

2nd edition

# The **Constituents** of **Medicinal Plants**

An introduction to the chemistry and  
therapeutics of herbal medicine



ANDREW PENGELLY

# The Constituents of Medicinal Plants

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Andrew Pengelly has lectured widely in colleges and universities throughout Australia, New Zealand and the United States. He is a founding editor of the *Australian Journal of Medical Herbalism* and a fellow of the National Herbalists Association of Australia, having served many years as executive director and vice president.

He is now a full-time lecturer in Herbal Therapies at the School of Applied Sciences at the University of Newcastle, where he also conducts research into Australian medicinal plants. He lives in Cessnock with his wife, Pauline Pettitt.

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An introduction to the  
chemistry and therapeutics  
of herbal medicine



ANDREW PENGELLY

with a Foreword by Kerry Bone

  
ALLEN & UNWIN

This book is dedicated to the  
lavender lady—my wife, Pauline Pettitt.

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## FOREWORD



As Andrew Pengelly observes in his introduction to this text, the field of medicine has long been divided between the so-called ‘rationalist’ and ‘vitalistic’ approaches. The same dichotomy exists today among herbal practitioners. But as herbal medicine moves increasingly into mainstream acceptance, it is more and more being placed under the rationalist microscope. And not without good reason: our recent understanding of the therapeutic uses of plants has revealed a number of significant issues which have the potential to impact on the quality, safety and efficacy of herbal products. It is therefore essential that all practitioners and students of herbal medicine, whatever their philosophical leanings, have the tools to understand and effectively manage these issues as they pertain to the wellbeing of their current or future patients. An effective understanding of modern herbal practice fundamentally begins with a sound knowledge of the phytochemistry and related therapeutics of medicinal plants.

Given this, Andrew Pengelly’s much revised second edition of *The Constituents of Medicinal Plants* is a welcome arrival. In this text he comprehensively covers the major phytochemical classes found in plants and their implications for human therapy. Key features are the many chemical structures and the wide-ranging discussion of their pharmacological activities.

A major advantage is that this book assumes only a basic understanding of chemistry, which makes it an ideal primer for students and practitioners alike. In addition, it provides a simple yet comprehensive introduction to the field which does not fall into the trap of being overly reductionist or technical. Rather, it adapts the technical information to existing knowledge, in the process helping to better define the traditional understanding that underlies the practice of herbal medicine. As such, this book provides both a unique education and a rationale for practitioners to broaden the range of clinical

indications for many existing medicines. Useful technical data for better understanding potential adverse reactions and interactions with pharmaceutical drugs is another important learning outcome.

The author is a well known and respected authority on medicinal herbs who through his teaching and journal articles has helped to pioneer the scientific understanding of herbal practice in Australia.

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## PREFACE



This is a book about plant chemistry written by a herbalist with no claims of being a chemist. Having a driving ambition to understand the nature of herbal medicines—in particular what makes them work—I delved head first into the previously alien world of atoms, molecules and bonds. Having learned enough to be engaged to teach the topic to budding herbalists and naturopaths, I set about formalising the teaching notes—the result is the original (1996) edition of this text.

To say that I was surprised to see the book turn into a standard reference overnight would be an understatement. After all, there are other, more scholarly texts in the marketplace, and others formally trained as chemists who are eminently more qualified to write on the subject. Nevertheless the book has found a place in the libraries of many renowned herbal authorities and teachers, as well as being used by students in colleges and universities around Australia, New Zealand, England and the United States. While many students seem to regard it as the ‘medicine they have to have’, other students (and teachers) have been attracted to the book by its very simplicity. Perhaps, having had to learn the hard way from the ‘bottom up’ myself, I have been able to present information that is quite technical and complex in a manner that is relatively digestible.

*The Constituents of Medicinal Plants* was never designed as a pure exposition of chemical structures—I leave that to the analytical chemists. My belief is that the structures give us an important insight into the way herbal medicines act, and are a way of rationalising many of the traditional applications that have been passed down over the centuries. The structures also give us valuable information into the potential for adverse reactions and interactions with pharmaceutical drugs.

In this new edition I have not departed from the original

philosophy—to describe the structures as a means of explaining a herb's activity in a way that benefits the practice of medical herbalism. I have, however, become rather fascinated by the molecular structures and I hope I can pass some of that enthusiasm on to the reader. For those who have not studied chemistry or biochemistry previously I have extended the introductory chapter in an endeavour to explain how organic compounds are named and represented in structural drawings, but this cannot substitute for an introductory text in organic chemistry.

Two new chapters have been added—on fixed oils and triterpenoids—while the original phenol chapter has been divided into two. The new polyphenol chapter gives greater recognition to the plant tannins, as well as including a more comprehensive review of the flavonoids—previously grouped with glycosides.

Completion of the second edition would not have been possible without the encouragement and assistance of many individuals. Australia is fortunate to have herbalists of such high esteem as Denis and Ruth Stewart, Nick Burgess, Kerry Bone, Anne Cowper, David MacLeod, Robyn Kirby and Rob Santich. All have inspired and encouraged me throughout my career and I give them a big 'thank you'. I am also indebted to Dr Doug Stuart, my supervisor and mentor at the University of Newcastle. I am most grateful to my wife Pauline Pettitt for her constant support and love. Last but not least I am indebted to all the readers, students and herbalists who, over the years, have given me such positive feedback that I was compelled to write this second edition.



# INTRODUCTION TO PHYTOCHEMISTRY



## Introduction

The field of medicine has long been divided between so-called ‘rationalist’ and ‘vitalistic’ principles. While the rationalist/scientific model has held sway (at least in the Westernised nations) for the last couple of centuries, vitalistic concepts of health and healing have made a comeback in the recent decades. A vast array of natural healing modalities—both ancient and new—have emerged, and some are even challenging orthodox medicine for part of the middle ground. Alternative medicine has become Complementary and Alternative Medicine (capitals intentional), or CAM for short; however, the question is often asked: ‘Is there any scientific evidence that proves any of these therapies work?’

Of all the various complementary therapies, perhaps medical herbalism can be made to fit the orthodox model most easily. Given that many of the pharmaceutical drugs in use are derived from plants directly or indirectly, it is obvious that at least some plants contain compounds with pharmacological activity that can be harnessed as medicinal agents. While few would disagree with that proposition, there are many who persist in referring to herbal medicines (along with other ‘alternative remedies’) as unproven and therefore of little or no clinical value. Increasingly, the public—and particularly the medical establishment—are demanding herbalists and other complementary therapists provide scientific evidence for the efficacy and safety of their practices. While this is an admirable objective, it cannot be achieved overnight, given the complexities of the herbs themselves, the variety of formulas and prescribing methods available and the difficulties in adapting medical models to the herbal practice.

Indeed there are many inside the medical establishment who question the validity of double-blind controlled trials and

‘evidence-based medicine’ in general (e.g. Black 1996; Vincent and Furnham 1999). In a formal evaluation procedure, the quality of randomised controlled trials of interventions using complementary medicines was found to be more or less the same as those using conventional biomedicine—although the overall quality of evidence in both cases was generally regarded as poor (Bloom *et al.* 2000). This assessment supports the point made by Black that ‘the difference in the standards of evidence for orthodox and complementary therapies may not be as great as generally assumed’ (Black 1996).

## Phytochemical basis of herbal medicines

Since herbal medicines are products of the biological world, their properties and characteristics can be studied using the accumulated skills and knowledge embedded in the natural sciences—especially botany and chemistry or biochemistry. Through an understanding of simple principles of chemistry we see there is a similarity in the molecules that make up plants and humans, while foods and medicines derived from plants provide a chemical continuum between these two kingdoms. The more we comprehend these natural processes, the easier it is for us to intervene using biological agents (in this case herbs) to alleviate diseased states in our fellow humans.

To the scientist or pharmacist a plant’s constituents may be regarded as an unholy mixture of mainly unwanted chemicals, to be refined with the objective of identifying and isolating an ‘active principle’. Herbalists on the other hand aim at a holistic approach—one that values the sum or totality of a plant’s constituents—even those considered by the pharmacist to be worthless. In order to study the activity of a given herb, it is often necessary to purify it or isolate a specific compound—an example of the reductionist approach that characterises the biomedical model.

While many of the studies referred to in this book are a product of such reductionist research, the results or findings should not be devalued in principle. Isolation of and experimentation with single constituents provides information that can be adapted to a more holistic understanding of a herb’s action. Knowledge of individual constituents is also essential for developing quality assurance methods, extraction procedures, understanding of pharmacological activity and pharmacokinetics and—most importantly—understanding of

potential toxicology and interactions with pharmaceutical drugs. It is not merely a necessary step in the isolation and synthesis of plant-derived drugs.

## Understanding organic chemistry

It does not require a science degree to gain an understanding of the fundamental chemical structures found in medicinal herbs, but some knowledge of organic chemistry is desirable. Hence reference to any good introductory text on organic chemistry or biochemistry will help those who haven't done an elementary course at tertiary level.

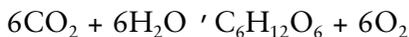
I am indebted to some of the great scientists and herbalists who have inspired me with their knowledge of the subject, making the job of learning phytochemistry much easier for the non-chemist—teacher, student and practitioner alike. I refer especially to Terry Willard, Jean Bruneton, G. E. Trease and W. C. Evans, Varro Tyler, Kerry Bone, Jim Duke, Peter Waterman and—in the field of essential oils—Arthur Tucker and Joy Bowles (with apologies to the many worthy individuals I have omitted). I highly recommend the publications of these pioneers—many are listed in the references.

In this chapter we review some of the basic chemical principles and terminology that are used throughout the book, along with an introduction to the biosynthetic processes through which plants manufacture their chemicals.

## Biosynthesis of organic compounds

### Photosynthesis

Photosynthesis is a process by which the leaves of plants manufacture carbohydrates and oxygen, using carbon dioxide from the air and water absorbed from the roots. The following equation should be familiar to anyone who studied biology at high school.



This reaction is only possible under the influence of sunlight and in the presence of specialised plant cells known as chloroplasts, which contain the light-trapping pigment chlorophyll.

## Biosynthetic pathways

Virtually all chemical compounds found in plants derive from a few well-studied metabolic pathways. The so-called ‘pathways’ begin with chemical products of photosynthesis and glycolysis (glucose metabolism)—simple starting molecules (precursors) such as pyruvic acid, acetyl coenzyme A and organic acids. A series of intermediate compounds are formed which are quickly reduced—with the assistance of specific enzymes—into other, often unstable intermediate compounds, until finally a complex, stable macromolecule is formed. Metabolic pathways involve a series of enzymes specific for each compound.

## Primary and secondary metabolites

The biosynthetic pathways are universal in plants and are responsible for the occurrence of both primary metabolites (carbohydrates, proteins, etc.) and secondary metabolites (phenols, alkaloids, etc.). Secondary compounds were once regarded as simple waste products of a plant’s metabolism. However, this argument is weakened by the existence of specialist enzymes, strict genetic controls and the high metabolic requirements of these compounds (Waterman and Mole 1994). Today most scientists accept that many of these compounds serve primarily to repel grazing animals or destructive pathogens (Cronquist 1988).

Biosynthetic reactions are energy consuming, fuelled by the energy released by glycolysis of carbohydrates and through the citric acid cycle. Oxidation of glucose, fatty acids and amino acids results in formation of ATP (adenosine triphosphate), a high-energy molecule formed by catabolism (enzymic breakdown) of primary compounds. ATP is recycled to fuel anabolic (enzymic synthesis) reactions involving intermediate molecules on the pathways.

Whereas catabolism involves oxidation of starting molecules, biosynthesis or anabolism involves reduction reactions, hence the need for a reducing agent or hydrogen donor, which is usually NADP (nicotinamide adenine dinucleotide phosphate). These catalysts are known as coenzymes and the most widely occurring is coenzyme A (CoA), made up of ADP (adenosine diphosphate) and pantetheine phosphate.

The most common pathways are:

- Pentose ' glycosides, polysaccharides
- Shikimic acid ' phenols, tannins, aromatic alkaloids
- Acetate–malonate ' phenols, alkaloids
- Mevalonic acid ' terpenes, steroids, alkaloids

## The structures of organic compounds

### Of elements and atoms

An **element** is a substance that cannot be divided further by chemical methods—it is the basic substance upon which chemical compounds are built. The Periodic Table classes all known elements in a systematic manner based on the increasing number of electrons and protons (which are equal), starting with **hydrogen** (number 1 as it has 1 electron and 1 proton).

**Atoms** are the smallest particle within elements. They are made up of protons and neutrons (in the nucleus) and electrons (in orbits around the nucleus). Each orbit represents an energy level and these give the atom stability. Electrons in the outer orbit, or valence shell, control how the atom bonds. When atoms are linked together by chemical bonds they form **molecules**.

To achieve chemical stability, an atom must fill its outer electron shell, and it does this by losing, gaining or sharing electrons. These are known as valence electrons and the valence is specific for each element.

### Chemical bonds

A **bond** is a pair of electrons shared by the two atoms it holds together. There are many types of chemical bonds including hydrogen, ionic and covalent bonds. In organic chemistry (based on the element carbon) we deal mainly with covalent bonds, which may occur as single, double or triple bonds.

**Covalent bonds** have a shared pair of electrons between two atoms—they neither gain nor lose electrons, as ionic bonds do. They occur in elements towards the centre of the Periodic Table, the most significant element being carbon. Covalent bonds are stronger than hydrogen or ionic bonds and don't form solutions with water. They may be polar or non-polar depending on the relationship between the electric charges emitted by the respective atoms.

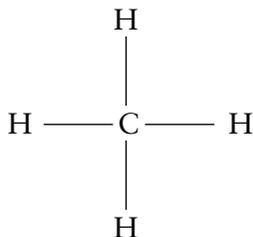
The bonding properties of elements are related to their valence, that is, the number of electrons they need to fill their outer shells. The most abundant elements found in living organisms (including herbs) are:

|          |   |
|----------|---|
| Hydrogen | H |
| Oxygen   | O |
| Nitrogen | N |
| Carbon   | C |

The bonding properties, or valence bonds, are 1, 2, 3, 4 respectively, hence the HONC rule (Perrine 1996):

H forms 1 bond  
 O forms 2 bonds  
 N forms 3 bonds  
 C forms 4 bonds

From the HONC rule we learn that *carbon must always be linked to other atoms through four bonds*. For example, the formula for **methane** is CH<sub>4</sub>. We can draw it in a way that represents the bonding arrangement:

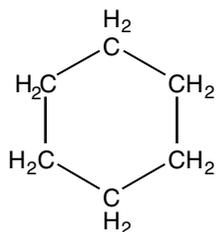


### Acyclic, cyclic and heterocyclic compounds

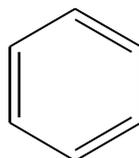
The atoms of organic compounds are arranged as either open chains (acyclic or aliphatic) or closed ring systems (cyclic). Each corner or kink in the ring (or chain) indicates a CH<sub>2</sub> group, although these are usually abbreviated to C or omitted. Each line represents a bond.

Unsaturated ring systems are those in which the carbons are linked by double or triple bonds, while saturated rings do not contain any double bonds. In the diagram below, the **cyclohexane** ring is a saturated ring with each carbon labelled. The **benzene** ring, the

central structure of thousands of organic compounds, is an unsaturated six-carbon ring, generally illustrated as a hexagon containing three double lines for the conjugated (alternating) double bonds. The labels are omitted in this example. Compounds containing one or more benzene rings are known as **aromatic** compounds.



cyclohexane ring

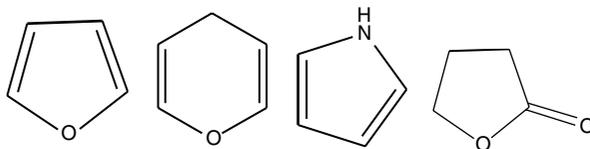


benzene ring

Once you have looked at these structures often enough, the labelling of atoms is unnecessary—since only one arrangement of atoms is possible for each bonding configuration according to the HONC rule. See if you can count the number of bonds held by each carbon atom in the cyclohexane ring above—there must be four.

