TEACHING TOOLS IN PLANT BIOLOGY™: LECTURE NOTES

Medicinal Plants: Past, Present, and Future

Plants are amazing chemical factories. Like other organisms, they produce a shared set of small-molecule metabolites, referred to as primary metabolites, which in plants probably number <10,000. Collectively, organisms in the plant kingdom also produce a vast array of at least 200,000 specialized metabolites that are not conserved but instead are usually restricted to a single plant family, genus, or species (metabolite number estimates are from Pichersky and Lewinsohn, 2011). These specialized metabolites (formerly called secondary metabolites) are the most rapidly evolving aspect of plant metabolism, and the compounds often have defensive or signaling functions.

Many of these specialized compounds have biological activities toward microbes and invertebrate or vertebrate animals. Among these are some of the most important medicines used for the treatment of human illnesses or diseases. Many of the drugs we use today come from plants, some of which have been used for healing purposes for hundreds or thousands of years. Plant-derived medicines are often grouped together with medicinally active compounds derived from microbes, fungi, or animals into the category of natural compounds (to differentiate them from synthetic compounds), but here we limit our discussion to those derived from plants. We exclude most of the health-promoting phytonutrients found in food and focus on those plants and compounds ingested to treat ailments. (The many food plants that can contribute to disease prevention are described in Teaching Tools in Plant Biology 21: Plants, Food, and Human Health.)

More than half of the top 150 prescribed drugs in the United States have at least one compound derived from plants, and ~80% of the world’s population depends on plants or plant extracts as their major source of healthcare. There is a keen interest in screening plants for potential medicines, but with over 250,000 species of flowering plants alone, the task is immense. Some scientists have turned to traditional healers and folklore to help identify plants that might be medicinally active, and others are looking at plant families that are particularly rich in medicinal compounds. New approaches, such as metabolomics, metabolic engineering, and systems and synthetic biology, are contributing toward the identification, characterization, and production of plant-derived medicines. This article looks at the history of medicinal plants, ongoing efforts to identify novel medicinal compounds from plants, herbal remedies in traditional and contemporary medicine, and the regulations and policies that govern the use of plant extracts as medicines.

HISTORICAL USES OF PLANTS AS MEDICINES

Prehistory through the Middle Ages

Throughout most of human history, plants have been important sources of medicines. Herbal remedies came about by observing nature and by trial and error and were passed down from generation to generation over hundreds or thousands of years. Very early uses of plants as medicines are revealed by archeological data. For example, 77,000-year-old bedding material found in South Africa included leaves from a plant still valued for its toxicity to mosquitoes, Cryptocarya woodii, and an analysis of chemicals isolated from 50,000-year-old Neanderthal teeth suggested that the individual consumed chamomile (Matricaria recutita) or related medicinal plants prior to death.

The earliest written record of plant medicine comes from Sumerian clay tablets that date from ~4000 years ago, which include descriptions of the medicinal use of opium (Papaver somniferum), thyme (Thymus spp), licorice (Glycyrrhiza glabra), willow (Salix alba), fig (Ficus spp), and many other plants. Assyrian and Babylonian artifacts include similar descriptions. “Herbals” are texts that contain the names, descriptions, and medicinal uses of plants, descriptions of where they can be found, methods for storage and shelf life of the harvested materials, along with recipes for extractions, tinctures, or potions. One of the best known and most complete of the ancient herbals is the Egyptian Ebers Papyrus, a 70-foot-long medical scroll discovered in the 1870s. It lists 800 recipes and refers to the use of aloe (Aloe vera), wormwood (Artemisia spp), peppermint (Mentha piperita), henbane (Hyoscyamus niger) for worms, castor oil (Ricinus communis), mandrake (Mandrakora officinarum), garlic (Allium sativum), juniper (Juniperus spp), frankincense (Boswellia spp), senna (Senna spp), elderberry (Sambucus nigra), bayberry (Myrica spp), onion (Allium cepa), opium, thyme, and honey, just to name a few.

The practice of traditional medicines in China dates back at least 4500 years. The Shen Nong Ben Cao Jing (previously sometimes written Pun-Tsao) is considered by some as the oldest list of medicinal herbs. This herbal describes the gathering, preparation, and use of medicines derived from 252 medicinal plants, 67 medicinal animals, and 46 mineral drugs. It describes thousands of herbal cures, including the use of Chaulmoogra oil from the Hydnocarpus genus to treat leprosy and the use of ma huang (Ephedra spp, Chinese ephedra), which contains ephedrine, to improve circulation, reduce fevers, and treat lung disorders.

The Rig Veda is a 3500-year-old collection of Hindu sacred verses that forms the foundational works of Ayurveda, or traditional Indian medicine. These descriptions include location of plants and methods for storage and shelf life of the harvested material.
Ayurveda medicine is still practiced by up to 80% of the Indian population.

