Proceedings in Life Sciences

New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity

Edited by H. Wagner and P. Wolff

New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity

Proceedings of the First International Congress on Medicinal Plant Research, Section A, held at the University of Munich, Germany September 6—10, 1976

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With 152 Figures

Springer-Verlag Berlin Heidelberg New York 1977

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Cover motive: Left: a shoot of *Maytenus buchananii*, a bush or tree growing in Central West Africa, belonging to the Celastraceae. Right: structure of maytansin, isolated from the plant.

ISBN 3-540-08292-1 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-08292-1 Springer-Verlag New York Heidelberg Berlin

Library of Congress Cataloging in Publication Data. International Congress on Medicinal Plant Research, 1st, University of Munich, 1976. New natural products and plant drugs with pharmacological, biological or therapeutical activity. (Proceedings in life sciences) Includes bibliographies and index. 1. Materia medica, Vegetable—Congresses. I. Wagner, Hildebert, 1929—. II. Wolff, Peter Maria, 1932—. III. Title. [DNLM: 1. Drugs—Congresses. 2. Plants, Medicinal—Congresses. W3 IN632M 1976/QV766 161 1976n]. RS164.I56.1976. 615'.32. 77-8846.

Printed in Germany.

Offsetprinting and bookbinding: Brühlsche Universitätsdruckerei Lahn-Gießen.
2131/3130-543210

Preface

The fact that, of the approximately 600,000 plant species existing on the earth, only some 5 % have been specifically investigated chemically or pharmacologically, is a challenge to chemists spezializing in natural substances and to pharmacologists. In view of the limited number of research capacities and the ever-diminishing financial means, this challenge can only be met if, together with an improvement and refinement of methods of analysis, medicinal plant research is carried out on a broader interdisciplinary basis, with comparable, scientifically recognized screening methods, and if it is better coordinated, with greater use of modern documentation means. It is thus necessary in the future to concentrate specifically on projects leading to the development of new medicinal preparations.

The plenary lectures hold in the present symposium of the 1st International Congress for Research on Medicinal Plants reflect these efforts and tendencies. At the same time they provide a survey of some of the fields of medicinal plant research which are at present most actual and most intensively researched. They range from plant screening, isolation and structure elucidation of new principles, to the therapeutical optimization of a natural product.

The lectures given at this congress show clearly the necessity, in addition to national phytochemical societies, for a central international organisation, in which all active medicinal plant researchers in the world are included. Their aim should be to provide the impulse for more optimal, rational research, aimed at the solution of specific projects.

The symposium was generously supported by the Deutsche Forschungsgemeinschaft (Bonn) and various chemical and pharmaceutical industries.

June, 1977

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Problems and Prospects of Discovering New Drugs from Higher Plants by Pharmacological Screening

N. R. FARNSWORTH and A. S. BINGEL

A. Introduction

There are probably very few in attendance at this Congress who have not experienced the frustrations of initiating research on plants alleged to have interesting biological activity, only to find that the activity could not be confirmed or demonstrated in animal models. Perhaps even more frustrating to most of you, has been the often nonreproducible nature of biological effects initially shown by a plant extract. Difficulties involved in preparing plant extracts into suitable dosage forms that would allow accurate amounts of the extract to be administered to an animal are further complications that bring frustration to this type of research. A difficult-to-explain phenomenon, associated with the administration of active plant extracts to animals, is the failure to produce consistent dose-response curves such as those usually obtained when pure chemical compounds are evaluated. Behind all of these problems, we find the most important deterrent to the search for new potential drugs in plants, i.e. apathy on the part of industrial firms, foundations, academic institutions, and government agencies to provide adequate funds for long enough periods of time so that a program of this type would be expected to yield clinically useful agents.

It is our suspicion that the organizers of this Congres invited us to prepare this manuscript for one of two reasons. First, there may have been a desire to confirm the rumor that the presentation would be illustrated with visual aids designed to prevent the frequently sedative atmosphere characteristic of many scientific meetings. Second, these same organizers may have felt that we would be able to provide answers to the universal problems associated with the search for new drugs from higher plants alluded to previously. While we may be able to provide the hoped-for visual aids, it may not be possible to provide the hoped-for answers.

Perhaps the most important aspect of this presentation will be to provide evidence that the current misconceptions attributed to the lack of importance of plant products as drugs have little basis, and that the problems alluded to above may not really be insurmountable.