Ring systems in which the rings are composed entirely of hydrocarbons ( $\text{CH}_2$ ) are called **homocyclic** (e.g. benzene). Ring systems containing two or more different atoms are called **heterocyclic**. Such ring systems usually contain several carbon atoms and one or more atoms of other elements, usually nitrogen, oxygen or sulphur. Over 4000 heterocyclic systems are known from plant and animal sources. They sometimes occur fused to a benzene ring or to another heterocyclic ring, to give bicyclic systems. Some of these heterocyclic rings resist opening and remain intact throughout vigorous reactions, as does the benzene ring.

Some important parent heterocyclic compounds are shown below:



furan

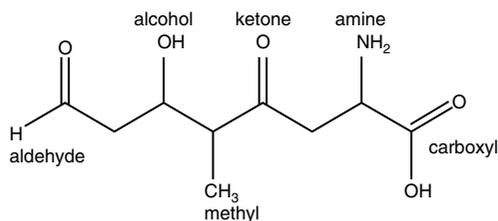
pyran

pyrrole

lactone

## Functional groups

Another feature of organic compounds is the presence of functional groups. These are groups of atoms attached to carbon chains or rings which are often involved in chemical reactions. The different classes of functional groups are distinguished by the number of hydrogen atoms they replace. Common ones include **alcohol**, **ketone**, **aldehyde**, **amine** and **carboxylic acid** (see the diagram below).



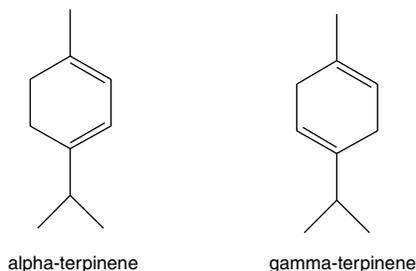
Imaginary hydrocarbon chain with functional group attachments

Functional groups are usually labelled in the shorthand manner shown above—even though the hydrocarbon chain (or ring) remains unlabelled. Functional groups exert a significant influence on the behaviour of molecules, especially small molecules such as those found in essential oils.

## Isomerism

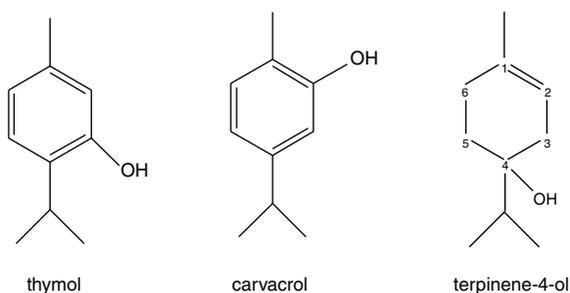
The mystery surrounding organic chemical structures is partly due to the three-dimensional shapes of these molecules: carbons tend to form tetrahedrons rather than planar (two-dimensional) structures. This allows for two or more positions of atoms on the same basic molecule. There are several types of isomers.

1. **Structural isomers**—compounds with the same molecular formula but a different arrangement of bonded atoms. The positioning of a double bond is indicated by prefixing the name of the compound with alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ ) or delta ( $\delta$ )—as in the example of terpinene on page 9.
2. **Positional isomers** differ in the position of their functional group. They may be compounds whose side chains are attached at different locations around the carbon ring. For example, the phenol **coumaric acid** may contain a hydroxyl (OH) group at any of three locations, known as *ortho* (*o*-coumaric acid), *meta* (*m*-coumaric



acid) or *para* (*p*-coumaric acid). **Thymol** and **carvacrol** are positional isomers due to the different positions of the hydroxyl group on the monoterpene skeleton.

In modern chemistry the positional isomer delegations (*ortho*, *meta* and *para*) are becoming obsolete, since the positions can be indicated by a simple ‘numbering’ system. Hence in the case of terpinene-4-ol, the major constituent of tea tree oil, the number 4 designates the position of attachment of the hydroxyl group to the ring, and the term ‘*para*’ is not required.



3. **Stereoisomers** have the same bonds or connectivity, but a different three-dimensional orientation of atoms.

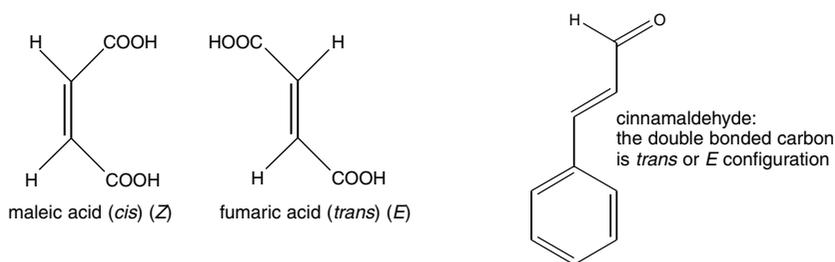
a. **Geometric (*cis-trans*) isomers** differ in the placement of functional groups on one side or other of the double bond:

- i. *cis* designates the stereoisomer with like groups on the same side of the double bond
- ii. *trans* designates the stereoisomer with like groups on opposite sides of the double bond

*Cis-trans* isomerism is responsible for significant differences in the properties and odours of many essential oils containing identical chemical constituents.

In modern chemistry texts the *cis/trans* nomenclature has been replaced by a notational system known as *E-Z* where *E* corresponds to *cis* and *Z* to *trans*. This system is less ambiguous as it is based on a more precise atomic number criterion for ranking substituents. In this system, when the higher atomic number atoms are on opposite sides of the double bond the configuration is *E* (Carey 2000).

The organic acids **maleic acid** and **fumaric acid** are *cis-trans* or *Z-E* isomers (see diagram below), while cinnamaldehyde—responsible for the odour of cinnamon—occurs in the *trans* or *E* form only.



**b. Enantiomers**—non-superimposable mirror images known as chiral\* molecules. They are also known as **optical isomers**—molecules that rotate plane-polarised light by identical magnitudes but in different directions:

- i. Dextrorotary: (*d* or +) rotates light clockwise (to the right)
- ii. Laevorotary: (*l* or -) rotates light anticlockwise (to the left)
- iii. Racemic mixture: (*dl* or  $\pm$ ) an equal amount of enantiomers

**c. Diastereomers**—stereoisomers that do not have a mirror image relationship. These molecules have more than one chiral centre. Tartaric acid, and also maleic and fumaric acids, are examples of diastereoisomers.

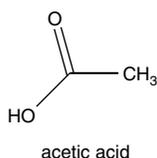
## Organic acids

Organic acids are of such widespread occurrence that they are not strictly secondary metabolites; in fact many occur during the citric

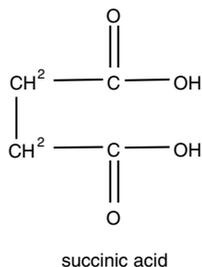
\* Chiral comes from the Greek word for hand—it refers to the property whereby the right hand is a mirror image of the left hand.

acid or Krebs cycle. They are water-soluble colourless liquids with characteristic sharp tastes.

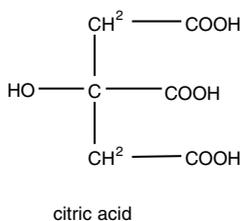
**Monobasic acids** contain a single carboxyl group (COOH). They include the fatty acids as well as **isovaleric acid**, a sedative principle found in *Valeriana officinalis* and *Humulus lupulus*. One of the most important in this group is **acetic acid**, the main constituent in vinegar. Acetic acid is the precursor of lipids as well as some essential oils and alkaloids.



**Polybasic acids** contain two or more carboxyl groups and generally have a slight laxative effect. They include **oxalic**, **succinic** and **fumaric acids**, the last one occurring in *Fumaria officinalis*.



**Hydroxyl acids** include a hydroxyl group (OH) with a pair of carboxyl groups. **Citric acid** and **tartaric acid** are the most common examples. **Lactic acid** is an exception in that it has only one carboxyl group. Lactic acid is enantiomeric—racemic forms occur in soured milk products.



**Aromatic acids** such as **benzoic acid** are sometimes classed with the organic acids; however, they are products of the shikimic acid pathway and are discussed further in Chapter 2.

## Synergism

While this book by necessity deals, in the main, with the properties of isolated plant constituents, the reader is reminded of the phenomenon of synergy—where the interaction of two or more agents results in a combined effect that is greater than the sum of the individual parts (i.e. of the additive effects). This process is often referred to in herbal medicine circles (e.g. for *Hypericum perforatum*) although it is a difficult one to prove. The primary application of this concept is in the traditional methods of combining herbal medicines in formulas; however, in recent times it has also been applied using the combined effects of active constituents within the same herb.

A review of herbal synergism is outside the scope of this text. However, for readers who would like to pursue the topic there is literature available and attempts are being made to qualify and quantify the processes involved (e.g. Duke and Bogenschutz-Godwin 1999; Williamson 2001).

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## PHENOLS



### Simple phenols

Phenols are one of the largest groups of secondary plant constituents. They are aromatic alcohols since the hydroxyl group is always attached to a benzene ring.

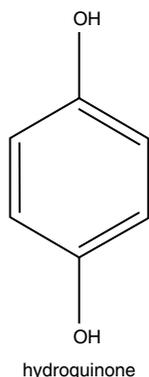


Like all alcohols the names of phenols always end in the letters 'ol'. In addition the ring system may bear other substitutes, especially methyl groups.

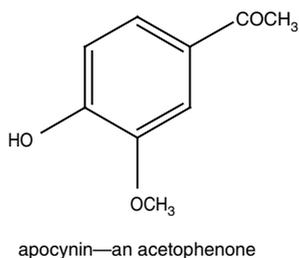
Simple phenols consist of an aromatic ring in which a hydrogen is replaced by a hydroxyl group. Their distribution is widespread among all classes of plants. General properties of simple phenols are bactericidal, antiseptic and anthelmintic. Phenol itself is a standard for other antimicrobial agents.

The simplest phenols are  $C_6$  structures consisting of an aromatic ring with hydroxyl groups attached. These include pyrogallol and hydroquinone.

Addition of a carboxyl group to the basic phenol structure produces a group of  $C_6C_1$  compounds, including some of widespread distribution among plants and with important therapeutic activity. The most important of these are gallic acid and salicylic acid.



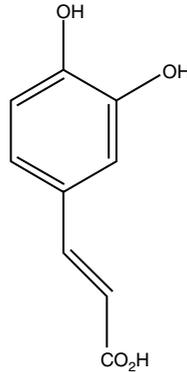
A rarer type of simple phenols with  $C_6C_2$  structures are known as acetophenones. Some of these have demonstrated antiasthmatic activity, particularly **apocynin** and its glycoside androsin, which are derived from *Picrorhiza kurroa* (Dorsch *et al.* 1994).



## Phenylpropanoids

These are  $C_6C_3$  compounds, made up of a benzene ring with a three-carbon side chain. The most important are the hydroxycinnamic acids: **caffeic acid**, ***p*-coumaric acid**, **ferulic acid** and **sinapic acid**. They can be derived from different stages of the shikimic acid pathway. These acids are of much benefit therapeutically and are non-toxic. They may also occur as glycosides.

Modification of the side chain of these acids produces alcohols such as coniferyl alcohol, which act as precursors to the formation of lignins (high-molecular-weight polymers that give strength and structure to stems of herbs and tree trunks). By modification of their  $C_3$  side chains or changes in substitution patterns of their aromatic nucleus, hydroxycinnamic acids are able to form a host of secondary



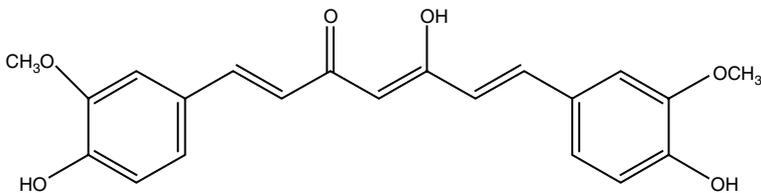
caffeic acid

compounds including phenolic ethers, lignans, coumarins, glycosides, dimers such as rosmarinic acid and curcumin from the roots of turmeric, and the depsides cynarin and chlorogenic acid.

Caffeic acid is an inhibitor of the enzymes DOPA-decarboxylase and 5-lipoxygenase. It is an analgesic and anti-inflammatory, and promotes intestinal motility (Adzet and Camarasa 1988). It is of widespread occurrence and is found in green and roasted coffee beans.

**Cynarin** (1.5 dicaffeoyl-D-quinic acid), the major active principle of globe artichoke, *Cynara scolymus* (Asteraceae), is formed from the bonding of two phenolic acids, caffeic and quinic acids. Cynarin is a proven hepatoprotective and hypocholesterolaemia agent.

**Curcumin** is the yellow pigment from the turmeric rhizome *Curcuma longa* (Zingiberaceae). Curcumin and its derivatives are diarylheptanoids. They have significant anti-inflammatory, hypotensive and hepatoprotective properties (Ammon and Wahl 1990).



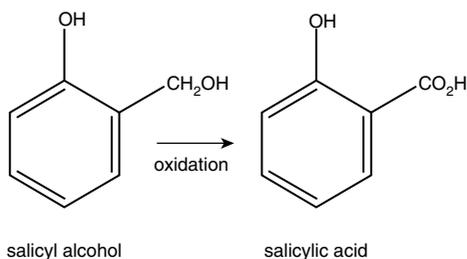
curcumin—diferuloylmethane

The simple phenol hydroquinone (see above) is derived from hydroxybenzoic acid. Upon glucosylation, arbutin, a simple phenol glycoside, is formed.

**Arbutin** occurs in leaves of the pear tree (*Pyrus communis*) and *Arctostaphylos uva-ursi*, and is a urinary tract antiseptic and diuretic. Arbutin is hydrolysed to hydroquinone in alkaline urine, this effect being strictly localised in the urinary tract. It is indicated for urinary tract infections, in particular cystitis, urethritis and prostatitis.

## Salicylates and salicins

**Salicylic acid** is a carboxylated phenol, that is, carboxylic acid and a hydroxyl group added to a benzene ring. It is rarely found freely in plants, but usually occurs as glycosides (e.g. salicin salicortin), esters and salts. In humans the glycosides are first hydrolysed to the aglycone salicyl alcohol with the aid of intestinal bacteria. Upon oxidation in the liver and bloodstream salicylic acid is produced (Mills and Bone 2000). Salicylic acid undergoes hepatic biotransformation and most is excreted in the urine as salicylic acid conjugates. **Aspirin** is a synthetic derivative of salicylic acid. Salicin-containing herbs such as willow bark are primarily used as analgesics, anti-inflammatories and febrifuges. The anticlotting effect of salicins is much milder than for aspirin, and the well-documented tendency to gastric haemorrhage associated with aspirin is not a problem in salicin-containing herbs (Bisset 1994). However, caution is required in using them in individuals with aspirin or salicylate sensitivity.



Salicylic acid was first prepared in pure form from meadow-sweet—*Filipendula ulmaria* (family Rosaceae) in 1838. It was first synthesised by the German chemist Kolbe in 1860. The subsequent synthesis of acetylsalicylic acid in 1899 by the Bayer Company resulted in aspirin.

