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Old Yet New—Pharmaceuticals from Plants

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Many people are surprised to learn that about 25% of the pharmaceuticals prescribed by doctors in the developed world have, as their origins, the chemicals produced by flowering plants. If compounds produced by fungi and some animals are included, the figure is above 40% (*1*). White tablets are not readily associated with the dark liquids and bitter tastes traditionally associated with the use of plants as medicines, but the living world is increasingly recognized as a source of molecules with a realized or potential value in the treatment of disease. This article explores some of the contributions made in this area over the last two centuries and illustrates the value of interdisciplinary research, since progress depends on a combination of expertise and skills in botany, chemistry, biochemistry, and pharmacology. The name given to this interdisciplinary subject is pharmacognosy and its renaissance in Western science has been the subject of several recent reviews (*2*–*5*).

Origins

Almost every culture within the wide diversity of the world's population and habitats uses its local plants as medicines in some form or another. Some of the most ancient records detail the use of plants in this way in ancient Babylon, Egypt, India, and China. Plant material was dried, crushed, or extracted to give products that today would be called *botanical medicines*, *herbal medicines*, or *phytotherapeuticals*, and the resurgence of interest and use of these forms of medicine in the developed world is one of the fascinating aspects of society in the last 20 years. It is remarkable that many plants that can be identified from the old sources are still known and used in some form today, as "herbals" or as conventional pharmaceuticals containing a single chemical substance obtained from the plant. However, it should not be forgotten that a large part of the world's population still relies on plants and their crude extracts as their only affordable source of medicine.

In contrast to the use of extracts in former times and still today in many cultures, modern Western scientific medicine prefers to use single substances. This has arisen from the rationalist and reductionist approach of the scientific method and the requirement to ensure consistent efficacy and quality. The story of drug development and discovery has thus largely been a story of the extraction, synthesis, modification, and design of molecules.

This article focuses on the role that molecules from plants play in the development of the armory of drugs available to treat disease. However, it should not be forgotten that the use of mixtures of molecular types to treat disease is fast gaining acceptance as the preferred choice in some areas of mainstream therapy (e.g. of cancer and HIV infection), so it will be interesting to see whether plant extracts, which are also complicated mixtures, gain more respectability as therapeutic agents in orthodox medicine in the next few years.

Why Do Plants Produce Bioactive Molecules?

The ability of extracts of some plants to produce an obvious response in humans or animals has been known for a long time. Some might induce sleep, others would cause a violent emptying of the bowels, and a few, in quite small doses, might cause death. Over the last 200 years, the chemicals responsible for these effects have been isolated from many of these plants and their structures have been determined. Although a few have relatively simple structures, many are very complicated and one can only applaud the ingenuity and persistence of those who took much time and effort to determine them.

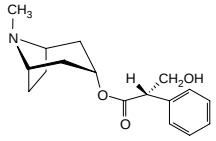
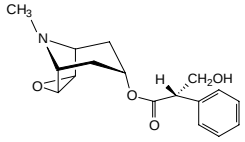
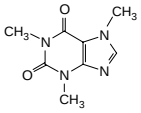
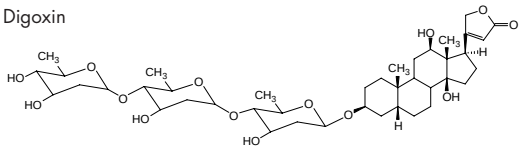
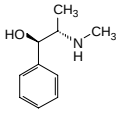
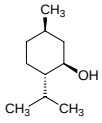
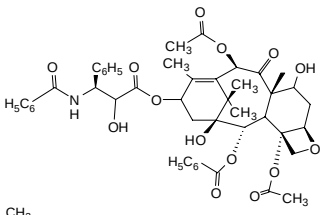
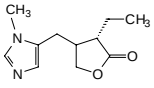
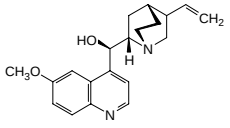
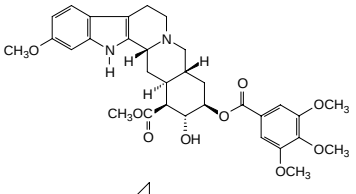
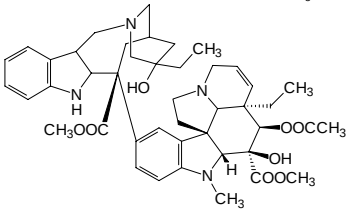
The ability of plants and some other living organisms to produce stereospecific molecules with very complex skeletons is one aspect that makes them attractive as sources of novel molecules, since some structures are beyond the imagination of even the most fanciful synthetic chemist.

Several theories have been advanced to explain the phenomenon of chemical complexity and diversity found in the botanical world, but the one most widely accepted at present is that the plant produces these compounds as part of its survival strategy (*6*). Since mammals are either threats to plants as herbivores or helpful as dispersal agents for seeds, it is not surprising that plants produce compounds that interact with mammalian physiology. The means by which plants were selected by humankind for treating various illnesses is not known, and some animals are known to utilize plants for the same purpose, but there is no doubt that this selection process has been a common activity in practically all human societies.

