

The Ethnobotanical Approach to Drug Discovery

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Medicinal plants discovered by traditional societies are proving to be an important source of potentially therapeutic drugs

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In 1785 William Withering, a British physician, reported that ingestion of dried leaves from the foxglove plant eased dropsy, an accumulation of fluid now known to be caused by the heart's failure to pump adequately. Withering credited an unexpected source for his information. "I was told," he wrote, that this use of foxglove (a member of the genus *Digitalis*) "had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed."

Digitalis has been helping cardiac patients ever since. Today two of its components—the glycosides digoxin and digitoxin—are prescribed to hundreds of thousands of people throughout the world every year. Indeed, these glycosides currently serve as the treatments of choice for rapid atrial fibrillation, a dangerous cardiac irregularity. Given the importance of *Digitalis*, we have no doubt that many readers of *Scientific American* are alive in 1994 because Withering investigated the secret remedy of "an old woman in Shropshire."

PAUL ALAN COX and MICHAEL J. BALICK met in the late 1970s, when they were doctoral students at Harvard University. Cox is dean of general education and honors and professor of botany at Brigham Young University. He is also president of the Society for Economic Botany. Balick is Philecology Curator of Economic Botany and director of the Institute for Economic Botany of the New York Botanical Garden in Bronx, N.Y. He is also past president of the Society for Economic Botany. Cox and Balick, who are collaborating on a book about ethnobotany for W. H. Freeman and Company, serve as advisers to a variety of governmental, academic and industrial research groups and foundations.

A decade ago this story would probably have been regarded as nothing more than a historical anecdote, of little relevance to contemporary drug discovery. By the mid-1980s most pharmaceutical manufacturers had abandoned exploring folk uses of plants in their search for new drugs. Now, however, the pendulum is beginning to swing back toward an appreciation that plants used in traditional medicine can serve as a source of novel therapeutic agents.

Such appreciation has emerged in part because of recent discoveries made by a small but growing group of ethnobotanists—researchers who study the relationships between plants and people. Fieldwork exploring the medicinal uses of plants by indigenous peoples in remote parts of the world, coupled with the introduction of sophisticated assays able to determine whether plants exert a biological effect, has facilitated the discovery of bioactive molecules made by medicinal plants. Some of these molecules show promise as possible therapies for a range of diseases, including AIDS and cancer.

In the U.S. the drug development process is a long and arduous one, designed to ensure that therapies released to market are effective and safe. It can thus easily take many years for a substance to become commercially available as a drug. There seems little doubt, however, that within a decade several new agents derived from ethnobotanical research will be introduced. We cannot claim that most drugs of the future will be found in this way. Yet the strategy, as will be seen, has many merits.

Until the 1950s, almost all pharmaceutical research relied heavily on vascular plants as sources of medicines. Flowering plants and ferns (as opposed to microscopic organisms and fungi) have given rise to about 120 commercially sold drugs and account for some

25 percent of all prescriptions issued every year in North America. Many of these agents are now synthesized in the laboratory, but others are still isolated from plants. Most were discovered by studying indigenous uses of plants.

For instance, the drug reserpine, which is still occasionally prescribed in the U.S. for hypertension, was isolated from the root of the climbing shrub *Rauvolfia serpentina* (Indian snakeroot) after scientists began analyzing Ayurvedic remedies—the traditional treatments used by the peoples of India. Other examples include aspirin, opiates, pilocarpine (prescribed for glaucoma and dry-mouth syndrome) and two cancer treatments—vincristine and vinblastine. Vincristine and vinblastine, both of which are still extracted from *Catharanthus roseus* (rosy periwinkle), have been prescribed for pediatric leukemia and Hodgkin's disease, respectively, since the 1960s.

Plants have been a rich source of medicines because they produce a host of bioactive molecules, most of which probably evolved as chemical defenses against predation or infection. Nevertheless, several forces conspired by the close of the 1970s to cause plants to lose much of their appeal as drug sources for the pharmaceutical industry. Microorganisms and fungi that inhabit soil, which are easy to collect and culture, had provided a dazzling array of antibiotics. Advances in synthetic chemistry and molecular biology promised to supply new means for designing drugs in the laboratory. And few major discoveries of plant-derived drugs had followed the identification of vincristine and vinblastine. Given these conditions, many pharmaceutical firms simply stopped searching for therapeutic compounds in higher plants.

