. Siri von Reis Altschul of the Botanical Museum of Harvard University completed and published an index of significant notes on food and medicinal uses of plants taken over a period of 4 years from the 2,500,000 specimens in the phanerogamic herbaria at Harvard University.[6-7] This systematic search yielded more than 7500 reports, many of which bear investigation by modern methods in view of their verified folk uses. The same botanist is now conducting a similar search in the herbarium of the New York Botanical Garden, which promises to uncover equally significant new hints for the phytochemist and pharmacologist.

Archaeological Material

Other minor or limited approaches for phytochemical research may on occasion arise from other aspects of ethnobotany. One of the most interesting lies in the study of plant remains from archaeological sites.

Ancient peoples may have had different uses of plants. There are a number of examples. What can explain the extensive remains of *Lithosperum ruderale,* known to possess antifertility properties, in certain archaeological sites in the southwestern United States?[51] The abundance of the remains militates against its use as a contraceptive agent. It could not have been a food. The remains of coca leaves in very early Peruvian mummy bundles may, of course, indicate that the ancients simply used the plant as a narcotic; but perhaps it indicates more basic employment in ethnomedicine.[111] The recent discovery in the tomb of a Bolivian shaman, dated about 500 A.D., of *Ilex guayusa* (Fig. 11) for preparation as a snuff, and with indications that it may also have been applied rectally in the form of an enema, suggests that these Indians employed a caffeine-rich plant in ways no longer known or employed in the modern world.[92] The recovery of large stores of seeds of the

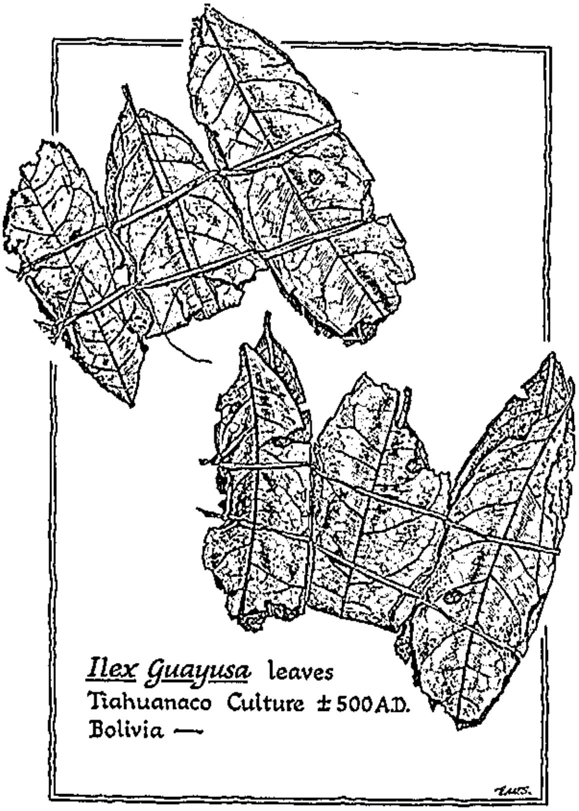


Fig. 11. *Ilex guayusa* leaves from the Tiahuanaco culture of Bolivia. (Drawing by E. W. Smith)

Fig. 12. Richard Spruce, one of the greatest explorers of the Andes and Amazon. He spent 14 years in the middle of the last century in South America, collecting many toxic, medicinal, and narcotic plants and carrying out extensive research on rubber and quinine. (Drawing by E. W. Smith)

sapindaceous *Ungnadia speciosa* in dry cave sites in the American Southwest has given impetus to phytochemical investigation of this seed. It could not have been used as a food; it is toxic. Why was it there in large bags—in a site dated 1500 B.C.?[2] Could it have had some strange ceremonial use as a poison or narcotic—a use now totally forgotten? These and many other hints from digging into the past relationship of ancient man and the Plant Kingdom may help orient modern research into the wealth of biodynamic constituents of plants.

ON THE HORIZON: THE WHY AND WHERETO OF FUTURE RESEARCH

Why should we look to the Plant Kingdom for new biodynamic principles? This question—at least to a botanist—might seem to be so trivial and juvenile as not to deserve the attention of a serious answer. Yet it must be taken up, if only because it has so often been asked. The answer in brief is that the Plant Kingdom still represents a vast storehouse of unknown compounds and it is only by further examination of its riches that we will be able to make progress in the design of new medicines and the further understanding of our ecological heritage.

