products of chemistry

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Medicines and Drugs from Plants[1]

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Long before scientists began investigating nature's chemicals and the living creatures that synthesize them, human beings were making extracts, tinctures, and other preparations from plants and animals. Thousands of years before the discovery of antibiotics, some of these natural preparations served as medicines to relieve pain or heal sickness. Others were poisons useful in hunting and warfare. A few acted as mind-altering or psychotropic drugs and found use in religion and recreation.

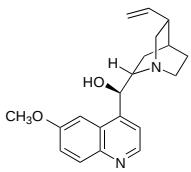
Altogether, these preparations had an enormous range of properties. One was a deadly poison from frog skin, and another was a remedy for fevers from tree bark. Poppies furnished a potent pain reliever, and a certain mushroom furnished a powerful hallucinogen. Concoctions of the most diverse sorts were common for millennia, ages before there were any biologists or chemists, or any concept of molecules and chemical compounds. All over the earth, people actively searched the natural world for beneficial preparations. Their success generally depended on trial and error, luck, and serendipity.

In the light of present knowledge, most of the active compounds in these preparations are probably plant or animal chemical warfare agents—that is, compounds organisms use to defend themselves or to attack their enemies. This is a reasonable guess, but it is only a guess because knowledge here is surprisingly limited. Human beings have been handling some of these compounds for centuries, but typically no one has investigated why they are present in the plants and animals that synthesize them.

The largest group of preparations from living organisms are medicines, and historically most of these have come from plants. Civilizations throughout the world have been turning plants into medicines for thousands of years, and they continue to do so today. In the centuries before modern medicine, synthetic chemistry, and the pharmaceutical industry, virtually all medicines came from plants. Today, more than three billion people outside the developed world depend on such remedies. Traditional medicine that relies heavily on plant and animal products is still practiced throughout China, often alongside modern Western techniques. In addition, Western medicine exploits medicinal species with considerable success. Laboratory investigators follow up leads from the traditional medications of many cultures, and they also screen previously unexamined plants and animals in the search for new active compounds. Research of the latter sort is responsible for Taxol, a compound from the stem bark of the Pacific yew (*Taxus brevifolia*) that has been much in the news as a critical anticancer drug (*1*).

Malaria and the Peruvian Fever Tree

Before the advent of antibiotics, drugs that could cure diseases were rare, and infection was a very common cause of death. The first chemical that effectively controlled an infectious disease appeared in Western medicine around 1630 when the Spanish conquerors of Peru discovered that a local tree bark was useful in overcoming certain fevers. They brought the bark of this "fever tree", as they called it, back to Europe, and its fame quickly spread across the continent. It soon proved to be a specific remedy for malaria, one of the world's most debilitating diseases. We now call the tree cinchona (*Cinchona officianalis* and related species) and know that the bark's main active principle is the alkaloid quinine (**1**). For nearly 300 years quinine was the only effective treatment for malaria.



1
the alkaloid quinine

Although the Spanish brought cinchona bark from Peru to Europe, it is unlikely that they discovered its medicinal properties by themselves. Indian civilizations had flourished in Peru for a thousand years before the Spanish arrived, and the Indians were excellent naturalists with a sophisticated pharmacopoeia of their own. Early Spanish chroniclers wrote admiringly of the Indians' knowledge of medicinal plants, and Spaniards exploited this knowledge for years. Within sixty years of the conquest in 1533, a steady stream of ships was carrying herbs, barks, and resins back to Spain for distribution throughout Europe. Direct evidence is lacking, but local Indians probably revealed the secret of cinchona bark to their Spanish overlords. If so, they deserve credit for the first step in bringing quinine to the wider world.

However cinchona bark and quinine reached the world beyond Peru, they quickly became medically important as the only remedy for malaria. The powdered bark itself was used until the 19th century, when in 1820 two professors at the School of Pharmacy in Paris, Pierre Joseph Pelletier and Joseph Caventou, isolated quinine from cinchona bark. After Pelletier and Caventou's work, cinchona bark could be assayed for its content of quinine and physicians could prescribe the drug more accurately.

Quinine is only one of thousands of medicines extracted from plants over the centuries. Historical connections between plants and medicines are complicated, and they are not always obvious. Well-known medicines sometimes have plant origins that have now disappeared from historical sight, and some plants familiar to us were the sources of medicines once popular but now no longer in use.

