PharmacognosyIII

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Phytotherapy and Pharmacognosy

Pharmacognosy is the science of biogenic or nature-derived pharmaceuticals and poisons. It deals with all medicinal plants, including those yielding complex mixtures, which are used in the form of:

1. Crude herbs (comminuted herbal substance).
2. Extracts (phytotherapy).
3. Pure compounds such as morphine.
4. Foods having additional health benefits and preventive effects (nutraceuticals).

Herbal medicines are often considered to be part of complementary and alternative medicine (CAM), and the use of herbal medicinal products (HMPs) and of CAM has increased across the developed world.

Phytotherapy is the use of plants, either in whole food form or in the form of standardized extracts and supplements, for healing purposes. Its roots trace all the way back to the beginnings of time and still stand strong in much of the world today.

Why pharmacist should take a course in phytotherapy?

The teaching of pharmacognosy has become even more relevant than previously over the last decade, as a result of the increasing use of herbal remedies (phytomedicines)by the public over the world. When entering a pharmacy today the section of herbs supplement is large enough to occupied the large increased in the number and type of these supplements, so, we need a pharmacist with rich knowledge base of traditional use and ethnobotany, combined with modern scientific, chemical, toxicological, pharmacological and clinical research- a position which some might consider under the term rational phytotherapy.

Types of drugs derived from plants:

- **Herbal drugs derived from specific parts of a medicinal plant:**

Botanical drugs which form the basis for herbal remedies or phytomedicines include, for example:

1. The herb of St John's wort (*Hypericum perforatum*), used in the treatment of mild to moderate depression.
2. The leaves of Ginkgo biloba, used for cognitive deficiencies (often in the elderly), including impairment of memory and affective symptoms such as anxiety.
3. The flower heads of chamomile (*Chamomilla recutita*), used for mild gastrointestinal complaints and as an anti-inflammatory agent.
4. The leaves and pods of senna (*Cassia spp.*), used for constipation.

▪ **Natural products or compounds isolated from nature:**

These are pure chemical entities, often used in the form of licensed medicines:

1. Morphine, from opium poppy (*Papaver somniferum*), used as an analgesic.
2. Digoxin and other digitalis glycosides, from foxglove (*Digitalis spp.*), used to treat heart failure.
3. Taxol, from the Pacific yew (*Taxus brevifolia*), used as an anticancer treatment.
4. Quinine, from Cinchona bark (*Cinchona spp.*), used in the treatment of malaria.

▪ **Nutraceuticals or 'functional foods':**

Many foods are known to have beneficial effects on health. Examples include:

1. Garlic, ginger, turmeric and many other herbs and spices.
2. Anthocyanin- or flavonoid-containing plants such as bilberries, cocoa and red wine.
3. Carotenoid-containing plants such as tomatoes, carrots and many other vegetables.

Important natural products and phytomedicines used in pharmacy and medicine

This part is devoted to plant-derived medicines arranged in therapeutic categories in a manner analogous to that of the British National Formulary (BNF), although the classification differs in some ways. For example, there is no section on immunological products and vaccines, or anesthesia, since plant medicines are not used for these purposes.

Both pure compounds and herbal medicines are included; isolated natural products are used mainly in conventional medicine and are treated in the same way as any other drug, and examples given include: morphine, codeine, digoxin, pilocarpine, atropine and colchicine. Many plant drugs are used as extracts, either in crude form, or modified and standardized in some way, and these are normally described as herbal products or phytomedicines. Many of these herbal drugs have now been incorporated into the European Pharmacopoeia (Eur. Ph.).

The gastrointestinal and biliary system:

Gastrointestinal (GI) and liver disorders account for minor, everyday complaints as well as major health problems. Dietary measures can improve symptoms that are caused, for example, by poor eating habits, but, if these are not successful, phytomedicines are also useful. In fact, natural products are still the most commonly used remedies in cases of constipation, diarrhoea and flatulence. Plants and their derivatives also offer useful treatment alternatives for other problems such as irritable bowel syndrome, motion sickness and dyspepsia. In the case of some liver diseases, phytotherapy provides the only effective remedies currently available.