B. Value of Drugs Obtained from Higher Plants

I. Commercial Value of Plant-Derived Drugs

To the best of our knowledge, data are not available outside the U.S.A. that allow one to calculate the actual number of prescriptions dispensed to patients that contain plant-derived drugs, nor the monetary value of such prescriptions. However, we can now document rather well that in the United States in the year 1973, the American public paid about $3 billion for prescription drugs that are still extracted from higher plants.

Recent data (1) claim that domestic sales of ethical drugs (*at the manufacturer's level*) in the U.S.A. totaled $6.3 billion in 1974 for human dosage forms, and that worldwide 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.

We have analyzed the National Prescription Audit (NPA) data in the U.S.A., which includes total new and refilled prescription sales for community pharmacies in the United States. Of the 1.532 billion prescriptions (3) 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 (2), then total prescription sales in community pharmacies for drugs from higher plants for that year amounted to about $1.59 billion. Further, microbial products (antibiotics, ergot alkaloids, immunizing biologicals, etc.) accounted for about 13.3 % of all prescriptions. 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), indicating perhaps two major points: (1) that natural products represent an extremely stable market in the United States, and (2) that, because of this stability, it can be safely assumed that the drugs represented in the survey are heavily relied on (prescribed) by physicians.

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 %

While it is true that the total percentage of prescriptions containing natural products decreased from 49.2 % in 1959 to 41.2 % in 1973, it is clear from Table 1 that the drop was attributed solely to a decreased use of microbial products, chiefly antibiotics. Thus, it can be stated that over the period 1959 to 1973, drugs from *higher plants* did not increase or decrease in frequency of use in the American prescription market. This is of interest because no new drugs from higher plants were introduced during the same span of time. It is our opinion that industry research and development investment for higher drug plant research during this same period of time *decreased* substantially. During the period 1959 to 1973, it is known that in the U.S.A. research programs in the pharmaceutical industry relating to the search for new drugs from higher plants were either phased out or reduced at Ciba, Smith Kline and French, Riker, G.D. Searle, and Eli Lilly and Co., and perhaps at other pharmaceutical companies as well.

National Prescription Audit figures for 1973 (3) indicate that 1.532 billion new and refilled prescriptions were dispensed from community pharmacies in the United States. At an average cost to the consumer of $4.13 per prescription (3), one can calculate a dollar value of $6.327

billion for the market in 1973. Thus, if a predicted 25.2 % of these prescriptions contained active principles of higher plant origin, the dollar cost to the consumer in 1973 would be estimated at $1.594 billion.

Now, how does one obtain the figure of $3 billion as the current value of higher plant medicinals in the U.S.A.? It can be estimated that somewhat less than the dollar volume representing the community pharmacy prescription market may be *added* to the $1.594 billion prescription market to account for the value of drugs dispensed in hospitals, government agencies, and the like. Thus, it seems logical and convenient to consider $3 billion as the annual value of drugs at the consumer level that are obtained from higher plants.

There is no way to estimate the importance and/or commercial value of drugs obtained from plants that are available to individuals without prescription, either in the U.S.A. or elsewhere, but this figure would probably be staggering.

Although our data are restricted to the U.S.A., it is safe to assume that plant-derived drugs are at least of equal importance in other countries of the world. Thus, it is safe to claim that there is little justification for the pharmaceutical industry to neglect plants as sources of new drugs on the base of infrequency of use, lack of importance of therapeutic effects, or inacceptability by the medical profession. That neglect could be based on a low dollar value, or poor profit potential, likewise, seems unjustified.

II. Role of Plant-Derived Drugs as Therapeutic Agents

To illustrate the importance of many higher plant drugs, the 12 most commonly encountered pure compounds, derived from higher plants and tabulated from the 1973 NPA prescription data, are presented in Table 2.

Table 2. Most commonly-encountered pure compounds from higher plants used as drugs in 1973 in the U.S.A.

Active plant principle	Total number of Rxs[a]	Percent of total Rxs
Steroids (95 % 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

Another interesting note is that in 1973, a total of 76 different chemical compounds of known structure, derived from higher plants, were represented in the prescriptions analyzed. Further, the assumption by many people is that most, if not all, of the higher plant-derived drugs of known structure are now produced commercially by synthesis. Nothing could be further from the truth. Of the 76 individual drugs just indicated, only seven are commercially produced by synthesis, emetine, caffeine, theobromine, theophylline, pseudoephedrine, ephedrine, and papaverine. This is not to imply that most of the naturally occurring drugs have not been synthesized; indeed they have. However, practical industrial syntheses for such important drugs as morphine, codeine, atropine, digoxin, etc. are not available. The alkaloid, reserpine, for example, can be commercially extracted from natural sources for about $0.75/g, whereas a multistep and difficult synthesis is available that yields reserpine at about $1.25/g. It should be obvious which of the two sources is used to produce this pharmaceutical.