In spite of this discouraging state

of affairs, in the late 1970s and early 1980s several groups of scientists independently set off to different corners of the world for the express purpose of finding innovative drugs through ethnobotanical research. Some of the researchers, such as Gunnar Samuelsson and Lars Bohlin of the University of Uppsala, were former students of the distinguished Swedish ethnobotanist Finn Sandberg. A number of American researchers trace much of their inspiration to another leading ethnobotanist, Richard Evans Schultes of Harvard University.

The two of us are among that latter group. When we were graduate students at Harvard in the late 1970s, Schultes encouraged us to continue our studies of traditional uses of plants in remote regions of the earth. Balick, in his doctoral work, extended Schultes's pioneering ethnobotanical research in the Amazon. Meanwhile Cox, who had been a missionary in Samoa for the Mormon church during his undergraduate years, returned to the South Pacific to study the ecology of the rain forest and the uses of plants by the Samoan people. After receiving our degrees, we continued to investigate herbal medicine in two culturally and geographically distinct areas: Central America (Balick) and Polynesia (Cox). Both of us have studied intensively with indigenous healers.

The ethnobotanical approach is actually one of several methods that can be applied in choosing plants for pharmacological studies. It is estimated that 265,000 flowering species grace the earth. Of these, less than half of 1 percent have been studied exhaustively for their chemical composition and medicinal value. In a world with limited financial resources, it is impossible to screen each of the remaining species for biological activity. Some kind of collection strategy is needed.

Investigators, for example, can gather vegetation randomly in an area supporting rich biological diversity. Unfortunately, random searches yield relatively few new drug possibilities. One notable exception is taxol. In 1992 the

ANDREW RAMCHARAN, a healer living in Belize, Central America, is collecting the leaves and flowers of the plant *Cornutia pyramidata* to include in a mixture used for skin rashes. Ethnobotanists interested in drug discovery often rely on healers to identify plants that are likely to contain potent bioactive chemicals. There is some urgency to this work: many healers are elderly and lack apprentices. As they die, much of their knowledge of local vegetation dies, too.

Food and Drug Administration approved taxol, derived from *Taxus brevifolia* (the Pacific yew tree), as a treatment for ovarian cancer and in 1994 approved it for treating metastatic breast cancer unresponsive to other therapies. Taxol was found in the course of a random-screening program conducted by the National Cancer Institute (NCI), which has maintained a plant-screening

program, with varying degrees of energy, since 1960. (Today the NCI employs several plant-gathering strategies. It also examines specimens not only for their anticancer effects but also for their ability to impede the functioning of the human immunodeficiency virus, or HIV, which causes AIDS.)

Other plant-collecting methods, including the ethnobotanical approach,



Drugs Discovered from Ethnobotanical Leads

The well-established drugs listed below are among dozens that were developed after scientists began to analyze the chemical constituents of plants used by traditional peoples for medicinal or other biological effects. For in-

stance, Western researchers isolated reserpine in 1952 from the climbing shrub *Rauvolfia serpentina* (photograph), which has been employed in India for many centuries to treat snakebite and mental illness.

DRUG	MEDICAL USE	PLANT SOURCE
Aspirin	Reduces pain and inflammation	<i>Filipendula ulmaria</i>
Codeine	Eases pain; suppresses coughing	<i>Papaver somniferum</i>
Ipecac	Induces vomiting	<i>Psychotria ipecacuanha</i>
Pilocarpine	Reduces pressure in the eye	<i>Pilocarpus jaborandi</i>
Pseudoephedrine	Reduces nasal congestion	<i>Ephedra sinica</i>
Quinine	Combats malaria	<i>Cinchona pubescens</i>
Reserpine	Lowers blood pressure	<i>Rauvolfia serpentina</i>
Scopolamine	Eases motion sickness	<i>Datura stramonium</i>
Theophylline	Opens bronchial passages	<i>Camellia sinensis</i>
Vinblastine	Combats Hodgkin's disease	<i>Catharanthus roseus</i>