Diarrhoea

Diarrhoea of sudden onset and short duration is very common, especially in children. It normally requires no detailed investigation or treatment, as long as the loss of electrolytes is kept under control. However, chronic serious cases of diarrhoea caused by more virulent pathogens are still a major health threat to the population of poor tropical and subtropical areas.

The World Health Organization (WHO) has estimated that approximately 5 million deaths are due to diarrhoea annually (2.5 million in children under 5 years).

The first line treatment is oral rehydration therapy using sugar-salt solutions, often with added starch, and the use of gruel rich in polysaccharides (e.g. rice or barley ‘water’) is an effective measure.

The polysaccharides of rice (*Oryza sativa*) grains are hydrolyzed in the GI tract; the resulting sugars are absorbed because the co-transport of sugar and Na from the GI lumen into the cells and mucosa is unaffected. Rice suspensions thus actively shift the balance of Na towards the mucosal side, enhance the absorption of water and provide the body with energy, and the efficacy of rice starch has been demonstrated in several clinical studies.

The treatment of diarrhoea in adults, particularly for travellers, may also include opiates or their derivatives, to reduce gastrointestinal motility. Many classical anti-diarrhoeal preparations contain opium extracts, or the isolated alkaloids morphine and codeine (e.g. kaolin and morphine mixture, codeine phosphate tablets), although these are controlled by law in some countries. Opioid derivatives such as loperamide, which have limited systemic absorption and, therefore, fewer central nervous system side effects, have superseded these agents to some extent but the natural substances are still used and are highly effective. Dietary fibre, including that found in bulk-forming laxatives (qv) can also be used to treat diarrhoea; in this case, the fiber is taken with only a small amount of water. There are other plant drugs which act in varying ways.

Tannin-containing drugs

Tannins are astringent, polymeric polyphenols, and are found widely in plant drugs. The most important herbs used in the treatment of diarrhoea include *Sangisorba officinalis* L., Black catechu, Oak bark, and even tea and coffee; however, many others are used in different countries. Tannin-containing drugs are generally safe, but care should be taken with concurrent administration of other drugs since tannins are not compatible with alkalis or alkaloids, and form complexes with proteins and amino acids.

Constipation

Constipation is often due to an inappropriate diet and lack of physical activity, for example, while being confined to bed during illness, or the result of taking other medication (especially opioids). It is characterized by reduced and difficult bowel movements, and is said to be present when the frequency of bowel movements is less than once in 2 or 3 days. Although the causes are not usually serious in nature, continuous irregularity in bowel movements should be investigated in case there is a risk of malignant disease. Constipation is often associated with other forms of discomfort such as abdominal cramps, dyspepsia, bloating and flatulence. Alternating diarrhoea and constipation are a symptom of irritable bowel syndrome.

Various types of plant-derived laxative are used:

- Stimulant laxatives (purgatives), which act directly on the mucosa of the GI tract.
- Bulk-forming laxatives, which act mainly via physicochemical effects within the bowel lumen.
- Osmotic laxatives, which act by drawing water into the gut and thus softening the stool. Osmotic laxatives may be mineral in origin, for example magnesium salts, or derived from natural products such as milk sugars.

Patients generally require rapid relief from constipation, and the immediate effect of stimulant and saline purgatives is very well known. Although there is no problem using them occasionally, or on a short-term basis (less than 2 weeks), or prior to medical intervention such as X-ray (Roentgen) diagnostics, long-term use should be discouraged. The exception is for patients taking opioids for pain management, who may need to use stimulant laxatives routinely.

