Medicinal Plants: Past, Present and Future (TTPB24) – Teaching Guide

Overview - Plants produce thousands of specialized metabolites, many of which have medicinal uses. More than half of the top 150 prescribed drugs in the US have at least one compound derived from plants, and about 80% of the world’s population depends on plants or plant extracts as a major source of healthcare. This lecture looks at the history of medicinal plants, herbal remedies in traditional and contemporary medicine, and ongoing efforts to identify novel medicinal compounds from plants. New approaches, such as metabolomics, metabolic engineering and systems and synthetic biology, are contributing towards the identification, characterization and production of plant-derived medicines.

Learning objectives
By the end of this lecture the student should be able to:
- Identify five cultures that have contributed to our historic knowledge of medicinal plants
- Evaluate the strengths and weaknesses of purified compounds versus plant extracts for medicinal uses
- Identify two or more reliable sources of information about any medicinal plant
- Identify five medicines derived from plants
- Summarize three different approaches used to identify plant candidates for drug-screening programs
- Compare the three classes of phytochemicals that represent most plant-derived medicines, and provide two examples of each
- Outline a currently-used metabolic engineering approach for drug synthesis
- Summarize the roles of plant science in providing access to medicines

Study / exam questions (understanding and comprehension)
- What evidences do we have that people have used plants as medicine before written history?
- Name three ancient cultures that created surviving written records of medicinal plant use. For each, list two medicinal plants used, and how the plants were used medicinally.
- What are four kinds of information you would expect to find in an herbal?
- Describe a situation in which you would use a purified plant-derived medicine, and one in which you would use a plant extract for medicinal purposes.
- Why is thebaine poppy considered safer than opium poppies?
- What is artemisinin, and what strategies are scientists using to increase its production?
- The world celebrated the total synthesis of taxol – why? And why is this method not currently used?
- What conditions is ginseng used for? How strong is the evidence to support this use? What factors complicate the documentation of ginseng’s efficacy?
What are two methods through which modern methods can help to make traditional medicines safer?

Based on current evidence, will you take Echinacea next time you feel a cold coming on? Why or why not?

What are three approaches being used to identify new sources of plant-based medicines?

Give an example each of a medicinally-active alkaloid, terpenoid and phenolic compound.

What is metabolic engineering? Describe three examples of plant metabolic engineering in use today.

Describe three ways that Western and traditional systems of medicine can work together.

Discussion questions (engagement and connections)

The Biodiversity Heritage Library (http://www.biodiversitylibrary.org/) has dozens of ancient Herbals digitized and on-line. Select an Herbal from the library and prepare a five-slide presentation about it. When was it published? Who wrote it, illustrated it, and published it? Can you find a familiar plant in it? How comfortable would you be self-medicating based only on this resource?

One of the most beautiful medicinal plant books is Köhler’s Medizinal-Pflanzen http://www.biodiversitylibrary.org/item/10836#page/3/mode/1up. Start with a picture you like in this book, research the plant.

Ask five friends or relatives about their use of plant-derived medicines, herbal medicines and supplements. How many different plants are used by your close circle? How do they obtain the information about the products they use? In your opinion, are they using these products appropriately?

Look up a medicinal plant in the WHO Monographs on Selected Medicinal Plants (http://apps.who.int/medicinedocs/en/d/Js2200e/). What kinds of information does this resource provide? Compare the information the WHO provides with the information you get from a Google search. How reliable is the information your Google search retrieves? What percentage of the top hits come from commercial sources? Would you feel comfortable using this product based on the information you get from the sources your Google search identified?

Investigate the mode of action of a medicinal plant. How have its effects been investigated? How strong is the evidence in support of its efficacy?

How would you investigate the mode of action of PHY906, the standardized formulation of Huang Qin Tang?

The ginseng case study raises the important point that practitioners of traditional medicine may value other attributes of the plants they use besides their chemical constituents. How important is it for scientists to consider these other values when introducing new methods for production of plant-derived medicines?
What is the current legal status of products containing ephedra? What evidence supports its banning? Do you think the US Food and Drug Administration made the right decision to ban it? Does everyone?

How are over-the-counter herbal supplements regulated? What agencies ensure that they are safe for consumers? Why do OTC supplements require less proof-of-efficacy than prescription drugs?

What advantages to “-omics” approaches bring to the study of medicinal plants? Give an example of an application.

Provide an example of how metabolic engineering is being used in the production of plant-based medicines.