Rauvolfia serpentina
INDIAN SNAKEROOT



Filipendula ulmaria
MEADOWSWEET



Papaver somniferum
OPIUM POPPY



Datura stramonium
JIMSON WEED



Cinchona pubescens
FEVER TREE



Catharanthus roseus
ROSY PERIWINKLE

are more targeted. In phylogenetic surveys, researchers choose close relatives of plants known to produce useful compounds. In ecological surveys, they select plants that live in particular habitats or that display characteristics indicating they produce molecules capable of exerting an effect on animals. Collectors might, for example, focus on specimens that seem to be immune from predation by insects. The absence of predation suggests a plant may produce toxic chemicals. Many chemicals that are toxic to insects also show bioactivity in humans, which means they might be capable of achieving some therapeutic effect.

Finally, the ethnobotanical approach assumes that the indigenous uses of plants can offer strong clues to the biological activities of those plants. For instance, if our colleagues at the NCI or at pharmaceutical firms asked us to focus on collecting plants that might serve as therapies for HIV, we would pay special attention to plants a society uses against diseases we know are caused by viruses. Plants exploited for their poisonous effects are also of interest. Blowgun poisons such as curare have in the past been found to contain compounds able to serve as anesthetics.

The history of drug discovery im-

plies that the ethnobotanical approach is the most productive of the plant-surveying methods, and recent findings confirm that impression. Some of the data were collected by Cox with his student Rebecca Sperry and with Bohlin and Mervi Tuominen of the University of Uppsala. This group found that 86 percent of the plants used by Samoan healers display significant biological activity in a variety of assays. Balick and Rosita Arvigo of the Ix Chel Tropical Research Foundation in Belize discovered that crude extracts of the plants that one healer (Don Elijo Panti, in Belize) considered to be his most powerful gave rise to four times as many positive results in a preliminary laboratory test for activity against HIV than did specimens collected randomly.

We should note, however, that few of the compounds exhibiting activity in laboratory tests will become new drugs. Some will turn out to be identical to, or less potent than, existing agents; others will prove too toxic for commercial use. Nevertheless, demonstrating activity in a bioassay is a necessary first step in the drug development process.

How do ethnobotanists choose the societies they study? Researchers differ in their criteria. Because not all cultures are equally likely to make use of plants having significant pharmaceutical activity, the two of us focus our efforts

on those possessing three characteristics. First, the societies should be located in a floristically diverse area, such as a tropical rain forest. Such diversity dramatically increases the number of plants available; it thus enhances the likelihood that plants with pharmacologically active molecules will be pressed into service.

Second, the societies should have remained in the region for many generations. Groups who have resided in one place for a long time presumably have had ample opportunity to explore and experiment with local vegetation. According to this requirement, aboriginal peoples who have populated Australia for many thousands of years would be a better choice for study than European settlers.

Third, the cultures must have a tradition in which healers transmit their plant knowledge from generation to generation, usually through apprentices. Consistent application of a given species for an ailment over millennia generates information rather analogous to that produced by large-scale clinical trials. Such repetitive, long-term use of botanical species can be expected to have identified both the most effective medicinal plants and those that are too toxic for use.

As these criteria suggest, we are especially interested in recording the spe-

cialized information possessed by healers; that is, knowledge not necessarily shared by most other individuals in the community. Many members of indigenous societies can identify some common plants that have medicinal uses, much as many Europeans realize that *Aloe vera* is helpful for burns. But only a healer might know the best plant to choose for treating serious or uncommon diseases, such as yellow fever.

Other ethnobotanists—notably, Brent Berlin of the University of California at Berkeley and Walter H. Lewis and Memory Elvin-Lewis of Washington University—prefer to study plants used by a broad array of villagers. This approach, called the consensus technique, is based on the supposition that awareness of highly effective medicinal plants will spread rapidly throughout a culture. We concentrate on seeking esoteric information because many healers no longer have apprentices. As healers die, their arcane wisdom is likely to be extinguished forever. Botanical insights that are widely held should be accessible longer.