Natural Compounds and Established Pharmaceuticals

Although Paracelsus had introduced the concept of "the active principle" in medicine in the 15th century, it was the introduction of modern chemistry in the late 18th and early 19th century that enabled compounds to be isolated as pure substances from plant extracts, particularly if they crystallized relatively easily. In many cases, these isolated compounds had much the same effect as the plant extract and so quickly replaced it as the important ingredient in medicines, although it is important to note that their chemical structure was often not fully elucidated until many years later. Serturner isolated the painkiller morphine, and other alkaloids such as codeine and narcotine, from opium (the dried latex of the poppy *Papaver somniferum*) in the first few years of the 19th century. These were the first natural compounds to be isolated and both are still very important drugs. Since then, many hundreds of compounds have been isolated from plants and many of these remain in widespread use in medicine (see Table 1). A more specific example is provided by the cardiac glycosides digitoxin, and more recently digoxin, from foxgloves (*Digitalis* species). The leaves of *Digitalis purpurea* were introduced into

Table 1. Some Established Pharmaceuticals Obtained from Plants

Name	Structure	Plant Source	Use in Medicine
Atropine		Deadly nightshade (*Atropa belladonna*) Henbane (*Hyoscyamus* spp.) Stramonium, jimson weed (*Datura* spp.)	Antispasmodic for gastrointestinal tract; pupil enlargement in eye
Scopolamine		As for atropine	Preoperative sedative; antiemetic in travel sickness
Caffeine		Coffee (*Coffea arabica*) Tea (*Thea sinensis*)	Central nervous system (CNS) stimulant
Digoxin		Woolly foxglove (*Digitalis lanata*)	Improvement in force of contraction to remedy congestive heart failure
Ephedrine		*Ephedra sinica* and other spp.	Relief of asthma and hay fever
Menthol		Peppermint (*Mentha* × *piperita*) and related species	Decongestant; cooling effect on nasal passages
Paclitaxel		Pacific yew (*Taxus brevifolia*)	Anticancer, especially for ovarian cancer
Pilocarpine		Jaborandi leaves (*Pilocarpus jaborandi*)	Glaucoma treatment; pupil contraction in eye
Quinine		Cinchona bark (*Cinchona* spp.)	Antimalarial
Reserpine		*Rauwolfia* spp.	Tranquillizer; hypotensive
Vinblastine		Madagascar periwinkle (*Catharanthus roseus*)	Anticancer, especially for leukemia

medicine by William Withering in England in 1785, after he carried out tests arising from his observation of their successful use by a local woman in treating dropsy. Dropsy was the name given to swelling of the limbs and tissues due to insufficient strength and frequency of the heartbeat, and it is now known that the glycosides reverse this situation. The dried leaves were used as powders or as tinctures at first, but eventually digitoxin was isolated and used as the pure chemical in pharmacy in the 19th century. The toxicity of digitoxin was too great and a very similar compound, digoxin, from the central European *Digitalis lanata*, replaced it and is still the drug preferred by many physicians to treat weak and irregular heartbeat (*7*).

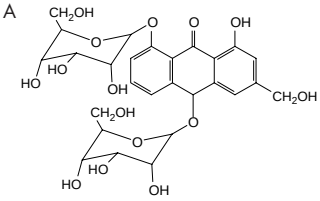
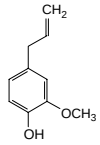
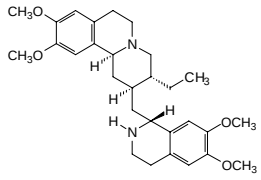
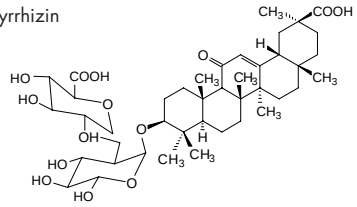
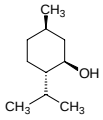
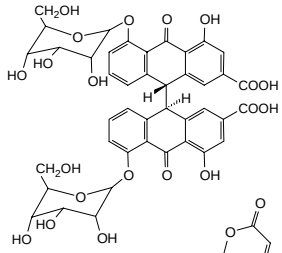
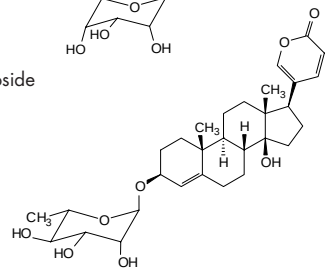
Not only the local European species were investigated, but also plants obtained during explorations by European nations around the world, which were already considered valuable medicines in the countries to which they were native. An extract of the bark of various *Cinchona* species had been used since the 16th century for treating malaria and in 1820 quinine was isolated from the bark. This alkaloid has ever since been a very important antimalarial, although currently, synthetic prophylactic compounds such as chloroquine predominate in the developed world.

As more compounds were isolated and their structure determined, patterns began to emerge making classification on a chemical basis possible, and terms such as *alkaloid* and *glycoside* were introduced. Over the years, with developments in separation science, it has become easier to isolate substances that do not crystallize readily or that exist in complex mixtures with closely related molecules. This, together with advanced spectroscopic methods, which give detailed information on the structure of the molecule, and sensitive tracer studies, which enable its route of

formation in the plant to be determined, has led to more precise definitions and the delineation of many more classes of compounds.

In several types of drugs, it has been found that no one single molecule predominating in quantity is responsible for the activity of the extract, since a mixture of related compounds is present. In these cases, although the chemistry is now known, the mixture is still used pharmaceutically. Some examples are given in Table 2.

