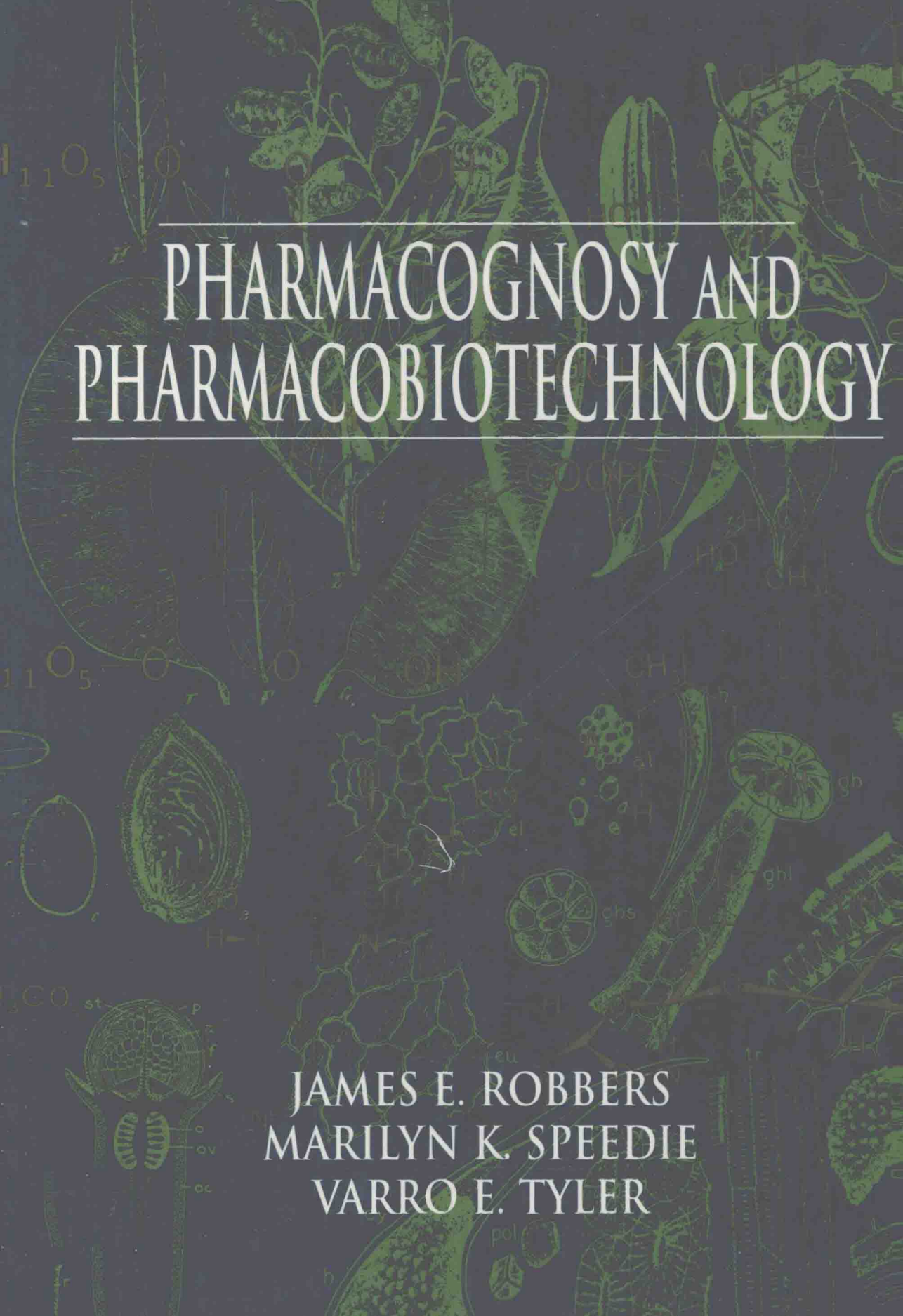

PHARMACOGNOSY AND PHARMACOBIOTECHNOLOGY

JAMES E. ROBBERS
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VARRO E. TYLER

PHARMACOGNOSY AND PHARMACOBIOTECHNOLOGY

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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Preface