It is such a simplistic statement that one might hesitate to make it in a serious discussion. We do not hesitate to make it—because one of the authors has spent his life exploring the tropical American forests for new biodynamic plants; the other has spent his life in an examination of the chemical peculiarities of hitherto uninvestigated plants and, as mentioned earlier, the probable function of these compounds as feeding deterrents and toxic agents against insects and phytopathogens. Such studies show the wide diversity of physiological activities which plants possess. Truly it may be said that plants live on their chemical wits![106]

We must now come to grips with the potential medicinal use for this extraordinary array of chemicals that Nature has provided for us.[22,24,76,77,102] We agree that the course of investigation into synthetic drugs should not be interrupted. Yet the study of synthetic compounds represents a simpler, more direct investigation relegated, more or less, to the chemist and the pharmacologist; and in very few cases has it led to a novel group of compounds based on a natural model. An in-depth chemical study of the complexity of perhaps half a million species of plants demands an interdisciplinary approach—an approach in which the botanist and the ethnobotanist must take the first step. But their work must be backed up closely by that of the chemist and the pharmacologist, preferably with field work as well as laboratory investigation. Certainly, this will lead to a better understanding of the *raison d'être* of all secondary compounds.[118]

What can we say about the future of our search for new biodynamic plant constituents?

When we realize that there are more than 50 classes of secondary organic constituents and that only a small percentage of plants have been phytochemically investigated—and even then usually only for one or 2 categories of constituents—the wide-open field for research must be obvious.

Furthermore, sophisticated modern chemical techniques can greatly amplify the horizon attainable by today's phytochemists. An excellent example is the increase in chemical understanding of *Cannabis,* one of man's oldest cultivated plants, going back nearly to the beginning of Old World agriculture some 10,000 years ago. Chemical study during the past 25 years has resulted in the discovery of more than 30 cannabinolic compounds,[62,65] and modern science believes that this most complex of plants may well have interesting, medically significant biodynamic constituents.

Even though it represents nothing more than an educated guess, we would venture to say that less than 10% of the organic constituents of the angiosperms are known—that fully 90% remain for discovery and investigation. Justification for doubt there might be. When one combines, however, the spectacular advances in the chemistry of secondary organic plant constituents with the many hints offered by modern chemotaxonomy and ethnobotany, then this "guess" may not appear to be too extravagant.

From the chemotaxonomic point of view, there are many clews as to where we might profitably search for further biodynamic constituents.[37] Such a search depends initially mainly on the pharmacologist to recognize the plant species and classes of compound which are of interest. Three examples should suffice. The importance of kava (from the piperaceous *Piper methysticum*) as an intoxicant has long been known,[30] but more recently it has been recognized that its main active constituent, kawain, (Fig. 13) and related styrylpyrones, are central-nervous-system-active muscle relaxants. Indeed, the drug is now used in clinical practice to alleviate nocturnal myospasms. Recently, atten-

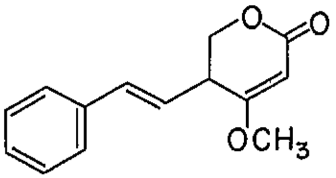


Fig. 13. Kawain, a styryl pyrone.

tion has been drawn to the antifungal activity of other styrylpyrones[47] which occur in related families such as the Lauraceae, and it seems obvious, in view of their potentially useful biodynamic properties, that we should devote more effort to an examination of their distribution and pharmacological evaluation.

A second group of potentially important compounds is the iridoids (Fig. 14). Until quite recently, their structures were unknown; but recently they have been shown to be active against several microorganisms.[47] These monoterpenoid lactones are obviously worthy of closer study, since their sesquiterpenoid congeners show extreme promise as antitumor agents.[62] The iridoids are usually circumscribed to the Scrophulariales and Gentianales, with about 50% of the families of these orders containing such compounds;[46] but they occur sporadically in other members of the "Rosalian complex" (Hamamelidae, Dilleniidae, and Rosidae). The fact that some iridoids act as insect pheromones and others as attractants to cats and other Felidae indicates their potential importance.

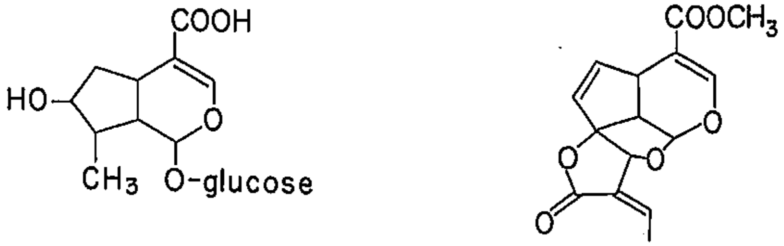


Fig. 14. Loganin (left), an iridoid, and isoplumericin, a fungicidal iridoid.