Table 2. Plants Still Used as Extracts

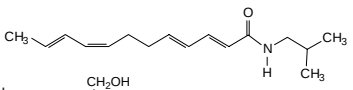
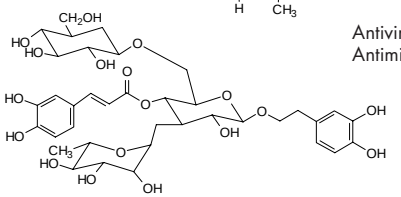
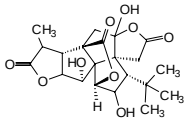
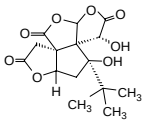
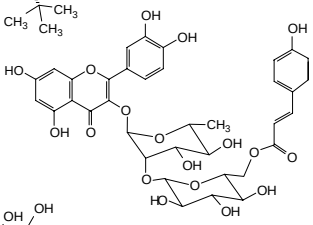
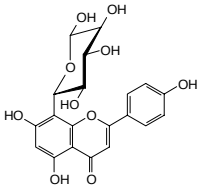
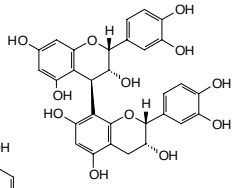
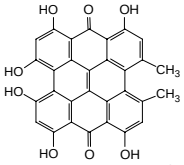
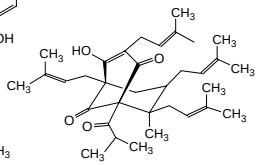
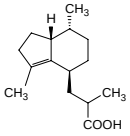
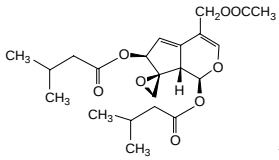
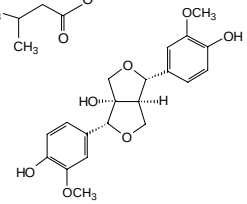
Pharmaceutical; Plant Source	Chemicals Present			Use in Medicine
	Type	Example	Structure	
Cascara bark; *Rhamnus purshiana*	Anthracene glycosides	Cascaroside A		Laxative
Clove oil; *Syzygium aromaticum*	Phenolic phenyl-propanoids	Eugenol		Topical antiseptic, analgesic
Ipecacuanha; *Cephaëlis pecacuanha*	Benzyliso-quinoline alkaloids	Emetine		Emetic, expectorant
Licorice; *Glycyrrhiza glabra*	Triterpene glycosides	Glycyrrhizin		Expectorant, antiinflammatory
Peppermint oil; *Mentha × piperita*	Monoterpenes	Menthol		Antispasmodic
Senna; *Cassia senna, Cassia angustifolia*	Anthracene glycosides	Sennoside A		Laxative
Squill *Urginea maritima*	Cardenolides	scilliroside		Expectorant

Herbal Medicines and Their Constituents

A fascinating trend in pharmacy in every developed country during the last two decades has been the enormous growth in the general public's use of powdered plant material or plant extracts containing the complicated mixtures of chemicals referred to above. These products are called by a variety of names such as *phytopharmaceuticals*, *phytomedicines*, and *herbal medicines* in European English, but are usually referred to as *botanicals* in the USA. In a few countries, most notably Germany, many of these preparations are used extensively in orthodox medicine; but in most countries they are, as yet, unaccepted by the majority of mainstream practicing physicians. Scientific interest in such pharmaceuticals is growing, and a less dismissive attitude to their therapeutic usefulness is becoming ever more evident (*8*). Several well-designed clinical studies have been undertaken that demonstrate a degree of efficacy for these plant extracts, and knowledge about the chemicals that contribute to the overall effect is fairly extensive. A detailed treatment of the constituents of these botanicals is beyond the scope of this article, which is mainly concerned with the contribution of the flowering plants to single chemical entity (SCE) pharmaceuticals, but several good books on the subject have been published (*9–11*). A selection of herbal extracts for which there is some hard clinical data is shown in Table 3, but some more general points should be mentioned concerning the chemical composition of this type of product.

The first, and very important, point that distinguishes herbal medicines from SCE pharmaceuticals is that the overall clinical effect is usually due to a mixture of compounds having a variety of pharmacological activities. The concept of a single "active principle" therefore does not really apply and it is very difficult to predict the activity on the basis of the content of only one compound. Thus the tranquillizing, anxiolytic, sleep-promoting herbal Valerian (*Valeriana officinalis*) contains the sesquiterpene valerenic acid, which inhibits GABA breakdown in the CNS, the monoterpene valepotriates, which cause smooth muscle relaxation and have a tranquillizing effect, and lignans, which bind to benzodiazepine receptors (*12*).

Table 3. Some Herbal Drugs with Some Clinical Evidence of Efficacy

Plant	Part Used	Claimed Therapeutic Benefit	Constituents Showing Activity		Activity of Constituents
			Type	Example of Structure	
Echinacea *Echinacea angustifolia* *Echinacea pallida*	Leaf juice, roots	Early-stage treatment of colds and 'flu	Polysaccharides Aliphatic amides		General immunostimulant Immunostimulant; antiinflammatory
			Phenolic compounds, e.g. echinacoside		Antiviral; Antimicrobial
Ginkgo *Ginkgo biloba*	Leaf extract	Improved peripheral bloodflow to reduce effects of aging on CNS function	Ginkgolides		Platelet Activating Factor (PAF) antagonist
			Bilobalide		Antioxidant
			Flavonoids		Vasodilator
Hawthorn *Crataegus oxyacanthoides* *Crataegus monogyna*	Leaves, fruit	Improved coronary function	Flavonoids, e.g. vitexin		Vasodilator
			Polycyanidins		cAMP-Phosphodiesterase inhibitor; control of intracellular calcium level
St. John's wort *Hypericum perforatum*	Aerial parts	Antidepressant	Hypericin		Monoamine oxidase inhibitor
			Hyperforin		Serotonin reuptake inhibitor
Valerian *Valeriana officinalis*	Underground parts	Tranquillizer, anxiolytic, aid to sleep induction	Valerenic acid		GABA reuptake inhibitor
			Valepotriates, e.g. valtrate		Anxiolytic; muscle relaxant
			1-OH Pinoresinol		Benzodiazepine receptor binder