## Main derivatives of salicylic acid

### *Glycosides*

- **Salicin**—found in willow bark (*Salix* spp.), poplar bark (*Populus* spp.) and *Viburnum* spp.
- **Populin**—*Populus* spp.
- **Gaultherin**—wintergreen (*Gaultheria* spp.)
- **Spiraein**—*Filipendula* spp.

### *Esters*

- **Methyl salicylate**—found in meadowsweet (*Filipendula* spp.), *Gaultheria* spp.
- **Salicylaldehyde**—*Filipendula ulmaria*
- **Acetylsalicylic acid** (aspirin)—aspirin is a synthetic derivative of salicylic acid

## Properties of salicins and salicylates

Various herbs containing derivatives of salicylic acid have long histories of use for relief of pain and inflammation in European and North American folk medicine.

Aspirin blocks synthesis of prostaglandins through acetylation of the enzyme cyclooxygenase. Whereas cyclooxygenase-2 (COX-2) is found mainly in inflamed tissues, cyclooxygenase-1 (COX-1) is present in platelets. The inhibition of COX-1 by aspirin is behind the well-documented blood-thinning effects of the drug, as well as other adverse reactions such as haemorrhage and gastric irritation.

Salicylic acid provides little inhibition of isolated cyclooxygenases, rather it prevents their formation in cells. Since they lack the acetyl group found in aspirin, natural salicylates do not have antiplatelet (blood thinning) effects (Meier and Liebi 1990).

Other actions associated with salicylic acid derivatives include central nervous system depression and antipyretic effects—they act to increase peripheral blood flow and sweat production, by direct action on the thermogenic section in the hypothalamus. This helps explain the use of salicin-containing herbs for neuralgias, sciatica, myalgia and headaches.

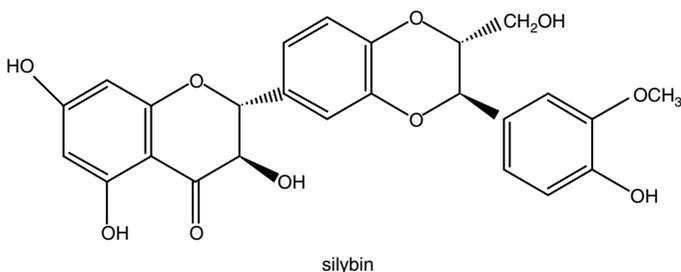
While some authorities have questioned the credibility of a genuine salicylate anti-inflammatory action in salicin herbs due to the low levels of active constituents found in traditional herbal preparations (Robbers and Tyler 1999), recent clinical investigations in Germany

have been based around high-dose willow bark extracts (120–240 mg salicin daily). These trials have demonstrated significant reduction of back pain with few side effects, and include a randomised double-blind study of 210 patients, reported in the *American Journal of Medicine* (Chrubasik *et al.* 2000).

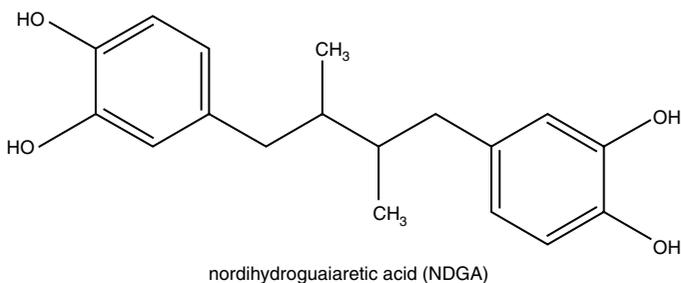
## Lignans

**Lignans** are dimeric compounds in which phenylpropane ( $C_6C_3$ ) units are linked between their side chains at the C-8 positions to form three-dimensional networks.

**Neolignans** are similar dimeric structures but unlike true lignans the linkage of their phenylpropane units does not occur at the C-8 positions. Hybrid lignans, or lignoids, are compounds with mixed biosynthetic origin. Examples are **flavonolignans** such as silybin from *Silybum marianum* and **xantholignans** from *Hypericum perforatum* (Bruneton 1995).

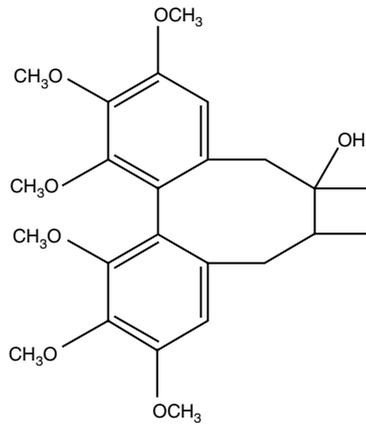


The simple lignan **nordihydroguaiaretic acid (NDGA)** from chaparral *Larrea tridentata* (Zygophyllaceae) is a potent antioxidant.



**Schizandrins** from *Schisandra sinensis* reverse destruction of liver cells by inducement of cytochrome P-450 (Huang 1993) while other lignans are antimicrobial, antiviral and antineoplastic. Many lignans, including those from flaxseed and stinging nettle root, are converted by intestinal bacteria to the active metabolites enterolactone and enterodiol, which are readily absorbed. These two lignans are also metabolites of dietary lignans found in grains and pulses. They have oestrogenic, antitumour and antioxidant properties, and are a major source of the class of compounds known as phytoestrogens.

Lignans from the mayapple (*Podophyllum peltatum*) show potent antiviral activity *in vivo* (MacRae *et al.* 1989).



schizandrin

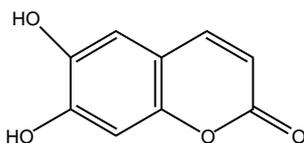
Recent research on lignans has focused on a range of compounds demonstrating cardiovascular activities such as inhibition of cyclic AMP phosphodiesterase, PAF antagonism, calcium channel antagonism and antihypertensive and antioxidant effects (Ghisalberti *et al.* 1997).

Lignans are also present in grains and pulses and their regular consumption has been shown to affect oestrogen levels in humans (Beckham 1995).

## Coumarins

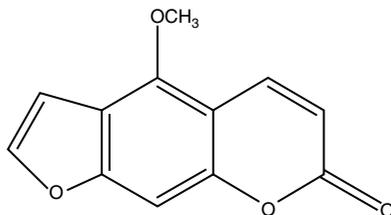
Coumarins are lactones of hydroxycinnamic acids, with cyclic  $C_6C_3$  skeletons.

Most simple coumarins are substituted with OH or OCH<sub>3</sub> at positions C-6 and C-7. They often occur in glycosidic form, for example **aesculin** is the glycoside of aesculetin.



aesculetin (6,7-dihydroxycoumarin)

Furanocoumarins have a furan ring at C-6 and C-7 (psoralen) or C-7 and C-8 (**angelican**) of the coumarin ring system; however, they are not phenolic in structure. Angelican and the structurally complex coumarin **archangelican** occur in the roots of angelica (*Angelica archangelica*) and have spasmolytic activity. The linear furanocoumarins **psoralen** and **bergapten** have photosensitising properties—utilised in treatments of vitiligo and psoriasis where the subject is concurrently exposed to solar radiation. Furanocoumarin contained in plants may produce phototoxic reactions in people with normal skin. They must be used with caution and prolonged sun exposure should be avoided. These coumarins are found in bishops weed (*Ammi majus*) and other species of the Apiaceae and Rutaceae families (Towers 1980). **Cimicifugin**, a linear coumarin found in *Cimicifuga racemosa* and *Angelica japonica*, shows hypotensive activity in animals (Harborne and Baxter 1993).



bergapten—a linear furanocoumarin

The furanochromone **khellin** is the active constituent of *Ammi visnaga* (Apiaceae), a significant antispasmodic and antiasthmatic herb, which also has a beneficial action on coronary blood vessels. Pyranocoumarins, which contain a pyran ring fused at C-7 and C-8, are also present in *Ammi visnaga* (Greinwald and Stoberneck 1990).

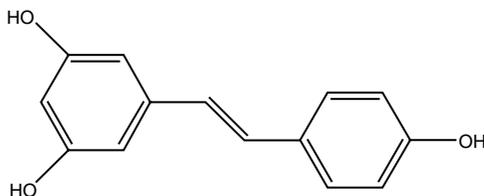
The distribution of coumarins is widespread. Originally isolated from tonka beans, they are abundant in particular plant families, for example Rubiaceae—*Asperula*; Poaceae—*Avena*; Fabaceae—*Medicago*, *Melilotus*; Rutaceae—*Ruta*, *Citrus* spp., *Murraya*; Apiaceae—*Angelica*, *Ammi*.

**Dicoumarol** (bishydroxycoumarin), used as a medical drug, was originally derived from *Melilotus* (sweet clover). **Warfarin**, the blood-thinning drug also used as rat poison, is a synthetic coumarin derivative. **Aflatoxin B<sub>1</sub>**, a complex coumarin found in the common mould *Aspergillus flavus*, is one of numerous toxic aflatoxins that contaminate food during storage.

Coumarins in general have antimicrobial and fungicidal activity. They are often described as blood thinning, though this activity is mainly restricted to dicoumarol, a product of incorrectly dried (or mouldy) hay.

## Stilbenes

Stilbenes are characterised by two benzene rings—one of which is usually phenolic—in a C<sub>6</sub>C<sub>2</sub>C<sub>6</sub> arrangement (Waterman and Mole 1994). The compounds were first studied for their antifungal effects in eucalypt trees and the wood of grapevines. The compound of most interest is **resveratrol**, a hydroxystilbene first isolated from the roots of the white hellebore (*Veratrum album* var. *grandiflorum*).



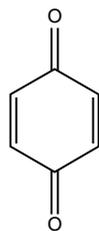
resveratrol—a hydroxystilbene

Hydroxystilbenes are found in a variety of plants, many unrelated. They are a prominent component of many species of the Polygonaceae family (*Rheum*, *Polygonum* spp.) but the richest source is found in grape skins and red wine (Creasy and Creasy 1998).

Resveratrol is an antioxidant, anti-inflammatory, antiplatelet and antiallergy agent with demonstrated cancer-preventative activity (Cheong *et al.* 1999; Steele *et al.* 1998). It has been shown to inhibit cyclooxygenase-2 (COX-2) *in vitro* (Subbaramaiah *et al.* 1998).

## Quinones

Quinones are polycyclic aromatic compounds in which one hexane ring contains two opposite carbonyl groups. Typically the quinoid structure is attached to one or more benzene rings, which may or may not have a phenol function, that is, hydroxyl group. The simplest quinone, benzoquinone, lacks the benzene ring altogether.



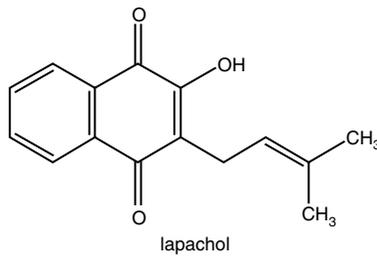
benzoquinone

Quinones form an important component of the electron-transport system in plants and mammals. **Ubiquinol**, the reduced form of coenzyme Q<sub>10</sub>, and **menaquinone** (vitamin K) have significant antioxidant properties, playing a major role in protecting cells from free-radical damage (Cadenas and Hochstein 1992). Any of four different metabolic pathways may be involved in quinone biosynthesis (Harborne and Baxter 1993). The largest subgroup are the anthraquinones, which occur mainly as glycosides and are referred to in Chapter 4.

## Naphthaquinones

**Naphthaquinones** are characterised by their dark pigmentation—**lawsone** is the active principle in the popular hair dye obtained from

the henna plant (*Lawsonia inermis*). Many 1,4 naphthaquinones—in which oxygen is double-bonded to carbon in the C-1 and C-4 positions in the ring—are recognised for their antimicrobial, anti-fungal and antitumour activities. These include **juglone** from walnut bark (*Juglans cineraria*), **lapachol** from pau d'arco (*Tabebuia impetiginosa*) and **plumbagone** from sundew (*Drosera rotundifolia*).



In 1968 lapachol was identified as an antitumour agent, showing significant activity against Walker 256 carcinosarcoma *in vivo*, particularly following twice daily oral administration (Rao *et al.* 1968). This result was confirmed in later studies. The isopentenyl side chain in lapachol is thought to play a pivotal role in this activity. In separate studies structural variations to the side chain of lapachol were found to be inactive, confirming the molecular specificity for lapachol's biological activity (De Santana 1968).

## Miscellaneous phenolic compounds

The basic phenolic structure occurs in many other classes of compounds found in medicinal herbs, including the following:

- Tannins—see Chapter 3
- Glycosides, e.g. most flavonoids, anthraquinones
- Essential oils, e.g. **thymol**
- Alkaloids, e.g. **oxyacanthine**

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## POLYPHENOLS—TANNINS AND FLAVONOIDS



### Tannins

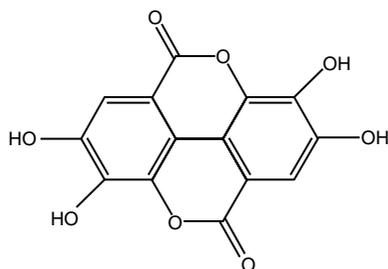
Tannins represent the largest group of polyphenols. They are widely distributed in the bark of trees, insect galls, leaves, stems and fruit. Tannins were originally isolated from the bark and insect galls of oak trees. They are the chief plant constituents responsible for astringency.

Tannins are non-crystalline compounds which in water produce a mild acid reaction. Their ingestion gives rise to a puckering, astringent sensation in the mouth and the taste is sour. They often occur as glycosides. Their ability to precipitate proteins into insoluble complexes enables humans to ‘tan’ animal hides and convert them to leather. This ability is also the basis of their astringent effects. Due to protein precipitation, the tannins exert an inhibitory effect on many enzymes, hence contributing a protective function in bark and heartwoods of woody plant species. Tannins also form precipitates with polysaccharides and some alkaloids including caffeine.

Tannins are high-molecular-weight compounds (500–5000) containing sufficient phenolic hydroxyl groups to permit the formation of stable cross-links with proteins, and as a result of this cross-linking enzymes may be inhibited. Almost all tannins are classified as either hydrolysable tannins or condensed tannins—some plants contain both kinds

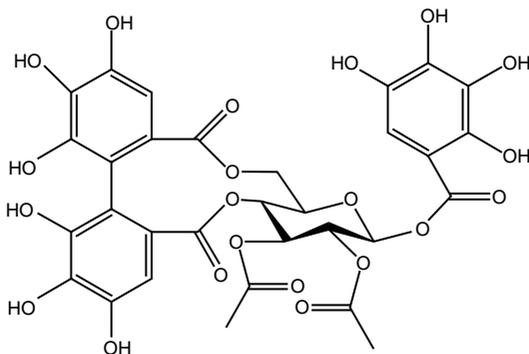
### Hydrolysable tannins

Hydrolysable tannins are derived from simple phenolic acids, particularly **gallic acid**, which is linked to a sugar by esterification. The gallic acid groups are usually bonded to form dimers such as **ellagic acid**.



ellagic acid

Hydrolysable tannins break down on hydrolysis to give gallic acid and glucose or ellagic acid and glucose, known as **gallotannins** and **ellagitannins** respectively. They are readily soluble in water and alcohol. Botanicals containing hydrolysable tannins include cranesbill (*Geranium maculatum*) and agrimony (*Agrimonia eupatoria*).



rugosidin D—section of molecule

### *Actions of hydrolysable tannins*

Actions of hydrolysable tannins include:

1. Protecting inflamed mucous membranes
2. Drying effect on mucous membranes, reduces hypersecretions
3. Reduce inflammation and swelling which accompany infections
4. Prevent bleeding from small wounds
5. Reduce uterine bleeding, for example menorrhagia, metrorrhagia
6. Binding effect in the gut—relieves diarrhoea, dysentery
7. Used externally as douches, snuffs, eyewash

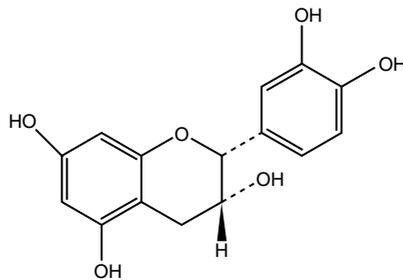
Apart from the general actions listed above, some specific actions have been demonstrated for a range of hydrolysable tannins and these are listed in Table 3.1.