The most important adverse effect of the long-term use of the stimulant laxatives and saline purgatives is electrolyte loss. Hypokalaemia, pathologically reduced levels of potassium (K), may even worsen constipation and cause damage to the renal tubules. The risk of hypokalaemia is increased with administration of some diuretics and hypokalaemia exacerbates the toxicity of the cardiac glycosides (e.g. digoxin), which are often prescribed for elderly patients.

Hyperaldosteronism, an excess of aldosterone production, which leads to sodium (Na) retention, and again to potassium loss and hypertension, is also a risk. In general, the use of bulk-forming or osmotic laxatives is preferred, unless there are pressing reasons for using a stimulant laxative.

Bulk-forming laxatives

These are bulking agents with a high percentage of fiber and are often rich in polysaccharides, which swell in the GI tract. They influence the composition of food material in the GI tract, especially via the colonic bacteria, which are thus provided with nutrients for proliferation. This in turn influences the composition of the GI flora and the metabolism of the food in the tract (including an increase in gas, or flatus). Bulkforming laxatives are generally not digested or absorbed in the GI tract, but pass through it largely unchanged.

Wheat bran, *Triticum aestivum* L.

Bran is less useful as a laxative (except when taken as a natural part of the diet, e.g. in breakfast cereal), since it contains phytic acid, which in high concentrations can complex with and, therefore, reduce the bioavailability of vitamins and minerals taken at the same time. However, in some patients, wheat bran (the husk from the grains of *Triticum aestivum*) is more effective than other swelling agents, and preparations containing it are available for prescribing. These are taken in water.

Osmotic laxatives

Osmotic laxatives, such as lactulose or lactose, which are dimeric sugars derived from milk, are a useful and widely used approach to the treatment of long-term constipation. Lactose is split in the GI tract into glucose and galactose, and galactose is not generally resorbed well. Consequently, the bacteria of the colon metabolize this sugar. The resulting acids, including lactic acid and acetic acid, have an osmotic effect, and the bacteria in the colon multiply more rapidly. This results in softening and increasing in the amount of feces, with a subsequent increase in GI peristalsis.

Stimulant laxatives

Stimulant laxatives are derived from a variety of unrelated plant species, which only have in common the fact that they contain similar chemical constituents. These are anthraquinones such as emodin and aloe-emodin, and related anthrones and anthranols. Anthraquinones are commonly found as glycosides in the living plant.

Several groups are distinguished, based on the degree of oxidation of the nucleus and whether one or two units make up the core of the molecule. Studies using

dianthrone glycosides such as sennosides A and B suggest that most of these compounds pass through the upper GI tract without any change; however, they are subsequently metabolized to rhein anthrone in the colon and caecum by the natural flora (mainly bacteria) of the GI tract.
Anthranoid drugs act directly on the intestinal mucosa, influencing several pharmacological targets, and the laxative effect is due to increased peristalsis of the colon, reducing transit time and, consequently, the re-absorption of water from the colon. Additionally, the stimulation of active chloride secretion results in an inversion of normal physiological conditions and a subsequent increased excretion of water.

Inflammatory gi conditions:

Gastritis and ulcers:

Inflammation of the gastric mucosa, or gastritis, is an acute inflammatory infiltration of the superficial gastric mucosa, predominantly by neutrophils. It is generally treated with antacids (magnesium and aluminium salts) and emollients (alginate, mucilages), but other phytomedicines are still occasionally used (e.g. chamomile and liquorice). These agents, especially liquorice, were used to treat gastritis and ulceration until superseded by the synthetic H2-receptor-blocking agents (cimetidine, ranitidine, etc. and proton pump inhibitors (omeprazole, lansoprazole).
Now that infection with Helicobacter pylori is known to be a causal factor in ulceration, antibiotic therapy is the first-line treatment of choice. Most pharmaceuticals for mild gastric inflammation contain a mixture of an emollient, to line and soothe the mucosa (e.g. an agar suspension), an antacid and possibly a carminative such as peppermint or anise oil.