Another aspect to be considered is that in some cases the compounds thought to be responsible for the effect have been shown to play only a minor part or not to be particularly significant. The antidepressant activity of *Hypericum perforatum* (St. John's wort) was at first thought to be due to the action of hypericin as a monoamine oxidase inhibitor; it is now thought that hyperforin is the major contributor and acts as a serotonin re-uptake inhibitor (*13*).

It should also be appreciated that the presence of other compounds such as saponins, flavonoids, and tannins may modify the solubility, bioavailability, and metabolism of the pharmacologically active compounds.

A reductionist experimental approach to these herbal medicines often leads to frustration, because the activity is often much decreased, or even lost, when the total extract is fractionated. This may be due to synergy or the protective role of one type of molecule for another (e.g. in preventing oxidative breakdown).

The value of determining the chemical constituents present might therefore be questioned, but such investigations are justified by the need to have some type of quantitative marker to allow good quality control to be effected. In addition, even though a compound may not be responsible for all the activity observed, it may still serve as a lead compound for more conventional SCE drugs, a classic example being the development of aspirin (see below). The process is essentially the same as that discussed below for ethnopharmacology as a basis for drug discovery, but no major pharmaceuticals have been developed in recent years from the conventional herbal drugs of North America and Europe.

Drugs from Nonmedicinal Plants—Yams and Yews

Not all drugs are obtained directly by isolation from the plant extract. A plant may not be included in the list of those with medicinal properties but may produce a type of molecule that is difficult to synthesize but is chemically similar to one known to be therapeutically useful. In these situations the expertise of chemists or biochemists is called upon to convert the plant compounds into the required ones or their analogues.

The foremost example of this category is the class of compounds known as steroids. It is arguable that some of the most far-reaching changes in society in the latter half of the 20th century would not have occurred were it not for the fact that steroids can be produced cheaply and in large amounts from plant material.

The medical importance of steroids arises from the fact that some of the major hormones in the body belong to this chemical group. Of particular importance are the sex hormones progesterone, estradiol, and testosterone and the adrenocorticoids, such as cortisone, which have an antiinflammatory effect. The value of progesterone in preventing miscarriage in progesterone-deficient pregnant women and of cortisone in treating conditions such as arthritis were demonstrated clinically in the middle decades of the 20th century, but supplies of the hormones could only be obtained at that time from slaughterhouse waste from animals, in which they occurred in small amounts. A different type of steroid was known to be present in large amounts in some plant species, and it was the American Russell Marker who developed a synthetic method of converting plant steroids obtained from Mexican yams (*Dioscorea* spp.) to the animal steroids (*14*, *15*). At about the same time, in the early 1950s, the use of progesterone-like compounds as oral contraceptives was being introduced and the availability of cheap steroids in large amounts facilitated the introduction of free or inexpensive female oral contraception. This not only made family-planning programs available worldwide but also contributed to the major changes in sexual morals and behavior in the West. Commercial steroids are now produced from several plants by a mixture of synthetic chemistry and transformations using microorganisms. Some of the relationships are shown in Figure 1.

A slightly different situation is shown by the recent demand for large amounts of the anticancer drug paclitaxel (Taxol) (*16*). This compound has been used clinically only for the last seven years but is now widely employed. It was first isolated from the bark of the Pacific yew *Taxus brevifolia*, but its supply was restricted because it is present in only small amounts; the trees needed to grow for 20 years to make harvesting economic, and removal of the bark killed the tree. In addition, there were major conservation concerns over harvesting the trees from the Pacific coast forests of the USA. Paclitaxel itself is not found in the leaves of *Taxus* spp;. but compounds known as baccatins are present, and methods have been devised whereby the baccatins are extracted from the leaves, especially of the plentiful European yew *Taxus baccata*. These are converted chemically to paclitaxel and another compound docetaxel (Taxotere), which is in clinical use in Europe (*17*, *18*). It is interesting that some fungal species that infect *Taxus* also produce taxanes, and culture of these fungi may provide the basis for a more economic and environmentally friendly method of obtaining this valuable pharmaceutical (*19*).

Using the Natural Molecule as a Template—Willow to Aspirin

In some cases it is not very suitable to use the isolated compound from a medicinal plant as a pharmaceutical . The plant may be difficult to grow or obtain; the compound may be unstable, it may not have a sufficiently strong effect, or most seriously, it might have undesirable side effects. In such cases, a common approach, particularly in the pharmaceutical industry, is to determine which parts of the molecule are responsible for the desired activity (this portion of the molecule is sometimes termed the *pharmacophore*) and which parts are not necessary or contribute to the undesired effects. The natural compound is thus used as a template in attempts to synthesize the pharmacophore, eliminate the undesired portions of the molecule, and synthesize related compounds so that structure–activity studies can be carried out (*20*).