Even more interesting information can be derived from the 1973 survey data. For example, 99 different crude plant drugs, or types of extracts from crude plant drugs, were found to be present in the prescriptions analyzed, involving about 38,300,000 prescriptions in 1973 (2.5 % of the total). Those found in the greater number of prescriptions are listed in Table 3.

Table 3. Most commonly encountered higher plant extracts used in prescriptions in 1973[a]

Crude botanical or extract	Total number of Rxs	Per cent of total Rxs[b]
Belladonna *(Atropa belladonna)*	10,418,000	0.68 %
Ipecac *(Cephaelis ipecacuanha)*	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 Biflavonoids *(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 (3) 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

One only needs to open the pages of any standard textbook of pharmacology to be impressed by the fact that virtually every pharmacological class of drug includes a natural product prototype that exhibits the classical effects of the pharmacological category in question; most of them are plant-derived (see Table 4).

Table 4. Typical plant principles used to illustrate pharmacological principles in standard textbooks

Type of pharmacological action	Type of compound	Name of compound
Centrally acting skeletal muscle relaxant	Alkaloid	Bulbocapnine
Analgesic	Alkaloid	Morphine, codeine
Smooth muscle relaxant	Alkaloid	Papaverine
Antigout	Alkaloid	Colchicine
CNS stimulant	Monoterpene	Camphor
	Sesquiterpene	Picrotoxin
	Alkaloid	Strychnine, caffeine, theobromine, theophylline
Local anesthetic	Alkaloid	Cocaine
Parasympatholytic	Alkaloid	Atropine, scopolamine
Parasympathomimetic	Alkaloid	Pilocarpine, physostigmine
Peripherally acting skeletal muscle relaxant	Alkaloid	*d*-Tubocurarine
Sympathomimetic	Alkaloid	Ephedrine
Ganglionic blocker	Alkaloid	Nicotine, lobeline
Cardiotonic	Cardiac glycoside	Digitoxin, digoxin
Antiarrhythmic	Alkaloid	Quinidine
Uterine stimulant	Alkaloid	Sparteine, ergot alkaloids
Antihypertensive	Alkaloid	Reserpine, *Veratrum* alkaloids
Psychotropic	Alkaloid	Reserpine
Cathartic	Anthraquinone	Anthraquinone glycosides
	Mucilages	Psyllium, agar
	Fixed oil	Castor Oil
Antimalarial	Alkaloid	Quinine
Antiamebic	Alkaloid	Emetine

III. Uses Other than as Drugs for Plant-Derived Chemicals

Natural drug products, many of which have been derived from higher plants, play an important role as useful investigative tools in pharmacological studies. Some such compounds are included in Table 4. Others are mescaline and LSD-derivatives in the study of psychiatric disorders; various toxins, e.g. tetrodotoxin, in the study of nerve transmission; cyclopamine in the study of teratogenesis; phalloidin for induction of hepatoxicity; and phorbol myristate acetate as a standard cocarcinogen in the investigation of potential carcinogens and cocarcinogens.

Other useful applications of plant derived chemicals can be cited; e.g. bixin as a coloring agent for foods; nordihydroguaiaretic acid as an antioxidant in lard; essential oils and their derived terpenes as perfumes and flavoring agents, etc. The economic value of these materials is difficult to estimate, but surely must be in the billion dollar category on a worldwide basis.

A number of laboratories feel that the major purpose for finding in plants new structures with biological activity is to provide templates for the synthesis of analogs and/or derivatives which will have equivalent or better activity than the parent molecule. This may indeed be an admirable purpose, and from a practical point of view, it may be advantageous with regard to patent protection. However, history shows that it is an exceptionally rare instance when a naturally occurring chemical compound that has found utility as a drug in man, will yield a derivative on structure modification that exceeds the value of the parent compound in drug efficacy.