A book entitled *Pharmacognosy and Pharmacobiotechnology* might for some seem to be an unusual combination of terminology and disciplines. The logic behind this combination is that, on the one hand, pharmacognosy, the forerunner of all other scientific disciplines in pharmacy and which has its origins in ancient civilizations, deals with drugs produced by plants, animals, and microorganisms. It includes all drug agents produced through a biosynthetic process. On the other hand, pharmacobiotechnology involves the production of natural product drugs by application of the remarkable progress made in recent years in molecular biology. It is the newest frontier in providing innovative approaches in drug discovery and patient treatment. In essence, therefore, this book deals with both the oldest and the newest drugs, the common thread being that all are natural products.

The goal of this textbook is to provide primary knowledge of natural product drugs to the pharmacy student in the professional program of study. It will also interest those students engaged in graduate studies in natural products as well as other health professionals seeking to understand the important role natural products have in drug therapy and drug discovery. Emphasis is placed on the biology and chemistry of these drugs as they relate to drug production and pharmaceutical and medicinal use. A chapter on pharmacobiotechnology is devoted to developing an understanding of the application of molecular biology to technology in the production of recombinant protein drugs and monoclonal antibodies.

With the exception of the antibiotics and the biologics, the drugs are organized on the basis of their biosynthetic and chemical relationships; this provides the fundamental basis for the conceptual understanding of natural products as drugs. The biosynthetic processes that have evolved in living organisms have led to the formation of unique, diverse chemical structures that possess an amazing variety of biological activities. Some of these chemicals are mainstays in drug therapy, and the never-ending variety of novel pharmacophores found in natural products has served as a stimulus to the medicinal chemist to use them as prototypes for structural modification in order to improve therapeutic effect. Pharmacognosists and natural product chemists have also been stimulated to search nature to find new leads for drug discovery.

The chapter on Antibiotics includes not only natural products but semisynthetic and synthetic anti-infective agents as well. This provides a complete picture of the armamentarium of drugs used to treat infectious diseases. The chapter on Biologics and Immunomodulators is a unique aspect of the book and discusses both immunologic agents and biologics related to human blood. Many of the latter are available for drug therapy only because of the advances in pharmacobiotechnology.

The demand for information on the safety and efficacy of herbal medicines is increasing at an extremely rapid rate. Although these so-called dietary supplements are not regulated by the Food and Drug Administration nor are legal standards of identity and purity monographed in current editions of the *United States Pharmacopoeia* or the *National Formulary*, many pharmacies sell them, and it is important for pharmacists to have a working knowledge of the basic principles involved in their use. For this reason, some of the more important herbal drugs have been included and are found in the appropriate chapters according to the chemistry of their active constituents.

At the present time, the world pharmaceutical market is rapidly expanding. Numerous new drug companies are being formed along with an accompanying increase in research and development efforts. In the search for new drugs, organisms from all parts of the

globe are being examined as sources for novel chemicals and bioactivity. The search ranges from plants of the tropical rain forests to animals and microorganisms from the seas. In addition, pharmacobiotechnology has had a major influence on increasing the speed of the drug discovery process by providing unique and valuable tools for drug screening, such as the cloning of receptor proteins for bioactivity assays. We believe that this book will enable the reader to understand the significant role of natural products in drug discovery and patient therapy. We hope that it will impart, at least in some small way, the excitement and awe associated with human knowledge about, and the use of, these wondrous chemicals from nature.

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Minneapolis, Minnesota Marilyn K. Speedie
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Contents

1

Introduction to Pharmacognosy

A BRIEF HISTORY OF PHARMACOGNOSY

From the earliest days of organized pharmaceutical and medical knowledge, all of the information pertaining to drugs and their usage in Western culture was designated "materia medica" (literally, medical matter). The most famous commentary on drugs, written by the Greek pharmaco-botanist Pedanios Dioscorides in the first century A.D., is titled *De materia medica libri cinque* (Concerning medical matter in five volumes). This treatise, which covered some 600 plant drugs plus a number of animal and mineral products, remained the authority in the field for about fifteen centuries.

Gradually, as the amount of knowledge about drugs increased, specialized disciplines became a necessity. In the early nineteenth century, materia medica began to undergo division into pharmacology (the actions of drugs) and pharmacognosy (all aspects of drugs, with lesser emphasis on actions). At the time, all medicines derived from natural sources, so that qualifier is not necessary.

