Medicines from Plants Trail

When faced with a predator, plants cannot get up and run away, so must protect themselves with an arsenal of chemicals. Because these chemicals tend to work by interfering with cellular activity in animals, many are useful to us as medicines.

Plants such as Willow or Ephedra have been known for thousands of years to be medically effective, while others such as the Madagascar Periwinkle have only recently been investigated. One of the reasons for conserving the world’s plant biodiversity is to help maintain the natural library of potentially useful drugs which can be derived from plants.

See an online version of this trail at www.botanic.cam.ac.uk/medicines
Medicines from Plants

Plants and plant extracts have been used as medicines for thousands of years. Indeed, the first Botanic Garden here in Cambridge was set up in 1762 as a ‘Physic Garden’, with plants arranged according to which area of the body they would treat. Some traditional remedies such as Willow and Foxglove have subsequently been shown to have a scientific basis to their use as treatments. However, many others were ineffective, particularly those identified using the theory of the ‘Doctrine of Signatures’, which ascribed therapeutic properties to plants based on their resemblance to body parts. Walnut kernels, for example, resemble brains, so walnuts were used to treat headaches and mental illness.

Plants, unlike animals, cannot get up and run away when faced with a predator, so must vigorously defend themselves against animals, bacteria, fungi and even other plants which want to eat them or invade their personal space. They do this with a bewildering array of chemicals, known as ‘secondary metabolites’: specialised compounds, each usually only made by one or a few species. Secondary metabolites generally fall into one of three categories: terpenoids, alkaloids and phenols.

Over 20,000 terpenoids have been described. They include steroids, resins, latexes and essential oils (which derive their name from the fact that they have an aroma characteristic of the ‘essence’ of the plant, rather than because they are essential for the plants’ survival). Some essential oils attract pollinators, while others prevent herbivory.
Alkaloids are often extremely poisonous to humans and other animals. Again, they deter herbivory – in the most extreme cases by killing the herbivore. They can also help plants dominate their patch of land – for example, Coffee (Coffea arabica) leaves contain caffeine, which they release into the soil when they fall and decay, and which inhibits the germination of other seedlings.

Phenols include tannins, which are common across the plant kingdom. Their astringent taste repels animals, and some interfere with the digestive processes of insects.

This amazing natural library of chemicals is vitally important to the process of discovering new medicines. Screening and development programmes are expensive, but effective drugs can bring enormous health benefits (and huge profits). Many of the plants providing precursors to these drugs are native to developing countries, and there is considerable international discussion about how the people living in those countries should benefit from the use of their natural resources. The Nagoya Protocol is a legal framework to ensure fair and equitable benefit sharing; as of December 2019 it has been ratified by 123 countries.
1 European Yew (*Taxus baccata*)

Yew trees contain **taxenes** and **taxanes**, two classes of terpenes which are highly poisonous to many animals and thus deter herbivory.

In the 1960s a natural products screening programme in the United States sampled bark from Pacific Yew (*Taxus brevifolia*) and found that at lower doses the active ingredient, taxol, reduced the growth rate of cancer cells. However, Pacific Yew bark only yields small quantities of taxol – it is estimated that three mature trees were required to treat one patient – and production required cutting down the trees.

Further investigations found that the European Yew has high levels of taxol throughout the plant. This led to the development of methods to extract taxol from European Yew clippings, which could be harvested without killing the tree. Prunings from Yew trees at the Botanic Garden have in the past contributed to making an anti-cancer drug, but it is now produced from cell cultures in laboratories.

2 Sea Grape (*Ephedra distachya*)

*Ephedra* is part of a curious group of plants called ‘gnetophytes’. These plants have hardly changed in the past 100 million years, and are thought to be relics of an ancient flora in which they were far more competitive and common.

The leaves of *Ephedra* are tiny and scale-like; gnetophyte leaves evolved independently from leaves in flowering plants. *Ephedra* produces the alkaloid **ephedrine**, which has been shown to interfere with insect thermoregulation and may also have effects on insect neurotransmitters. This may be the method by which the plant deters insect herbivores.

Ephedrine has been used for at least 2,000 years as a stimulant, as well as a treatment for asthma and bronchitis. Its chemical structure is very similar to that of compounds in the nervous system, and it mimics their effects. It is used to treat low blood pressure, but has side effects which include insomnia and a fast heart rate.
### Giant Reed (*Arundo donax*)

The Giant Reed can be truly giant, growing to over ten metres tall in good conditions. It reproduces using underground rhizomes which form thick networks extending up to a metre below ground.

The Giant Reed produces the alkaloid **gramine**, which is toxic to many animals, including several insects which might otherwise use the reed as a food plant. During efforts in the 1930s to investigate gramine as a pesticide, a researcher accidentally made it in a slightly different molecular configuration; upon testing a small quantity on his tongue, he found it had an anaesthetic effect. Further work led to the development of the anaesthetic Lidocaine.