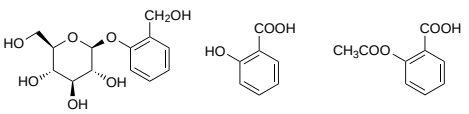
From Willow Bark to a Successful Drug

Probably the best-known and most widely used medicine associated with plants is aspirin. Although aspirin does not come from a plant, it was specifically designed to compete with several popular plant medicines. The active ingredients in these medicines all had similar chemical structures, and they were the inspiration for aspirin. The natural medicines were in wide use throughout the 19th century, but aspirin largely replaced them in the early 1900s.

Unlike quinine, the plant products that inspired aspirin have a well documented historical origin (*2*). They began with a discovery by an 18th-century English clergyman, the Reverend Edward Stone, who noted that, like cinchona bark, the bark of the white willow (*Salix alba*) has a bitter

taste. Cinchona bark was well known for treating fevers, and Reverend Stone suspected that willow bark might also be a fever remedy. Guided by his suspicion, Reverend Stone tested the medicinal properties of willow bark. He carefully dried the bark, powdered it, and used the powder to treat persons suffering from fevers. He treated about fifty cases over five years and concluded that willow bark was a "very efficacious" remedy for fevers. Reverend Stone's reasoning was faulty, but it had led him to an impressive discovery.

The active principle in Reverend Stone's willow bark was salicin (**2**), a compound related to salicylic acid (**3**). Other similar natural compounds were soon discovered, and experience over the next century showed that these salicylates, as they were called, effectively reduced fever, pain, and swelling and relieved gout, rheumatic fever, and arthritis. Such favorable medicinal properties led the chemical research laboratories of the Bayer company in Elberfeld, Germany, to seek a new salicylate for the drug market. The goal was to prepare a synthetic compound that could compete successfully with the natural salicylates then available. Nineteenth-century chemical knowledge and technology were adequate to the task, and Bayer's research led in 1897 to *O*-acetylsalicylic acid (**4**), which we now know as aspirin.



2 salicin **3** salicylic acid **4** aspirin

Aspirin has had an extraordinarily successful history, and worldwide consumption is now about 100 million pounds (over 45 thousand metric tons) of aspirin a year. Americans buy over 30 billion aspirin tablets annually. Most often people take aspirin for relief from simple headaches and other minor pains, but aspirin is also an important drug in treating rheumatoid arthritis and in preventing blood clots through blocking the aggregation of blood platelets. An exciting finding in recent years is that a regular low dose of aspirin diminishes the incidence of heart attack, probably owing to inhibited platelet aggregation. Another boost for aspirin came in mid-1993, when the American Cancer Society released a study suggesting that people who take aspirin regularly have a 40% lower death rate from cancers of the digestive tract.

Seeking a Different Reality

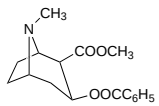
Medicines related to plants are the largest group of useful preparations that humans have derived from nature, but there is a much smaller group of agents that probably excite more interest. These are the natural mind-altering, or psychotropic, drugs. In general, these drugs act either to mimic or to block the action of a chemical compound that transports nerve signals in the brain. Some of these drugs cause hallucinations; others induce psychosis or euphoria. Still others act as sedatives, hypnotics, or stimulants.

Natural mind-altering drugs come mostly from plants or fungi. For several thousand years, they have inspired awe and reverence in peoples around the world, offering a miraculous escape from the everyday world into a spiritual realm. Because they appear to open the way into another world, psychotropic agents have held a prominent position in both religion and medicine. Many traditional cultures attribute sickness and death to malign spirits, so that medicine and religion become inseparable. For priests or healers to diagnose and treat diseases, they must conciliate the appropriate spirits. Under the influence of psychotropic drugs, a priest can enter the world of these spirits, communicate with them, and then work to heal the patient. Some traditional cultures limit access to mind-altering drugs to priests and other special members of society. Others make these drugs available to ordinary people as well.