The word "pharmacognosy," formed from two Greek words *pharmakon* (drug) and *gnosis* (knowledge), was long thought to have been introduced by C.A. Seydler, a medical student in Halle/Saale, Germany, who used the title *Analectica pharmacognostica* for his dissertation in 1815. However, recent historical research has found an earlier usage of "Pharmacognosis." J.A. Schmidt used that title in his *Lehrbuch der Materia medica,* published in Vienna in 1811, to describe the study of medicinal plants and their properties.

Later in the nineteenth century, chemists began to synthesize large numbers of organic compounds with structures of ever-increasing complexity, some of which were useful therapeutic agents. Because these products were considered to fall outside the realm of pharmacognosy, the discipline of medicinal chemistry, which had remained relatively dormant since the time of Paracelsus, took on increased vigor. Thus, there came to be three basic disciplines devoted to drugs: pharmacology, which dealt with drug actions and effects; pharmacognosy, covering all information on medicines from natural sources—plants, animals, and microorganisms; and medicinal chemistry, the science of synthetic drugs.

This situation prevailed until the mid-twentieth century, at which time pharmacognosy and medicinal chemistry began to merge. The reasons were both numerous and complex and need not be dealt with here. It is sufficient to point out that, in spite of the continued utilization of a large number of significant drugs of natural origin—antibiotics, oral contraceptives, serums and vaccines, and classic medicines from higher plants—both teaching and research efforts concentrated on synthetic drugs. Many individuals who continued to work with botanicals were educated principally in chemistry and adopted the designation *natural product chemists.*

Then, in the last decades of the twentieth century, three significant events occurred which have already produced fundamental changes in the attitude of both the public and scientists toward pharmacognosy. In the first place, lay persons discovered the utility of whole plant drugs—or herbs, as they are commonly called. Dissatisfaction with the effectiveness and the cost of modern medicine, abetted by an enhanced appreciation of things "natural" and "organic," has caused millions of persons throughout the world to gain a deep appreciation of the use of classical plant drugs for the treatment of many ailments, usually of the self-limiting variety. The "green" revolution, in terms of

herbal medicine, has now achieved astonishing popularity in the United States. Although not yet understood or encouraged by an ultraconservative Food and Drug Administration that classifies most plant drugs as dietary supplements or food additives and places severe limitations on labeling, there is little doubt that consumer demand will promote an ever-increasing interest in classic plant drugs for use as traditional herbal remedies.

In the second place, major pharmaceutical manufacturers have recognized that plants with folkloric reputations as remedies probably provide the best source of constituents that can serve either as new drugs or as prototypes for them. Because the patent situation renders it difficult to obtain market exclusivity for many classic plant remedies long in use, the search for botanical remedies has turned to exotic plants in remote areas such as the tropical rainforests. Major pharmaceutical companies have now developed cooperative agreements with individuals or organizations seeking medicinal plants in such countries as Brazil, Costa Rica, China, Mexico, Borneo, and even Samoa. This intensive effort is certain to yield positive results in the form of new plant drugs in the reasonably near future.

And finally, the greatest revolution of all, which is still in its infancy as far as drug discovery is concerned, has begun in the field variously described as recombinant DNA technology, genetic engineering, or more specifically, pharmacobiotechnology. This involves the transfer of genetic material from one organism to another, permitting the latter to produce in quantity a component of the former that is useful as a drug. The first commercial application of the technique in pharmacognosy has been a process utilized by the Eli Lilly Company which allows the production of human insulin by a special nondisease-producing strain of *Escherichia coli* bacteria that has been genetically altered by the addition of a gene for human insulin production.

Another early commercial product resulting from this methodology was tissue plasminogen activator, alteplase or tPA, a thrombolytic agent. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator obtained from a line of human melanoma. This is inserted genetically into a line of Chinese hamster ovary cells which then secrete the enzyme alteplase into the culture medium from which it is recovered, purified, and marketed. These examples demonstrate the feasibility of recombinant DNA technology in the production of commercial amounts of useful proteinaceous drugs. Details of them and other natural products produced by the technique will be discussed subsequently in this text.