This also does not discount the value of such model compounds as cocaine, yielding information that led chemists to produce related local anesthetics such as procaine and its congeners, nor the value of the large number of synthetic anticholinergic drugs that were designed from the tropane nucleus and which have their own specific advantages.

Finally, the value of plant-derived chemical compounds as building blocks for semisynthetic derivatives cannot be underestimated. The classical example is the use of diosgenin as the primary starting material for the synthesis of the majority of steroidal hormones currently used in medicine.

C. Apathy in Plant-Derived Drug Development

Although estimates vary, the most commonly-quoted figure as to the number of species of higher plants that can be found growing on planet Earth is 250,000 to 500,000. One also often hears educated "guestimates" that "less than 5 % (or 10 % or 15 %) of these plants have been investigated for pharmacologically active principles." However, no one has adequately determined what parameters must be considered before one can state that a particular plant has indeed been "investigated for pharmacologically active principles." With respect to attempting to estimate how many plants have been investigated *as potential sources of new drugs*, our more than *six* years experience at computer coding the world literature concerning chemical constituents and pharmacological activities of living organisms leads us to believe that no reasonable estimate can be made.

For example, for the past dozen or so years, what might be considered to be the most extensive pharmacological investigation of plants ever has been carried out by the National Cancer Institute (Drug Research and Development Branch). About 20,525 different species of plants were screened for animal antitumor activity (4). However, the fact that 90 % of these were shown to be devoid of antitumor effects against the one or two tumor systems (of several hundred known) selected for the "screen" surely does not preclude the sample plants from having chemical entities of potential use as medicaments in a variety of other diseases or conditions. Therefore, although one might be able to say that 4 - 8 % of higher plants have been investigated for *antitumor* activity, these plants must still be considered "uninvestigated" with respect to the many other important drug actions that they might possess.

What is the financial gamble in developing a new drug, synthetic or natural? This figure is difficult to determine, mainly because of the complications involved in assessing and calculating drug development costs. Do we consider the cost of discovering the compound? of preclinical testing? of clinical evaluation? of preparing FDA approval forms? One cannot use the figure of $722.7 million, published by the U.S. drug industry as indicative of its total 1974 budget for company-financed research and development of human pharmaceuticals in the United States (1). This figure is not specific for new drug entities, but includes costs for developing "me too" products, new dosage forms, etc. If we nevertheless did use that figure and considered also that in 1973, only 19 single *new* drugs were introduced on the market in the United States (5), then the research and development costs per drug would amount to $38 million. Since other sources (6), however, state that, taking into consideration the factors mentioned above, the total cost of research and development of each new drug before it reaches the market may be only from $2.5 to $4.5 million, then it becomes obvious that the total research and development costs of pharmaceuticals, published by the drug industry, are far from being atributable primarily to NEW drugs.

If one accepts the more conservative figure, ca. $3 million, as the cost to develop a new drug to a marketable form (estimated cost from inception to marketable dosage form, including clinical trials, etc.), and if the industry currently invests a maximum of $0.15 million per year for research on drugs from higher plants, then one could expect, on an average, that only *one* new drug from higher plants would be marketed every 20 years. From our experience it seems doubtful that more than three or four pharmaceutical firms in the U.S.A. are currently engaged in any type of meaningful research on higher plants as sources of new drugs. We further suggest that $0.15 million annually is a generous estimate of the current cost of such research to the American pharmaceutical industry. What might happen if the financial commitment to research in this area were at the same level as for the development of synthetic drugs?

Let us now consider the fact that in the U.S.A. during the period 1954 to 1973, eight new drugs from higher plants were introduced as prescription items; reserpine, deserpidine, rescinnamine, sparteine, Rauwolfia whole root, alseroxylon fraction products, vincaleukoblastine (vinblastine), and leurocristine (vincristine). One might argue that, during the past 20 years, even at a low level of research funding for developing new drugs from higher plants, one new drug has been marketed every 2.5 years, on the average. Because the expectation by the parameters previously discussed is one plant-derived drug every 20 years, while the actual situation is one every 2.5 years, research and development costs in this area appear to be a "bargain."

Why have the pharmaceutical industry and government agencies turned their heads against further exploitation of a market now estimated in the U.S.A. at $3 billion at the consumer level? The answer can be expressed simply that there are major examples, from the not-too-distant past, in which modest investments of time, money, and effort, have not paid off. Let me cite just a few to illustrate the point.

A few years ago, one of our leading pharmaceutical houses in the U.S.A. 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 Ph.D staff of chemists,