This approach has led to the introduction of several major groups of drugs, including probably the best-known drug in all the world, aspirin. Aspirin (acetylsalicylic acid) is made completely synthetically but its development is based on the traditional use in Europe of plants such as willow (*Salix* spp.) and meadowsweet (*Filipendula ulmaria*) to treat rheumatism and general aches and pains. In the early 19th century compounds were isolated from these plants that could be hydrolysed to give salicylic acid, which showed the same effects as the extracts of the plants (Fig. 2). Salicylic acid was used in medicines but large doses were needed; it had an unpleasant

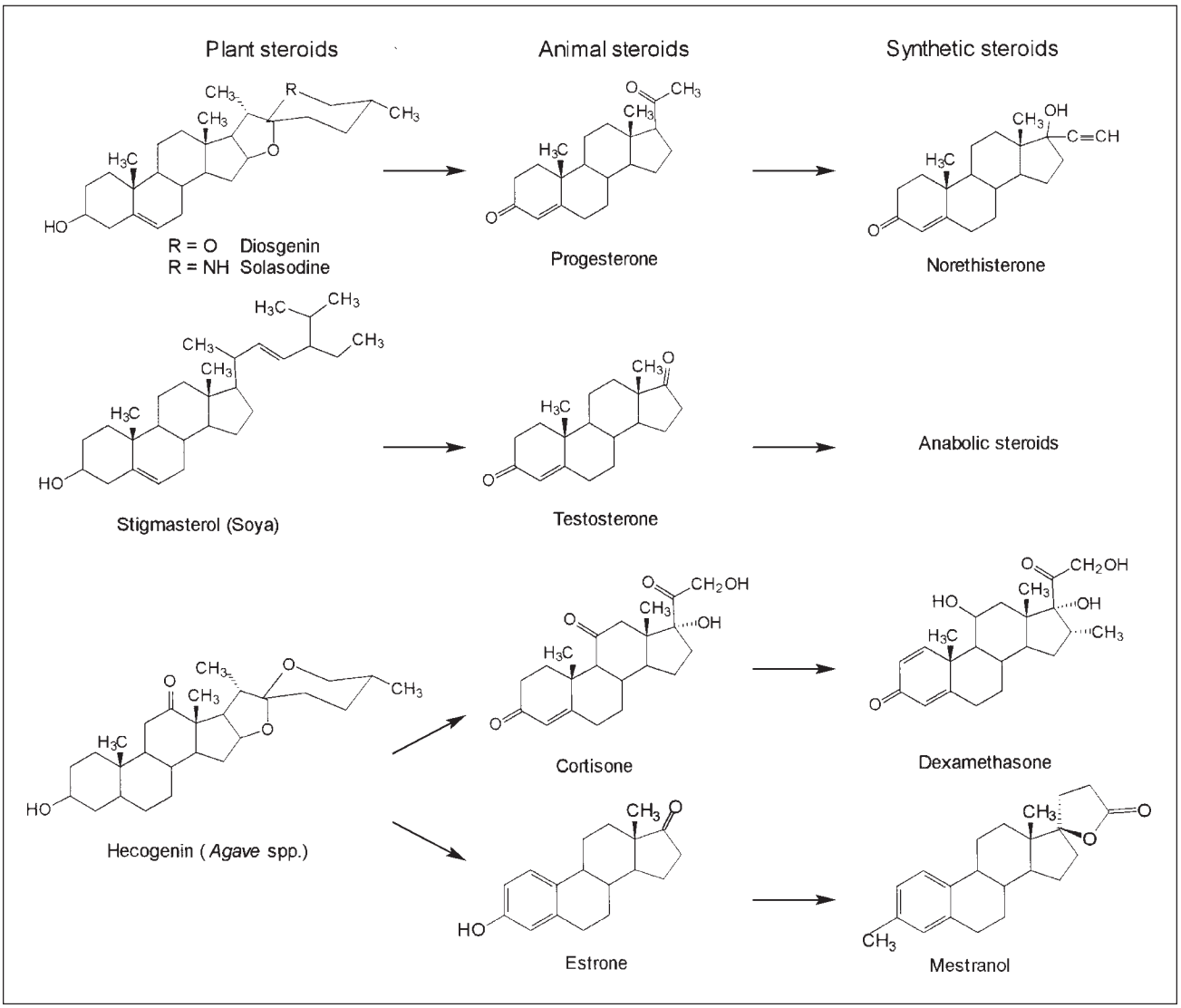


Figure 1. Steroids from plants.

taste and was not well tolerated by the stomach. Derivatives of salicylic acid were made to try to overcome these problems, and in 1899 the acetyl derivative, synthesized by the Bayer company in Germany, was introduced as aspirin into clinical use (*21*). Not until almost 100 years later was its ability to block the synthesis of compounds such as prostaglandins discovered as the basis of its activity. It is important to realize that not only aspirin but the whole array of nonsteroidal anti-inflammatory agents such as ibuprofen has resulted from this exploration of the naturally occurring salicylates.