Psychotropic drugs have turned up in cultures in all parts of the world, but they are much more common in the New World than the Old. It is not clear why this geographical bias exists, because there is no botanical reason to think that psychotropic drugs are more prevalent in New World plants. What is clear is that, for at least fifteen hundred years, native peoples of the Western Hemisphere have used local plants to prepare a remarkable variety of concoctions to eat, drink, smoke, or chew (*3*). When Columbus landed in Hispaniola on his second voyage in 1496, he found the Taino Indians using something they called *cohoba* to communicate with the spirit world. Cohoba is a powerful hallucinogenic snuff made by drying and grinding large beans that the Indians harvested from the yopo tree (*Anadenanthera peregrina*). A little later in Mexico, the Spanish invaders discovered ololiuqui, an Aztec hallucinogenic drink made from the seeds of the snakeplant (*Turbina corymbosa*).

Farther south, the conquistadores found a milder psychotropic agent. The Incas in Peru chewed the leaves of the coca plant (*Erythroxylon coca*) as a stimulant and analgesic. The habit was not widespread among the working people, because coca leaves were also a form of currency. However, the Spaniards were soon urging coca on the Incas they forced into service as gold miners. They had discovered that coca was an ideal drug for impressed workers: it suppresses hunger and sustains heavy manual labor.

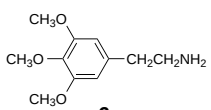
Coca was in use in Peru a thousand years before the Spanish arrived, and the Incas' modern descendants continue to chew coca leaves, currently at the rate of about thirteen million pounds a year. Perhaps more meaningful for us, the active principle in coca is cocaine (**5**). Clandestine drug laboratories in northern South America process tons of coca leaves to supply cocaine as a recreational drug to an evidently insatiable American market. Cocaine and the quick money it promises have brought drug gangs, chaos, and murder to cities and towns across the United States.



5 cocaine

Several other ancient New World drugs are also still in active use. One of the best known is the hallucinogen peyote. Ritual use of peyote was established long before the Spanish arrived in Mexico, and it is still practiced by a number of Indian tribes there. In addition, peyote is legally protected in the United States for use in the ritual of the Native American Church, an institution that claims 250 thousand members. In 1993, the United States Congress reconfirmed this traditional use of peyote as a matter of religious freedom.

The drug at the center of these activities comes from the peyote plant, a small, round, gray-green cactus (*Lophophora williamsii*) that grows from the Rio Grande Valley in Texas south to north-central Mexico. In several American Indian languages, the word for "peyote" is the same as the word for "medicine". The main active principle in peyote is the alkaloid mescaline (**6**), which is concentrated in the upper portion of the cactus. To harvest peyote, the round tops of the growing cactus are cut off parallel to the ground and then dried. These dried



6 mescaline

discs, or mescal buttons, are tough and essentially indestructible. A peyote user simply takes a button into his or her mouth, moistens it with saliva, and swallows it. In earlier times many Indian tribes made pilgrimages to gather peyote in areas where it grew. Now, members of the Native American Church as far north as Canada mail-order supplies of mescal buttons from Texas.

Discovering Plant Medicines: Who Was First?

People have been nibbling at unfamiliar plants for ages, looking for new foods and for new sources of medicines and other useful preparations. Someone, or maybe several people, somewhere in South America, must have first noted the salubrious effects of cinchona bark and passed this information on to others in the community. Each of thousands of plant medicines discovered over thousands of years has its history, but early peoples seldom left records for posterity. We cannot hope to unearth the detailed history of most of their findings. We often have a discovery but know nothing about the discoverer.

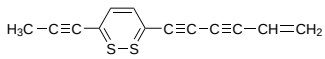
There is another, perhaps less obvious uncertainty associated with the origins of plant medicines. Humans are not the only creatures that regularly investigate plants for new foods. Many other species do the same. Is it possible that some of these other species also discover medicines and pass this knowledge on in their own communities? Do other species use plants to fight diseases the way humans do? If so, the history of plant medicines could be older than the history of mankind.

Biologists have long discussed circumstantial and anecdotal evidence that other species use medicines. Because anecdotal information is questionable, reports from professional animal behaviorists about animals and medicines have aroused considerable attention. One of the most provocative of these is a report concerning the peculiar way chimpanzees (*Pan troglodytes schweinfurthii*) select and eat the young leaves of certain herbaceous plants (*Aspilia rudis* and related species) (*4*).