Interestingly, healers often practice both as generalists and specialists. In Belize, caregivers provide some level of primary health service to residents of their villages and surrounding regions, yet they often also have unique areas of expertise. Hortense Robinson of Ladyville specializes in midwifery and other health care concerns of women and children. Andrew Ramcharan of Rancho focuses on treating snakebite in an area that harbors many venomous snakes. The knowledge such healers possess can be quite remarkable. In the islands of Samoa, most healers are female and specialize in herbal medicine; only bone setters are commonly male. The herbalists, or *taulasea*, typically make use of more than 100 species of flowering plants and ferns.

We find healers mainly by asking people to identify the individuals to whom they turn when they are sick. Having located healers, we take pains to explain our mission to them and to tribal chiefs. This process is analogous to “informed consent” in clinical settings. The interactions go most smoothly if Western researchers are trained in both botany and anthropology and have a good understanding of the societies they visit. If the healers are amenable to teaching us, we spend many weeks, months or even years with them and take careful notes on the properties and uses of the plants they show us. During such fieldwork, we attempt to live in accordance with local customs, and we usually learn the local language.

When, with the guidance of the healers, we have decided on the plants we want to collect, we gather a kilogram (about two pounds) of each species. (Prior to collection, we always obtain permission from the healers, village chiefs, landowners and governments.) Whenever possible, we collaborate with local scientists or students. We save four or five samples of a plant to serve as “voucher,” or reference, specimens. These specimens are pressed flat, dried and labeled carefully. The labels indicate species name and indigenous name and application, as well as any directions needed for locating the plant again. Eventually the specimens are deposited in herbaria (collections of preserved plants) in several parts of the world for consultation by other botanists.

We then prepare the rest of the material for transport to our laboratories. Typically we dry the plants or preserve them in aqueous alcohol. Later, in the laboratory, we or our colleagues usually extract different kinds of molecules from the plants by immersing them in various solvents. Next, we separate out the solvent and deliver the resulting solvent-free extracts (or sometimes the plant samples themselves) to collaborators at other universities, governmental agencies or drugmakers for screening.

In the 1960s standard screening assays for many potential drugs consisted of injecting test material into a rodent and waiting to see if the animal fell ill, got well or displayed some other change in behavior or health. Screen-

ing was thus a time-consuming, costly and imprecise endeavor. Thirty years later bioassays are faster (usually being automated) and are significantly more specific. At the NCI, tiny amounts of material can be screened rapidly against an array of up to 60 distinct human tumor cell lines. Many other assays assess the ability of an extract to influence the activity of a single enzyme involved in the biochemical interactions that underlie a disease. For example, scientists looking for an AIDS treatment might evaluate whether the extracts inhibit the activity of the enzyme reverse transcriptase in cells. Reverse transcriptase is coded for by the genetic material of HIV and is needed for replication of the viral particles.

When an extract displays significant activity in a bioassay, we return to the field with our local collaborators and retrieve a bulk sample of the original plant, typically 50 to 100 kilograms' worth. Chemists need these extra supplies in order to isolate the molecule responsible for the observed activity and to determine (by spectroscopic techniques) its structure. Newly emerging techniques that require very little plant material may render such return collection trips unnecessary.

Once the molecular structure is identified, researchers compare it with that of known chemicals. If the isolated molecule is novel, or has already been found but has not been studied as a possible drug, it may be analyzed further as is. In other cases, a synthetic version will be examined instead—that is, if workers can determine how to con-



ETHNOBOTANIST MICHAEL J. BALICK, one of the authors, is drying plants that were collected by his colleagues in Belize. Drying is one of the techniques by which investigators preserve their specimens in the field.

struct the substance and can do so at a reasonable cost. Still other times, the molecule will serve as raw material that is altered to produce some desired activity. Even if an isolated molecule or a synthetic version clearly cannot serve as a drug for some reason, its discovery might suggest previously unconsidered avenues for attacking a disease.

After investigators settle on a test molecule having significant activity—also known as a lead compound—evaluation proceeds as it would for any other potential drug. Researchers study the compound for such characteristics as its strength of binding to a particular target molecule and its toxicity to cells. If it passes these tests, a company or governmental agency may decide to invest the money needed (an estimated \$200 million) to bring it to market. At that point, it becomes a drug candidate. To make its way to pharmacy shelves, the drug candidate must prove its worth in additional laboratory analyses and in clinical trials.