**Table 3.1 Specific actions of hydrolysable tannins**

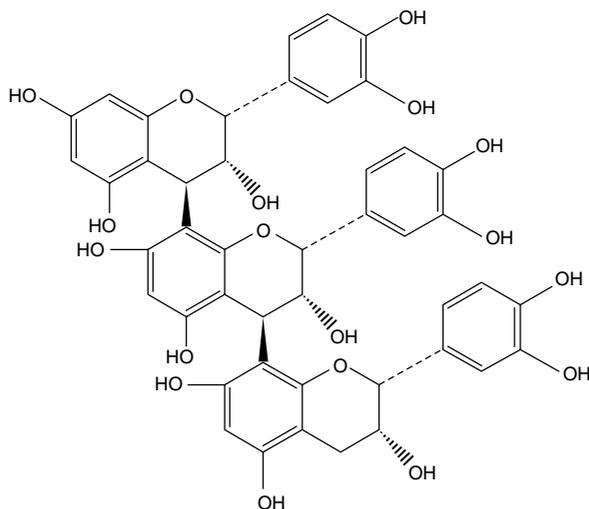
| Compound         | Plant origin  | Action  |
|------------------|---|---|
| Sanguiin         | <i>Rubus idaeus</i>                                   | Cytotoxic   |
| Rugosin D        | <i>Filipendula ulmaria</i>                            | Antitumour  |
| Gallotannic acid | <i>Quercus</i> spp.                                   | Astringent,<br>antihaemorrhagic                             |
| Oenthein B       | <i>Epilobium</i> spp.                                 | Inhibitor of 5 $\alpha$ reductase,<br>aromatase, antitumour |
| Hamamelitannin   | <i>Hamamelis virginicus</i>                           | Antioxidant   |
| Geraniin         | <i>Geranium maculatum</i> ,<br><i>Phyllanthus</i> spp | Cytotoxic, hypolipidaemic                                   |
| Agrimoniin       | <i>Agrimonia eupatoria</i>                            | Astringent, antidiarrhoeic                                  |

## Condensed tannins

**Condensed tannins** or **phlobotannins** are polymers of flavan-3-ols (catechins) and flavan-3,4-diols (leucoanthocyanins). Upon hydrolysis condensed tannins form insoluble red residues or phlobaphenes. They are only partially soluble in water and alcohol; the addition of glycerine aids solubility. The basic catechin-type molecules are of low molecular weight—hence they are not true polyphenols and have low astringency.



epicatechin



trimeric procyanidin from grape seed

**Oligomeric procyanidins (OPCs)** are a major subcategory of condensed tannins in which two or more molecules of catechin and/or epicatechin are linked by simple carbon bonds. OPCs are present in popular beverages such as green and black teas and red wine. They are responsible for many of the benefits associated with red wines, including findings of lower mortality from cardiovascular and cerebrovascular diseases among low to moderate wine drinkers (Jones 1995). Green tea is especially rich in the beneficial epigallocatechin, which is a potent antioxidant and vascular tonic.

OPCs are extracted commercially from grape seeds and pine bark, often under the proprietary name of **Pycnogenol®**. A similar product is produced in New Zealand's South Island from the bark of *Pinus radiata*. The pycnogenol group were first isolated by Professor Jacques Masquelier of the University of Bordeaux while searching for agents that might enhance or extend the activity of vitamin C. Based on these and subsequent investigations the following activities have been demonstrated for grape seed extract (Bombardelli and Morazzoni 1995; Bone 1997; Masquelier *et al.* 1979):

- Antioxidant activity 20 times stronger than vitamin C
- Ability to trap hydroxyl free radicals, lipid peroxides and free radicals
- Delay onset of lipid peroxidation

- Inhibit damaging effects of enzymes associated with degradation of connective tissue structures
- Vascular protective activity
- Antiatherogenic activity

### Tannins as digestive inhibitors

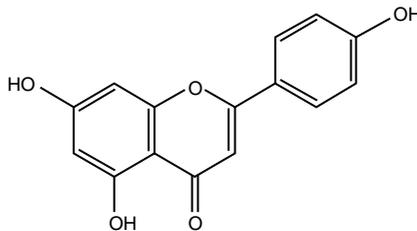
Consumption of tannins may lead to reduced absorption of proteins and other nutrients (Johns 1990:63). This can also lead to problems in compounding herbal medicines since there is a tendency to cause precipitates in some cases. For the same reason it is not considered wise to drink tea with meals; however, herb teas are generally low in tannins (Blake 1993).

### Flavonoids

These compounds occur as yellow and white plant pigments (Latin *flavus* = yellow). **Rutin** was discovered in rue (*Ruta graveolens*) in 1842—it later became known as vitamin P (permeability factor).

### Chemistry

Flavonoids occur both in the free state and as glycosides. Their chemical structure is based on a C<sub>15</sub> skeleton consisting of two benzene rings connected by a three-carbon chain, that is, C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub>. The three-carbon chain is generally closed to form a heterocyclic ring (the C-ring). Flavonoids are products of both the shikimic acid and acetate pathways, being formed by the condensation of a phenylpropanoid precursor with three malonyl coenzyme A units.



apigenin—a flavone

Almost all plants studied have been shown to contain a series of closely interrelated flavonoids with different degrees of oxidation and/or hydroxylation patterns. While there are numerous structural classes within the flavonoids, the most commonly occurring are flavones (e.g. **apigenin**) and flavonols (e.g. **quercetin**).

### Role in plant physiology

Flavonoids are universal within the plant kingdom—they are the most common plant pigments next to chlorophyll and carotenoids. They are recognised as the pigments responsible for autumnal leaf colours as well as for the many shades of yellow, orange and red in flowers. Their functions include protection of plant tissues from damaging UV radiation, acting as antioxidants, enzyme inhibitors, pigments and light screens. The compounds are involved in photosensitisation and energy transfer, action of plant growth hormones and growth regulators, as well as defence against infection (Middleton 1988). The plant response to injury results in increased synthesis of flavonoid aglycones (including phytoalexins) at the site of injury or infection.

Flavonoids can be considered as important constituents of the human diet—average consumption is estimated at approximately 1 g flavonoids per person per day, although the amount of absorbed flavonoids may be much lower. Flavonoid glycosides are poorly absorbed until undergoing hydrolysis by bacterial enzymes in the intestine, whereupon their aglycones can be absorbed. However, recent studies suggest a fair level of absorption of flavonol glycosides from the small intestine can also occur (Gee and Johnson 2001).

Flavonoid aglycones that reach the large bowel are subject to ring fission by intestinal bacteria, a process in which the middle (non-aromatic) carbon ring is split apart into smaller fission metabolites. These metabolites are readily absorbed and some are known to possess therapeutic benefits in their own right (Bone 1997). Due to the process of enterohepatic circulation, the therapeutic benefits of flavonoid metabolites are sustained over a relatively long duration.

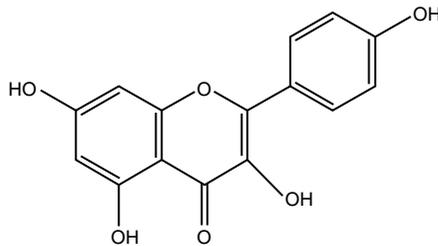
The proposition outlined above has been challenged following recent investigations, the results showing that higher levels of dietary quercetin were absorbed by ileostomy patients as glycosides from the small intestine.

## Therapeutics

Experiments have proven flavonoids affect the heart and circulatory system and strengthen the capillaries. They are often referred to as ‘biological stress modifiers’ since they serve as protection against environmental stress (Middleton 1988). They are also known to have synergistic effects with ascorbic acid. Their protective actions are mainly due to membrane stabilising and antioxidant effects.

Therapeutic effects of flavonoids such as antioxidant, antiviral, hepatoprotective, antiatheromatous, anti-inflammatory and anti-hypertensive have been widely reported, though it must be remembered these effects are dependent on their degree of absorption. Rutin and hesperidin among others are effective in reducing permeability of blood capillaries and are widely used for peripheral vascular disorders.

In the Zutphen Elderly Study (in Holland) carried out on 805 men aged 65–84 years, dietary intake of flavonoids was calculated during a five-year period. The study indicates that the intake of flavonoids is inversely associated with mortality from coronary heart disease and, to a lesser extent, myocardial infarct. The main source of flavonoids in the men’s diets were tea, onions and apples. These flavonoids include **quercetin**, **kaempferol** and **myricitin** as well as the catechin-type condensed tannins found in black tea (Hertog *et al.* 1993).



kaempferol—a flavonol

Epidemiological studies with dietary flavonoids have also demonstrated an inverse association with incidence of stroke (Rice-Evans 2001). Antitumour activity has been demonstrated in flavonoids. **Nomilin** in citrus induces glutathione-S-transferase (GST), which aids in detoxification of carcinogens. Quercetin inhibits cytotoxic

T lymphocytes *in vitro*. *In vitro* studies also suggest flavonoids such as **tangeretin** and **nobiletin** from citrus fruits may inhibit mutagenesis produced by mutagens from cooked food, thereby playing a role in prevention of carcinogenesis (Calomme *et al.* 1996).

Animal studies show many flavonoids protect liver cells from damage induced by toxins such as carbon tetrachloride. **Silymarin**, the flavonolignan complex from *Silybum marianum*, is an inducer of phase 1 detoxication, and protects liver mitochondria and microsomes from lipid peroxidation. This protection also occurs with the flavonoids quercetin and taxifolin. Silymarin causes hepatic regeneration and increases hepatic glutathione *in vivo*.

### Enzyme inhibitors

The presence of numerous aromatic hydroxyl groups on flavonoids enables them to easily attach to enzyme surfaces averting potent inhibition of some enzyme systems in humans (Miller 1973). Examples include:

1. Aldose reductase—causes diabetic cataracts. Quercetrin is regarded as a very potent inhibitor of this enzyme. Others include nepetrin and its glycoside nepitin from *Rosinarinus officinalis*, as well as glycosides of luteolin and kaempferol (Pathak *et al.* 1991).
2. Xanthine oxidase—causes hyperuricaemia leading to gout and renal stones. It is postulated that free hydroxyl groups at C-5 and C-7 are important for inhibition of xanthine oxidase (Pathak *et al.* 1991).
3. Tyrosine protein kinase—causes increased pre-malignant cells.
4. Lipoxygenase and cyclooxygenase—involved with production of inflammatory prostaglandins, leukotrienes and thromboxanes, that is, dual inhibitors. Arachidonic acid derivatives.
5. Cyclic nucleotide phosphodiesterase (PDE)—key enzyme in promotion of platelet aggregation.

Flavonoids such as **baicalein** from *Scutellaria baicalensis* and *S. lateriflora* inhibit pro-inflammatory metabolites including certain prostaglandins and leukotrienes. Quercetin and others are effective inhibitors of the release of histamine induced by various agents. They inhibit a number of stages of inflammation including granulation tissue formation in chronic arthritis (Middleton and Drzewiecki

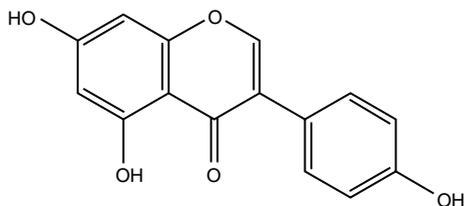
1984). Flavonoids offer the advantage of a high margin of safety and lack of side effects such as ulcerogenicity over the classical anti-inflammatory drugs.

Diseases associated with increased permeability of blood capillaries include diabetes, chronic venous insufficiency, haemorrhoids, scurvy, varicose ulcers and bruising. Buckwheat, *Fagopyrum esculentum* (Polygonaceae), contains 8% rutin if grown under suitable ecological conditions. Tissue examinations of animals with induced oedema plaques in corneal and conjunctival tissue showed that after treatment with 180 mg rutin from buckwheat herb (tablets) the oedema was flushed out and the fragility of the vascular system was reduced. Photographic documentation shows quite distinctly the return to normal of the tissues after a period of 30 days (Schilcher and Muller 1981).

Lipid peroxidation, the oxidative degradation of polyunsaturated fatty acids, is implicated in several pathological conditions—ageing, hepatotoxicity, haemolysis, cancer, atherosclerosis, tumour promotion and inflammation. Selected flavonoids may exert protective effects against cell damage produced by lipid peroxidation stimulated by a variety of toxins, owing to the antioxidant properties of the compounds (Pathak *et al.* 1991).

## Isoflavones

Isoflavones are flavonoid isomers whose distribution is largely restricted to the Fabaceae (legume) family. They have been classified with the flavonoids although they rarely occur in the glycosidic form. They have structural similarities to oestrogens so they are also classed amongst the phytoestrogens, compounds that bind to oestrogen receptors but whose oestrogen activity is relatively low.



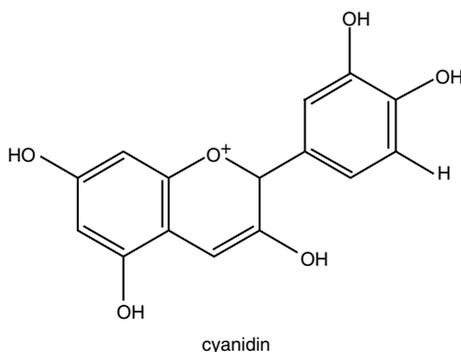
genistein—an isoflavone

Clinical trials have supported the efficacy of isoflavones such as **genistein**, found in soymilk and other soy products, in prevention of breast tumours and other cancers, as well as alleviating hot flushes and other symptoms associated with the menopause (Albert *et al.* 2002). Isoflavones are also found in liquorice (*Glycyrrhiza glabra*), alfalfa (*Medicago sativa*), black cohosh (*Cimicifuga racemosa*) and red clover (*Trifolium pratense*).

## Anthocyanins

Anthocyanin pigments are found in flowers and red, blue and black fruits. They are present in the plant as glycosides of hydroxylated 2-phenylbenzopyrylium or flavylum salts. The aglycones (non-sugar portion) are known as anthocyanidins—only six are of widespread occurrence.

Chemical structure has a significant influence on anthocyanin colours. As the number of sugar hydroxyl and methyl groups in the B-ring (at the top right) increases, the colour changes from orange to



blue as the visible absorption maximum shifts to longer wavelengths. Hence **cyanidin** turns orange-red and **delphinidin** bluish-red in methanolic solutions (Mazza and Miniati 1993). The presence of flavone co-pigments, chelating metals or aromatic acyl substitutes tends to produce a blueing effect (Cseke and Kaufman 1999).