The origins of Western medicine start with the Greek physician Hippocrates and later Galen, whose writings refer to the use of more than 500 plant species. Another Greek, Theophrastus, has been described as the father of botany, and his book “Historia Plantarum,” which describes the natural habitats, geographic distributions, collection, and preparation of medicines, spices, and perfumes, was used for over 2000 years. “De Materia Medica” was written by Pedanius Dioscorides, a Greek physician traveling with the Roman army and is one of the most influential herbalists ever written. This five-volume book, considered to be a precursor to modern pharmacopeia, described 4740 medicinal usages, from aromatic oils, salves, and ointments to narcotics and poisons. Furthermore, Dioscorides recognized that plants’ medicinal properties are affected by cultivation and harvesting practices. For example, he observed that opium poppy latex collected in early morning is more potent than that collected later in the day.

Evidence of medicinal plant use in other parts of the world is scarce due to the scarcity of written records. The earliest Aztec herbal written by a native physician, Martin Cruz, was published in Mexico around 1552. In 1570, a Spanish doctor recorded around 1200 medicinal plants used by Aztecs, many found in large Aztec botanical gardens. Tobacco (Nicotiana tabacum) was mentioned in a number of texts describing its use in recipes to cure health problems from gout to stomach upset.

Numerous medicinal texts were written in the Arab world, combining their herbal and pharmacological knowledge with those of the Greeks, Romans, and Asians. The Persian Avicenna Ibn Sina (980 to 1037) produced one of the most famous medical encyclopedias of this period, The Canon of Medicine (1025), and a second book based on plants and their healing properties. These books introduced clinical trials, randomized controlled trials, and efficacy tests, becoming the basis of today’s clinical pharmacology. They were used as medical authorities for the next 500 years both in the east and west.

 Herbalists from the time of Dioscorides through the mid 1600s ascribed to the “Doctrine of Signatures,” which stated that a plant’s shape, texture, and color could indicate what part of the body it might heal. Mandrake and ginseng have roots shaped like men (or women) therefore could be used to treat any number of human sicknesses. Plants were given “signatures,” names to indicate what part of the body they might treat (e.g., spleenwort, boneset, brighteyes, and maidenhair fern). The Swiss physician Paracelsus, “the father of chemical pharmacology” (1493 to 1541), popularized this notion.

Age of Herbals and Physic Gardens

After the fall of Rome, herbal manuscripts were maintained, translated, and copied in monastery libraries, and monks and nuns gathered and raised herbs that they used to treat the sick. Charlemagne (742 to 814) is credited for commanding that his royal gardens contain medicinal plants, therefore establishing the basis for later botanic and physic gardens. From the 15th through 17th centuries, numerous herbals were published and printed in Europe, many based on ancient texts, and botanical, medicinal, or physic gardens were founded by monasteries, medical schools, physicians, and apothecaries (pharmacists). Herbal medicines were an important part of medical treatment, but, starting in the early 1800s, herbal medicines began to fall out of favor as advances in chemistry opened the door to purified drugs.

Case Study: Digoxin and Cardiac Glycosides

The use of glycosides purified from foxglove (Digitalis purpurea) as treatments for cardiac problems originates with its use as an herbal remedy. Early studies were performed by William Withering, who was a medical doctor and a botanist. He was active in the late 1700s, a time when rationalism and science were applied to all of life from agriculture to politics. Prior to his studies on Digitalis, he wrote the first natural history of British flora that used the Linnaean system of classification. According to legend, Withering observed the successful treatment of a patient with a heart condition by a woman using an herbal therapy. By virtue of his botanical knowledge, Withering recognized that of the 20 or more herbs used in the medicine, the active constituent was probably from the plant foxglove. From 1775 to 1784, he studied and standardized the preparation of foxglove for medicinal purposes, culminating in his book published in 1785, “An Account of the Foxglove, and Some of its Medical Uses.” Although Withering’s work preceded the advances in chemistry that were to follow, and he did not purify the active chemical compounds from the plants, he laid the foundation for the science of medicinal phytocchemistry. The active ingredients, cardiac glycosides, were later purified, and they continue to be prescribed for the treatment of heart problems.

FROM 1800 TO THE PRESENT: THE QUEST FOR ACTIVE COMPOUNDS

Beginning early in the 19th century, many drugs and medicines used the purified active compounds isolated from medicinal plants rather than the complex extracts or decoctions. One of the most famous was the extraction of salicin from willow bark in the 1820s. Willow had been used for centuries as a painkiller, antipyretic, and anti-inflammatory agent. Improvements to lessen salicin’s adverse physiological effects eventually led to the production of aspirin, which was the first major medicine sold in tablet form.