Finally, consider the search for novel natural products with antitumor activity.[62] It is obvious from a glance at the structures of the most active compounds that they are sesqui- or di-terpenoids which contain methylene and, especially, 5-membered-ring lactone systems. Obviously, a fuller examination of the Compositae, with its wealth of such compounds,[40] would be worthwhile, especially in view of the well known contact allergies which many species of this family impart.[63]

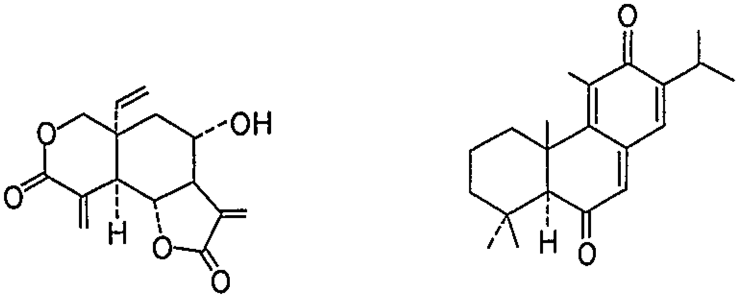


Fig. 15. Vernolepin (left), a cytotoxic sesquiterpenoid lactone, and taxodione, a Walker carcinosarcoma-256-inhibitory diterpene.

It is less obvious that ethnobotany can suggest numerous and diverse indications of as yet wholly uninvestigated biodynamic activity. It may, however, suffice to point out a few instances that have resulted from our recent work in tropical South America. When one realizes how these observations are circumscribed by the number of researchers, in time and geographical region, one may easily appreciate how many more observations could be made with a larger corps of researchers working over a longer period of time and across the 5 continents.

New and chemically unexplained arrow poisons, collected in the last few years in the northwest Amazon, have been found in plants belonging to *Virola* (Myristicaceae) (Fig. 16), *Schoenobiblos* (Thymeliaceae), *Ocotea* (Lauraceae), and *Swartzia* (Leguminosae), none of which has been chemically well investigated. The genus *Ryania* contains species which are among the most toxic plants of the Amazon. Several species of the closely related Caryocaraceae, Marcgraviaceae, Quiinaceae, and Humiriaceae—all poorly studied chemically and all apparently lacking alkaloids—are elements of the toxic flora of tropical South America.[88,90] A curious ichthyotoxic plant, *Patinoa ichthyotoxica* (Bombacaceae), employed by the Tikuna Indians in fishing, has not been chemically analyzed.[89]

Members of the Bignoniaceae and Monimiaceae are also frequently indicated as toxic elements in the neotropical flora. A recently described species of the pepper family, *Piper erythroxyloides*, is chewed by the Motilines of northern Colombia for its tongue-numbing effect,[95] due possibly to the presence of styrylpyrones. The Connaraceae, allied to the richly alkaloidal family Leguminosae, has species known or employed by natives as poisons; but in spite of this wide recognition and the size (some 350 species) and phylogenetically interesting relationships of the family, it is chemically almost unstudied.[88,90] The Ericaceae, especially in the Andean highlands, deserves much deeper investigation. *Aristolochia* (Fig. 17), now attracting attention because of interesting new compounds that it contains,

Fig. 16. *Virola theiodora.* (Drawing by E. W. Smith)

some of which appear to be cytotoxic, has rather striking uses in aboriginal medicine in the Amazon.

The Rubiaceae, a large family which—partly because of many economic plants such as *Cinchona* and *Coffea*—has received consistent chemical study, merits greater attention along lines that ethnobotanical studies may indicate. Intensification of chemical studies in this family is indicated by the recent discovery of N,N-dimethyltryptamine in the leaves of *Psychotria viridis*, used in South American hallucinogenic preparations.[60] Furthermore, a number of species of rubiaceous plants have recently been cited as poisonous or as ingredients of poisonous preparations: *Duroia, Psychotria, Palicourea, Retiniphyllum,* among other genera.[88,90]

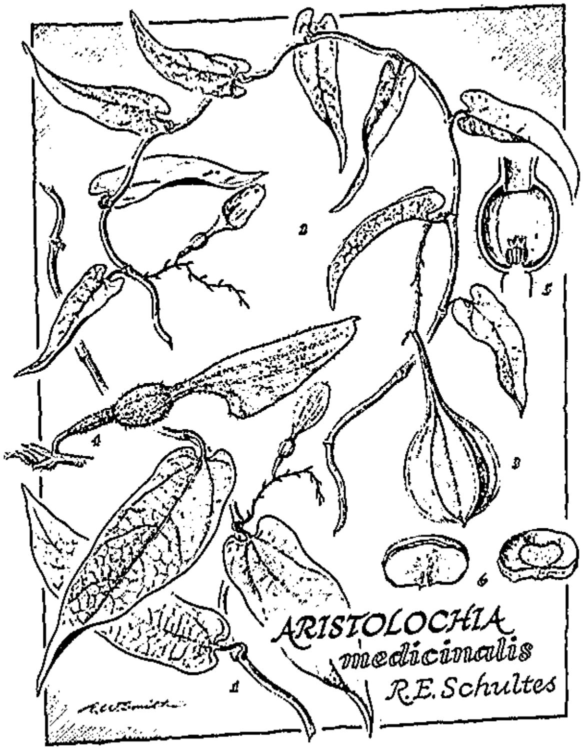


Fig. 17. *Aristolochia medicinalis.* (Drawing by E. W. Smith)