Alginate

Alginate or alginic acid is an anionic polysaccharide distributed widely in the cell walls of brown algae including Laminaria, and *Ascophyllum nodosum*. Raw or dried sea weed is washed with acid to remove cross-linking ions that cause the alginate to be insoluble. It is then dissolved in alkali, typically sodium hydroxide, to produce a viscous solution of alginate.
The solution is filtered to remove the cell wall debris and leave a clear alginate solution. Alginate binds with water to form a viscous gum and acts as a protective coating over the walls of the stomach and oesophagus.

Dyspepsia and biliousness

Dyspepsia and ‘biliousness’ are closely associated with eating habits and are very common complaints.

Patients describe the symptoms as nausea, pain and cramps, distension, heartburn and the 'inability to digest food', often experienced after rich meals. The condition is treated either with cholagogues or with bitter stimulants. A cholagogue is an agent that stimulates bile production in the liver, or promotes emptying of the gallbladder and bile ducts. Although clinical evidence is largely lacking, but they should not be used in cases of bile duct obstruction or cholestatic jaundice. Phytomedicines used as bitter stimulants, such as Gentian and Wormwood, act directly on the mucosa of the upper part of the GI tract and especially of the bitter receptors on the tongue, stimulating the secretion of saliva and gastric juices and influencing the secretion of gastrin. An aperitif containing 'bitters', taken about half an hour before eating, stimulates gastric and biliary secretion; however, it is not known whether these effects are restricted to patients with a reduced secretory reflex, or whether an increase also occurs in healthy people.

Artichoke:

Cynara scolymus L. this well-known member of the Asteraceae yields the globe artichoke, which is the large flower head of the plant. The medicinal part is the leaf, which is used to treat indigestion and dyspepsia, and to lower cholesterol levels.

Constituents: The leaf contains the bitter sesquiterpene lactone cynaropicrin, several flavonoids and derivatives of caffeoylquinic acid, including cynarin.

Therapeutic uses and available evidence:

Antihepatotoxic effects, cholagogue activity and a reduction of cholesterol and triglyceride levels have been reported, and are now known to be due to inhibition of cholesterol biosynthesis. Clinical studies have shown that artichoke leaf extract can improve parameters such as fat intolerance, bloating, flatulence, constipation, abdominal pain and vomiting, and increase bile flow, at a daily mean dose of 1500 mg. Artichoke extract is also useful in irritable bowel syndrome.

Nausea and vomiting

'Travel sickness' or 'motion sickness' is particularly common in children and is caused by the repetitive stimulation of the labyrinth of the ear. It is most common when travelling by sea, but also happens in cars, airplanes and when horse-riding. Vomiting, nausea, dizziness, sweating and vertigo may occur. Prophylactic treatment includes the use of antihistamines (mainly phenothiazines) and cinnarizine, and natural compounds such as the antimuscarinic alkaloid hyoscine, found the Solanaceae family. Morning sickness of pregnancy is also common but few (if any) synthetic drugs are licensed for such a use because of fears of toxicity to the unborn child. Ginger can be a useful antiemetic for this condition, as well as for travel sickness.

Hyoscine (scopolamine)

The alkaloid hyoscine is usually isolated from Datura or *Scopolia spp*. It is a popular remedy for motion sickness, given at an oral dose of 400 mg or, more recently, as a transdermal patch containing 2 mg of the alkaloid, which is delivered through the skin over 24 h.
Hyoscine is also used as a premedication, usually in combination with an opiate, to relax the patient and dry up bronchial secretions prior to administration of halothane anesthetics.