Which countries have not ratified the Convention on Biological Diversity? What is the 2010 Nagoya protocol, and what are its goals? How do these international agreements affect the search for novel plant medicines?
Lecture synopsis
Introduction (1 - 4)
Plants produce thousands of specialized metabolites, many of which have medicinal uses. More than half of the top 150 prescribed drugs in the US have at least one compound derived from plants, and about 80% of the world’s population depends on plants or plant extracts as a major source of healthcare. This lecture looks at the history of medicinal plants, herbal remedies in traditional and contemporary medicine, and ongoing efforts to identify novel medicinal compounds from plants. New approaches, such as metabolomics, metabolic engineering and systems and synthetic biology, are contributing towards the identification, characterization and production of plant-derived medicines.

HISTORICAL USES OF PLANTS AS MEDICINES (5 – 13)
People have used plants as medicines since pre-history. Archeological studies suggest that humans used plants to promote health as long as 77,000 years ago. Written records extend back about 4000 years. Herbals (lists of medicinal plants and their uses) from Egypt, China, India, Persia, Greece, still survive. 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: Digitoxin and cardiac glycosides (12 - 13)
One of the earliest “modern” treatises on a medicinal plant was William Withering’s “An Account of the Foxglove, and Some of its Medicinal Uses” from 1785, which laid the foundations for modern medicinal phytochemistry.

FROM 1800 TO THE PRESENT: QUEST FOR ACTIVE COMPOUNDS (14 – 28)
The first medicinally active plant compound, morphine, was purified in 1805. This story and several others are recounted below. The question of which is better, a plant extract or a purified compound, is important and will be revisited; the simple answer is, there is no simple answer, and both are needed in global healthcare.

Case Study: Morphine and other opiates (16 – 18)
Morphine is one of several alkaloids found in the opium poppy, Papaver somniferum, one of the most powerful analgesics known, and was the first medicinally active plant compound to be purified. Although it can be synthesized, the methods are not very efficient and so most opiates are derived from plants. Morphine is also very addictive and subject to abuse. Thebaine poppies carry a mutation that allows them to accumulate thebaine but not morphine. These poppies are less subject to illicit abuse, but the thebaine can be used for the manufacture of oxycodone, and have become important resources for the production of opiates.

Case Study: Antimalarials – quinine and artemisinin (19 – 22)
Malaria is a devastating disease caused by a plasmodium protozoan carried by mosquitoes. Spanish priests observed the indigenous Indians using the powdered bark of the Cinchona tree as a remedy, and in 1820 the active alkaloid called quinine was purified. Cinchona bark is still used, because quinine cannot be synthesized effectively. However, quinine-resistance is widespread in the plasmodia. Currently, one of the most important therapies is artemisinin, from the plant Artemisia annua. Yields from the plants are low and variable, so projects are underway to increase its production in the plant, and also to produce it through semisynthetic methods.
**Case study: Taxol and camptothecin (23 – 26)**
Taxol and camptothecin are plant-derived compounds that interfere with cancer cell division. Taxol was identified from *Taxus brevifolia* in a random screening project, and purified in 1966. It is a large complex molecule; one of its early researchers described it as “the kind of structure that only a tree would make.” Initially, taxol was extracted from the bark stripped from the tree, but it was quickly realized that this harvesting was unsustainable. It can be made synthetically, but with difficulty. Currently, taxol is produced in a cell-culture system and semisynthetically, from an intermediate isolated from the leaves of *Taxus baccata*. Harvesting the branches and leaves doesn’t kill the trees. Camptothecin is isolated from *Camptotheca acuminata*, a plant used in traditional Chinese medicine. Due to side effects associated with camptothecin, two less-toxic derivatives are used therapeutically.

**Case study: Vinca alkaloids, fortuitous findings (27)**
Vinca alkaloids are effective therapies for cancers of white blood cells. They are derived from Madagascar periwinkle (*Catharanthus roseus*, formerly known as *Vinca rosea*). These plants are important sources of a large number of alkaloids, as described below.

**Not all conditions will be treatable by single compounds (29)**
Some chronic diseases are pleiotropic in nature and unlikely to be treated by a single compound. Examples of diseases or illnesses that won’t be cured by a single magic bullet are: AIDS, diabetes, metabolic syndrome, obesity, and Alzheimer’s. Many traditional remedies are composed of several plants. Perhaps some of their effects come from multiple active compounds acting together? There is some evidence to support this idea.

**THE BEST OF BOTH: PLANT-BASED MEDICINES, PRESENT AND FUTURE (30 – 49)**
Today’s healthcare challenges demand an approach to medicinal plants that embraces the traditional and the modern. Traditional remedies can be mined for novel single-compound drugs, but also can be studied and optimized to enhance their multifactorial benefits.