In presenting this brief history of the initial development, decline, and renascence of the discipline of pharmacognosy, the comments have been purposely limited to its place in Western culture. That is not to say that drugs of plant and animal origin have played insignificant roles in the Asiatic culture represented by such countries as China and India. In China, the drug encyclopedia *Pen-ts'ao kang mu*, compiled by Li Shih-Chen and published in 1596 A.D., listed more than 2000 drugs of natural origin. Some 5000 native plants are used as medicinal herbs in that country today. The *Vedas* of India, a collection of hymns predating 1000 B.C., included more than 1000 healing herbs, many of which continue to be used in Ayurvedic medicine.

The problem is that, until now, these cultures have made only minor contributions to Western medicine. The useful plant drugs *ma-huang* (ephedra) from China and rauwolfia from India are notable exceptions. However, the philosophical precepts upon which Chinese and Ayurvedic medicines are based are entirely different from those of the West. Both of the former believe that disease is caused by an imbalance of certain "elements" or "humors" in the body reminiscent of the long-discredited four-humors doctrine of the Greek physician Hippocrates (ca. 4600 to 361 B.C.). Drug research based on such philosophical principles has not proven productive. It is only when the herbal remedies are evaluated by Western methods, as was the case with ephedra and rauwolfia, that useful drugs result. That is a task remaining to be done for many thousands of potentially useful medicinal plants.

VALUE OF NATURAL DRUG PRODUCTS

Compounds from natural sources play four significant roles in modern medicine. In the first place, they provide a number of extremely useful drugs that are difficult, if not impossible, to produce commercially by synthetic means. These include such diverse groups of compounds as the alkaloids of the opium poppy, of ergot, and of solanaceous plants; the cardiotonic glycosides of digitalis; most of the antibiotics; and all of the serums, vaccines, and related products. Natural sources also supply basic compounds that may

be modified slightly to render them more effective or less toxic. The numerous variations of the morphine molecule serve as examples here. A third role of natural products is their utility as prototypes or models for synthetic drugs possessing physiologic activities similar to the originals. Procaine and similar local anesthetics are commonly cited representatives of this category. Examples of all three types of compounds and their relationships are given in Table 1–1.

There is a fourth role for natural products that is quite different from the above but is nonetheless important. Some natural products contain compounds that demonstrate little or no activity themselves but which can be modified by chemical or biological methods to produce potent drugs not easily obtained by other methods. For example, taxol may be synthesized from baccatin III, which occurs more or less abundantly in the leaves of various yew species, whereas taxol itself is found only in the bark of the scarce Pacific yew. Proper chemical and biological treatment of stigmasterol, which occurs abundantly in soybean oil, permits the large-scale production of hydrocortisone or related corticosteroids, compounds that occur in nature in only small amounts. The importance of natural products as precursors of significant drugs cannot be overemphasized.

Some 25 years have passed since the last detailed survey of the use of natural products and their constituents in medicine was conducted. However, the conclusions reached then from a survey of 1.05 billion new and refilled prescriptions are still widely quoted in the literature. It is probable that, with the exception of certain details to be mentioned later, the findings would be similar today.

In the prescriptions studied, about 25% were for drugs containing higher plant principles. Taken by itself, however, this figure can be misleading. About 10% of the total prescriptions (40% of those with plant constituents) were for hormonal principles, including progestins, corticosteroids, estrogens, and anabolic agents. Obviously, these are not isolated directly from higher plants but, instead, are produced from precursors obtained from that source. In other words, they fall into the fourth category of natural products previously discussed. Many of the narcotic analgesics are classified in the second category, namely, chemical modifications or derivatives of such compounds as morphine. The point is, the 25% figure frequently quoted does not consist of isolated plant drugs *per se* but also includes derivatives with various related or unrelated activities prepared from plant precursors.