Fig. 18a. Habit of *Brunfelsia grandiflora* subsp. *schultesii* in the Leticia area of Amazonian Colombia. This plant, known locally as chiric sanango, is an important element in folk medicine and is presently under investigation for possible cardiovascular activity. (Photograph by T. Plowman)

Fig. 18b. Flower of *Brunfelsia grandiflora* subsp. *schultesii* (Solanaceae). (Photograph by T. Plowman)

Notwithstanding the great amount of chemical attention devoted to the Solanaceae for such a long time as a result of economic interest in tobacco, tomato, and potato, the use of many other members in medicine, the large number of narcotic or hallucinogenic species, and the spectacular poisons of the nightshade family, there remains a vast field for modern phytochemical investigations in this family of some 90 genera and nearly 3000 species. In fact, some of the hallucinogenic uses of several genera in this family—*Brunfelsia*[68] (Fig. 18), *Cestrum*,[97] *Iochroma*,[97] *Latua*[69] (Fig. 19), *Petunia*[32]—remain either unstudied or have had only cursory chemical investigation.[87,97]

The Lythraceae should also be placed high on the priority list, if only because of the recent discovery of several new quinolizidine alkaloids in the Mexican auditory hallucinogen *Heimia salicifolia*.[87,97] Ethnobotanical observations also suggest the advisability of looking at the biodynamic constituents of such rather unlikely families as the Amarantaceae, Araceae (Fig. 20), Cucurbitaceae, and Olacaceae.[90] A thorough chemical study of the Malpighiaceae is long overdue[96] and

Fig. 19. *Latua pubiflora* of the Solanaceae is a strict endemic of central Chile and has a reputation as a potent poison and hallucinogen. It has recently been recollected after many years. Tropane alkaloids have been reported from this species. (Drawing by J. B. Clark)

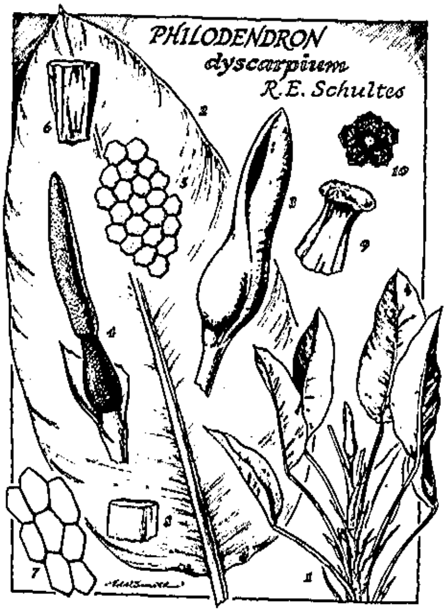


Fig. 20. *Philodendron dyscarpium*, a member of the Araceae and native to quartzitic savannas in Amazonian Colombia. The inflorescences of the plant are widely used in the region as oral contraceptives, but the plant has not been pharmacologically or chemically studied. (Drawing by E. W. Smith)

has recently been stimulated by the discovery of N,N-dimethyltryptamine in leaves of *Banisteriopsis rusbyana* (Fig. 21), an additive to the hallucinogenic drink ayahuasca, caapi, or yajé prepared basically from the β-carboline-rich species *B. caapi* or *B. inebrians.*[70] The discovery and frequency of folk uses of tropical American members of the Apocynaceae—a family certainly accorded a great amount of chemical study in recent years—urge further and more novel examinations of many as yet unstudied genera of the American tropics for new biodynamic elements. Virtually nothing is known of active principles in the tiny Andean families Desfontainiaceae and Gomortegaceae, members of which are employed as intoxicants in Chile.[87,97]

It would be easy to extend this list. To do so, however, would merely emphasize and reemphasize the great and still almost unrecognized and unused orientation that serious and critical evaluation of all sorts of ethnobotanical information can provide modern laboratory researchers in natural-products chemistry.[110] When one considers the opportunities that daily present themselves around the world, the almost limitless potentialities may easily be appreciated.

Progress in natural products research has, in many respects, been slow in coming. One of the major factors in resurgence of activity has certainly been academic interest in the use of chemistry in plant classification: chemotaxonomy, biochemical taxonomy, molecular taxonomy. What has been termed the "biochemical period" in taxonomy started about 1950,[27] a date that curiously and perhaps significantly coincides roughly with the period during which so many of the new "wonder drugs," mostly from plants, were discovered: muscle relaxants from South American arrow poisons; antibiotics from moulds, actinomycetes, bacteria, lichens, and other plants; rutin from a number of species; cortisone precursors from sapogenins of several plants, especially *Strophanthus* and *Dioscorea*; hypertensive agents from *Veratrum*; cytotoxic principles from *Podophyllum*, *Vinca*, and other sources; khellin from *Ammi visnaga*; reserpine from *Rauwolfia*; hesperidin from the citrus group; bishydroxycoumarin from *Melilotus*;