Rich sources of anthocyanins are grape skins and bilberries (*Vaccinium myrtillus*)—along with other members of the *Vaccinium* genus including blueberries. Bilberry has long been associated with effects on microcirculation and is used in diabetic neuropathy and

ophthalmology. Despite the presence of oligomeric procyanidins (OPCs) and flavonoids, experimental and clinical studies have found most of the potency of bilberry lies in the anthocyanin fraction. A superoxide anion scavenging effect has been demonstrated *in vitro* and *in vivo* for bilberry anthocyanins (Martin-Aragon *et al.* 1999), while numerous anthocyanin-containing berries were shown to possess superoxide radicals scavenging and antilipoperoxidant activities (Constantino *et al.* 1994).

Anthocyanins have long been associated with collagen-stabilising activity, protecting the body's connective tissue from degradation during inflammatory illnesses (Mills and Bone 2000).

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## GLYCOSIDES



### Introduction

Glycosides are a group of compounds characterised by the fact that chemically they consist of a sugar portion (or moiety) attached by a special bond to one or more non-sugar portions. Chemically they are hydroxyls of a sugar that are capable of forming ethers with other alcohols, or esters with acids.

Glycosides are broken down upon hydrolysis with enzymes or acids to:

1. a sugar moiety = glycone; and
2. a non-sugar moiety = aglycone/active portion.

These may be phenol, alcohol or sulfur compounds.

The bond between the two moieties may involve a phenolic hydroxyl group in which case an O-glycoside is formed. In other cases carbon (C-glycosides), nitrogen (N-glycosides) or sulfur (S-glycosides) may be involved. Glycosidic bonds are of extra significance since they link monosaccharides together to form oligosaccharides and polysaccharides.

Most glycosides can be classed as ‘prodrugs’ since they remain inactive until they are hydrolysed in the large bowel with the help of specialised bacteria, leading to the release of the aglycone—the truly active constituent.

Classification of glycosides is based on the nature of the aglycone, which can be any of a wide range of molecular types, including phenols, quinones, terpenes and steroids. Since glycosides are so heterogenous in structure they are not easy to learn as a specific group and are described together here for convenience.

## Distribution

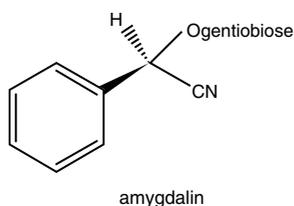
Glycoside distribution is widespread throughout the plant kingdom. They occur in the seeds of pulses, in swollen underground roots or shoots (yams, sweet potatoes), flowers and leaves. Some are toxic, especially cyanogenic and cardiac glycosides. Cooking may render them non-toxic. Glycosides are mostly soluble in water and organic solvents, though the aglycones tend to be somewhat insoluble in water.

Despite the widespread distribution of some glycoside classes we often find that the same botanical families consistently contain the same aglycone types; for example:

- Brassicaceae—glucosinolates
- Rosaceae—cyanogenic glycosides
- Scrophulariaceae—phenylpropanoid, iridoid, cardiac glycosides
- Asteraceae—phenylpropanoid, flavonoid glycosides
- Polygonaceae—anthraquinones

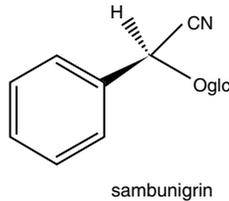
## Cyanogenic glycosides

In cyanogenic glycosides the element nitrogen occurs in the form of hydrocyanic acid, also known as prussic acid—one of the most toxic of all plant compounds. A number of amino acids are known precursors of these glycosides. **Amygdalin** from the bitter almond is derived from the aromatic amino acid phenylalanine. Amygdalin is hydrolysed in the presence of the enzyme amygdalase and water, involving a two-stage process to produce glucose along with an aglycone made up of benzaldehyde (scent of bitter almonds) and odourless hydrocyanic acid.



The occurrence of cyanogenic glycosides is widespread. Amygdalin and **prunasin** are very common among plants of the Rosaceae, particularly the *Prunus* genus. This includes not only the bitter almond but also the kernels of apricots, peaches and plums. Marzipan flavour is also derived from amygdalin. Cyanogenic glycosides are found in other food plants, including linseed and manioc—a traditional flour in South America, where the plant is boiled and water discarded to remove the toxin. The glycosides are characteristic of several other plant families including the Poaceae (grasses) and Fabaceae (legumes).

**Sambunigrin** (D-mandelonitrile glucoside) from the leaves of the elder tree—*Sambucus nigra* (Caprifoliaceae)—is isomeric to prunasin.



## Toxicology

Toxicity of hydrocyanic acid involves inactivation of the respiratory enzymes, leading to dizziness and high facial colour. In high doses the whole of the central nervous system ceases to function and death follows. However, large doses of raw plant material (> 3.5 mg/kg) are required for a toxic effect to occur. Our bodies are able to neutralise cyanides by converting them to thiocyanates, which are eliminated in the urine (Bruneton 1995), however, this capacity can be overloaded if doses of cyanide are sufficiently high.

## Therapeutic actions

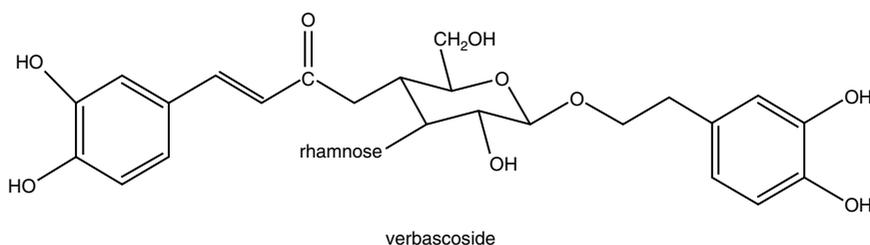
An amygdalin-containing drug called **laetrile** has been used as a cytotoxic agent in cancer, though its use is now restricted. In small quantities these glycosides do exhibit expectorant, sedative and digestive properties. Wild cherry bark, from *Prunus serotina*, is an excellent cough remedy and tonic, as well as a flavouring agent used in cough syrups. It is of benefit as a tea for bronchitis. The main antitussive principle is prunasin.

## Phenylpropanoid glycosides

Classic phenylpropanoid glycosides (PhGs) have only been known since 1964 when the first—**verbascoside**—was isolated from *Verbascum sinuatum*. Since then over 100 PhGs have been reported, but verbascoside is by far the most widespread, having been identified in more than 60 species from 14 plant families. These glycosides consist of three basic units:

1. a central glucose;
2. a C<sub>6</sub>C<sub>2</sub> moiety, usually a dihydroxy-2-ethanol; and
3. a C<sub>6</sub>C<sub>3</sub> moiety, usually a hydroxycinnamic acid.

The aromatic units can be differentially derived and other saccharides are usually linked to one or two of the free hydroxyls of the central glucose. The precursors to the non-sugar moieties are tyrosine and cinnamic acid—products of the shikimic acid pathway (Cometa *et al.* 1993).



PhGs are common in the following families:

- Scrophulariaceae—*Verbascum* spp.; *Rhemannia glutinosa*; *Digitalis purpurea*
- Plantaginaceae—*Plantago asiatica*; *P. lanceolata*
- Asteraceae—*Echinacea pallida*; *E. angustifolia*
- Lamiaceae—*Stachys* spp.; *Teucrium* spp.; *Ocimum sanctum*
- Verbenaceae—*Verbena* spp.; *Lantana camara*

### Therapeutic actions

Eight phenylpropanoid glycosides from steamed *Rhemannia glutinosa* demonstrated immunosuppressive activity *in vivo*—the most

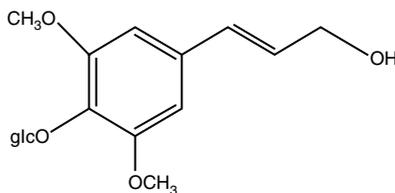
potent of these was **verbascoside** (Sasaki *et al.* 1989). In other studies verbascoside demonstrated mild to moderate antitumour activity, as well as analgesic and neurosedative actions (Pieretti *et al.* 1992). The antitumour activity is linked to inhibition of PKC (protein kinase C), an enzyme involved in cellular proliferation and differentiation (Herbert *et al.* 1991). It has recently been proposed that the antitumour activity of mistletoe (*Viscum album*) is also associated with inhibition of PKC by phenylpropanoids (Panossian *et al.* 1998).

**Echinocoside**, a trisaccharide (similar to verbascoside with an extra saccharide) found in *Echinacea angustifolia* and *E. pallida*, has proven antibiotic and antiviral properties, and was once thought to be the main active constituent of Echinacea. Echinocoside and other phenylpropane derivatives of Echinacea are proven antioxidants—together they protect skin against collagen degradation as a result of UV damage (Facino *et al.* 1995). However, subsequent investigations revealed other compounds (e.g. alkylamides, polysaccharides) to be of greater significance in the overall action of Echinacea.

Numerous other activities have been reported for PhGs, particularly from *Plantago* spp. and *Forsythia* spp. A comprehensive review of the pharmacological activities of this group is available (Cometa *et al.* 1993).

Given the simple structures and high reactivity of phenylpropane molecules, a variety of glycoside forms exist—including many that don't conform to the classic PhGs structure. **Syringin**—also known as **eleuthroside B**—from *Eleutherooccus senticosus* is an example. In this case glucose is part of a functional group attached to the benzene ring.

Several phenylpropanoid derivatives have been identified as contributing to the adaptogenic activity (adaptability to stress) in species such as *Eleutherooccus senticosus*, *Rhodiola rosea* and *Ocimum*



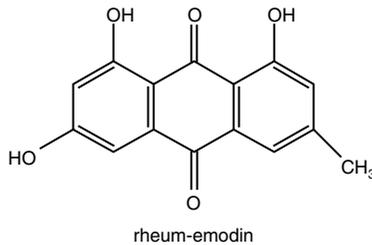
syringin—eleuthroside B

*sanctum* (Wagner, Norr and Winteroff 1994). These non-specific but well-documented effects have been linked to the structural similarity of phenylpropanoids to catecholamines such as **epinephrine** and **L-dopa**. Some closely related phenylethane derivatives such as **salidroside** from *Rhodiola rosea* are reported to have similar activity (Panassian *et al.* 1999).

## Anthraquinones

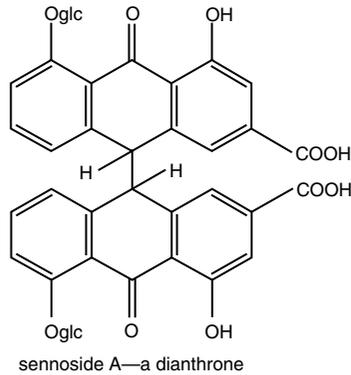
**Anthraquinones** are yellow-brown pigments, most commonly occurring as O-glycosides or C-glycosides. Their aglycones consist of two or more phenols linked by a quinone ring. Hydroxyl groups always occur at positions 1 and 8, that is, 1,8-dihydroxyanthraquinones.

The main anthraquinone-containing plants are cascara sagrada (*Rhamnus purshiana*), senna, rhubarb, aloes, dock and St John's wort. **Rheum-emodin** is a typical simple anthraquinone from rhubarb root (*Rheum palmatum*).



As anthraquinones are yellow-brown pigments many have been used historically as dyes for textiles, for example dyer's madder (*Rubia tinctoria*). They are also known as anthracene glycosides, since **anthracene** was the first compound isolated, by French chemists Dumas and Lambert, in 1832.

Experimental investigations with the most widely prescribed anthraquinones—**sennosides A and B**—show they pass through the stomach and small intestine unaltered, but that in the caecum and colon they are converted to dianthrone (their aglycones) by microorganisms. The **dianthrone**, which remain unabsorbed, are further transformed into **anthrone** and anthraquinone, producing hydra-gogue and laxative effects in the process (Adzet and Camarasa 1988).



The laxative effect is thought to occur as a result of increased peristaltic action and inhibition of water and electrolyte resorption by the intestinal mucosa. There is no evidence of direct irritation of the bowel mucosa (Bruneton 1995).

### Therapeutic actions

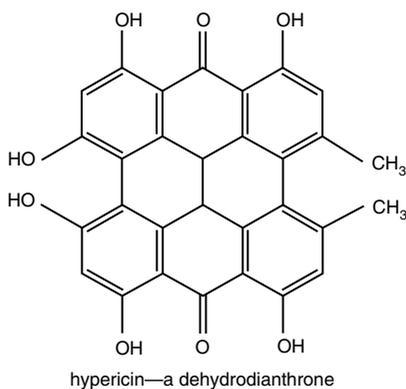
The composition of glycosides and their derivatives in anthraquinone-containing plants determines their effectiveness as laxatives. The gentlest acting laxatives in this group belong to the buckthorns (*Rhamnus catharticus* and *R. frangula*) and rhubarb (*Rheum palmatum*). In both cases the herbs are aged for at least a year during which the more irritant anthraquinone derivatives are converted to milder acting compounds. The presence of tannins also tends to moderate the laxative effect.

Aloes (*Aloe barbadensis*) and *Senna* spp. are the other commonly used laxative agents in this class. Senna leaves and pods are indicated for emptying bowels before X-ray investigations, and before and after abdominal operations (Bisset 1994). Senna syrup is commonly prescribed for children and may be used during pregnancy and lactation for limited periods. Otherwise anthraquinones are contraindicated during pregnancy. The duration of action is around eight hours, and they are usually taken before bed at night.

Due to the stimulant effect of these laxatives, they are contraindicated in irritable/spastic colon conditions. A slight overdose can produce griping and discomfort, an effect that is generally counterbalanced by the presence of carminatives such as peppermint or coriander oil. It is unwise to rely on these remedies alone when

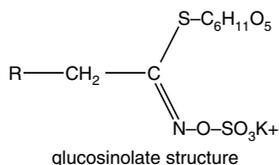
treating chronic constipation, since dependence can result. The anti-septic effects of anthraquinones deter the growth of enteric pathogens. Some anthraquinones and naphthaquinones significantly inhibit Epstein-Barr virus early antigen activation at low doses (Konoshima *et al.* 1989).

**Hypericin**, the dark-red pigment from *Hypericum perforatum*, is a dehydrodianthrone, structurally an anthraquinone. However, it does not break down to anthrone in the bowel and is without laxative action. Hypericin has been thoroughly investigated and used (generally in *Hypericum* extracts standardised to hypericin content) for antidepressant and antiviral activities (Bombardelli and Morazzoni 1995).



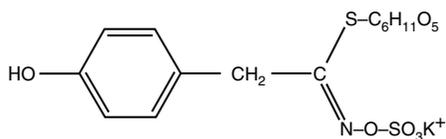
## Glucosinolates (mustard oil glycosides)

These are pungent-tasting compounds found mainly in the Brassicaceae family. More than 70 individual glucosinolate compounds are known, varying only in the character of their side chain. These glycosides are formed by decarboxylation on amino acids such as tyrosine, phenylalanine and tryptophan (see Table 4.1).



**Sinigrin** (potassium isothiocyanate), the glycoside from seeds of the black mustard (*Brassica nigra*), is hydrolysed on bruising or heating by the enzyme myrosinase to an unstable aglycone—allyl isothiocyanate. Depending on conditions other thiocyanates and highly toxic nitriles may be formed, the latter when plants are subjected to very hot water (> 45°C). A huge variability in relative abundance of the glycosides and their degradation products exists, associated with factors such as pH, season and genetic variety (Macleod 1975).

At least 300 species of Brassicas have been studied for their glucosinolate content. The compounds are mainly concentrated in the seeds, although they can be found anywhere in the plants. They can



sinigrin from white mustard seed

always be identified by their spicy, pungent taste—responsible for the flavour of mustard seeds, horseradish root, cress and rocket leaves as well as cabbage and its relatives such as broccoli. They also occur in the garden nasturtium, *Tropaeolum majus* (Tropaeolaceae) and cress (*Lepidium sativum*), in the form of **glucotropaeolin**, which is hydrolysed to the antibiotic compound benzyl isothiocyanate.