So far the rigorous ethnobotanical field searches that have been conducted since the early 1980s have generated many lead compounds. Some of these have been identified as drug candidates, and a few may eventually reach pharmacy shelves. We cannot be sure of the exact number of leads or drug candidates, because most pharmaceutical makers will not discuss products in the early stages of development. We do know, however, that many of the lead compounds derived from ethnobotanical research exhibit potent antiviral, antifungal or anticancer effects—properties that are sorely needed in the pharmaceutical arsenal.

Two drug candidates that have reached clinical trials are being developed by Shaman Pharmaceuticals in South San Francisco, Calif. The active component in both drugs is derived from a plant that grows in Central and South America. One formulation shows promise against respiratory viruses. The second version may be administered topically for treating infections caused by the herpes simplex virus.

Another exciting agent in the drug pipeline is a powerful antiviral compound called prostratin. The story of prostratin's identification serves as a good paradigm of the drug discovery process. When Cox was in Samoa in 1984, several healers told him that they treat yellow fever by giving patients brews made by steeping in water pulverized wood of the rain-forest tree *Homalanthus nutans*. Cox collected samples and brought them to the U.S., where he prepared freeze-dried solvent

extracts. Because of the prevailing attitudes at the time, no drug companies were inclined to analyze his specimens.

Fortunately, Michael R. Boyd and Gordon M. Cragg of the NCI agreed to test them. The extracts exhibited strong activity against HIV in the test tube. Chemists John H. Cardellina II and John A. Beutler, also at the NCI, then discovered that the active component was a chemical called prostratin. The chemical was known but was not being studied as a drug, because it was a phorbol, a class of chemicals that promotes the development of tumors.

Worry over tumor promotion initially dampened interest in prostratin at the NCI. But Cox argued that if this particular phorbol stimulated the growth of cancer, its carcinogenic properties would have become evident in Samoa; its continued use by healers suggested it was safe. When Peter M. Blumberg, a cell biologist at the NCI, examined the drug's carcinogenic effect in mice, he found, to his co-workers' surprise, that it did not promote tumor formation, even though it activated an enzyme (protein kinase C) that participates in malignancy. The NCI is now planning to accept bids from drug companies for the right to investigate prostratin further as a possible drug.

An additional compound identified through Cox's ethnobotanical research highlights the striking precision of the knowledge possessed by many healers. Samoan *taulasea* apply the bark of a local tree, *Erythrina variegata*, to the skin to treat inflammation. In describing this tree, they insisted that only one of the two types of *E. variegata* in the region was helpful. Sure enough, when a team led by Vinod R. Hegde and Mahesh G. Patel of Schering-Plough Corporation in Kenilworth, N.J., evaluated the ability of bark samples to inhibit an enzyme involved in inflammation (phospholipase A₂), they found the healers were absolutely correct. Bark from only one variety of *E. variegata* displayed anti-inflammatory activity. From that bark, the team isolated the active component—a chemical known as a flavanone. The chemical is now under development as a topical anti-inflammatory at Schering and at Phyton Catalytic in Ithaca, N.Y.

In Thailand a team led by Hans T. Beck of the New York Botanical Garden and Weerachai Nanakorn, then of the Royal Forest Department in Bangkok, learned from healers that the roots of *Curcuma comosa*, a relative of the ginger plant, eased stomach pains and other gastrointestinal disorders. Tannis Jurgens and colleagues at Merck & Co., in

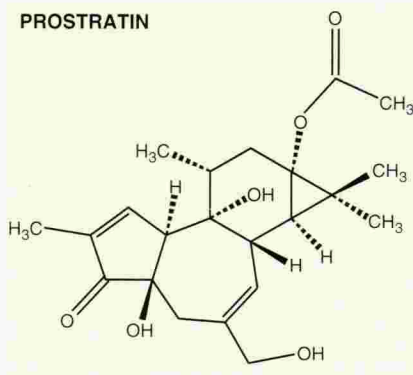
Rahway, N.J., then isolated from the roots a novel compound that kills parasitic worms in the stomach. The compound is now under investigation as a potential treatment for parasitic diseases. In Peru, Lewis and Elvin-Lewis obtained samples of a tree sap that Jivaro Indians and others apply for hastening the healing of wounds. The active ingredient in the sap, called taspine, is being tested for that same purpose in animals. If those tests are successful, human trials are likely to follow.