Irritable bowel syndrome, bloating and flatulence

Irritable bowel syndrome (IBS) is characterized by pain in the left iliac fossa, diarrhoea and/or constipation. Symptoms are usually relieved to some extent by defecation or the passage of wind, and can be treated successfully by the use of bulk laxatives with or without antispasmodic (carminative) drugs.
Natural remedies include peppermint oil and other essential oil carminatives, and some of the tropane alkaloids. Atropine has been replaced by hyoscine, in the form of the Nbutyl bromide, which, as a quaternary ion, is poorly absorbed from the GI tract and, therefore, has fewer antimuscarinic side effects. Artichoke extract is also useful in irritable bowel syndrome. Carminatives are usually taken with food; they produce a warm sensation when ingested and promote postprandial elimination of gas. Plant-based carminatives are usually rich in essential oil, such as the fruits (‘seeds’) of species of the Apiaceae (celery family) and some members of the Lamiaceae (mint family). Many condiments such as cumin and caraway have carminative effects and are used as spices because of their taste and their pharmacological effect. It seems likely that not only is the essential oil responsible for the effect, but the other components (e.g. the flavonoids) also contribute.

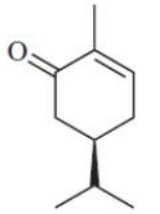
Umbelliferous fruits

The fruits (not ‘seeds’ as they are commonly known) of several members of the celery family (Apiaceae or Umbelliferae) are used as carminatives as they are rich in essential oil and have an antispasmodic effect. Many of these species are also important as spices.

Caraway, *Carum carvi* L. (carvi fructus)

Caraway is the fruit of a mountain herb common in many regions of Europe and Asia.
Constituents: The essential oil (3–7%) consists mainly of (þ)- Carvone and (þ)-limonene, accounting for 45–65% and 30–40%, respectively, of the total oil. Carvone is considered to be the main component responsible for the spasmolytic action.

Therapeutic uses and available evidence: The fruits are used in cases of dyspepsia, minor GI cramps and flatulence. Little modern clinical evidence is available but caraway has long been used in products such as infant gripe water. The aqueous extract, and even more so the essential oil, acts as a spasmolytic and has antimicrobial activity.



(–)-Carvone

Liver disease

Liver damage, cirrhosis and poisoning should only be treated under medical supervision. There is a useful phytomedicine derived from herbs are widely used for liver disease, although with less clinical evidence in support. Herbs used for 'biliousness' are also used in mild liver disease.

Milk thistle, *Silybum marianum* (silybi mariani fructus)

The seeds of the milk thistle, *Silybum marianum* (L.) Gaertn. (Asteraceae), yield a flavolignan fraction known as silymarin.

Constituents: The active constituents of the extract silymarin are flavolignans, mainly silybin (¼silibinin), with isosilybin, dihydrosilybin, silydianin, silychristin and others.

Therapeutic uses and available evidence:

In many parts of Europe, silymarin is used extensively for liver disease and jaundice. It has been shown to exert an antihepatotoxic effect in animals against a variety of poisons, particularly those of the death cap mushroom Amanita phalloides. This fungus contains some of the most potent liver toxins known (the amatoxins and the phallotoxins), both of which cause fatal haemorrhagic necrosis of the liver.

Silymarin has been used at doses of 420 mg daily to treat patients with chronic hepatitis and cirrhosis; it is also partially active against hepatitis B virus, is hypolipidaemic and lowers fat deposits in the liver in animals. This extract can be used not only for serious liver disease, but also for general biliousness and other digestive disorders.

Turmeric, *Curcuma domestica* val. (curcumae domesticae rhizoma)

Turmeric is used in Asian medicine to treat liver disorders and well as inflammatory conditions. For details regarding the drug and its constituents. Related species include Javanese turmeric which is mostly used for dyspepsia and other gastrointestinal problems. Turmeric and curcuminoids are hepatoprotective against liver damage induced by various toxins, including paracetamol (acetaminophen), aflatoxin and cyclophosphamide; they protect against stomach ulcers in rats, and have antispasmodic effects.
Turmeric is also hypoglycaemic in animals, and hypocholesterolemic effects have been observed both in animal and human clinical studies, although clinical studies for liver disease are lacking. In addition, turmeric is antibacterial and antiprotozoal in vitro. Turmeric is well tolerated but the bioavailability is poor and daily doses of at least 2g are normally used.