### Therapeutic actions

The main use for the Brassicas in general is culinary. In commerce black mustard has largely been replaced by brown mustard (*Brassica juncea*) in recent times, since the latter species is better adapted to mechanical harvesting (Tucker and DeBaggio 2000). Apart from providing a rich source of nutrients, black and brown mustard seeds act to stimulate appetite and digestion. Mustard seeds are rich in mucilage and essential fatty acids as well as glucosinolates. Seed oils act as rubefaciants or irritants when applied topically, causing local vasodilation. Mustard poultices have been used historically to break up congestion in the lungs and

**Table 4.1. Glucosinolates and their precursors**

| <b>Glycoside</b>                      | <b>Aglycone</b>                                 | <b>Precursor</b>    | <b>Herb</b>  |
|---------------------------------------|---|---------------------|--|
| Sinigrin                              | Allyl<br>isothiocyanate                         | Homome-<br>thionine | <i>Brassica nigra</i> ,<br><i>B. juncea</i> ,<br><i>B. oleracea</i>  |
| Sinalbin                              | <i>p</i> -hydroxybenzyl<br>isothiocyanate       | Tyrosine            | <i>Brassica alba</i>   |
| Gluconasturtiin                       | Phenylethyl<br>isothiocyanate                   | Phenylalanine       | <i>Armoracia<br/>rusticana</i><br><i>Nasturtium<br/>officinale</i>   |
| Glucobrassicin                        | 3-indolylmethyl<br>isothiocyanate               | Tryptophan          | <i>Brassica oleracea</i> ,<br><i>B. sativus</i> var.<br><i>niger</i> |
| Glucotropaeolin                       | Benzyl<br>isothiocyanate                        | Phenylalanine       | <i>Tropaeolum<br/>majus</i><br><i>Lepidium sativum</i>               |
| Progoitrin                            | 2-hydroxy-3-butenyl<br>isothiocyanate           | Tyrosine            | <i>Brassica oleracea</i>   |
| Alliin<br>Allyl cysteine<br>sulfoxide | Allicin<br>Allyl disulfide<br>Diallyl disulfide | Cysteine            | <i>Allium sativa</i>   |

bronchioles, though care must be taken not to induce skin lesions.

Taken internally the glucosinolate herbs are effective decongestants for sinus and bronchial conditions (e.g. horseradish and garlic tabs), while also acting to stimulate digestion and circulation. Large doses may induce emesis. As with many sulfur compounds glucosinolates exhibit antibiotic effects.

Benzyl isothiocyanate, obtained by hydrolysis of glucosinolates in *Tropaeolum majus*, is cytotoxic and active against several human tumour cell lines (Pintao *et al.* 1995). *Nasturtium* is traditionally used for acute bronchitis and in dermatology for skin rashes, mild burns and dandruff (Bruneton 1995).

**Glucobrassicin**, widely distributed among the edible Brassicas, produces a number of metabolites known as indoles. Indoles are

thought to be also responsible for some of the well-documented cancer-protecting properties of Brassicas, and they are preserved after cooking. Brassica indoles have been shown to induce tumour-inhibiting enzymes *in vivo* (Brinker 1991).

## Toxicology

Volatile oil of black mustard seed consists purely of glucosinolates, and should never be used internally or externally. The oil is classified as severely toxic and irritant to skin and mucous membranes, and the oral LD<sub>50</sub> is a very low 0.15 (Tisserand and Balacs 1995). Inhalation of the oil induces severe irritation of the eyes and nasal membranes. Essential oil derived from horseradish root (*Cochlearia armoracia*) is equally toxic.

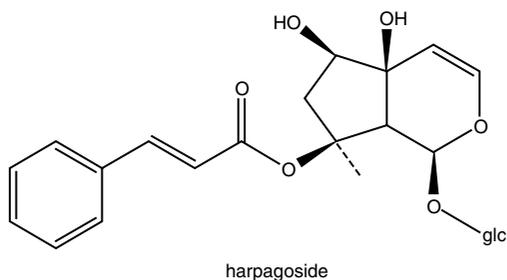
Powdered black mustard seed is the form in which fomentations and other topical medications are traditionally prepared. The *Botanical Safety Handbook* notes that ingestion of large quantities can produce irritant poisoning; however, it can be used safely at appropriate doses. The handbook further advises that external use should not be sustained for longer than two weeks, and is contra-indicated in children under six years of age. Severe burning can occur after 15–30 minutes' application of the pure powder, but the potency can be reduced by mixing with a carrier such as cornstarch (McGuffin *et al.* 1997).

Hypothyroid individuals should avoid oral consumption of glucosinolate herbs and foods except in low quantities.

## Iridoid glycosides

Iridoids are synthesised through the mevalonic acid pathway and are technically known as cyclopentan-*[c]*-pyran monoterpenoids. They occur mainly as glycosides although non-glycosidic iridoids also occur—these are covered in Chapter 5. The name iridoid is derived from the common Australian meat ant *Iridomyrex detectus*, from which it was first detected in 1956 (Sticher 1977). Iridoid glycosides are derived from plants belonging to many families, most notably the Rubiaceae, Lamiaceae, Scrophulariaceae and Gentianaceae.

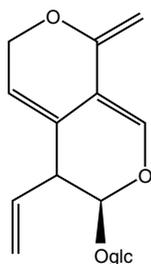
Harpagoside, an anti-inflammatory compound found in devil's claw, *Harpagophytum procumbens* (Pedaliaceae), and figwort, *Scrophularia nodosa* (Scrophulariaceae), combines a phenylpropanoid structure with a typical iridoid glycoside.



The first iridoid glycoside to be identified was **asperuloside** from woodruff—*Asperula odorata* (Rubiaceae). Other compounds of therapeutic significance include **aucubin** from plantain, *Plantago* spp. (Plantaganaceae), **procumbin** from devil's claw and **loganin** from bogbean, *Menyanthes* spp. (Menyanthaceae).

### Secoiridoids

These glycosides are formed by the opening of the five-carbon ring of the iridoid **loganin**. They include **amarogentin**, **gentiopicroside** from gentian, *Gentiana* spp. (Gentianaceae), **picroliv** from *Picrorhiza kurroa* (Scrophulariaceae) and **oleuropein** from olive leaves, *Olea europea* (Oleaceae).



gentiopicroside—a secoiridoid glycoside

### Therapeutic actions

Iridoids are the most bitter of all plant compounds, often responsible for the so-called 'bitter principle'. On a scale for bitter value devised by Wagner and Vaserian (described in Sticher 1977), amarogentin and related secoiridoids were the most bitter of all compounds tested. The taste is perceptible at a dilution of 1 part in 50 000. Bitters are

known to stimulate release of gastrin in the gastrointestinal tract, leading to increase in digestive secretions including bile flow. Bitters improve appetite and assist pancreatic function. They are regarded as cooling remedies, useful for fevers and inflammations.

Various iridoids have been identified as antimicrobial, laxative, choleric and hepatoprotective—especially picroliv (Sticher 1977; Visen *et al.* 1993). While anti-inflammatory activity has been identified in aucubin and others, in most cases it is relatively weak. In the case of **harpagoside** this may depend on the degree of hydrolysis that occurs in the gut since the aglycone (harpagogenin) was found to be less active than the glycoside itself (Recio *et al.* 1994).

Recently much research has been devoted to olive leaf and the secoiridoid oleuropein. Apart from antimicrobial properties, the traditional hypotensive use for the herb has been verified through demonstration of coronary vasodilatory activity (Zarzuelo *et al.* 1991). Investigations by Hansen *et al.* (1996) reveal the presence of a dihydroxyphenyl ethanol fraction with calcium channel antagonist activity, leading to isolation of a new secoiridoid—**oleacein**. Subsequently oleacein was identified as a potent angiotensin converting enzyme (ACE) inhibitor, offering further evidence for hypotensive action. It appears the combination of iridoid glycosides with phenolic derivatives in medicinal herbs may produce synergistic effects that we are only beginning to understand (Cometa *et al.* 1993).

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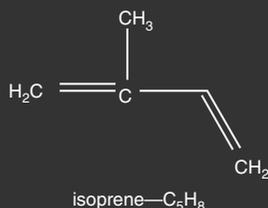


## TERPENES



### Introduction

Terpenoids, or terpenes, comprise one of the most important groups of active compounds in plants with over 20 000 known structures. All terpenoid structures may be divided into isoprene (five-carbon) units containing two unsaturated bonds. They are synthesised from acetate via the mevalonic acid pathway.



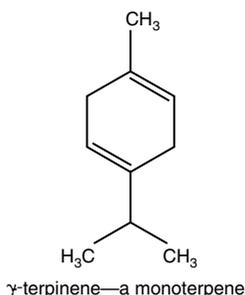
During the formation of the terpenes, the isoprene units are linked in a head to tail fashion. The number of units incorporated into a particular terpene serves as a basis for the classification of these compounds, as shown below:

|               |                |   |
|---------------|----------------|---|
| Isoprene      | $C_5H_8$       |   |
| Terpene       | $(C_5H_8)_n$   |   |
| Monoterpene   | $C_{10}H_{16}$ | Essential oils, e.g. menthol, iridoids                  |
| Sesquiterpene | $C_{15}H_{24}$ | Bitter principles, especially<br>sesquiterpene lactones |
| Diterpene     | $C_{20}H_{32}$ | Resin acids, bitter principles                          |
| Triterpene    | $C_{30}H_{48}$ | Saponins, steroids                                      |
| Tetraterpene  | $C_{40}H_{64}$ | Carotenoids   |
| Polyterpene   | $(C_5H_8)_n$   | Rubber  |

## Monoterpenes

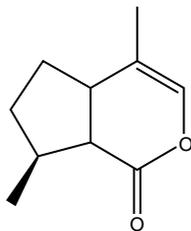
These are the major class of chemical compounds found in essential oils. Among the most widely occurring monoterpene oils are cineole from *Eucalyptus* spp. and pinene from *Pinus* spp. These are covered in Chapter 7.

Biosynthesis involves condensation of two  $C_5$  precursors giving rise to geranyl pyrophosphate, a  $C_{10}$  intermediate from which monoterpenes are derived (Harborne and Baxter 1993). Condensation of geranyl pyrophosphate with  $C_5$  precursors gives rise to diterpenes, and the other classes of terpenoids are similarly formed.



## Iridoids

The bitter iridoid monoterpenes usually occur as glycosides (see Chapter 4). Non-glycosidic iridoids include the sedative **valepotriates** found in valerian—*Valeriana* spp. (Valerianaceae). They are closely related to **nepetalactone**, the volatile component of essential oil of catnip, *Nepeta cataria* (Lamiaceae), responsible for attracting cats to the plant.



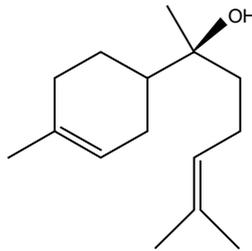
nepetalactone—a monoterpene iridoid

**Paeoniflorin**, a monoterpene glucoside, is a major constituent found in the Chinese herb *Paeonia lactiflora* (Ranunculaceae). The herb is anti-inflammatory, sedative, antipyretic and antispasmodic (Huang 1993).

## Sesquiterpenes

These C<sub>15</sub> compounds occur mainly as ingredients of essential oils or as  $\gamma$ -lactones. They are thought to have evolved as phytoalexins or antifeedants, compounds synthesised by plants as a response to fungal attack and herbivore grazing (Bruneton 1995; Cronquist 1988).

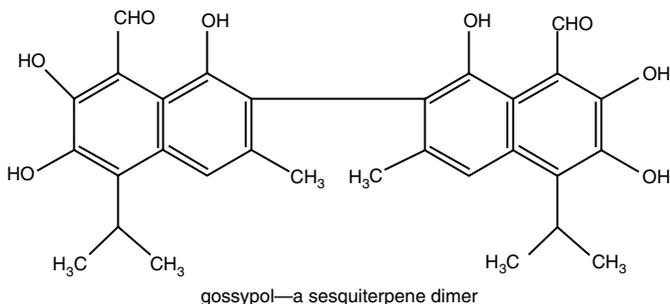
Their main occurrence is also in essential oils, usually in combination with monoterpenes, although they have higher melting points. Essential oil of Roman chamomile, *Anthemis nobilis* (Asteraceae), contains the blue-coloured sesquiterpene **chamazulene**, while German chamomile (*Chamomilla recutita*) contains the anti-inflammatory sesquiterpenes **bisabolol** and **bisabolol oxides**.



bisabolol—a sesquiterpene

**Gossypol** from the cotton plant *Gossypium herbaceum* (Malvaceae) is a sesquiterpene dimer, in which the isoprene units are arranged into two bonded aromatic structures.

Gossypol has been used in China as an antifertility agent in men. It is thought to act primarily on the testicular mitochondria, by inhibiting  $\text{Ca}^{2+}$  uptake at the presynaptic endings (Huang 1993). Despite the high efficacy (> 99%) of gossypol its long-term use as an infertility agent is limited by undesirable side effects which include irreversible infertility (Hamburger and Hostettmann 1991).



Sesquiterpenes are significant constituents of myrrh resin (*Commiphora molmol*). Recent studies indicate that sesquiterpenes are responsible for local anaesthetic, antibacterial and antifungal properties (Dolara *et al.* 2000).

### Sesquiterpene lactones

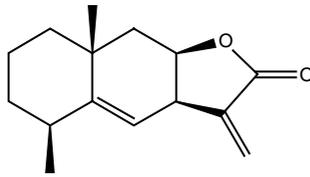
Over 3000 different sesquiterpene lactones are known, and a large number of them occur in the Asteraceae family—in which they are considered a signature group of compounds. They often occur as mixtures of several related compounds, and tend to concentrate in leaves and flowers. Structurally they consist of one and a half terpenes (or six isoprene units) attached to a lactone ring. Many of their names end in the suffix ‘olide’ indicating the presence of the lactone group.

Being such a large group, the lactones are classified into four main subgroups according to their ring structures (Harborne and Baxter 1993; Rodriguez *et al.* 1976):

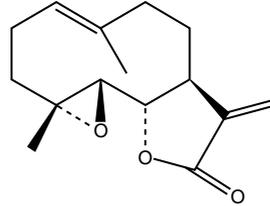
- Eudesmanolides—two fused six-membered rings
- Germacranolides—ten-membered ring
- Guaianolides—a five-membered ring fused to a seven, methyl substituent at C-4
- Pseudoguaianolides—as above but with methyl substituent at C-5

Some Asteraceous medicinal plants and their main sesquiterpene ingredient are listed in Table 5.1.