Cocaine is another drug that has become a household name because of its notoriety as a drug of abuse. It is the major active substance in the leaves of *Erythroxylum coca* and *Erythroxylum truxillense* bushes, known and used for centuries in the high plateau of the Andes in South America. The leaves of these plants are dried and powdered to make a paste with alkaline plant ash, which is then used to form a small quid that is held in the mouth inside the cheek. This practice appears to be primarily used to counteract fatigue and cope with the low oxygen levels and harsh living conditions of the Andean plateau. When cocaine was isolated in the latter half of the 19th century, it was shown to produce a short-acting stimulation of the central nervous system and a feeling of numbness, but it was also soon found to be addictive. The numbness was traced to the ability of cocaine to act as a local anesthetic, blocking transmissions along the nerves to the brain, which had very useful medical applications in minor surgery. The unwanted addictive and CNS-stimulant effects of cocaine, as well as its short half-life, restricted its use, and consequently much work was undertaken to synthesize analogues that had no CNS-stimulant or addictive properties but retained the local anesthetic effect with a longer duration of action. This work led to the introduction of compounds such as lidocaine, now extensively used for minor operations, as in dentistry. The introduction of an amide bond, in place of the ester linkage found in cocaine, and steric hindrance, due to the surrounding methyl groups, reduce the rate of hydrolysis and loss of activity of the lidocaine molecule (*22*). A series of local anesthetics analogous in structure to cocaine is shown in Figure 3.

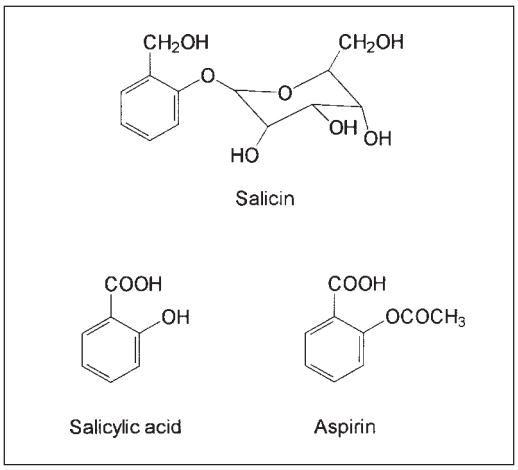


Figure 2. Salicylates and aspirin.

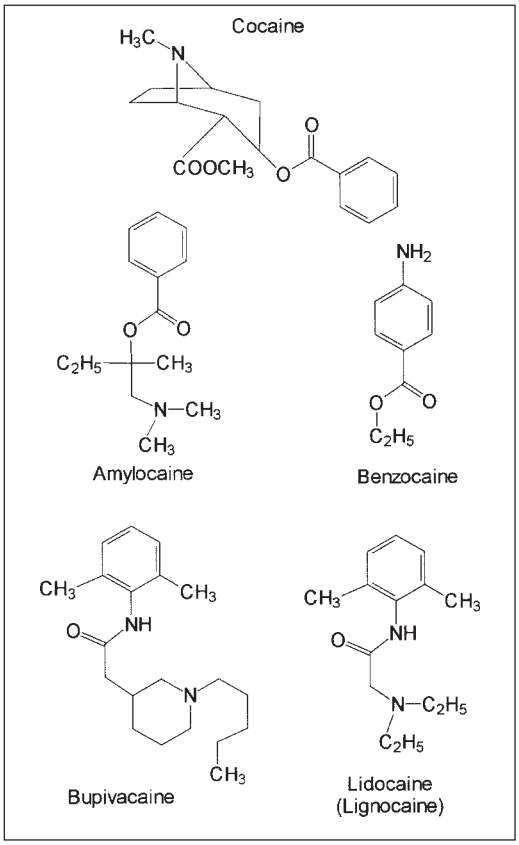


Figure 3. Local anesthetics derived from cocaine.

A selection of other important synthetic drugs that have been developed using naturally occurring compounds as templates is given in Table 4.

New Drug Discoveries from Plants—How Are They Made?

In spite of much work carried out over the last two centuries, it is estimated that about 90% of the world's flowering plant species still have not been investigated in detail for their chemistry or biological activity. It is predicted that 25% of today's flowering plant species will be lost by 2025 C.E. and the question inevitably arises of how those most suitable for investigation should be selected. In many cases selection is now made with the object of performing a bioassay, often of the high-throughput, automated variety, and this selection may be either random or targeted.

Random Selection

Random selection consists of acquiring a large number of samples from a locality or from a collection of plants, such as in a botanic garden, and submitting them to a particular biological test. No criteria for the selection are formulated, with the possible exception of trying to ensure as wide a diversity of species and habitats as possible. This approach is often taken when the target disease is unknown or not common in traditional medicine, and some success has been achieved in this respect with the large screening program carried out by the National Cancer Institute for novel anticancer and anti-HIV molecules from plants. The anticancer drug taxol (Paclitaxel), one of the most important clinically used drugs introduced in the last decade, was discovered by this process and several types of anti-HIV molecules are in clinical trials (*23*).

