Higher plants—the sleeping giant of drug development

Norman R. Farnsworth and Ralph W. Morris

Recent figures[1] claim that domestic sales of ethical drugs (at the manufacturers' level) totaled $6.3 billion in 1974 for human dosage forms and that world-wide sales of combined veterinary and human dosage forms totaled $11.3 billion in the same year. One can probably double these industry figures to estimate the cost of human and/or veterinary drugs to the consumer.

With an estimated $12.6 billion being spent annually for human drug dosage forms in the United States, the main thrusts of this article are (*a*) to point out (and emphasize) the value of drugs derived from higher plants (excluding antibiotics and other fungal products, animal products, biologicals, and completely synthetic entities), (*b*) to point out the importance of these drugs to the armamentarium of the physician, and (*c*) to suggest several reasons why higher plants essentially are being neglected in new drug development research programs. Several examples illustrative of the material under consideration will be made from the personal experience of the authors.

Reliance on Higher Plants as Sources of Drugs

Farnsworth has previously pointed out the importance of all types of natural products in the American prescription market.[2-5] We have analyzed the National Prescription Audit (NPA) data,[6] which includes the total for new and refilled prescription sales by community pharmacies in the United States. Of the 1.532 billion prescriptions dispensed during 1973, 25.2% contained one or more active constituents obtained from higher plants (seed plants). If one considers that in 1973 the average prescription price to the consumer was $4.13,[6] then total prescription sales in community pharmacies for drugs from higher plants for that year amounted to about $1.59 billion. Furthermore, microbial products (such as antibiotics, ergot alkaloids, and immunizing biologicals) accounted for about 13.3% of all prescriptions, and animal-derived prescriptions accounted for about 2.7% of the total.

In order to determine whether or not 1973 was an atypical year, a computerized analysis was carried out on the American prescription market from NPA data each year for the period 1959 through 1973. Although the total number of prescriptions increased dramatically over this 15-year period, the percentage of natural-product prescriptions remained rather constant (Table 1). This may indicate that (*a*) natural products represent an extremely stable

Table 1—Comparison of Natural-Product Containing Prescriptions Dispensed in Community Pharmacies (1959 and 1973).

Year	Higher Plants, %	Microbes, %	Animals, %	Total %
1959	25.5	21.4	2.3	49.2
1973	25.2	13.3	2.7	41.2

Norman R. Farnsworth, PhD, is a Professor of Pharmacognosy, Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612.

Ralph W. Morris, PhD, is a Professor of Pharmacology, Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612.

Table 2—Most Commonly Encountered Pure Compounds From Higher Plants Used as Drugs in 1973.

Active Plant Principle	Total Number of Rxs[a]	Percentage of Total Rxs
Steroids (from diosgenin)	225,050,000	14.69
Codeine	31,099,000	2.03
Atropine	22,980,000	1.50
Reserpine	22,214,000	1.45
Pseudoephedrine[b]	13,788,000	0.90
Ephedrine[b]	11,796,000	0.77
Hyoscyamine	11,490,000	0.75
Digoxin	11,184,000	0.73
Scopolamine	10,111,000	0.66
Digitoxin	5,056,000	0.33
Pilocarpine	3,983,000	0.26
Quinidine	2,758,000	0.18

[a] Total number of Rxs in 1973 was 1.532 billion.
[b] Produced commercially by synthesis; all others by extraction from plants.

cies, and the like. Thus, it seems logical and convenient to consider $3.0 billion as the annual value of drugs obtained from higher plants at the consumer level.

Apathy in Supporting Research on Drugs from Plants

It should be remembered that although estimates will vary, the most commonly quoted figure as to the number of higher plants to be found growing on planet Earth is about 500,000. One often finds quoted educated "guestimates" that "less than 5% (or 10% or 15%) of plants have been investigated for pharmacologically active principles." One could really debate the point as to what has to be considered before a plant is "investigated for pharmacologically active principles." After more than 5 years of experience at computer coding the world literature concerning the chemical

Table 3—Most Commonly Encountered Higher Plant Extracts Used in Prescriptions in 1973.[a]