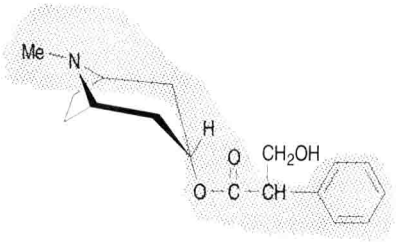
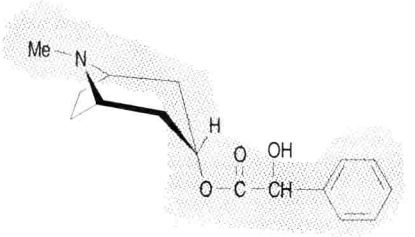
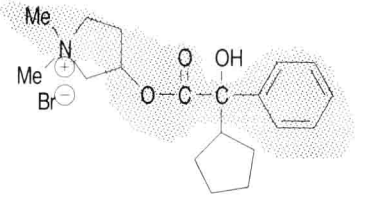
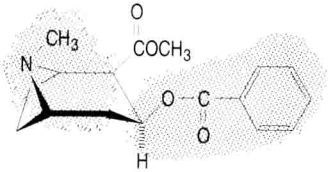
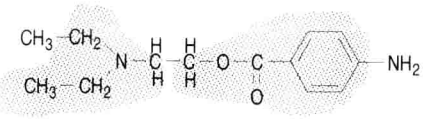
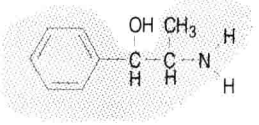
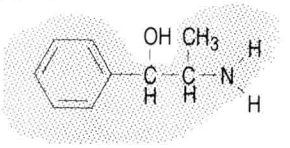
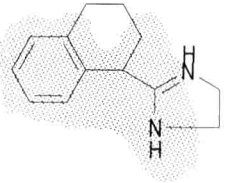
Nearly 12% of the total prescriptions surveyed were for microbial-derived products; about 6% were animal derived; 7% were mineral in character. The remaining 50% was composed of synthetic chemical agents. In summary, the survey indicated that approximately 50% of prescriptions filled in 1967 contained one or more natural drug products, broadly defined so as to include various molecular modifications.

No similar in-depth survey has been conducted since that time, but a 1991 prescription audit revealed little change in the overall 25% figure for prescriptions containing one or more natural products. Conclusions regarding the significance of certain medicines from natural sources may also be drawn from a general knowledge of the pharmaceutical marketplace. The 6% figure for animal-derived drugs was not and is not representative of the use of such products in the United States. Most serums, vaccines, and the like are either utilized in hospitals or administered in various types of clinics where no identifiable prescription is ever written. Various blood products also fall in this category.

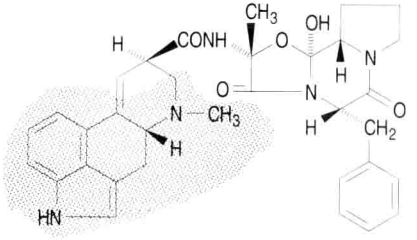
In 1967, the use of antibiotics and antineoplastic agents from natural sources was much less than at present, the variety and application of such principles having increased markedly in recent years. The change of hydrocortisone from prescription to OTC status and the nearly ubiquitous use of contraceptive medication by females of child-bearing age have certainly resulted in a marked increase in the quantities of plant-derived hormones employed. Further, the advent of a fairly large number of drugs produced by pharmacobiotechnological procedures has certainly promoted an increased use of natural drug products. In addition, the therapeutic use of crude drugs (herbs) and their galenical products (phytomedicinals) by the American public has reached an all-time high. As previously explained, most of these are not technically classified as drugs in this country, but the therapeutic use and utility of many of them cannot be denied. Sales of such products in the United States in 1994 were estimated at approximately $1 billion at the wholesale level in comparison to total sales of about $55 billion by U.S. pharmaceutical manufacturers. Herbal products thus represent a small but ever-increasing percentage of the total market.