Apart from their benefit as digestive bitters, many of these



alantolactone—an eudesmanolide  
sesquiterpene lactone



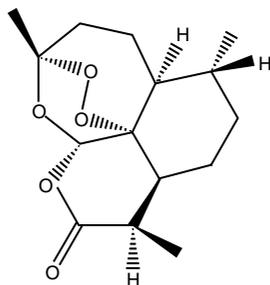
parthenolide—a germacranolide  
sesquiterpene lactone

**Table 5.1 Sesquiterpene lactones from the Asteraceae**

| Species                     | Sesquiterpene lactone |
|-----------------------------|-----------------------|
| <i>Achillea millefolia</i>  | Achillin              |
| <i>Inula helenium</i>       | Alantolactone         |
| <i>Artemisia annua</i>      | Artemisinin           |
| <i>Artemisia absinthum</i>  | Absinthin             |
| <i>Cnicus benedictus</i>    | Cnicin                |
| <i>Arnica montana</i>       | Helenalin             |
| <i>Tanacetum parthenium</i> | Parthenolide          |

compounds have anti-inflammatory, antimicrobial and antiprotozoal actions. Their biological activities have been reviewed by Rodriguez *et al.* (1976). **Parthenolide** from feverfew (*Tanacetum parthenium*) has been widely acclaimed for its benefits in treatment and prevention of migraine headaches, while **artemisinin**, from sweet Annie (*Artemisia annua*), is widely used to treat malaria. In the latter compound the presence of the endoperoxide group attached to the guaianolide-type sesquiterpene structure is responsible for the antiparasitic action. Recently artemisinin has also been found to elicit antitumour activity *in vitro* (Beekman *et al.* 1998). Antibiotic action has been demonstrated for **alantolactone** from *Inula helenium* (Boatto *et al.* 1994).

Further studies with tincture of Arnica have verified an anti-inflammatory effect. The lactone **dihydrohelenalin**, and particularly its ester derivatives, is able to inhibit cytokines TNF- $\alpha$  and IL-1 by regulation of their transcription factors, in a similar way to glucocorticoids (Klaas *et al.* 2001).



artemisinin—a sesquiterpene  
lactone endoperoxide

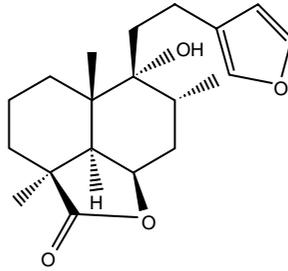
## Allergic contact dermatitis

Numerous sesquiterpene lactone-containing plants of the Asteraceae family are known to cause contact dermatitis in humans. In one case a patient developed acute dermatitis of the right hand with severe blistering following a single application of Arnica tincture (Hormann and Korting 1995). The presence of an  $\alpha$ -methylene group in the chemical structure is thought to be a prerequisite for production of dermatitis (Rodriguez *et al.* 1976). Essential oil of costus (*Saussurea costus*), in which costuslactones are the major components, was formerly used in perfumery; however, it has been identified as a powerful sensitiser and is now rarely used (Tisserand and Balacs 1995).

## Diterpenes

These are the most bitter tasting of all terpenoid compounds, responsible for the acclaimed stomachic and tonic properties of herbs such as **marrubiin** in horehound, *Marrubium vulgare* (Lamiaceae), and **calumbin** from calumba, *Jatrorrhiza palmata* (Berberidaceae). They occur as acyclic, cyclic, bi- tri- and tetracyclic compounds (referring to the number of carbon rings present), while many are also lactones. Some are chiral molecules, indicated by the prefix 'ent'—for enantiomers.

Diterpenes tend to be most abundant in the Lamiaceae family, for example *Salvia officinalis*, or common sage, which has antiviral diterpenes (Tada *et al.* 1994) and **forskolin** from *Coleus forskohlii*. Forskolin has demonstrated a range of activities, including vasodilatory, antihypertensive, bronchodilatory, positive inotropic action on

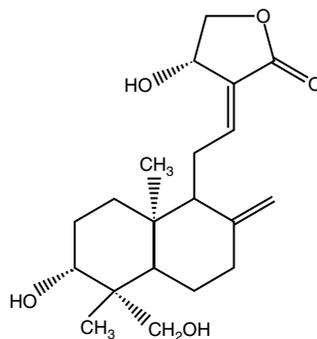


marrubiin—a furanic  
labdane diterpene

the heart, decreases intraocular pressure, and inhibition of platelet aggregation (Hamburger and Hostettmann 1991; Bruneton 1995).

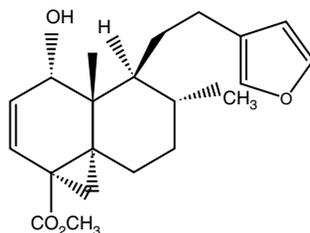
**Taxol** is a complex diterpene from the yew tree, especially the Pacific yew—*Taxus brevifolia* (Taxaceae). Taxol and its derivatives are used as prescription drugs for cervical and breast tumours (Lenaz and De Furia 1993). It has an antimetabolic effect, associated with an interaction of taxol with the tubulin-microtubule system (Hamburger and Hostettmann 1991).

The Indian herb *Andrographis paniculata* (Acanthaceae) contains diterpene lactones, glucosides and dimers including **andrographolide** (Bone 1996). Hepatoprotective activity has been demonstrated, supporting the traditional use for liver and digestive disorders (Chander *et al.* 1995). Andrographolide and its derivatives have been proven to produce substantial immune-enhancing effects, supported by clinical studies in bacterial and respiratory infections (Melchior *et al.* 2000).



andrographolide—a diterpene lactone

The Australian hop bush, *Dodonaea viscosa*—which is also distributed across parts of Oceania, Africa, Southern Asia and Central America—is a rich source of diterpenoids, some of which are pharmacologically active. Ent-labdanes such as **hautriwaic acid** have been shown to produce spasmolytic effects on isolated guinea-pig ileum, involving interference with calcium influx into the smooth muscle cells (Mata *et al.* 1997). Current attention is focused on a new subtype of clerodane diterpenes to be isolated, known as **methyl dodonates** (Ortega *et al.* 2001).



methyl dodonate A—  
a tricyclic clerodane diterpene

## Bitter principles

The term ‘bitter principle’ is used in reference to any one of a group of unrelated constituents responsible for the bitter taste characteristic of many herbs. Most are derived from terpenes, though non-terpene structures such as certain flavonoids and alkaloids are included with the bitters.

Bitters have certain physiological effects regardless of their chemical structure, since the bitterness itself directly stimulates tongue receptors, in turn sending signals via the gustatory nerve for the release of a cascade of gastric secretions and hormones. The effects are to stimulate appetite and digestive processes generally, increasing bile flow, regulating blood sugar levels and counteracting food sensitivities and allergies (Mills 1997). Bitters are regarded as cooling remedies, and hence are also useful for fevers and inflammation.

Recent research indicates up to 80 different bitter taste receptors in humans. These are genetically linked to loci that influence bitter perceptions—hence individuals have vastly different abilities to perceive bitter tastes (Drewnowski and Gomez-Carneros 2000). This genetic variability (polymorphism) has been interpreted as a protective mechanism for identification of bitter poisons; however, it can also

lead to rejection of healthy foods such as grapefruit and salad greens by many people, and the familiar problem of non-compliance with herbal medicines!

Table 5.2 is a list of herbal bitter constituents along with known bitterness indices, calculated from the maximum dilutions of constituents at which bitterness is still detectable (Wagner *et al.* 1984).

**Table 5.2 Bitter principles in herbs**

| Name                            | Class of compounds     | Main constituents                       | Bitterness index                                 |
|---------------------------------|------------------------|---|--|
| <i>Centaureum</i> spp.          | Secoiridoid glycosides | Swertiamarin<br>Gentiopicroside         | Plant > 2000<br>Flowers 12 000                   |
| <i>Gentiana lutea</i>           | Secoiridoid glycosides | Gentiopicrin 2–3.5%<br>Amarogentin 0.5% | 12 000<br>58 × 10 <sup>6</sup><br>Root 10–30 000 |
| <i>Harpagophytum procumbens</i> | Secoiridoid glycosides | Harpagoside<br>Procumbide               | Root 600–2000                                    |
| <i>Menyanthes trifoliata</i>    | Monoterpene alkaloid   | Foliamenthin<br>Gentianin               | Leaf 4–10 000                                    |
| <i>Olea europea</i>             | Secoiridoid glycoside  | Oleuropein 2%                           |  |
| <i>Plantago lanceolata</i>      | Iridoid                | Aucubin 2–2.4%                          |  |
| <i>Cnicus benedictus</i>        | Sesquiterpene lactones | Cnicin<br>Artemisiifolin                | Herb 800–1800                                    |
| <i>Artemisia absinthium</i>     | Sesquiterpene lactones | Absinthin 0.2%                          | 12 700 000<br>Herb 10–25 000                     |
| <i>Cynara scolymus</i>          | Sesquiterpene lactones | Cyanaropicrin                           |  |
| <i>Marrubium vulgare</i>        | Diterpenes             | Marrubiin 0.3–1%                        | 65 000   |
| <i>Bryonia alba</i>             | Triterpenes            | Curcubitacins                           |  |
| <i>Quassia arama</i>            | Secotriterpenes        | Quassin 0.1–0.15%                       | 17 × 10 <sup>6</sup><br>Wood 40–50 000           |
| <i>Citrus aurantium</i>         | Flavanone glycosides   | Neohesperidin<br>Naringin               | 500 000<br>Peel 600–1500                         |
| <i>Humulus lupulus</i>          | Phloroglucinols        | Iso-humulone<br>Lupulone                |  |

## Triterpenes

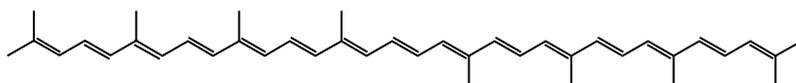
Triterpenes represent a very large group of medicinal plant compounds, and so a separate chapter has been devoted to them (Chapter 6).

## Tetraterpenes

The main group of interest is the carotenoids, over 600 of which are found in nature—providing red, orange and yellow pigments to fruits and vegetables. Some—in particular  $\alpha$  and  $\beta$  **carotene**—act as provitamins, converted to vitamin A by the human digestive system.

Carotenoids are chemically characterised by long hydrocarbon chains with conjugated double bonds. They are synthesised from phytoene, a  $C_{40}$  intermediate formed by condensation of two molecules of geranylgeranyl pyrophosphate (Harborne and Baxter 1993).

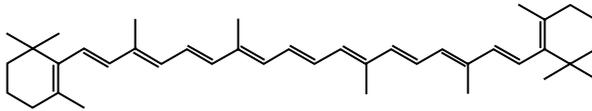
**Lycopene** is a deep-red pigment, found in tomatoes and other pink-red fruits and vegetables. It has a simple acyclic structure, and is considered the prototype molecule for the carotenoid family.



lycopene—an acyclic carotenoid

Lycopene is one of the most widely consumed carotenoids; however, it lacks provitamin A activity. Through cyclisation at one or both end groups of lycopene, carotenes are formed, containing one ( $\delta$  and  $\gamma$  carotenes) or two ( $\alpha$  and  $\beta$  carotenes) ionone rings. **Vitamin A** (all-*trans*-retinol) consists of a  $\beta$ -ionone ring with a side chain of three isoprenoid units. Hence  $\alpha$  and  $\beta$  carotenes provide two molecules of retinol in the human body whereas  $\delta$  and  $\gamma$  carotenes provide only one. In reality, carotenoids are incompletely absorbed and 6  $\mu\text{g}$  of  $\beta$  **carotene** is equivalent to 1  $\mu\text{g}$  retinol equivalent (RE). Carotenoids with hydroxylated ionone rings (e.g. **lutein**) provide no vitamin A activity (Eitenmiller and Landen 1999).

Despite having no provitamin A function, carotenoids such as lycopene and lutein are still biologically active. High serum lycopene



beta-carotene

concentrations have been linked to a reduced risk of atherosclerosis, while preventative effects against heart disease and cancer have also been reported. As an antioxidant it is a powerful quencher of oxygen free radicals compared to other carotenoids (Bruno and Wildman 2001). Lycopene appears to play a particular role in reducing the risk of prostate cancer (Criston *et al.* 2000).

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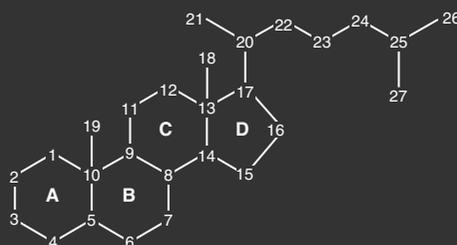


## TRITERPENOIDS AND SAPONINS



### Introduction

Triterpenoid compounds are derived from a  $C_{30}$  precursor, squalene, which was first isolated from shark liver (Bruneton 1995). They have similar configurations to steroids (found in plants and animals) whose  $C_{27}$  skeletons are also derived from squalene. According to convention, the rings are labelled A–D (or E if present) and the carbons are numbered as shown on the diagram.



triterpenoid numbering convention

The triterpenoids are a large and diverse group made up of several subclasses:

- Free triterpenes
- Triterpenoid saponins
- Steroidal saponins
- Cardiac glycosides
- Phytosterols
- Curcubitacins
- Quassinoids

## Phytosterols

Sterols such as **stigmasterol** and **sitosterol** are essential components of cell membranes, and they are also used as the starting material in the production of steroidal drugs. Phytosterols are characterised by a hydroxyl group attached at C-3 and an extra methyl or ethyl substituent in the side chain not present in animal sterols (Harborne and Baxter 1993).

Phytosterols are minor but beneficial components of the human diet since they may inhibit growth of tumours and help in regulation of blood cholesterol. Therapeutically they are important constituents of the following herbs.

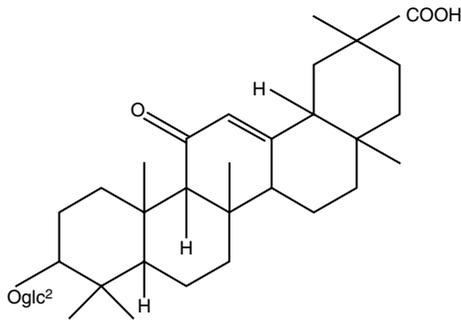
- *Withania somniferum* (Solanaceae), known as ashwaganda in Ayurvedic medicine, contains steroidal lactones called **withanolides** which exhibit antitumour and hepatoprotective activities.
- Recent experiments on stinging nettle root (*Urtica dioica*) demonstrate a potent inhibition of enzymes involved in benign prostatic hyperplasia. Steroidal compounds including **stigmast-4-en-3-one** are thought to be responsible for this activity (Hirano *et al.* 1994).
- In *Commiphora mukul*—myrrh (known as guggal in India)—the resin contains steroids known as **guggulsterones**, which lower blood cholesterol and triglycerides via stimulation of thyroid function (Bruneton 1995).

## Saponins

Saponins are compounds whose active portions form colloidal solutions in water, which produce lather on shaking and precipitate cholesterol. They occur as glycosides whose aglycones are triterpenoid or steroidal structures. The combination of lipophilic (fat-soluble) aglycones at one end of the molecule and hydrophilic (water-soluble) sugars at the other end gives them the ability to lower surface tension, producing the characteristic detergent or soap-like effect on membranes and skin.