Fig. 21. Leaves of chagropanga, *Banisteriopsis rusbyana*, employed as an additive to the narcotic ayahuasca drink. The leaves of this plant contain high concentrations of N,N-dimethyltryptamine. Comisaria del Putumayo, Puerto Limón, Colombia. (Photograph by T. Plowman)

Fig. 22. Among the Indians of the northwest Amazon, the Kofán tribe of Colombia and Ecuador appears to have one of the richest ethnopharmacopoeas. They employ a great variety of plants in preparing their sundry arrow poisons, many of which have not yet been chemically investigated. The photograph shows 2 curare-makers preparing the bark of a species of Strychnos, one of the ingredients of a type of arrow poison. (Photograph by R. E. Schultes)

and sundry others—not to mention new psychoactive structures of potential value in experimental psychiatry from both cryptogamic and phanerogamic sources.

CONCLUSION

Nearly a century ago there was still little interest in or even comprehension about concentrated searches for new biodynamic principles in plants, especially when guided chemotaxonomically. As early as 1897, however, Helen Abbott wrote:[1]

> *The vegetable kingdom does not usually claim our attention for its intellectual attainments, although its members would certainly seem to possess greater chemical skill than a higher race of beings exhibits in laboratories. There has been comparatively little study of the chemical principles of plants from a purely botanical view. It promises to become a new field of research.*

This it has become. Can we use it to full advantage in our search for new biodynamically active plants?

In conclusion, we might well quote from an extraordinarily significant lecture given in 1859 at the Medical Society of the University of Nashville by George S. Blackie, M.D.—a lecture fraught with modern concepts but which has been forgotten and ignored.[13] Dr. Blackie, among many other points, said the following:

> *Need we wonder that the philosophers of ancient Greece pursued their philosophic discussions in the groves of Academus; that the modern Brahmin 'neath the sacred Banyan contemplates the wonders of his god; that the ancient Druids performed their learned and religious rites under the shade of the mighty oak; that the Persian monarch, struck with wonder and awe, decked the planetree with the jewels of his host, and the ancient priestcraft of Egypt planted groves around the shrines of their divinities?*

Peoples whom we have chosen to consider members of less-advanced societies have consistently looked to the Plant Kingdom—without which no animal life on earth could have evolved—for the betterment of life. Should we as chemists, pharmacologists, and botanists—with so many and varied means at our disposal—not take a lesson from them?

REFERENCES

1. H. D. de S. Abbott, *J. Franklin Inst.*, 124, 161 (1887).
2. J. M. Adovasio and G. F. Fry, *Econ. Bot.*, 30, 94 (1976).
3. S. K. Agarwal and R. P. Rastogi, *Phytochemistry*, 13, 2623 (1974).
4. Vernon Ahmadjian and Mason E. Hale, *The Lichens*, New York, NY: Academic Press, 1973.
5. Siri von Reis Altschul, *Lloydia*, 30, 192 (1967).
6. Siri von Reis Altschul, *Bot. Mus. Leafl., Harv. Univ.*, 22, 333 (1970).
7. Siri von Reis Altschul, *Drugs and Foods from Little Known Plants: Notes in Harvard University Herbaria*, Cambridge, MA: Harvard University Press, 1973.
8. T. E. H. Aplin and J. R. Cannon, *Econ. Bot.*, 25, 366 (1971).
9. Y. Asahinat and S. Shibata, *Chemistry of Lichen Substances*, Amsterdam: A. Asher & Co., Ltd., 1971.
10. William A. Ayer, B. Altenkirk, S. Valverde-Lopez, Bryce Douglas, Robert F. Raffauf, and J. A. Weisbach, *Can. J. Chem.*, 46, 15 (1968).