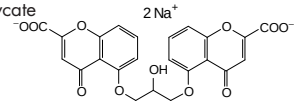
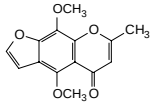
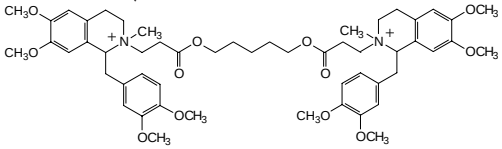
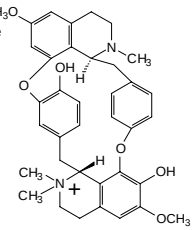
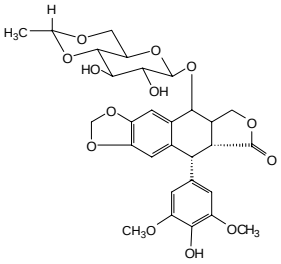
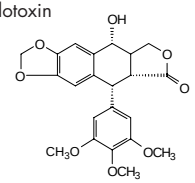
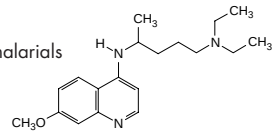
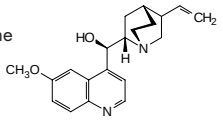
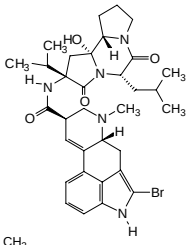
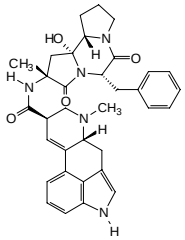
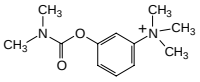
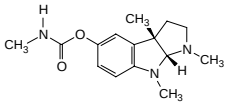
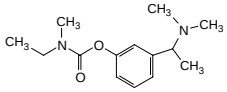
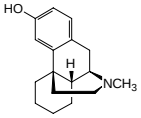
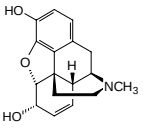
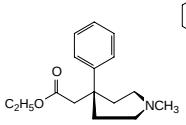
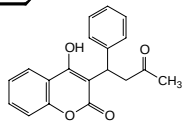
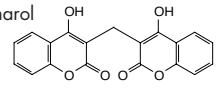
Some sections of the pharmaceutical industry have also negotiated contracts with countries and botanical gardens to supply samples for screening, but the relatively low "hit rate" achieved has resulted in some companies seeking a more targeted approach. Some recent studies have shown that this is more likely to lead to novel compounds of interest (*24*).

Targeted Selection

Targeted selection processes may be based on one of several parameters, but ethnopharmacology is probably that most widely used, especially in academic research (*25*). Ethnopharmacology is the study of the use of local materials by an ethnic group or community after several generations of living in their particular local ecosystem. Many important drugs have been derived from plants used in traditional medicine, but there are many communities whose heritage of knowledge is being lost through globalization, urban drift, destruction of habitats, and forced migration. There has been a resurgence of interest in accumulating and testing this knowledge (*26*), and several novel compounds discovered in recent years have aroused interest as compounds for clinical use or as lead molecules for pharmaceutical development. A few of these are shown in Table 4.

The ethnopharmacological approach has two major drawbacks. The first is that the biological activity may be due to a known compound or group of compounds, and this may become obvious only in the later stages of a costly and time-consuming research process if no other investigation is carried out simultaneously. A common example of this is the report of finding antimicrobial activity in aqueous plant extracts that is due to the phenolic "tannin" compounds present. Duplicate isolation of known compounds is overcome by using extraction methods that eliminate types of unwanted compounds or by employing dereplication procedures. The latter methods often use a separation system linked with a spectrophotometer and computer, which can check the details of mass spectra or NMR spectra and compare them against a database containing the parameters in question for a large number of compounds,

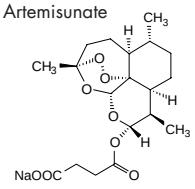
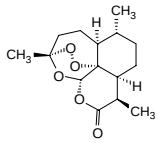
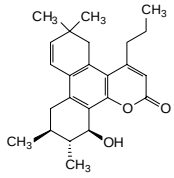
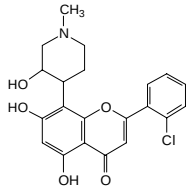
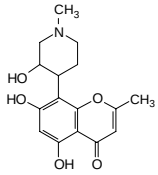
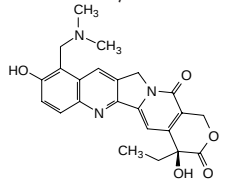
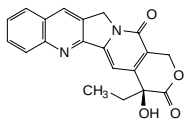
Table 4. Some Important Drugs Synthesized Using Natural Molecules as Templates

Drug, Structure	Template Molecule, Structure	Plant Source	Traditional Use	Clinical Use of Drug
Sodium cromoglycate 	Khellin 	*Ammi visnaga*	Treatment of bronchial complaints	Antiasthmatic
Atracurium (and other muscle relaxants) 	Tubocurarine 	*Chondodendron tomentosum*	Paralyzing dart poison	Muscle relaxant during anaesthesia
Etoposide 	Podophyllotoxin 	*Podophyllum peltatum*	Purgative	Anticancer
Chloroquine (and related) antimalarials 	Quinine 	*Cinchona* spp.	—	Antimalarial
Bromocryptine (also cabergoline, methysergide) 	Ergotamine 	*Claviceps purpurea*	To aid childbirth	Treatment of Parkinson disease
Neostigmine 	Physostigmine 	*Physostigma venenosum*	Ordeal poison	Treatment of myasthenia gravis
Rivastigmine 				Treatment of early symptoms of Alzheimer disease
Dextromethorphan 	Morphine 	*Papaver somniferum*	Analgesic, soporific	Cough suppressant
Pethidine 				Analgesic
Warfarin 	Dicoumarol 	*Melilotus alba* (action of microorganisms after harvesting)	—	Anticoagulant

frequently referred to as a "library" (*27*). The second problem often encountered is that the activity connected with an extract may be lost upon fractionation, indicating that a mixture of substances is necessary for the desired effect due to synergistic or other complementary relationships between the constituents.