Many drugs are compounds that are purified from plants, or derivatives of the natural products, of which several are examined more closely below, but first it’s worth considering the question, “Which is better, a plant extract or the purified compound?” There is no simple answer. The plant extract can include more than active compound and have a multifactorial effect that can’t be replicated by a single compound. Plant extracts are usually cheaper than pharmaceutical-grade medicines. However, there is also a problem of batch-to-batch variation in potency and the possibility of contaminants, and there can be supply shortages. Furthermore, medicinal plants are routinely overharvested, and several are endangered. Purified compounds are chemically defined and provide consistent supply.
and precise dosages. Purified compounds can also be starting points for the production of more effective drugs or drugs with fewer side effects (such as aspirin from salicylic acid). However, the extensive testing and clinical trials needed for regulatory approval of a new compound mean that these drugs can be prohibitively expensive for most people. Clearly, both plant extracts and purified compounds are needed in global healthcare.

**Case Study: Morphone and Other Opiates**

Opium, which is a complex mixture of alkaloids isolated from the seed capsules or other parts of the poppy *Papaver somniferum*, has been used as a pain reliever (analgesic) and sedative since before recorded history. Morphine, one of several biologically active alkaloids present in opium, was the first medicinally active plant compound to be purified and the first to be sold as a commercial product. Morphine was purified in 1805 by a young pharmacist, Friedrich Sertürner, who is also credited for naming his new compound after Morpheus, the Greek god of dreams. Sertürner’s work laid the groundwork for the subsequent purification of many other plant alkaloids, such as codeine and noscapine, which are effective cough suppressants. Derivatives of these natural compounds are also important medicines. Diamorphine, commonly known as heroin, is a more potent synthetic derivative of morphine, and oxycodone is a derivative of the alkaloid thebaine that is used as a time-released painkiller.

Morphine is the best of drugs and the worst of drugs. Its pain-relieving properties are unmatched. It is the most widely used treatment for pain, with more than 230 tons of morphine used medicinally each year. During a ceremony honoring Friedrich Sertürner, a celebrant said, “Without morphine I would not want to be a physician.” However, opiates can be highly addictive substances. Morphine and other opiates act by binding to neurotransmitter receptors. With prolonged opiate use, the activity or amount of receptor produced by the target cells can decrease, so more medication is needed for pain relief. Users can develop a dependency or addiction and suffer debilitating withdrawal symptoms.

The potential for misuse means that these drugs are controlled substances and that there is an active illegal trade in them. In most countries, it is legal to grow poppies but illegal to harvest opium from them. Although synthetic methods have been established for the production of these alkaloids, they are not commercially viable, and most opiates are derived or derivatized from plant extracts. (Methadone, used to treat opiate dependency, is a structurally dissimilar synthetic opioid.) Most of the opiates used medicinally in the United States come from plants grown and harvested legally in India or Tasmania, but the black market demands for opioids means that poppies are also grown for illicit purposes. Safer poppies have been developed, such as the thebaine poppy that carries the *thebaine oripavine poppy* mutation that blocks the production of morphine and codeine, so that the plants accumulate thebaine and oripavine, precursors for the production of painkillers. Other studies have used viral-induced gene silencing and RNA interference methods to manipulate the production of secondary metabolites in poppy and to investigate further this unique biochemical pathway.

**Case Study: The Antimalarials Quinine and Artemisinin**

Malaria is a deadly disease that has affected humans since our earliest written records and occurs in tropical and swampy regions all over the world. Malaria kills about a million people a year, mostly children, and millions more are chronic sufferers of its debilitating effects. It is caused by a plasmodium protozoan, which is carried from human to human by mosquitoes. Malaria is treatable by drugs that target the protozoan, and the two most effective treatments, quinine and artemisinin, come from plants.

Quinine comes from the bark of the Cinchona tree (*Cinchona* spp) native to the Peruvian region of South America. In the 17th century, Spanish priests observed the indigenous Indians using the powdered bark as a remedy for fevers, and they brought it back to Europe. The effectiveness of this treatment led to a great demand for it, which threatened the natural Cinchona forests. In 1820, the active compound, an alkaloid called quinine, was isolated by the French chemists Pelletier and Caventou. More than 100 years passed before a method was developed to synthesize it. The first synthetic pathway, published by Woodward in 1944, was inefficient in part because the product was a mixture of stereochemical isoforms. In the 21st century, improved methods to synthesize the active stereoisomer were published, but in each case, the synthetic route was not economical compared with the purification of the natural product from the bark. Furthermore, strains of plasmodia resistant to quinine and other antimalarials have emerged, so alternate drugs are often used.

Records in China dating back nearly 2000 years describe qing hao, also known as sweet wormwood (*Artemisia annua*), as a treatment for fevers or malaria. The active compound, an endoperoxide sesquiterpene lactone named artemisinin, was first purified and characterized in the 1970s by Chinese scientists. Artemisinin has proven to be an effective therapy against malaria, but it is usually provided as a combined therapy with other drugs to slow the rate at which the protozoan develops resistance to it.

The amount of artemisinin extracted from plants is variable but usually low. The worldwide demand cannot be satisfied from the gathering of wild plants, so it is cultivated throughout Asia and Africa. Nevertheless, the supply of artemisinin is sometimes limited, and prices are often prohibitively expensive. Further enhancements in artemisinin production are needed. Two approaches are being followed to address this issue: plant breeding and synthesis.