When one considers that plant-derived ste-

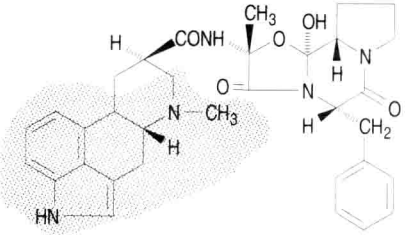
Table 1–1
Examples of Plant Drugs Serving as Prototypes or Models for Other Medicinals

Natural (Activity)	Closely Related Semisynthetic	Prototype-Derived Synthetic
Atropine (Anticholinergic) 	Homatropine 	Glycopyrrolate 
Cocaine (local anesthetic) 	—	Procaine 
Ephedrine (adrenomimetic) 	Phenylpropanolamine 	Tetrahydrozoline 

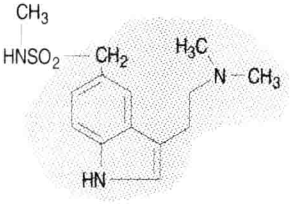
Ergotamine
(antimigraine)



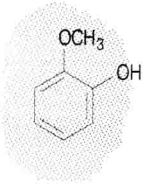
Dihydroergotamine



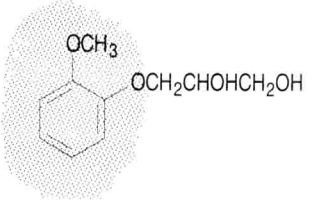
Sumatriptan



Guaiacol
(expectorant)



Guaifenisin



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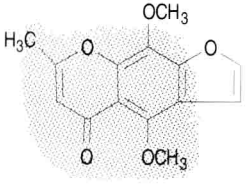
Khellin
(antiasthmatic)



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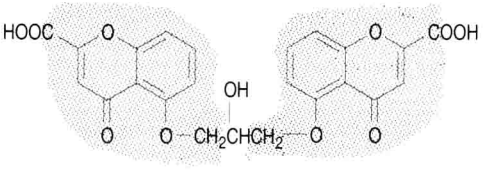
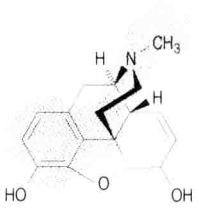
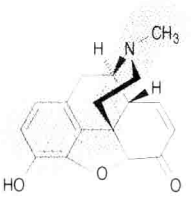
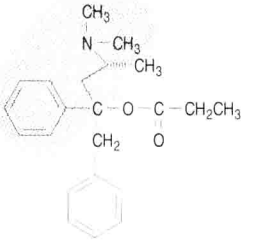
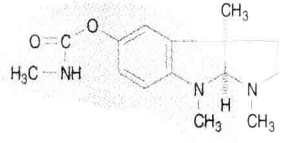
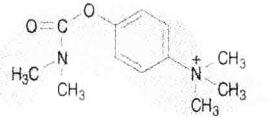
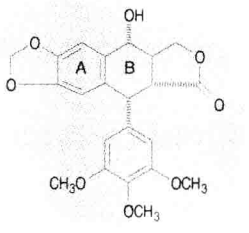
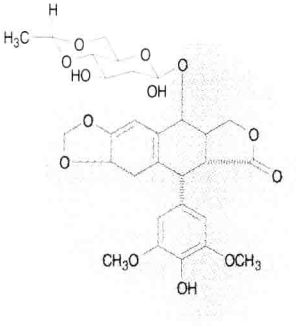
Cromolyn

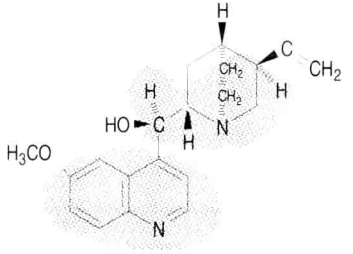


(continued)

Table 1–1
Examples of Plant Drugs Serving as Prototypes or Models for Other Medicinals—*(Continued)*

Natural (Activity)	Closely Related Semisynthetic	Prototype-Derived Synthetic
Morphine (narcotic analgesic) 	Hydromorphone 	Propoxyphene 
Physostigmine (cholinergic) 	—	Neostigmine 
Podophyllotoxin (antineoplastic) 	Etoposide 	—

Quinine
(antimalarial)