11. E. C. Bate-Smith in *Chemistry in Botanical Classification* (G. Bendz and J. Santesson, editors), Stockholm: Nobel Foundation, 1974, p. 93.
12. E. C. Bate-Smith and T. Swain, *Lloydia*, 28, 313 (1965).
13. George S. Blackie, *Botany as an Ally of Medicine*, Nashville, TN: John T. S. Fall Book and Job Printer, 1859.
14. Helmuth M. Bottcher, *Wonder Drugs—A History of Antibiotics* (E. Kawerau, translator), Philadelphia, PA: J. B. Lippincott Co., 1964.
15. V. J. Chapman, *Seaweeds and Their Uses*, London: Methuen & Co., Ltd., 1970.
16. Clyde M. Christensen, *The Molds and Man*, Minneapolis, MN: University of Minnesota Press, 1951.
17. Donovan S. Correll *et al.*, *Econ. Bot.*, 9, 307 (1955).
18. C. F. Culbertson, *Chemical and Botanical Guide to Lichen Products*, Chapel Hill, NC: University of North Carolina Press, 1969.
19. E. Yale Dawson, *Marine Botany*, New York, NY: Holt, Rinehart & Winston, 1966.
20. J. Erdtman in *Phytochemistry*, Vol. 3 (L. P. Miller, editor), New York, NY: Van Nostrand Reinhold Co., 1973, p. 327.
21. J. W. Fairbairn, *Lloydia*, 27, 79 (1964).
22. Norman R. Farnsworth, *J. Pharm. Sci.*, 55, 225 (1966).
23. Norman R. Farnsworth, *Pharm. Ztg.*, 113, 1293 (1968).
24. Norman R. Farnsworth in *Phytochemistry*, Vol. 3 (L. P. Miller, editor), New York, NY: Van Nostrand Reinhold Co., 1973, p. 351.
25. L. Fowden in *Phytochemistry*, Vol. 3 (L. P. Miller, editor), New York, NY: Van Nostrand Reinhold Co., 1973, p. 400.
26. R. Darnley Gibbs, *Lloydia*, 28, 279 (1965).
27. R. Darnley Gibbs, *Chemotaxonomy of Flowering Plants*, Montreal: McGill-Queens University Press, 1974, p. 1.
28. William D. Gray, *The Relation of Fungi to Human Affairs*, New York, NY: Henry Holt, 1959.
29. Mason E. Hale, Jr., *The Biology of Lichens*, London: Edward Arnold, 1967.
30. Rudolph Hänsel, "The Phytochemistry and Biological Activity of Kava," presented at Plant Constituents of Pharmacological Activity, a symposium at Chelsea College, London, 1972.
31. *Phytochemical Ecology* (J. B. Harborne, editor), London: Academic Press, 1972.
32. S. L. Haro Alvear, *Shamanismo y Farmacopea en el Reino de Quito*, Istit. Ecuator. Cienc. Nat. Contrib. No. 75 (November 1971).
33. N. Harper, G. A. Cooper-Driver, and T. Swain, in press.
34. T. G. Hartley, E. A. Dunstone, J. S. Fitzgerald, S. R. Johns, and J. A. Lamberton, *Lloydia*, 36, 217 (1973).
35. Jonathan Hartwell, *Lloydia*, 30, 379 (1967); 31, 71 (1968); 32, 79 (1969); 32, 153 (1969); 33, 97 (1970); 33, 288 (1970); 34, 103 (1971); 34, 204 (1971); 34, 310 (1971); 34, 386 (1971).
36. R. Hegnauer in *Comparative Phytochemistry* (T. Swain, editor), London: Academic Press, 1966, p. 211.
37. R. Hegnauer, *Chemotaxonomie der Pflanzen*, Vols. 1-6, Basel: Birkhauser Verlag, 1962, 1963, 1964, 1966, 1969, and 1973.
38. Roger Heim and R. Gordon Wasson, *Les Champignons Hallucinogènes du Mexique*, Paris: Muséum National d'Histoire Naturelle, 1959.
39. Francisco Hernández, *Nova Plantarum, Animalium et Mineralium Mexicanorum Historia*, Rome: B. Deuersini et Z. Mosotti, 1651.
40. W. Herz in *Chemistry in Botanical Classification* (G. Bendz and J. Santesson, editors), Stockholm: Nobel Foundation, 1974, p. 153.
41. Albert Hofmann, *Therapiewoche*, 17, 1739 (1967).