A less common approach, but one that finds some favor, especially with those searching for novel pesticides, is to select plants according to ecological features, such as survival from common predators. An interesting example of this, although not strictly pharmaceutical, is the discovery of the insect moulting hormone, juvabione. Larvae of the European bug *Pyrrhocoris apteris* did not develop to maturity if paper from

Table 5. Some Drugs of Current Interest Developed from Naturally Occurring Molecules

Compound, Structure	Biological Activity	Lead Compound		Comments
		Structure	Botanical Source	
Artemisunate 	Antiplasmodial for treatment of chloroquine-resistant malaria		Artemisin; *Artemisia annua*	Used in Chinese medicine for treating fevers
Calanolide A 	Anti-HIV reverse transcriptase inhibitor		*Calophyllum lanigerum, Calophyllum teysmanii*	Discovered by random screening
Flavopiridol 	Anticancer tyrosine kinase inhibitor		Rohitukine; *Amoora rohituka*	Bark of related species used to treat rheumatism
Topotecan (also irinotecan) 	Anticancer inhibitors of topoisomerase I		Camptothecin; *Camptotheca acuminata*	Little relevant usage; discovered by random screening

the American balsam fir *Abies balsamea* was used to line their containers, but there was no problem if paper derived from the common European pulping species was used. It was found that juvabione was produced by the American species and carried through to the finished paper product, but none of this compound was produced by the European species used in making paper (*28*).

A more fruitful approach for many types of bioactive molecule is to make selection according to the hypothesis that botanically related species often produce similar constituents. Thus, once a species has been found to contain an interesting compound, other species of the same genus or family will be examined for the presence of larger amounts of the compound of interest or for chemically related compounds, to enable some profile of structure–activity relationships to be constructed. The presence of larger concentrations of reserpine in species other than *Rauwolfia serpentina* was discovered using this botanical method, and such an approach is used as a justification for the work underlying a significant part of the papers published dealing with the isolation of novel compounds.

Such an approach requires botanical expertise but also an understanding of chemical structural types and their detection. This latter skill is the basis for the final type of targeted approach, which involves screening plants chemically to detect the presence of a certain chemical skeleton known to be associated with biological activity. For example, many indole alkaloids are bioactive and can be detected by a simple chemical test. This test can then be used as a way of concentrating on those species that contain detectable amounts of the compounds.

In Vitro Assays and Targeted Drug Discovery Processes

A multitude of small-scale in vitro bioassays have been developed over the last two decades (*29*, *30*). These were originally based on cultured cells or isolated enzymes, but in recent years the development of molecular biology techniques such as gene isolation, the polymerase chain reaction, and the cloning of receptors has enabled the targets for bioassays to be much more specific. Binding assays are commonly used to determine if an extract or compound has an affinity for a receptor and thus might act as an agonist or antagonist.

It should be noted that although small-scale in vitro assays are now commonly used in Western countries, they are not ideal because they cannot accurately predict how a plant extract or compound may affect a system in vivo. The case could be made for in vivo or clinical studies, using animals or humans respectively, to be the first stage of the screening process, since as noted above, in vitro tests are not always good predictors. Reasons for this are the difficulty of modeling the disease in a single system and the fact that the effects of metabolism and toxicological manifestations are not usually taken into account. An additional negative factor in the use of in vitro systems is that they select only compounds acting on known mechanisms and so could well miss those that might have a successful effect in vivo but that act by a completely different mechanism.

In vivo systems have their disadvantages also, since financial and social pressures militate against the use of animals until later stages in the discovery process. However, in some countries, where labor costs are lower and there is little pressure from society against the use of animals in research, animals are used much more frequently in initial screening procedures.

Future Prospects for Novel Pharmaceutically Useful Compounds from Plants

A recent review emphasizes the significant contribution that plants and fungi are still making to drug discovery (*31*). Some molecules of current interest are shown in Table 5.

Besides work on the flowering plants and fungi that have provided so many useful pharmaceuticals, extensive work is being done to determine naturally occurring bioactive molecules

from other parts of the living world, such as the oceans (*32*). With an estimated less than 10% of the world's angiosperms adequately investigated for chemical constituents and biological activity, it is reasonable to suppose that more interesting compounds that will pave the way to new drugs will be discovered from flowering plants. In addition, recent advances in biotechnology have widened the possible range of new compounds that might be produced by plants (*33*). Some of these are briefly discussed below.

Plant tissue culture was originally conceived as a useful method for producing expensive compounds in a way similar to the production of the antibiotics such as penicillin from culture, thus overcoming problems due to supply irregularities and harvesting occurring only once a year. The expectations of this technique have not been fully realized in practice, partly because the cells of many species produce different compounds in culture than when part of the normal plant. This has been exploited commercially by some companies who grow plant cells in culture with the aim of discovering novel compounds, and the possibilities are made greater by the introduction of elicitors, precursors, and suitable enzymes into the medium (*34*).

Another aspect of the rapidly expanding area of biotechnology that can be applied to the production of novel compounds is genetic transfer and manipulation. This may not only may make it possible to produce in common crop plants or weeds compounds formerly known only in exotic or endangered species; it also opens up avenues for the formation of novel compounds by introduction of genes into plants whereby enzyme activity on precursors leads to compounds not previously found in the species (*35*). These developments are still in their infancy, but it will be interesting, and probably exciting, to see developments ten years hence.

The potential of plant constituents as substrates for combinatorial chemistry synthesis is also arousing some current interest. Combinatorial chemistry can produce many new compounds, but its potential is restricted if there is little novelty in the starting materials (*36*). Originally amino acids and peptides were the main type of compounds used in combinatorial synthesis; but the vast variety of chemical structures produced by living organisms is now recognized as a valuable resource, and so many new derivatives of naturally occurring molecules are likely to be made and screened (*36*).

It can be concluded, therefore, that the old story of plants as sources of medicines is still far from over, and indeed, new chapters are starting to be written.

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