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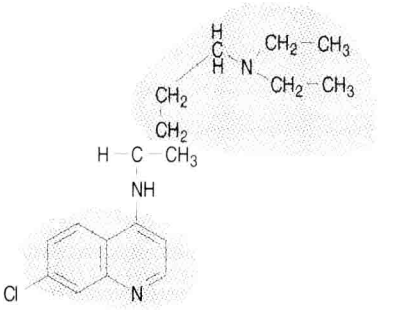
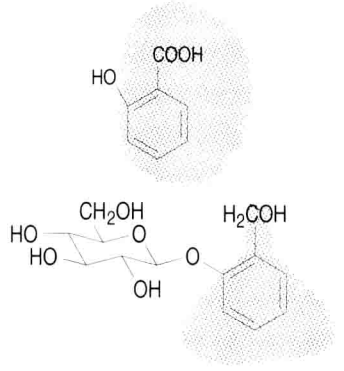
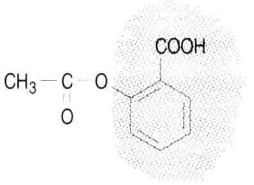
Chloroquine



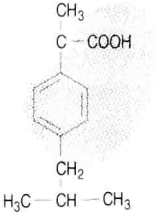
Salicin and Salicylic Acid
(Analgesic)



Aspirin



Ibuprofen



roids alone account for about 15% ($22 billion) of the $150 billion world pharmaceuticals market, that the annual market for taxol is estimated to reach $1 billion by the year 2000, that the antineoplastic agents vinblastine and vincristine have sales amounting to $100 million per year, that the market for psyllium seed products amounts to some $300 million annually, and that nicotine and scopolomine patches now have combined sales of more than $1 billion per year, it is obvious that natural products continue to play important economic as well as therapeutic roles in modern medicine. Based on figures of this nature, it must be concluded that natural drugs from higher plants, microbial sources, and animals have at least held firmly to the 43% market share they enjoyed in 1967. If one considers expanded OTC usage, they have probably increased their numerical share of the total drug market, even considering the large increase in synthetic drugs currently available.

In any case, research developments have blurred the dividing line between natural and synthetic products. The naturally occurring alkaloid ephedrine is now usually produced by chemical synthesis involving the reductive condensation of L-l-phenyl-l-acetylcarbinol with methylamine. Diazepam, a benzodiazepine tranquilizer, long thought to be of purely synthetic origin has since been found to occur naturally in small amounts in both plants and animals. This erosion of rigid classificational limits is one of the factors that has caused instruction in pharmacognosy to be combined with that in medicinal chemistry in many educational programs in American colleges and universities. Still, it must not be forgotten that a healthy market share approaching 50% of the significant drugs utilized in medicine today are natural in origin. It is the function of this volume to discuss the significant features of these important medicines.

PRODUCTION OF NATURAL DRUG PRODUCTS

Because of their diverse origin from plant, microbial, and animal sources, the production of natural drug products takes many different forms. Higher plants may be collected in the wild (wildcrafted), or cultivated, or both. In the case of those obtained from our ever-dwindling natural resources, special attention must be paid to quality control. Collectors, for the most part, are relatively uneducated individuals, not versed (and sometimes not caring) about the details of plant taxonomy. Their produce is sometimes misidentified or adulterated. It may also be harvested at the wrong time of year for maximum yield of desired constituents, improperly dried and stored, and subject to insect or rodent infestation. Obviously, quality control is important in such cases.

However, it is not always easy to determine the quality of plant materials. If they are maintained in whole form, identification is simple; but if they are finely comminuted, even qualified experts have difficulty, especially with mixtures. Once the plant material has been extracted, only suitable analytical techniques will give a true picture of quality. Such procedures may be chemical, physical, or biological in nature. Various chromatographic procedures that enable the analyst to compare the profile of the sample being tested with that of a product of known quality are most useful.

Unless wildcrafting is carefully and conscientiously carried out, natural reserves tend to become depleted. This is the situation that now exists in much of the United States, Western Europe, and even parts of Asia with respect to popular drug plants. This phenomenon ultimately results in the commercial cultivation of drug plants, but this industry is also beset with problems.

In the first place, the market is generally quite limited; and it often requires special techniques and procedures that are difficult to conduct, especially on a limited scale. Unless mechanization can be effected—a difficult task in small-scale crop production—it is labor intensive and therefore not feasible in technologically advanced nations where wages are high. For this reason, only a few such specialty crops are cultivated presently in the United States.