**Traditional Chinese and Traditional Indian Medicine (31 – 32)**
Traditional medicines in China and India have centuries of evidence to support them, and are widely used in the two most populated countries in the world. Their efficacies are only recently being recognized in the rest of the world, but it is clear that there is much to be learned from them.

**Drugs and therapies from traditional medicines (33 – 38)**
Traditional practices in China alone have identified more than 11,000 plant species with medicinal properties. Globally, about half of the traditional remedies examined have shown some promise in clinical trials.

**Case Study: Huang Qin Tang – from TCM to clinical trials (34 – 35)**
Huang Qin Tang is a nice example of a multifactorial therapy, because eliminating any one plant from the mixture eliminates its effectiveness. Because Huang Qin Tang’s benefits cannot be replicated by a single compound, it is being developed as a complex, multifactorial drug, with the recognition that the benefits it confers to an organism probably depend upon the concerted action of several active components acting synergistically.

**Case Study: Ginseng – panacea? (36 – 37)**
Globally, ginseng (*Panax* spp.) is the most widely used medicinal herb. World-wide sales of ginseng exceed $300 million. Ginseng is said to benefit the cardiovascular system and has been used for thousands of years to increase resistance to stress and boost vitality. 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.

Case Study: Ephedra (ma huang) – use and abuse (38)
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. 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.
Like morphine, ephedra is a potent beneficial drug that offers the potential for abuse. Its
over-the-counter sale as a weight loss aid has been banned in the US since 2004, although
it is still available in the US from TCM healers.

21st century science can be applied to ancient medicines (39 – 40)
21st century science is being applied to traditional medicines for drug discovery, and
standardize the formulations. Without significantly raising the prices of these medicines, it is
possible to increase their safety and effectiveness. Relatively low-cost methods can be used
to assay for contaminants thus making these medicines safer.

Over-the-counter herbal medicines (41 – 44)
Many herbal products are sold directly to the consumer as over-the-counter botanical dietary
supplements; in 2007 Americans spent nearly $15 billion on non-vitamin herbal dietary
supplements. 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.

Case Study: Echinacea purpurea, cure for the common cold? (43)
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.

Finding sources for new drugs (45 – 49)
It is thought that many of the more than 250,000 species of flowering plants harbour
medicinally important compounds, but the challenge is deciding which plants to pursue.
Some plant families are more likely than others to produce medicinally active compounds,
and the understanding of the phytochemistry of medicinal compounds can narrow the scope
of the search.

Classes of phytochemicals with medicinal properties (50 – 59)
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. . The
most prominent classes of medicinally active chemicals are alkaloids, phenolics and
terpenoids.

-Omics, systems, semi-synthetic methods and metabolic engineering (60 - 73)
The study of medicinal plants benefits from many exciting new breakthroughs in “-omics” approaches (e.g. genomics, transcriptomics, proteomics, metabolomics) as well as new semi-synthetic 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. 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. Examples of these efforts include the production of reduced caffeine coffee by RNAi-mediated silencing of 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 re-engineering of Madagascar periwinkle (72 – 73)**
Madagascar periwinkle (*Catharanthus roseus*) produce a family of ~130 monoterpenoid indole alkaloids (MIAs) derived from a single precursor, strictosidine. Through altering the substrate specificity of strictosidine synthase, and adding enzymes to modify strictosidine substrates, the range of MIAs can be expanded, providing new candidates for medicinal compounds.

**Recognizing the value of and protecting biodiversity (74 – 76)**
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.

**HEALTH CARE FOR ALL (77 – 79)**
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 (WHO) noted that less than 1% of the new drugs developed in the past 25 years target diseases of the poor, and 90% of R&D spending goes into diseases that affect the richest 10%. Globally, most people 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 analysed 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.

**SUMMARY AND FUTURE PROSPECTS (81 – 82)**
The study of medicinal plants requires many types of expertise, including Western medicine, traditional medicine, ethnobotany and phytochemistry. It’s an exciting and constantly evolving discipline with a very real applied outcome.
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<td><strong>Health care for all</strong>. Global access to health care is very unequal. Although medicinal plants can be sources for new pharmaceutical drugs, they are also one of the only sources of medicines for most of the world. Plant science has a role in improving health care for everyone, rich or poor.</td>
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| 80 - 81 | **Summary**. The study of medicinal plants requires many types of expertise, including Western medicine, traditional medicine, ethnobotany and phytochemistry. It’s an exciting and constantly evolving discipline with a very real applied outcome.