Crude Botanical of Extract	Total Number of Rxs[b]	Percentage of Total Rxs
Belladonna (*Atropa belladonna*)	10,418,000	0.68
Ipecac (*Cephaelis ipecacuanhae*)	7,047,000	0.46
Opium (*Papaver somniferum*)	6,894,000	0.45
Rauwolfia (*Rauvolfia serpentina*)	5,822,000	0.38
Cascara (*Rhamnus purshiana*)	2,451,000	0.16
Digitalis (*Digitalis purpurea*)	2,451,000	0.16
Citrus Bioflavonoids (*Citrus* spp.)	1,379,000	0.09
Veratrum (*Veratrum viride*)	1,072,000	0.07

[a] Compounded prescriptions represented less than 2.0% of total prescriptions and were excluded from the survey data that were compiled and analyzed. The drugs indicated above were in standard dosage forms and not in multicomponent, extemporaneously prepared prescriptions.
[b] Total Rx volume in 1973 was 1.532 billion prescriptions.

against further exploitation of a market now estimated at $3.0 billion at the consumer level? The answer can be expressed simply that there are major examples, from the not-too-distant past, in which moderate investments in time, money, and effort have not paid off. Let us cite just a few to illustrate the point.

A few years ago, one of our leading pharmaceutical houses made the decision to initiate a modest effort in the search for new drugs in plants. At that time, the company had no staff trained in the problems and approaches to developing such a program. Thus, it surveyed the employment records of its staff of PhD-level chemists, and determined that one individual had indicated on his employment form that he was also interested in natural products chemistry. He was an excellent organic chemist and had decided that the best approach would be to collaborate with a trained botanist in a country rich in medicinal folklore. This botanist was directed to ship several plants each month to the pharmaceutical firm where extracts were made and subjected to a broad array of pharmacological screens. It should be noted that, in many instances, the pharmacological screens did not include animal models to detect the type of activity for which the plant was allegedly used by the natives. As time passed, the pharmacology staff became irritated at "thick, black, sticky extracts that clogged up their syringes, and which, for the most part, did not give dramatic activity."

After about 2 years the program was dropped, and the results of the pharmacological evaluation of 100 or more of the plants were published. An examination of the fine print in the article revealed that indeed many of these plants elicited remarkable pharmacological effects. It was difficult to envision a pharmaceutical firm making such information known to the scientific community without following through on the isolation of the active principles. An inquiry brought to light the fact that since cooperation of the pharmacologists could not be enlisted, and because the results of the crude extract testing were not dramatic enough,* the program was dropped and the chemist was allowed to publish the data.

It was subsequently determined, through talking with colleagues of the botonist, that many of the plants eventually published as having interesting activity, had been only tentatively identified. Indeed, several eventually were found to have been incorrectly identified. The botanist had not been consulted prior to publication of the results to determine the exactness of the identifications; thus, even though many interesting pharmacological leads appear to be apparent in this publication, a follow-up by other interested investigators would undoubtedly result in utter frustration.

A second example can be cited in which another pharmaceutical firm initiated a program through which leads were obtained by searching books on medical botany concerning the floras of primitive countries. Interesting uses for plants were noted and orders were placed for the collection of 1-kg quantities of each plant for initial pharmacological screening. As is well known by workers in the field, commercial plant suppliers usually operate by notifying their botanist collaborators to collect specific plants (giving them the Latin name and any other pertinent information). In most cases, the botanist recognizes the Latin name of the plant as one which is known popularly by the natives under some common vernacular name. A native in the area who is knowledgeable in herbal medicine is dispatched to collect 2 kg of "the bark of capinuri" (as a hypothetical example). Almost anyone can tell you the result from this point on. The native collects what to him is "capinuri," but a native in an adjoining village or province might collect an entirely different plant that he knows as "capinuri." This is not too difficult to understand; even here in this country, if a person were asked

* If a crude extract has only 1.0% of active principle, is it reasonable to equate the qualitative and/or quantitative response against that produced by a pure chemical compound?

to collect 2 kg of "periwinkle," that person could conceivably return with any one of four or five different species of plants (and each quite distinctly unrelated). Thus, the shipment of "capinuri" is shipped to the pharmaceutical firm (invariably the collector will not supply a voucher herbarium specimen of the plant being collected for future reference). The extract from the "capinuri" shows very interesting pharmacological effects, and the commercial supplier is requested to obtain another 500 lb of the bark of the specified Latin name plant. Our supplier again notifies his contact (usually several months or years later), and perhaps a different native is dispatched to collect the 500 lb of "capinuri." Again, no voucher specimen is made and the 500 lb of bark, after extraction and testing for confirmation of the original activity, is found to be devoid of that activity!