One of these is American ginseng, a shade-grown root crop that because of its high price lends itself to small scale production even in this country. Used primarily by inhabitants of the Asian rim nations, ginseng is becoming popular as a kind of tonic in both Europe and America. In the United States it is approved by the FDA only as a food for beverage purposes; but it is extensively cultivated here, especially in Wisconsin. Ginseng exports from this country in 1992 amounted to approximately $90 million.

Another plant drug grown extensively in the United States is ginkgo leaves. One plantation of 10 million trees, grown as bushes so the leaves can be harvested mechanically, occupies more

than 1000 acres in South Carolina. The leaves are dried and shipped to Europe for processing. Ginkgo biloba extract (GBE) is a best-selling drug there.

Volatile-oil-producing plants, such as peppermint, are also extensively cultivated in parts of the United States, especially in Indiana and the Pacific Northwest. All of the operations involved, including the initial distillation of the oil from the harvested plant material, are highly mechanized to reduce labor costs. As is the case with other drug plants, cultivation permits selection of high-yielding varieties and also allows the time of harvest to be controlled to maximize yields.

Nevertheless, most of the drug plant cultivation takes place outside the United States. Even a specialty crop, such as ergot, that involves mechanical inoculation of rye plants with spores of a selected fungus, is produced in Eastern Europe. This kind of field cultivation must necessarily compete successfully on an economic basis with saprophytic production of the alkaloids obtained by growing the organism in submerged culture. Large fermenters are employed for this purpose in a manner analogous to antibiotic production.

An alternative method of drug plant cultivation involves production of the desired secondary constituents by cell-culture techniques. Although this method may be utilized in certain specialized cases, there are many limitations, including slow growth of the cells, expensive media and production facilties, low yields of desired metabolites, and a tendency to store desired constituents in the cells rather than to excrete them into the media where they may be more easily recovered. Studies have shown that stress conditions, such as interaction with an appropriate pathogen, may stimulate the production of certain desired constituents in plant-cell suspension cultures, but slow growth of the cell biomass is still a problem. Probably this method of drug production will not become truly useful until the plant genes that code for enzymes catalyzing the desired biosynthetic reactions can be transferred into more rapidly growing bacterial or fungal cells.

Microbial metabolites used as drugs, especially the antibiotics and related antineoplastic agents, are produced by fermentation. This usually involves growing the desired organism in aerated tanks holding thousands of gallons of a sterilized nutrient medium. At the proper time, the cell growth is separated from the culture broth, the latter is extracted, and the extract is then purified to yield the desired component. In some cases, such as with the cephalosporins, the constituent produced by fermentation is subjected to various chemical reactions to produce by semisynthesis the desired drug product.

Production of genetically engineered drugs is basically quite similar to the fermentation techniques used for antibiotics. The principal difference is that a gene controlling the formation of the desired component is transferred from its original source to a fast-growing microbial or animal cell line, thereby allowing quantity production in a relatively short period of time. Because the technique is relatively new and considerable experimentation is required to develop a single commercial product, most drugs produced by recombinant DNA technology are quite costly, a factor that tends to limit their use.

In addition to desired components, undesirable constituents may also be synthesized by genetically modified organisms. This was vividly demonstrated in 1989 when tryptophan produced by a Japanese manufacturer using a strain of bacteria so modified was implicated in 1,400 cases of eosinophilia myalgia syndrome, a serious blood disorder. At least 19 deaths were recorded. Subsequent investigation revealed the tryptophan was not the causative agent. Instead, two toxic contaminants produced by the modified organisms and not removed during the purification procedure were at fault. Nevertheless, the FDA acted to remove tryptophan from the dietary supplement market. This episode points up the necessity for thorough testing of all genetically engineered foods and drugs prior to marketing.

In the specialized sense, the term *biologics* refers to animal derivatives, such as serums, antitoxins, and globulins or to microbial products, such as vaccines, toxins, and tuberculins that confer protection against pathogenic microorganisms. Products in the first category are prepared from the blood of animals, usually following some sort of special treatment designed to increase the concentration of desired components. Those of the second type are produced by inoculating an appropriate culture medium, which in some cases may consist of living tissue, with the proper pathogen. After appropriate purification, the product is ready for drug use. Even though they may lack immunizing activity, human blood and its various fractions or derivatives are usually considered to be biologics.

A whole spectrum of natural drug products exists, and their precise method of production is