The probability that drug companies, universities and Western scientists will profit financially from information provided by healers in traditional societies raises a serious question: What is being done to protect the interests of healers and their communities? We are well aware that the healers with whom we work provide significant intellectual guidance. Indeed, we refer to them as "colleagues," "guides" and "teachers," instead of as "informants." Given the significant participation of indigenous peoples in our research programs, we believe they are entitled to the same intellectual property rights enjoyed by other investigators. Hence, we do all we can to see that those rights are protected.

For instance, in the case of prostratin, the NCI and Brigham Young University, where Cox is a professor, have guaranteed that a significant part of any royalties earned from the drug will be returned to the Samoan people. Virtually all ethnobotanists active in drug research are involved in making similar arrangements for the cultures they study. In fact, now that ethnobotanical inquiry is expanding, formal guidelines are being devised.

To many cultures, protecting the forests around them is more important than receiving money. Hence, many researchers are devoting effort to protecting the rain forests in the regions where they work. For example, Thomas Eisner of Cornell University helped to convince Merck & Co. to invest \$1 million in a project designed to inventory and ultimately preserve a part of the Costa Rican rain forest. In return, Merck can study chemicals extracted from living organisms in Costa Rica's national parks and elsewhere.

Four village-owned and village-managed reserves encompassing 64,000 acres have now been formed in Samoa with funds raised through the Seacology Foundation of Provo, Utah (an organization Cox helped to create). These protected territories include the Falealupo Rain Forest Reserve, the site where the plant that produces prostratin was



SAMOAN HEALER MARIANA LILO, who died in 1993, is shown cutting the stem of *Homalanthus nutans*. She went on to macerate the wood and steep it in hot water, producing a brew to be drunk by patients with yellow fever (a viral disease). The active ingredient, prostratin (above), was isolated by the National Cancer Institute, which plans to license it to a drug company for investigation as a possible treatment for HIV infection. Prostratin is one of a range of potential drugs that have been discovered through recent ethnobotanical research.



first collected. In the U.S. territory of American Samoa, Cox participated in establishing the 50th national park of this nation. By mandate of Congress, the park will allow and encourage Samoan healers to continue to use medicinal plants in a sustainable way—that is, in a way that guarantees their ongoing availability.

Balick and Arvigo and their colleagues Gregory Shropshire of the Ix Chel Tropical Research Foundation and Leopoldo Romero of the Belize Association of Traditional Healers recently helped to establish the world's first ethnobiomedical forest reserve. It is an entity designed specifically to ensure that medicinal plants will be available for local use. The protected area, called the Terra Nova Rain Forest Reserve, comprising almost 6,000 acres of forest in the Yalbak region, is to be managed by the Association of Traditional Healers. The reserve was created not only to provide needed medicinal plants but also to teach young people about their uses. It is hoped that such teaching will encourage youth to preserve the knowledge of their elders. Researchers will also be collaborating with the healers to devise ways to make sure that medicinal plants are harvested sustainably.

In spite of its apparent successes, ethnobotany is unlikely to ever become a major force behind commercial drug discovery programs. Its application is limited by the paucity of properly trained ethnobotanists who have the

time to conduct rigorous, long-term fieldwork in remote areas of the world. Also, many funders of drug research still perceive the ethnobotanical approach as archaic, unscientific and unworthy of attention.

Yet the demonstrated ability of ethnobotany to generate exciting leads for drugs suggests to us that, for the near future at least, the approach will occupy an expanding role in drug development. Those who understand the value

of such work are truly in a race against time. In Samoa, two healers who first provided Cox with information leading to the discovery of prostratin—Epensa Mauigoa and Mariana Lilo—died in 1993. Generations of accumulated medical wisdom died with them. Ethnobotanists can capture much of the remaining knowledge, but only if the research effort is expanded soon. Sadly, plant knowledge seems to be disappearing even faster than the forests themselves.

FURTHER READING

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