The yield of artemisinin from a plant depends on the plant genotype and the environmental conditions in which it is grown, and these can vary tremendously. Plants producing consistently higher yields are being developed through selective breeding. One approach is to take advantage of natural genetic variation to identify gene loci correlated with increased production of artemisinin. For example, as artemisinin is produced in glandular trichomes on the leaf surface, selecting plants with more trichomes or larger leaves may increase yields. Genes encoding steps in the biosynthetic pathway can also contribute to the natural variation in artemisinin production. Another approach may be to target specific genes, such as the biosynthetic genes for a metabolic engineering approach in transgenic plants.

A different approach has been to identify synthetic methods for artemisinin production, which can allow artemisinin to be
produced year-round and on demand. The greatest success so far has involved a semisynthetic approach in which the reaction takes place partly in yeast cells and partly in vitro. Semisynthetic artemisinin is already being produced, and research to increase yields is ongoing. However, it is unlikely that this approach will meet all of the needs for artemisinin because it is more expensive than the drug isolated from plants and currently is not being produced in amounts sufficient to meet the demands. Improvements in plant yields and semisynthetic production, including perhaps using precursor-rich plant extracts as starting materials, may both be needed to produce the quantities required for the large-scale antimalarial treatments that will decrease the numbers of deaths attributed to this disease.

Case Study: Taxol and Camptothecin

In the mid-20th century, a phytochemical screening program was initiated to identify natural products with beneficial health effects. Through this program, thousands of plant samples were extracted, analyzed chemically for certain compounds (e.g., steroids), and subject to biological assays to determine their antibiotic, antiviral, and antitumor properties. Some of the plants were selected by random screening, and others were identified from traditional medicines. Two major drugs that are effective anticancer drugs emerged from this program: taxol and camptothecin.

Taxol, later named paclitaxel, was initially characterized from extracts of the bark of the Pacific yew (Taxus brevifolia), which had been included in a large-scale collection of plant materials from the Pacific Northwest. The yew extract showed an unusually high level of cytotoxicity against a cell culture derived from human cancer cells. Taxol was purified in 1966 and its structure determined in 1970. Its mechanism of action was subsequently shown to be through its binding and stabilization of tubulin that interfered with cell division. Interest in taxol’s anticancer properties led to large numbers of trees being harvested annually. At one point in the 1980s, it was estimated that 360,000 trees a year would have to be harvested to meet the demands for taxol. Taxol is a large, complex molecule not readily amenable to synthesis, but in 1994, two groups published a method for the complete synthesis of taxol. However, these methods are very expensive and produce low yields. Today, most taxol is produced semisynthetically from a precursor harvested from the needles of European yew (Taxus baccata) that occurs at much higher levels than taxol. The precursor, 10-deacetyl-baccatin III, can be chemically converted into taxol. Thus, branches can be harvested from trees on a yearly basis without sacrificing the tree. Another approach uses a plant cell fermentation process that starts with cultured plant cells. This method not only protects the trees from overharvesting, but also avoids the use of hazardous chemicals required for the synthetic route. The cultured plant cell fermentation approach is an example of “green” (environmentally friendly) chemistry, and the company Bristol-Myers Squibb that developed it received the Greener Synthetic Pathway award in 2004 from the U.S. Environmental Protection Agency.

Another drug that was identified through this phytochemical screening program, camptothecin, was isolated from Camptotheca acuminata, a tree native to China. This tree is used in traditional Chinese medicine (TCM) and is known as xi shu, meaning “happy tree.” Camptothecin and its derivatives very specifically target the enzyme topoisomerase I, which is needed to relax DNA supercoiling during DNA replication. Due to side effects associated with camptothecin, its two less toxic derivatives, irinotecan and topotecan, are used therapeutically. An unexpected outcome of this research was the discovery that topoisomerase I is a good target for tumor-suppressive drugs. As a consequence, focused studies searching for inhibitors of topoisomerase I have been performed, leading to the identification of unrelated but effective therapies.

Not All Conditions Will Be Treatable by Single Compounds

In spite of the successes described above, not all ailments are likely to find a single “magic bullet” compound that cures or prevents them. The examples shown above include drugs that bind cell receptors (morphine), drugs that target pathogenic agents (quinine and artemisinin), and drugs that affect single cultured cells (taxol and camptothecin), which allows them to be screened and identified in vitro. The vinca alkaloids were discovered more or less by accident through animal studies. Diabetes, the condition vinca alkaloids were initially intended to treat, still is without a simple treatment (other than insulin therapy, which is not very effective for type 2 diabetes). Many human ailments are pleiotropic in nature and involve dysfunction of multiple systems, tissues, cells, and signaling pathways and so may not be treatable by a single chemical compound. The search for therapies for these ailments returns us to the traditional remedies.