42. Patricia K. Holmgren and Wil Keuken, *Index Herbariorum*, Utrecht: Oosthoek, Scheltema & Holkema, 1974.
43. Bo Holmstedt and G. Liljestrand, *Readings in Pharmacognosy*, London: Pergamon Press, 1963.
44. S. Huneck in *Prog. Phytochem.*, Vol. 1 (L. Reinhold and Y. Liwschitz, editors), New York, NY: Wiley, 1968, p. 223.
45. *Algae and Man* (Daniel F. Jackson, editor), New York, NY: Plenum Press, 1964.
46. Soren R. Jensen, Bent J. Nielsen, and Rolf Daldgren, *Bot. Not.*, 128, 148 (1975).
47. K. Jewers, "Recent Studies on Lactones of Possible Pharmacological Interest," presented at Plant Constituents of Pharmacological Activity, a symposium at Chelsea College, London, 1972.
48. James Jiu, *Lloydia*, 29, 250 (1966).
49. D. A. Jones in *Phytochem. Ecol., Proc. Phytochem. Soc. Symp., 1971* (J. B. Harbourne, editor), London: Academic Press, 1972, p. 103.
50. L. D. Kapoor, A. Singh, A. Kapoor, S. W. Stivastava and S. N. Stivastava, *Lloydia*, 38, 221 (1975).
51. Karen Krag, "The Use of *Lithosperum ruderale Dougl.* as a Contraceptive," [unpublished manuscript], Botanical Museum of Harvard University, 1974.
52. S. Morris Kupchan, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 33, 2288 (1974).
53. D. Lavie in *Chemistry in Botanical Classification* (G. Bendz and J. Santesson, editors), Stockholm: Nobel Foundation, 1974, p. 181.
54. John Lindley, *The Vegetable Kingdom*, 2nd edition, London: Bradbury & Evans, 1847.
55. Carolus Linnaeus, *Species Plantarum* (introduced by W. T. Stearn) London: Quaritch Ltd. (Ray Society Facsimile Edition), 1957, p. 155.
56. Björn Lüning, *Acta Chem. Scand.*, 18, 1507 (1964).
57. Björn Lüning, *Phytochemistry*, 6, 857 (1967).
58. Björn Lüning in *The Orchids* (Carl L. Withner, editor), New York, NY: John Wiley & Sons, 1974, p. 349.
59. B. A. Lynch-Brathwaite, E. J. Duncan, and C. E. Seaforth, *Planta Med.*, 27, 173 (1975).
60. Ara H. Der Marderosian, K. M. Kensinger, J.-M. Chao and F. J. Goldstein, "The Use of Hallucinatory Principles of a Psychoactive Beverage of the Cashinahua Tribe (Amazon Basin)" in *Drug Dependence*, No. 5, 1970, p. 7.
61. Lynn Margulis in *Handb. Genet.*, Vol. 1 (Robert C. King, editor), New York, NY: Plenum Press, 1974, p. 1.
62. *Marijuana—Chemistry, Pharmacology-Metabolism and Clinical Effects* (Rafael Mechoulam, editor), New York, NY: Academic Press, 1973.
63. John C. Mitchell in *Recent Adv. Phytochem.*, Vol. 9 (V. C. Runeckles, editor), New York, NY: Plenum Publishing Co., 1975, p. 119.
64. Koji Nakanishi in *Recent Adv. Phytochem.*, Vol. 9 (V. C. Runeckles, editor), New York, NY: Plenum Publishing Co., 1975, p. 283.
65. John L. Neumeyer and R. A. Shagoury, *J. Pharm. Sci.*, 60, 1433 (1971).
66. Bernard Ortiz de Montellano, *Science*, 188, 215 (1975).
67. *Chemistry of the Alkaloids* (S. W. Pelletier, editor), New York, NY: Van Nostrand Reinhold Co., 1970.
68. Timothy Plowman, *Bot. Mus. Leafl., Harv. Univ.*, 23, 245 (1973).
69. Timothy Plowman, Lars Olaf Gyllenhaal, and Jan-Erik Lindgren, *Bot. Mus. Leafl., Harv. Univ.*, 23, 61 (1971).
70. J. Poisson, *Ann. Pharm. Fr.*, 23, 241 (1965).
71. Efrén C. del Pozo in *Ethnopharmacologic Search for Psychoactive Drugs* (D. Efron, editor), Washington, DC: U.S. Government Printing Office (Public Health Service Publ. No. 1645), 1967, p. 59.