The chimpanzees select each leaf with elaborate care, sometimes closing their lips over a leaf and holding it for a few seconds before deciding whether to pluck it from its branch. They place each chosen leaf in their mouth, roll it around, and rub it with their tongue against the inside surface of their cheek. Then they swallow the leaf without chewing it, even though *Aspilia* leaves are covered with bristly hairs and must be difficult to swallow whole. Chimpanzees do chew other leaves that they pick and eat, but they treat *Aspilia* leaves differently and seem to consider the whole experience unpleasant. The behaviorists saw one chimpanzee vomit while feeding on the plant, although afterward he seemed healthy and vigorous for the rest of the day. Another chimpanzee wrinkled his nose repeatedly as he swallowed the leaves.

Were these chimpanzees taking medicine? Several observations strengthen the possibility. Chimpanzees cannot gain much nourishment from *Aspilia*. They never chew the leaves, and leaves retrieved from feces appear fresh, perhaps folded once or twice but otherwise hardly damaged in their passage through the digestive tract. The indigenous Africans value *Aspilia* as a medicinal plant. They use the leaves and roots in treating a number of topical ailments, such as burns and wounds, as well as for stomach pains and worms.

The chimpanzees' curious habit of not chewing the leaves is reminiscent of the preferred mode of administering a few drugs in human medicine. The best known of these is nitroglycerin, which acts directly on the heart to alleviate the chest pains of angina pectoris. The patient holds a pill of nitroglycerin under his tongue, and the drug is absorbed directly into the blood. In this way nitroglycerin enters the circulation more rapidly than if swallowed. It can reach the heart without destruction by liver enzymes or by stomach acid. In the same way, perhaps *Aspilia* leaves are a more effective medicine if they are not chewed. This is a reasonable possibility, because they contain thiarubrine-A (**7**), which is an antibiotic that is destroyed by acids (*5*). Chimpanzees may get more thiarubrine-A into their circulation by direct absorption through the mouth than they would from leaves that were chewed, swallowed, and exposed to stomach acid.



7
thiarubrine-A

Other observers have reported similar leaf-swallowing behavior by baboons (*Papio anubis* and *P. hamadryas*), and there are also descriptions of chimpanzees eating other species of medicinal plants. These observations reinforce the argument that these primates are indeed taking medicine. Such studies led to the first symposium to discuss research in zoopharmacognosy, as this area of investigation has been named. In early 1992 the American Association for the Advancement of Science (AAAS) sponsored a meeting at which behaviorists discussed suggestive evidence that not only primates, but also bears, dogs, and cats use medicines.

What about the Future?

If other living species do in fact exploit plants to improve their health, mankind may have been using plant medicines since its earliest days. But what about the future? Will plants continue to be an important source of human medicines? Nowadays, biomedical scientists uncover the details of one disease after another. Clinical medicine has available new magic bullets each year. In this hi-tech world, plant medicines may seem a bit quaint. History and romance apart, do we really care any longer about barks and berries with therapeutic properties?

The short answer is that we still need plants. About a quarter of the drugs in prescription medicines today are derived from plants. A survey in the mid-1980s indicated that American consumers spend about eight billion dollars a year on plant-derived prescription drugs. According to more recent figures, the 20 top-selling drugs in the United States have annual sales of 700 million to 2 billion dollars each, and six of these drugs come from plants.

Pharmaceutical companies have recently increased their investment in the search for new medicinal plants. One reason for this is the prevalence of diseases and conditions that we cannot yet combat with specifically designed drugs. There are still no magic bullets for AIDS or cancer. There is no pill for treating stroke. Plant products sometimes offer the best available treatment for such conditions.

Why should plants produce compounds that are effective against AIDS or stroke, when these are threats that plants never face? Why should defenses fashioned by innumerable generations of evolution to oppose a plant's enemies sometimes be effective against quite different human afflictions? It is not obvious why this is so, but a fascinating possibility is that, on a molecular level, nature's bag of chemical tricks may be limited. Perhaps plant and human predators sometimes employ closely related means of attack that can be blocked by the same defense.

This suggestion may seem unreasonable, but it is related to recent discoveries about how evolution operates.