THE BEST OF BOTH: THE PRESENT AND FUTURE OF PLANT-BASED MEDICINES

Increasingly, medical practitioners, healers, and government agencies are recognizing that the future of medicine brings
Traditional Chinese and Traditional Indian Medicine

TCM is one of the oldest and most widely used forms of medicine. It accounts for ~40% of all health care delivery in China today. Its views of health and the body are different from those of Western medicine and involve a focus on balancing different properties and energies. Many of its therapies are involved in restoring balance through the use of massage, exercise, and acupuncture, as well as thousands of different herbal and alternative medicines. Highly trained practitioners are important in TCM to diagnose and treat the malady. Familiar remedies derived from TCM include Ginkgo biloba, artemisinin, and ginseng (described further below).

Traditional Indian medicine, Ayurveda, is used by up to 80% of the more than one billion inhabitants of India. Like TCM, Ayurveda is very holistic in its approach. It includes massage and exercise alongside herbal medicines prepared and dispensed by trained practitioners. Traditional Indian medicinal drugs include the senna glycosides, derived from Senna alexandrina and related species, which are used as laxatives and in dieters tea for weight loss; curcumin from the plant turmeric or haridra (Curcuma longa); and withafarin A, from ashwagandha (Withania somnifera).

Drugs and Therapies from Traditional Medicines

The use of plants as medicines dates back several thousand years. How well do these remedies stand up to the analytical tools of modern science? Generally, they fare quite well. About half of the traditional remedies examined have shown some promise in clinical trials. Thus, these long-established remedies are another good starting point for drug discovery. Traditional practices in China alone have identified more than 11,000 plant species with medicinal properties, far more than have been pharmacologically analyzed. Many TCMs involve more than one ingredient, which complicates their analysis, but may also be key to their efficacy, as seen for the case of Huang Qin Tang.

Case Study: Ginseng

Globally, ginseng (Panax spp) is the most widely used medicinal herb. The two most studied species are Panax ginseng (Asian ginseng) and Panax quinquedentata (American ginseng). Herbal preparations of ginseng involve the dried root, which can be preserved in several ways and sold as pills, powders, teas, etc. Worldwide sales of ginseng exceed $300 million. Ginseng is used alone and also as a component of complex preparations. Ginseng is said to benefit the cardiovascular system and has been used for thousands of years to increase resistance to stress and boost vitality. It is used therapeutically for its immunomodulatory, anti-inflammatory, and antitumor activities. The active agents in ginseng are thought to be the ginsenosides, also known as ginseng saponins. There are as many as 40 different ginsenosides. The composition and amounts of these can vary according to ginseng species, plant age, and environmental and storage conditions. Some ginsenosides act as scavengers of free radicals or stimulate production of antioxidants. Others have been shown in vitro to bind to and act as agonists to mammalian receptors, such as the glucocorticoid and androgen receptors. Determining the functions of ginsenosides in humans is complicated by the low bioavailability of the compounds and metabolic processes that affect their activity. Furthermore, different ginsenosides have different physiological properties, and the ginsenoside composition of extracts varies with growth condition and extraction methods, adding a layer of complexity to the analysis of clinical data.

Wild plants have been overcollected to the point of endangerment in Asia and North America, a fate shared by many medicinal plants. Although ginseng is cultivated for medicinal purposes, wild plants command a premium price and continue to be overharvested. Production of ginsenosides in cell and root cultures can increase production and may curtail the
overharvesting of wild plants. However, there are also cultural and nonscientific issues involved in the consumption of ginseng (and many other medicinal plants). For example, many farmers’ livelihoods depend upon the sustainable production of ginseng. The introduction of cell culture–derived ginseng could have serious impacts on those who practice traditional production methods. Furthermore, the shape of the root has traditionally been a consideration in its price and its uses; given their long traditional associations with the root itself, how would traditional healers respond to a chemically identical but nevertheless very different extract from cultured cells? Beliefs and traditions can be powerful allies in the healing process, and understanding these cultural factors is essential for the success of any venture to introduce new medicines or therapies. Perhaps, like vanillin, there is room in the marketplace for both the traditional (more expensive) and synthetic (cheaper) product.

Case Study: Use and Abuse of Ephedra

An extract of the dried stems of Ephedra sinica (common name ephedra) has been used to treat colds, asthma, and respiratory complaints for thousands of years. The plant produces several related alkaloids, including ephedrine, which is an agonist of α- and β-adrenergic receptors. By stimulating these receptors, ephedrine causes an enhanced heart rate, stimulation of the central nervous system, and dilatation of the bronchi and bronchioles. Thus, besides alleviating the symptoms of asthma, it also increases energy level and raises the metabolic rate, so it became popular both as a performance enhancer for athletes and as a weight loss drug. Unfortunately, several strokes, seizures, and deaths were attributed to over-the-counter ephedra-containing supplements. Its over-the-counter sale as a weight loss aid has been banned in the United States since 2004, although it is still available in the United States from TCM healers. Its use by athletes in competitive sporting events is also banned. Like morphine, ephedra is a potent beneficial drug that offers the potential for abuse.