72. Robert F. Raffauf, *Lloydia,* **25**, 255 (1962).
73. Robert F. Raffauf, *Handbook of Alkaloids and Alkaloid-containing Plants,* New York, NY: John Wiley, 1970.
74. Robert F. Raffauf, *Econ. Bot.,* **24**, 34 (1970).
75. Siri von Reis, *Econ. Bot.,* **16**, 283 (1962).
76. Thomas Reynolds, *Chem. Ind. (London),* 443 (1971).
77. Thomas Reynolds, *Chem. Ind. (London),* 603 (1975).
78. E. C. Rice, *Allelopathy,* New York, NY: Academic Press, 1974.
79. Trevor Robinson, *The Organic Constituents of Higher Plants,* 3rd edition, North Amherst, MA: Cordus Press, 1975.
80. Paul J. Scheuer, *Chemistry of Marine Products,* New York, NY: Academic Press, 1973.
81. E. Schoffeniels and T. Swain, *Biochem. Syst. Ecol.,* **2**, 1 (1974).
82. Richard Evans Schultes, "A Contribution to our Knowledge of *Rivea corymbosa*—the Narcotic Ololiuqui of the Aztecs," Botanical Museum of Harvard University, Cambridge, MA, 1941.
83. Richard Evans Schultes, *Econ. Bot.,* **14**, 257 (1960).
84. Richard Evans Schultes, *Lloydia,* **25**, 257 (1962).
85. Richard Evans Schultes, *Rhodora,* **65**, 97 (1963).
86. Richard Evans Schultes in *Ethnopharmacologic Search for Psychoactive Drugs* (D. Efron, editor), Washington, DC: U. S. Government Printing Office (Public Health Service Publ. No. 1645), 1967, p. 33.
87. Richard Evans Schultes, *Annu. Rev. Plant Physiol.,* **21**, 571 (1970).
88. Richard Evans Schultes in *II Simposio de la Biologia Tropical Amazónica* (J. M. Idrobo, editor), Leticia, Colombia: Association for Tropical Biology, 1970, p. 177.
89. Richard Evans Schultes, *Bot. Mus. Leafl., Harv. Univ.,* **23**, 129 (1972).
90. Richard Evans Schultes, *Arnoldia (Boston),* **32**, 198 (1972).
91. Richard Evans Schultes in *Plants in the Development of Modern Medicine* (T. Swain, editor), Cambridge, MA: Harvard University Press, 1972, p. 103.
92. Richard Evans Schultes, *Etnol. Studier.,* **32**, 115 (1972).
93. Richard Evans Schultes, *Bull. Am. Orchid Soc.,* **42**, 785 (1973).
94. Richard Evans Schultes in *Recent Adv. Phytochem.,* Vol. 9 (V. C. Runeckles, editor), New York, NY: Plenum Publishing Co., 1975, p. 1.
95. Richard Evans Schultes, *Rhodora,* **77**, 165 (1975).
96. Richard Evans Schultes, *Bot. Mus. Leafl., Harv. Univ.,* **24**, 121 (1975).
97. Richard Evans Schultes and Albert Hofmann, *The Botany and Chemistry of Hallucinogens,* Springfield, IL: Charles C. Thomas Publishers, 1973.
98. D. C. Seigler, *Phytochemistry,* **14**, 9 (1975).
99. S. J. Smolenski, H. Silinis, and N. R. Farnsworth, *Lloydia,* **38**, 225 (1975).
100. Djaja Doendoel Soejarto, "The Plant Kingdom and the Search for Antifertility Agents," [unpublished manuscript], Botanical Museum of Harvard University, Cambridge, MA, 1975.
101. *Chemical Ecology* (Ernest Sondheimer and John B. Simone, editors), New York, NY: Academic Press, 1970.
102. G. H. Stout and R. E. Schultes in *Phytochemistry,* Vol. 3 (L. P. Miller, editor), New York, NY: Van Nostrand Reinhold Co., 1973, p. 381.
103. K. L. Su, E. J. Staba, and Y. Abul-Hajj, *Lloydia,* **36**, 72 (1973).
104. T. Swain in *Plants in the Development of Modern Medicine* (T. Swain, editor), Cambridge, MA: Harvard University Press, 1972, p. 125.
105. T. Swain in *Chemistry in Botanical Classification* (G. Bendz and J. Santesson, editors), Stockholm: Nobel Foundation, 1974, p. 81.
106. T. Swain, *Nova Acta Leopold.,* in press.

107. T. Swain and G. A. Cooper-Driver in *Phylogeny and Classification of the Ferns* (A. C. Jeremy, J. A. Crabbe, and B. A. Thomas, editors), London: Linnean Society, 1974, p. 111.
108. A. N. Tackie, D. Duuma-Bedu, P. A. Lartey, P. L. Schiff, J. E. Knapp, and D. J. Slatkin, *Lloydia*, **37**, 6 (1974).
109. Armen Takhtajan, *Flowering Plants: Origin and Dispersal* (C. Jeffrey, translator), Edinburgh: Oliver and Boyd, 1969.
110. Lord Todd in *Philip Morris Sci. Symp. Proc., 1st, 1973* (Nicholas J. Fina, editor), New York, NY: Philip Morris Incorporated, 1973, p. 27.
111. Margaret A. Towle, *The Ethnobotany of Pre-Columbian Peru*, Chicago, IL: Aldine Publishing Co., 1961.
112. P. Train, J. R. Henrichs, W. A. Archer, "Medicinal Uses of Plants by Indian Tribes of Nevada," in *Contributions Toward a Flora of Nevada*, No. 45, Beltsville, MD: USDA Plant Ind. Station, 1941 (revised edition, 1957).
113. G. E. Trease and W. C. Evans, *Pharmacognosy*, 10th edition, London: Balliere Tindall, 1972.
114. Rolla M. Tryon, personal communication.
115. William B. Turner, *Fungal Metabolites*, London: Academic Press, 1971.
116. S. Henry Wassén in *Plants in the Development of Modern Medicine* (T. Swain, editor), Cambridge, MA: Harvard University Press, 1972, p. 1.
117. John Mitchell Watt in *Plants in the Development of Modern Medicine* (T. Swain, editor), Cambridge, MA: Harvard University Press, 1972, p. 67.
118. R. H. Whittaker, *Science*, **163**, 150 (1969).
119. R. H. Whittaker and P. P. Feeny, *Science*, **171**, 757 (1971).
120. Carroll M. Williams in *Chemical Ecology* (E. Sondheimer and J. B. Simone, editors), New York, NY: Academic Press, 1970, p. 103.
121. *Rumphius Memorial Volume* (H. C. D. de Wit, editor), Baarn, Holland: Drukkerij Hollandia N.V., 1959.
122. Robert E. Woodson, Heber W. Youngken, Emil Schlittler, and Jurg A. Schneider, *Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology*, Boston, MA: Little, Brown and Co., 1957.
123. Heber W. Youngken, Jr., *Lloydia*, **32**, 407 (1969).