At one time several years ago, it was known to some that more than 20 plants with extremely interesting pharmacological effects had been obtained at the aforementioned pharmaceutical firm, but the pharmacological effects of most of the plants could not be duplicated on subsequently collected samples. The obvious answer to the mystery (by those in charge of the operation) was that this simply represented the trials and tribulations of botanical-chemical-pharmacological research and/or biological variation from one batch of plant material to the next. Could not all of this have been avoided if all parties concerned were more aware of the need for proper precautions in documenting botanical specimens so that identical collections could be made at a later date?

A third vivid and unfortunate example, and perhaps the most costly one known to these writers, is illustrated by a physician who approached a major pharmaceutical firm stating that for a modest sum (we are told $500,000), he would spend some time in a primitive jungle area and observe medicine men using plants as drugs. He, as a physician, would be able to ascertain the condition of the patient, confirm the diagnosis of the disease, and assess the effects of herbal remedies prescribed by the medicine man. In cases where the herbal remedy was judged effective, the physician would then collect large quantities of the plants and ship them to the drug firm.

Because this was a novel approach, the physician was funded, and he went off to the jungle. He did everything that he agreed to do. He collected several large samples of plant material, carefully numbered each sample, and prepared pressed voucher specimens of each sample, so that botanists could later identify each sample. He identified each of the voucher specimens by writing the correct identifying number on a leaf of each specimen with a ball point pen! The voucher specimens were carefully dried (concurrently the leaves became brittle) and the bulk samples of plant material and the voucher specimens (not carefully packaged) were shipped to the drug firm. The voucher specimens were turned over to a botanist who found either that many of the leaves had crumbled, or that the identifying numbers were illegible; virtually none of the voucher specimens were found to be identifiable. Obviously there was no further interest in testing the bulk samples collected, because if any showed interesting activity, it would be impossible to recollect larger samples for additional studies.

These are only a few of the many examples that could be cited if space were available, and it is a certainty that such examples become widely publicized. Is it any wonder that administrators allocating funds for research programs are reluctant to initiate projects to explore the possibility of finding new drugs from plants? On the other hand, is it not more reasonable to look at the tremendous untapped potential of new drug development from higher plants from a positive viewpoint, and to make a *commitment* to a *major* program that would include sufficient time, adequate funds, and the acquisition of a variety of specialists who are trained in and who could recognize the problems inherent in this area, so that the obvious oversights in the examples cited could be avoided?

Acknowledgments

The authors would like to thank Dr. Raymond A. Gosselin, Massachusetts College of Pharmacy, and Mr. James A. Donahue, Lea, Inc., for making available the 1959-1973 NPA-RPA data for analysis; Dr. John Ruggiero, Pharmaceutical Manufacturers Association, for providing industry reports on research and development expenditures; and Dr. Arthur Nelson, Assistant Professor of Pharmacy Administration, University of Illinois at the Medical Center, College of Pharmacy, and Dr. Joseph D. McEvilla, School of Pharmacy, Temple University, for valuable suggestions and constructive criticism of certain parts of this manuscript.

References

1. *Annual Survey Report, 1973-1974.* Pharmaceutical Manufacturers Association, Washington, 1975.

2. Farnsworth NR: Drugs from higher plants. *Tile & Till 55*(2): 32-36, 1969.

3. Farnsworth NR: Drugs from microbes. *Tile & Till 55*(3): 48-51, 1969.

4. Farnsworth NR: Drugs from animals. *Tile & Till 55*(4): 66-71, 1969.

5. Farnsworth NR: Importance of secondary plant constituents as drugs. In Miller LP, Ed: *Phytochemistry*, Vol III, Van Nostrand Reinhold, New York, 351-380, 1973.

6. *National Prescription Audit Ten Year Summary, 1959-1968,* and subsequent supplements. R. A. Gosselin, Dedham, Mass., and Lea, Ambler, Pa., 1969.

7. *National Prescription Audit General Information Report,* 12th ed. Lea, Ambler, Pa., 1972.

8. DeHaen P: *Non-Proprietary Name Index.* Paul DeHaen, New York, 1974.

9. Clymer HA: The changing costs and risks of innovation in drug development. In *Research Management,* Wiley, New York, 375-388, 1970.