Lidocaine is still used today, and is now synthesised artificially. However, the plant has numerous other uses. Because of its fast growth it is often used as fuel for electricity production, and its straight stems can be used in construction. It is also the plant most often used to make reeds for woodwind instruments.

### Foxglove (*Digitalis purpurea*)

Foxgloves produce **digoxin**, a chemical known as a ‘cardiac glycoside’, which acts to increase the heart’s output force and the amount of blood pumped on each beat. The entire plant (including the root and the seeds) is toxic. This toxicity is one of the plant’s natural defences against animals which would otherwise eat it.

Foxglove extract was first described as a treatment for heart conditions in the late 1700s. However, it was difficult to determine the quantity of the active ingredient in plant extracts, and there is only a small difference between the amount which is medically effective and the amount which will cause poisoning. Because of this, it is now used less frequently than other similar drugs.
1. *Taxus baccata*
2. *Ephedra distachya*
3. *Arundo donax*
4. *Digitalis purpurea* ★
5. *Cinchona officinalis*
6. *Catharanthus roseus*
7. *Hypericum perforatum* ★
8. *Echinacea purpurea* ★
9. *Ginkgo biloba*
10. *Papaver somniferum* ★
11. *Dioscorea nipponica* ★
12. *Atropa belladonna* ★
13. *Artemisia annua* ★
14. *Salix alba*

Plants marked ★ are annuals or biennials and will not be visible all year round.
Fever Tree (Cinchona officinalis)
The bark of the Fever Tree contains quinine, an alkaloid which is produced as a defence against insects. Caterpillars which would otherwise eat the leaves greatly dislike the taste of quinine, and will leave the tree untouched.

Cinchona is native to South America, and is named for the (probably false) story that its bark cured the wife of the Count of Chinchón. It was instrumental in allowing Europeans to combat malaria and colonise Africa, and was used to produce quinine until more efficient drugs were synthesised in the 1940s. Cinchona bark is still used to produce quinine for tonic water, though making this at home is not recommended – careful measurement is needed, with overdose leading to ‘cinchonism’: symptoms include ringing of the ears, headache, blurred vision, dizziness, nausea, confusion and diarrhoea.

Madagascar Periwinkle (Catharanthus roseus)
Alkaloids tend to taste bitter, so alkaloid-filled leaves are avoided by grazing herbivores. Many also interfere with processes in animal cells, which makes them poisonous. The Madagascar Periwinkle produces over 120 such alkaloids, including vincristine and vinblastine.

The Madagascar Periwinkle has been used for centuries as a folk remedy for diabetes, and this led to studies investigating its use as a medicine. These studies showed little effectiveness in treating diabetes, but great potential in stopping the division of rapidly dividing cells, leading to its use in anti-cancer therapies, particularly for treating childhood leukaemia. The active ingredient vincristine is produced at a yield of only three grams per tonne of plant material and, for a while, farms were devoted to the growth of the plant. However, vincristine can now be synthesised in a laboratory.
7 **St John’s Wort**  
(*Hypericum perforatum*)

St John’s Wort, probably so called because it flowers around the date of the Feast of St John (24 June), produces **hyperforin** and **hypericin**. However, it is not clear what use they are to the plant. It is probable that they are involved in defence, as their levels increase in response to both herbivory and stress.

St John’s Wort has a long history of being used in folk medicines. It was often used in ‘theriac’, a concoction of dozens of ingredients fermented and matured together, which would supposedly cure assorted ailments. Today, it has become the subject of intensive research, as it has been shown to have antidepressive, antitumour and antiviral activity. St John’s Wort has an unusually high level of interaction with other drugs, and interferes with the effects of various anticoagulants, immunosuppressants and contraceptives.

8 **Purple Coneflower**  
(*Echinacea purpurea*)

The Purple Coneflower is native to eastern and central North America, where it grows on prairie grassland. It has been used for centuries by Native Americans to treat various ailments, including coughs, toothache, sore throats and tonsillitis.

*Echinacea* has become popular in Western herbal medicine in the last 100 years. However, no active ingredients have been identified within *Echinacea*, and its effectiveness has not been proven. Many studies have aimed to investigate whether taking *Echinacea* preparations after the onset of symptoms of a cold can shorten the cold’s duration. However, a 2014 review of these studies concluded that, although it seems possible that some *Echinacea* products are more effective than a placebo (‘sugar pill’) for treating colds, the overall evidence for clinically relevant treatment effects is weak. Additionally, trials investigating whether *Echinacea* can prevent colds have not shown any statistically significant effect.

1 Karsch-Völk et al, Cochrane Systematic Review, https://doi.org/10.1002/14651858.CD000530.pub3
Ginkgo biloba

Ginkgo trees were abundant in prehistoric times, but mostly died out as the Earth cooled during the Pliocene epoch, up to around 2.5 million years ago. Some trees survived in China, with many in modern times being cared for by monks in mountain monasteries, and from around 1100 AD it quickly spread throughout Asia, reaching Europe in the 1700s.