The emerging idea is that evolutionary development proceeds by tinkering with what is at hand rather than by launching grand new enterprises. Biologists are beginning to recognize that organisms develop new structures and capabilities by adapting already existing molecules to new uses. An evolutionary development may look quite novel, but close similarities between the new and the old may emerge on examination at the molecular level. If this idea is correct, if nature is generally conservative in fashioning novel capabilities, predators may have a limited number of weapons in their arsenals. Regardless of whether their victims are plants or humans or any of thousands of other creatures, there may be only a limited number of ways they can conduct their assaults.

Ethnobotanists, private pharmaceutical houses, and the National Institutes of Health (NIH) have all realized the advantages of plant-derived medicines, and all are screening plants for new drugs. Two sorts of programs are underway. The first centers on exploring systems of traditional medicine. Many cultures make use of traditional medicinal plants about which we have no modern scientific information. A careful enumeration of traditional Chinese remedies in 1980 listed 2,270 medicines. Most of these represent discrete species of plants, many of which are readily available in local markets in China. A study of herbal medicine in one small region of northern Thailand turned up 553 species of local plants in current use. The NIH's National Cancer Institute is now examining medicinal plants from China and Korea, and one encouraging lead turned up is an anticancer compound from a Chinese source.

In addition to plants used in traditional medicine, there are thousands of other species that have never been screened for possible biological activity. Biomedical scientists have examined thoroughly only about one-half of one percent of the world's higher plants for medically useful activity. The greatest concentration of unexamined species is in the tropics. (Of the known 250 thousand species of higher plants, about 110 thousand grow only in the New World tropics.) Several studies are now underway to explore this untapped source of natural compounds. One of the most interesting of these is a program sponsored by the American pharmaceutical house Merck & Company (*6*). In 1992, Merck agreed to pay the Costa Rican National Institute of Biodiversity one million dollars over two years for the right to search for new drugs in the tropical forests of Costa Rica. Local residents, who were first trained in collecting and identifying species, are now gathering samples and cataloging plants and animals. Biologists estimate that more than 500 thousand biological species are native to Costa Rica; fewer than 85 thousand of these have been scientifically described and catalogued.

An important feature of this agreement, which has since been renewed, is that Merck and the National Institute of Biodiversity will share royalties from any successful drugs that emerge from the survey. Half these royalties, as well as ten percent of the initial one million-dollar payment, are designated specifically for conservation work in Costa Rica. Conservationists have a strong interest in how this agreement works in practice, because it offers an attractive arrangement for saving tropical forests from further destruction. Cutting down a forest brings cash from the sale of timber and often provides land for a growing population of destitute peasants. These are immediate advantages that a developing country finds hard to resist. To forego the cash and protect its forests, a poor country requires an alternative source of profit from these national resources. Harvesting drugs may offer a way to make forests profitable without destroying them. If the country of origin shares in the profits, drug harvesting could turn a tropical forest into a sustainable national resource. A forest could have a long-term value much greater than the one-time profit realized from clearing it for timber and development.

The government of Costa Rica is seriously committed to maintaining its biological resources and dedicating them to improving the quality of life. As his first official act after his inauguration in May 1994, President José María Figueres opened a symposium on Costa Rican biodiversity and its value to the country. Other countries that are poor in cash but rich in biological resources, including Mexico, Nepal, and Indonesia, are watching the Costa Rican experiment with interest.

The search for new medicines in their forests may give developing countries an economic rationale for saving these scientifically unexplored areas (*7*). Furthermore, it may offer the developed world a welcome reason to favor preservation. People who have been unimpressed by efforts to save forests as reservoirs of biological diversity and ecological balance for their own sake may be more interested in maintaining these areas as sources of novel medicines that will benefit both the developed and the developing worlds.

In these surveys of uninvestigated species and traditional medicinal plants, there is always the possibility of finding a compound that is an immediately useful drug. It is more likely, however, that the plant chemicals discovered will serve as leads for drug development. Perhaps only minor modification will be necessary to convert a new compound into a good drug. In other cases new compounds will simply suggest unprecedented types of chemical structures for synthesis in the laboratory, much as the natural salicylates suggested the synthesis of aspirin a century ago.

Note

1. This article is based on the author's book *Bombardier Beetles and Fever Trees*; Addison-Wesley: Reading, MA, 1996.

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