21st Century Science Can Be Applied to Ancient Medicines

21st century science is being applied to traditional medicines with several goals in mind. One is drug discovery, with the assumption that, like artemisinin, some traditional medicines will be based on single compounds that can be developed into purified drugs. Even complex formulations like Huang Qin Tang can be improved by standardizing the formulations, which is important to achieve the level of reproducibility needed for clinical studies.

As described below, metabolomics and related methods can be applied to the medicinal plants, to understand better their biochemistry, and also to the animal or human under study, to investigate how it responds to the medicines. For example, the transcriptional responses or the changes in small molecule profiles of cells or animals responding to traditional medicines can be compared with their responses to other compounds to identify their modes of action.

Most people in the world cannot afford to buy pharmacologically produced or extracted compounds but rely mainly or entirely on traditional medicines, which are much less expensive. Without significantly raising the prices of these medicines, it is possible to increase their safety and effectiveness. For example, many medicines have been found to be contaminated with heavy metals or pesticide residues that can be concentrated to toxic levels upon drying or extracting the plant materials. Relatively low-cost methods can be used to assay for contaminants, thus making these medicines safer. The World Health Organization has created guidelines of Good Agricultural and Collection Practices and Good Manufacturing Practices, guidelines for herbal medicines to encourage more uniformity and safety.

Over-the-Counter Herbal Medicines

Many herbal products are sold directly to the consumer as over-the-counter botanical dietary supplements; in 2007, Americans spent nearly $15 billion on nonvitamin herbal dietary supplements. Top sellers include G. biloba, St. John’s wort (Hypericum spp), garlic, Echinacea spp, saw palmetto (Serenoa repens), and Kava kava (Piper methysticum). Because these supplements are not required to demonstrate medicinal benefit, there is often little rigorous data to support their efficacy. However, the incidence of direct harm is also rare. Unlike traditional practices in which herbal remedies are usually dispensed by trained practitioners, over-the-counter products are marketed directly to the consumer, and confusion and uncertainty about their use is widely reported. The National Center for Complementary and Alternative Medicine, an institute of the U.S. National Institutes of Health, provides up-to-date, evidence-based information about herbal compounds (http://nccam.nih.gov/health/herbsataglance.htm), as does the European Medicines Agency (http://www.ema.europa.eu).

Case Study: Echinacea

Echinacea products contain material from any of several species of the genus Echinacea, which includes purple coneflower (Echinacea purpurea) and narrow-leaf coneflower (Echinacea angustifolia). These plants are native to North America and have been used as medicines by Native Americans and First Nations for hundreds or thousands of years. Native Americans relied on oral histories and traditions, so no written records remain before their encounters with Europeans, but archaeological evidence and studies by ethnobotanists reveal many centuries of medicinal plant use, which continues today.

Echinacea is one of the most used herbal remedies, with global sales of over $300 million annually. It is thought to contribute to enhanced immune responses and is marketed particularly as a therapy for respiratory infections and colds. Clinical data to support these roles are mixed; some studies indicate a beneficial effect, whereas others show no effect. One study pointed to the effects being stronger on people who are sicker, and another indicated that the diversity of materials used in different studies (different species, different plant parts, and different methods...
Finding Sources for New Drugs

It is thought that many of the more than 250,000 species of flowering plants harbor medicinally important compounds, but the challenge is deciding which plants to pursue. One approach is to look at plants in families that seem to be more likely than others to produce medically active compounds. A few examples are the Myrtaceae, which includes eucalyptus and clove, Apocynaceae (periwinkle), Solanaceae (tobacco, nightshade [Solanum dulcamara], and pepper [Capsicum annuum]), Papaveraceae (poppy), and Taxaceae (Pacific yew).

Another approach has been to integrate knowledge of traditional medicines from different regions of the world. When mapped phylogenetically, groups of related plants whose medicinal properties have been discovered independently are revealed. The fact that different groups of humans have independently discovered these properties makes certain plant groups particularly attractive candidates for further investigation.

Modern analytical methods can be applied to known medicinal plants to identify chemical or genetic profiles, and these profiles can be used as indicators of medicinally active compounds. For example, if a few metabolic pathways involved in specialized metabolism are highly correlated with medicinal properties, high-throughput methods can be used to screen large numbers of plants for these molecular fingerprints and identify good candidates for further study. Although the biochemical diversity of medicinal compounds is immense, they are mostly derived from only a few dozen highly versatile central intermediates that serve as backbones.

Classes of Phytochemicals with Medicinal Properties

In spite of what some medieval botanists believed, plants do not make medicines to serve humans. Many of the medicinally active compounds found in plants are products of specialized metabolism and are believed to function for defense against herbivores or pathogens. A few types of chemicals are predisposed toward medicinal properties, allowing researchers to narrow their focus to certain classes of chemicals as they screen for active compounds. The most prominent classes of medicinally active chemicals are alkaloids, phenolics, and terpenoids.