Ginkgo extract has been shown to raise blood levels of nitric oxide, which increases the diameter of blood vessels. Because of this, many people take Ginkgo supplements with the aim of improving memory or protecting against the effects of dementia. However, the NHS Knowledge Service\(^1\) says that ‘Ginkgo biloba supplements may be of limited use in preventing dementia in generally healthy elderly people’.

\(^{1}\) https://www.nhs.uk/news/neurology/ginkgo-wont-stop-dementia/

Opium Poppy (Papaver somniferum)

The Opium Poppy (also known as the Breadseed Poppy) is widely grown as an agricultural crop. As well as providing seeds for food, its latex contains alkaloids which have painkilling properties, including morphine, codeine, and many others. The legal harvest of poppy seeds is around 80,000 tonnes per year, with around two thirds of production taking place in the Czech Republic, Turkey, Spain, Hungary and France. Eating poppy-seed bread before drug tests can produce false positive results, but further analysis can distinguish genuine opiate use.

Analysis of Poppy DNA indicates that Poppies became able to make morphine and other painkillers at least eight million years ago. Prior to this, Poppies could only make noscapine, another related chemical with only mild painkilling properties. It is likely that the chemicals which the plant now makes deter herbivores from eating the plant.
11 **Yam (Dioscorea nipponica)**

There are around 600 *Dioscorea* species, of which at least eight produce edible tubers known as Yams. Some wild Yams, including *D. nipponica*, produce saponins, which reduce the feeding rate and growth of animals which eat them, and thus act as a deterrent against herbivory. Yams are different to the Sweet Potato, *Ipomoea batatas*, which is related to Morning Glory.

One of these saponins bears a striking similarity to progesterone, a female sex hormone in mammals. Progesterone was marketed from the 1930s as a drug to prevent miscarriage and alleviate menstrual problems, but making it synthetically was complicated and expensive. Careful botanical research and screening highlighted Yam extract as a good starting material for a simple five-step synthesis process, which paved the way for larger-scale production of progesterone. Very similar chemicals are used today in contraceptive pills.

12 **Deadly Nightshade (Atropa belladonna)**

One of the most poisonous plants in the UK, Deadly Nightshade is a member of the potato family (Solanaceae), along with tomatoes and aubergines. All parts of the plant are toxic, especially the berries, which contain a mixture of alkaloids which affect the nervous system. One of them, atropine, causes sweating, vomiting, breathing difficulties, confusion, hallucinations and death.

In very small quantities, though, atropine has medical applications. Atropine eye drops dilate the pupils, which is useful in opticians’ analyses. (Wide pupils were also considered attractive in the 15th and 16th centuries, and Nightshade drops were widely used for this reason – indeed, Linnaeus named the species *belladonna*, Italian for ‘beautiful lady’.) Injections of atropine are used to treat a very slow heart rate and other cardiac problems. Atropine also inhibits the production of saliva, and is sometimes used for this during surgery.
Sweet Wormwood \textit{(Artemisia annua)}

Humans make use of several \textit{Artemisia} species for culinary purposes: Tarragon \textit{(Artemisia dracunculus)} is used to flavour sauces, while Common Wormwood \textit{(Artemisia absinthium)} gives the characteristic taste to absinthe. Sweet Wormwood has feathery leaves and a profusion of yellow flowers, and has been used for millennia in traditional Chinese medicine to treat malaria. The active ingredient, \textit{artemisinin}, is part of the group of aromatic chemicals known as terpenoids, widely found in flowering plants. It acts to inhibit growth of other plants, stopping them using nutrients which the Wormwood could itself use.

\textit{Artemisinin} was isolated as part of a Chinese research program in the 1970s, set up to screen thousands of chemicals to find a treatment for malaria. (It was discovered by Chinese scientist Tu Youyou; she received the Nobel Prize in 2015.) It acts by interfering with the cellular functions of the malaria parasite, though in recent years resistant strains of malaria have developed, and \textit{artemisinin} is now only used in conjunction with other antimalarial drugs.

White Willow \textit{(Salix alba)}

The bark of Willow trees is rich in \textit{salicylic acid}, a phenolic chemical which benefits the plant in multiple ways. It has antibiotic and antifungal properties, so protects against infection, and has been shown to prevent the growth of plants close by, a phenomenon known as allelopathy. In addition, \textit{salicylic acid} is used by plants to regulate the process of flowering.

Willow trees have been known for millennia to have medicinal properties: its use in pain relief is mentioned in the Ebers Papyrus, an ancient Egyptian text dating back to around 1500 BC. \textit{Salicylic acid} was identified as the active component of Willow bark in the 19th century, and in 1853 French chemist Charles Gerhardt synthesised \textit{acetylsalicylic acid} for the first time. This chemical, marketed by Bayer under the trade name ‘Aspirin’, is now one of the most commonly used drugs in the world.