Alkaloids are a very large and diverse group of metabolites and contribute the greatest number of known plant-derived medicines. There are ~12,000 known alkaloids, and they are thought to be present in ~20% of plants. They are structurally diverse and have diverse biochemical origins. Alkaloids are usually heterocyclic, nitrogen-containing compounds that are alkaline or slightly basic and taste bitter. The monoterpene indole alkaloids (MIAs) are a family of ~2000 compounds that includes the vinca alkaloids and primarily are found in Madagascar periwinkle and Rauvolfia serpentina (paragandha or snakeroot). Benzylisoquinoline alkaloids are a family of ~2500 compounds, including morphine, and are found in several plant families. Tropic alkaloids are more widely distributed in the plant kingdom and include nicotine and scopolamine, purine alkaloids include caffeine, and pyrrolizidine alkaloids are widespread in the plant kingdom and generally induced by herbivory. In humans, alkaloids can be stimulants (caffeine, cocaine, nicotine, and ephedrine), pain relievers (morphine), antitumor agents (vincristine and taxol), psychoactive agents or hallucinogens (dimethyltryptamine and mescaline), deadly poisons (strychnine, scopolamine, and coniine), or have any of several other biological activities (e.g., quinine).

Phenolics are a structurally diverse family of compounds defined as having one or more phenol groups; flavonoids, tannins, phenylpropanoids, etc., are all polyphenols. Medicinal phenolics include eugenol, a component of clove oil that is widely used as a treatment for toothache, coumarins (precursors for the synthesis of anticoagulants), and flavonoids and related compounds with diverse anti-inflammatory and antioxidant properties, such as the flavonoid epigallocatechin gallate from green tea, isoflavonoids like genistein from soybeans, tetrahydrocannabinol from Cannabis sativa, anthocyanins, and tannins.

Terpenoids are a very diverse and complex group of compounds made from five-carbon isoprene units. Monoterpenes, C_{10} compounds, include volatile compounds such as pinene and limonene, and are used therapeutically to aid respiration. Iridoids are also monoterpenes, often found as glycosides (conjugated to a sugar). Aucubin and valepotriates are iridoid glycosides with analgesic and anti-inflammatory properties found in Plantago lanceolata, Valerian officinalis, and other plants. Other medicinal active terpenoids include ginkgolides (from G. biloba), ginsenosides, taxol, and artemisinin.

Phylogenetic studies have revealed that some compounds that are present in widely divergent species may be the result of convergent or repeated evolution. Given that many of these compounds are derived from the highly conserved products of primary metabolism, such as isoprenes or amino acids, it not unreasonable to imagine that the ability to synthesize a compound has evolved more than once.

-Omics, Systems, Semisynthetic, and Other Methods for Metabolic Engineering

The study of medicinal plants benefits from many exciting new breakthroughs in “-omics” approaches (e.g., genomics, transcriptomics, proteomics, and metabolomics) as well as new semisynthetic methods for synthesis. Currently, the genomes, transcriptomes, proteomes, and metabolomes of many medicinal plant species are being investigated, with the goal of identifying the genes and proteins involved in the biosynthesis
of important compounds. Spatial, temporal, and environmental expression data are also being analyzed because many specialized metabolites are synthesized only in certain tissues or cells (e.g., trichomes) or only under certain conditions. In some cases, different enzymes in the biochemical pathway are expressed only in different cell types, which may be important for the regulation of production of the metabolite. The vast amounts of data being assembled require new methods for integration and analysis, and the development of new systems biology methods is being driven in part by the need to interpret these very diverse metabolic pathways.

Information about the biosynthetic pathway is invaluable for the design of methods to enhance the synthesis of the desired compounds, often referred to as metabolic engineering. In some cases, metabolic pathways can be introduced wholly into bacterial or yeast cells for large-scale fermentation production. As described earlier, genes from A. annua have been introduced into yeast for artemisinin production, and several groups have reported the successful production of various terpenoids, phenolics, and even some alkaloids in microbial cells. Alternatively, part of the pathyway can be introduced into yeast or bacterial cells along with a precursor derived from the plant, sometimes referred to as a semisynthetic method.

Although plant cells can be more difficult to manipulate than microbial cells, there are some advantages to their use for specialized metabolite production. For example, plant cells often already make the precursor molecules needed. Increasing the expression of a desired product can be as simple as increasing the expression level of a single enzyme, obviating the need to engineer the entire pathway. Plant cell cultures or hairy root cultures have been demonstrated to be effective systems for the production of several important metabolites (for some examples, see Leonard et al., 2009; Roberts, 2007; Dixon et al., 2012). Metabolic pathway can be manipulated in whole plants as well. Examples of these efforts include the production of reduced caffeine by RNA interference–mediated silencing of a biosynthetic enzyme, the morphine-free thebaine poppy described earlier, and sweeter-smelling lavender produced by elevated expression of an enzyme involved in terpenoid production.

**Case Study: Metabolic Reengineering of Madagascar Periwinkle**

Madagascar periwinkle produce a family of ~130 MIAs derived from a single precursor, strictosidine. Strictosidine is produced by the action of the enzyme strictosidine synthase, which conjugates the condensation of tryptamine (derived from the amino acid Trp) and secolagenin. Madagascar periwinkle can be propagated in cell culture or hairy root culture for large-scale metabolite production, and genes can be introduced stably by Agrobacterium rhizogenes–mediated transformation, making this plant amenable to metabolic reprogramming. In one study, a variant of the key enzyme strictosidine synthase with altered substrate specificity was identified through a mutagenesis and screening strategy in yeast. The gene encoding the variant enzyme was reintroduced into the plant, and hairy root cultures expressing it were shown to synthesize novel products. In a separate but related study, genes encoding enzymes that add halides (e.g., Cl and Br) to Trp were introduced into Madagascar periwinkle hairy root cultures, with the result that these plants synthesized halogenated tryptamine, and subsequently produced halogenated MIAs. Thus, the already diverse family of MIAs that periwinkles can produce has been made even more diverse, which one writer summarized as “gilding the periwinkle.”

**Recognizing the Value of Biodiversity**

Much of the world’s biodiversity can be found in tropical regions, but financial gains derived from this biodiversity often have not benefitted the people living in these regions. Increasingly, efforts are being made to encourage the preservation of biological diversity by ensuring that those who protect it benefit from the ultimate commercialization of products derived from it. The Convention on Biological Diversity, laid out in 1992, has been signed and ratified by most of the word’s countries. One of the key objectives of the Convention on Biological Diversity is “fair and equitable sharing of the benefits arising out of the utilization of genetic resources,” which was elaborated further on in the 2010 Nagoya protocol. It is hard to know how successful these efforts have been. Without the ratification of the United States, the leader in pharmaceutical research, the effect may be small. Nevertheless, a few companies have voluntarily signed agreements to ensure that their bioprospecting efforts benefit the host countries.

**HEALTH CARE FOR ALL**

The high cost of research and development means that pharmaceutical companies focus their efforts on diseases that affect the most affluent segment of the population, who can afford to buy the medicines they develop. The World Health Organization noted that <1% of the new drugs developed in the past 25 years target diseases of the poor, and 90% of research and development spending goes into diseases that affect the richest 10%. Bringing a drug from herbal remedy to patented pill is a hugely expensive undertaking, and private pharmaceutical companies cannot afford to pursue it unless they have a strong indication that they will recoup their expenses, through marketing it in the markets that can afford to buy it.

For the majority of the world’s population, prescription drugs are prohibitively expensive. Many rely primarily on herbal and traditional medicines. Implementing evidence-based practices can maximize the benefit of traditional medicines. In cases in which the active compound is known, the potency of traditional medicines can be batch analyzed and standardized. In cases where the active compound(s) cannot be identified, the standardization of cultivation conditions can contribute to a more uniform product. DNA barcoding techniques and mass spectroscopy are inexpensive methods that can confirm the identity of the plants in a medicine, and inexpensive analytical tests can screen for toxins and pesticides. As seen for artemisinin, scientific approaches can contribute to ensuring that the medicine is available in sufficient supplies to meet demand. The benefits of evidence-based medicine ought not to be restricted to the wealthy. The efforts of botanists, biochemists, and others to
enhance our knowledge of medicinal plants can lead to improved health for everyone.

**SUMMARY AND FUTURE PROSPECTS**

Plants are primary sources of medicines for most people in the world. Currently, more than half of the 150 most prescribed drugs have at least one component derived from plants. Bioprospecting to identify new plant-based medicines continues and the pharmacopoeia of traditional herbal medicines is being investigated as a source for novel therapies. In some cases, complex herbal medicines can provide therapeutic value greater than the sum of their parts.

Modern scientific methods can improve the efficacy and safety of medicinal plants. High-throughput methods and combinatorial chemistry can detect and create novel bioactive chemicals, and rapid and inexpensive assays to detect contaminants can be employed. The -omics approaches of the 21st century provide the tools needed to investigate the biosynthetic pathways of interesting phytochemicals in the plant and facilitate the metabolic engineering methods to increase the production of medicinal compounds. A particular emphasis is currently being placed on identifying natural products for the treatment of new or emerging diseases such as AIDS, and those associated with an aging, sedentary population, such as dementia and type 2 diabetes. These problems require multidisciplinary solutions and the contributions and skills of many, from botanist and chemist to health practitioner.

Medicinal plants, both known and yet to be discovered, are valued globally, not just locally. For many plants, climate change impacts are significant, as areas are cleared to make room for agriculture. The promise of new medicines and financial incentives may help to protect some wild lands are cleared to make room for agriculture. The promise of medicinal plants at risk of overharvesting. Species-rich ecosystems and the plants within them are disappearing from the planet as wild lands are cleared to make room for agriculture. The promise of new medicines and financial incentives may help to protect some areas, but conservation and environmental sustainability have to be valued globally, not just locally. For many plants, climate change is as great a threat as habitat destruction.

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