## Triterpenoid saponins

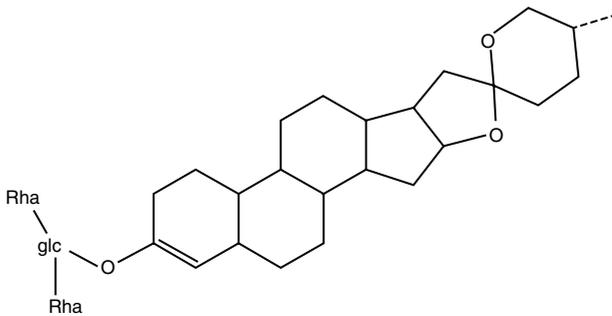
The most widely distributed triterpenoid aglycone is oleanolic acid, which forms a pentacyclic (containing five carbon rings) structure referred to as the oleanane-type ring system. **Glycyrrhetic acid** from liquorice root is an example. Other triterpenoid ring systems include ursane and lupane types as well as the dammarane type—represented by **ginsenosides** from *Panax ginseng* and **jujubosides** from *Ziziphus jujuba* (see Table 6.2).



glycyrrhizic acid from *Glycyrrhiza glabra*

## Steroidal saponins

These are not true triterpenes since their  $C_{27}$  ring skeletons cannot be broken down into isoprene units, although they have a common biosynthetic origin to triterpenes via the mevalonic acid pathway. They are sometimes referred to as nortriterpenes. Some including



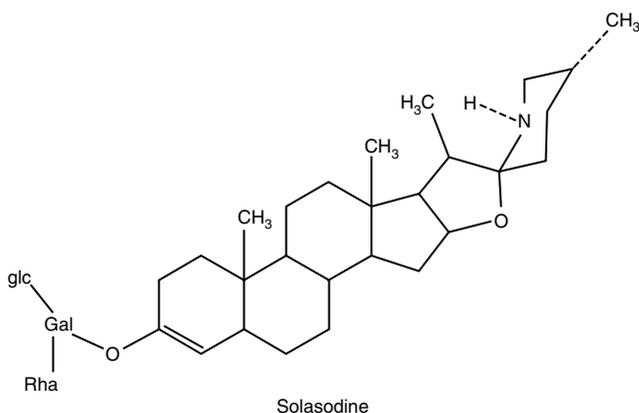
dioscin from *Dioscorea villosa*

diosgenin and hecogenin are used as precursors of sex hormones, cortisone and vitamin D. Steroidal saponins are thought to be responsible—at least in part—for the oestrogenic activity linked to herbs such as *Dioscorea villosa* and *Chamaelirium luteum*, though they are not classed among the phytoestrogens.

A subgroup of the steroidal saponins are the glycoalkaloids, in which the aglycone is a steroidal alkaloid (contains a nitrogen atom). The most common source of these compounds is the *Solanum* genus, including the common potato *Solanum tuberosum*.

Saponins can also be classified according to the way the aglycones are bonded to their sugar moieties:

- monodesmosidic saponins have their sugars and aglycones linked by a single OH group
- bisdesmodic saponins are linked by two OH groups or one OH and one carboxyl group.



The pharmacological activities of saponins were recently reviewed by Lacaille-Dubois and Wagner (1996). Apart from the local detergent and wound-healing effects, saponins have a range of systemic effects according to their chemical structures (see Table 6.1).

Due to their detergent effects noted earlier, saponins are capable of increasing permeability of membranes. They can cause haemolysis by destroying the membranes of red blood cells, thus releasing the haemoglobin—a major concern when saponins are injected as this may lead to anaemia and renal failure due to the sudden influx of haemoglobin into the bloodstream.

**Table 6.1 Systemic effect of various saponins**

|   |
|---|
| Anticancer: cytotoxic, antitumour, antimutagenic                  |
| Anti-inflammatory, antiallergic                                   |
| Immunomodulatory, antiviral                                       |
| Antihepatotoxic   |
| Antidiabetic: hypoglycaemic                                       |
| Antifungal  |
| Molluscicidal   |
| Cardiac activity: haemolytic, antithrombotic, hypocholesterolemic |
| CNS activity: anti-stress, sedative                               |
| Endocrine activity: adaptogenic, oestrogenic                      |
| Expectorant, diuretic   |
| Digestive—accelerate the body's ability to absorb nutrients       |

In an *in vitro* study using sheep erythrocytes, Takechi and Tanaki showed the haemolytic rates of steroidal saponins (bidesmosides) to be much higher than for triterpenoid saponins, suggesting that variation in haemolytic rate is linked to the structure of the aglycone. A possible explanation for the greater haemolytic effects of bidesmosides lies in their higher affinity for cholesterol on erythrocyte membranes (Takechi and Tanaki 1995).

When taken orally, saponins are absorbed rather poorly from the gut. Those that are absorbed are often in the aglycone form, following interaction with bacteria in the large bowel. The slow rate of absorption significantly slows the rate of haemolysis and associated toxicity (Mills and Bone 2000: 43). Saponins are regularly consumed in everyday foods such as cereals (Osbourn 2003) and, with few exceptions, do not demonstrate toxic effects in humans.

Many of the traditional herbal expectorants and diuretics contain significant amounts of saponins. Examples include senega (*Polygala senega*), poke root (*Phytolacca decandra*), golden rod (*Solidago virguarea*) and *Primula* spp. In large doses most of these species are mucous membrane irritants and emetics, hence their expectorant properties may well be reflex effects mediated by the vagus nerve.

Given their structural relationship to steroids, many saponins are renowned for their anti-inflammatory effects. Among the most potent are **saikosaponins** from *Bupleurum falcatum* and **boswellic acid** from *Boswellia serrata*. Saikosaponins are also immunomodulatory and hepatoprotective. Some saponins have been found to reduce

inflammation by inhibition of complement activity—these include some ginseng saponins, kaikasaponins and soyasaponins from kudzu (*Pueraria lobata*) (Oh *et al.* 2000). The presence of certain chemical groups within the saponin skeletons appears to influence anti-inflammatory activity, for example a carboxylic group at C-28 or C-30 (Recio *et al.* 1995).

Saponins, along with phytosterols, are known to play a role in reducing cholesterol plasma concentrations—probably owing to their structural similarities. Diosgenin, the aglycone of dioscin in wild yam (*Dioscorea* spp.), has been shown to reduce cholesterol absorption from the diet, which leads to increased hepatic synthesis and subsequent excretion in the faeces (Mills and Bone 2000). Many vegetables, including spinach, tomatoes and asparagus as well as legumes (especially soya beans), are rich in saponins—it is quite possible they also help reduce plasma cholesterol in this way. Saponins may also have liver-protecting effects—**soyasaponins** and **kudzusaponins** from kudzu root have been shown to be hepatoprotective in rodents (Arao *et al.* 1998).

Numerous triterpenoid saponins have been shown to inhibit pathogenic fungi, for example monodesmosides  $\alpha$  and  $\beta$  hederin from the common ivy (*Hedera helix*). Antifungal activity appears to be influenced by the number and kinds of sugar residues (Favel *et al.* 1994).

The main saponin-containing herbs and their aglycones are listed in Table 6.2.

**Table 6.2 Major saponin-containing herbs**

| Plant name                | Aglycone type                       | Saponin  |
|---------------------------|-------------------------------------|--|
| <i>Smilax officinalis</i> | Spirostan<br>sarsapogenins          | Sarsaparilloside, parilin  |
| <i>Avena sativa</i>       | Steroids<br>Triterpenes             | Avenacosides<br>Avenacin   |
| <i>Bacopa monniera</i>    | Dammarane type<br>Pseudojubilogenin | Bacopasaponins   |
| <i>Bupleurum falcatum</i> | Oleanolic acid                      | Saikosaponins  |
| <i>Panax ginseng</i>      | Protopanaxadiol<br>Protopanaxatriol | Ginsenosides R <sub>b</sub> –R <sub>d</sub><br>Ginsenosides R <sub>e</sub> –R <sub>g</sub> |
| <i>Hedera helix</i>       | Hederagenin                         | Hederin  |
| <i>Polygala senega</i>    | Presenegenin                        | Senegin  |

Table 6.2 (continued)

| Plant name                           | Aglycone type            | Saponin                       |
|--------------------------------------|--------------------------|-------------------------------|
| <i>Anagallis arvensis</i>            | Protoprimulagenin        | Primula acid                  |
| <i>Calendula officinalis</i>         | Oleanolic acid           | Arvenoside                    |
| <i>Beta vulgaris</i>                 | Glucuronide triterpenes  | Betavulgarosides              |
| <i>Centella asiatica</i>             | Ursane-type triterpenoid | Asiatosides                   |
| <i>Ziziphus jujuba</i>               | Dammarane type           | Jujubosides                   |
| <i>Lonicera japonica</i>             | Hederagenin              | Lonicerosides                 |
| <i>Glycyrrhiza glabra</i>            | Oleanolic acid           | Glycyrrhizin,<br>soyasaponins |
| <i>Symphytum officinale</i>          | Hederagenin              | Symphytoxide                  |
| <i>Solidago virguarea</i>            | Polygalacic acid         | Virguare saponins             |
| <i>Guaiacum officinale</i>           | Oleanolic acid           | Guaianins                     |
| <i>Dioscorea villosa</i>             | Steroid—diosgenin        | Dioscin                       |
| <i>Eleuthrococcus<br/>senticosis</i> | Oleanolic acid           | Eleuthrosides                 |
| <i>Aesculus<br/>hippocastanum</i>    | Aescigenin               | Aescin                        |
| <i>Saponaria officinalis</i>         | Gypsoside A              | Saponasides                   |
| <i>Ruscus aculeatus</i>              | Steroid                  | Ruscogenins                   |
| <i>Tribulus terrestris</i>           | Hecogenin                | $\beta$ -galactopyranosides   |
| <i>Pueraria lobata</i>               | Sophradiol               | Kaikasaponin                  |

## Herbal adaptogens

These agents are referred to as ‘harmony remedies’ by Stephen Fulder in his excellent book originally titled *The Root of Being: Ginseng and the Pharmacology of Harmony* (Fulder 1980), still one of the best analyses of this class of medicinal agent. The concept of adaptogens is based around enhancement of vitality and general resistance rather than treatment of specific illnesses.

‘By helping the body cope with stress, adaptogens can help accelerate learning speed, improve the memory, increase stamina in high performance athletes, alleviate small complaints and cut down infections by acting as a prophylactic’ (Wahlstrom 1987).

Examples of adaptogenic herbs include *Panax ginseng* and species, *Eleuthrococcus*, *Glycyrrhiza*, *Smilax* spp., *Dioscorea* spp., *Centella asiatica*, *Bupleurum* spp. and *Schisandra sinensis*.

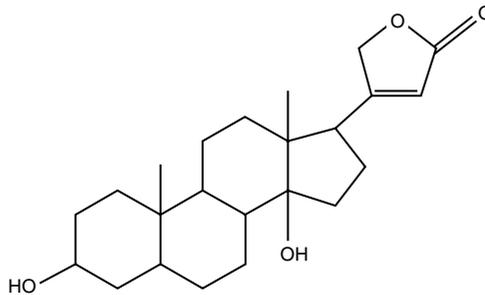
## Cardiac glycosides

These are glycosides possessing lactone rings attached in the  $\beta$  position at C-17. Sugar residues are linked glycosidically via the C-3 OH groups of the steroid aglycones. The aglycones have a tetracyclic steroidal nucleus with hydroxyl groups at positions C-3 and C-14. Most herbs that contain these compounds (and the compounds themselves) are scheduled for use by medical practitioners only; however, all health practitioners should have a basic understanding of their pharmacology since they are so widely prescribed in general practice.

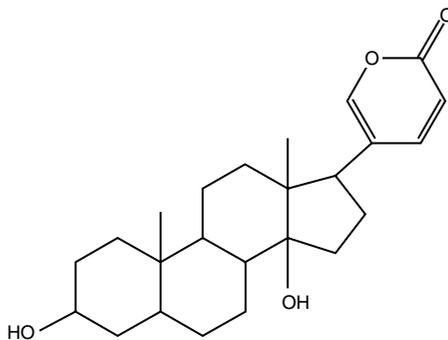
### Biogenesis

Aglycones are derived from mevalonic acid, but the final molecules arise from a condensation of a  $C_{21}$  steroid with a  $C_2$  unit (**cardenolides**) or  $C_3$  unit (**bufadienolides**).

Sugar moieties are composed of three sugar units: glucose, rhamnose and specific sugars such as digitoxose, which occur only in



cardenolide structure



bufadienolide structure

conjunction with cardiac glycoside. The sugar moiety confers on the glycoside solubility properties important in its absorption and distribution in the body. The presence of OH groups increases the onset of action and subsequent dissipation from the body. Glycosides with few OH groups tend to be lipophilic and are absorbed and eliminated more slowly (Bruneton 1995). The most widely used drug in this category is **digoxin**, which is actually a derivative of lantoside C, one of the glycosides in *Digitalis lanata* (Samuelsson 1992).

A select group of plant families are known to produce cardiac glycosides, the most notable being the Liliaceae, Scrophulariaceae and Apocynaceae. Some of the more important of the glycosides along with their plant source are listed in Table 6.3.

**Table 6.3 Plant sources of cardiac glycosides**

| Glycoside                      | Plant source               | Family           |
|--------------------------------|----------------------------|------------------|
| Digitoxin, gitoxin             | <i>Digitalis purpurea</i>  | Scrophulariaceae |
| Lanatosides A–E,<br>digoxin    | <i>Digitalis lanata</i>    | Scrophulariaceae |
| Convallotoxin,<br>convalloside | <i>Convallaria majalis</i> | Liliaceae        |
| Strophanthin                   | <i>Strophanthus gratus</i> | Apocynaceae      |
| Hellebrin                      | <i>Helleborus viridis</i>  | Ranunculaceae    |
| Proscillaridin,<br>scillaren A | <i>Urginea maritima</i>    | Liliaceae        |
| Odoroside, oleandrin           | <i>Nerium oleander</i>     | Apocynaceae      |

### Action of cardiac glycosides

Cardiac glycosides increase the force and speed of systolic contraction. In the failing heart they cause a more complete emptying of ventricles and shortening in length of systole. The heart has more time to rest between contractions. Increased cardiac output causes a lower heart rate and increases renal excretion. As to the pharmacology of digoxin itself, four main actions occur:

1. Positive inotropic effect—increases myocardial contractility due to direct inhibition of membrane-bound  $\text{Na}^+ \text{K}^+$ -ATPase leading to an increase in intracellular  $\text{Ca}^{2+}$ , that is,  $\text{Ca}^{2+}$  replacing  $\text{K}^+$ , leading to an in muscle contraction.

2. Increase in atrial and ventricular myocardial excitability—this may lead to arrhythmias.
3. Decrease in rate of atrioventricular conduction.
4. Increase in vagal tone and myocardial sensitivity to vagal impulses.

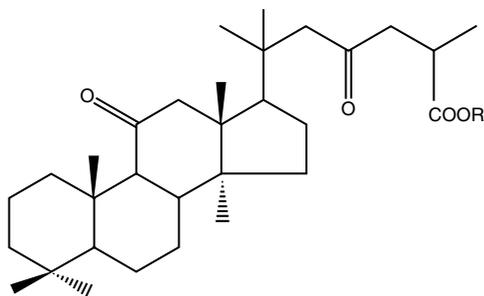
## Toxicity

These compounds have a low therapeutic index (0.5), meaning the therapeutic dose is not much lower than the toxic dose. Digitalis intoxication affects the body in many ways. There are gastrointestinal symptoms (nausea, vomiting, diarrhoea), vision disturbances, neurological symptoms (headache, neuralgia, drowsiness) and cardiovascular symptoms including worsening cardiac failure and arrhythmias. Disturbance of electrolytes occurs and potassium may need to be administered. There are also many contra-indications and drug interactions to be aware of. For a review of digoxin therapeutics and toxicology see Phillips and Johnston (1987).

## Free triterpenes

In a bioassay-oriented fractionation of *Calendula officinalis* flower extracts, the most potent anti-inflammatory activity was found to lie in the free triterpenes, rather than the saponins. While several active triterpenes were identified, the most active was faradiol monoester (Della Loggia *et al.* 1994).

Non-glycosidic triterpenes are found in large concentrations in some of the medicinal macrofungi—in particular reishi (*Ganoderma lucidum*) and *Poria cocos*. The most significant are highly oxygenated lanostane-type triterpenoids known as ganoderals and ganoderic acids from reishi. Well over 100 triterpenes have been isolated from the fruit and mycelium of *Ganoderma lucidum* (Kim *et al.* 2001). Triterpenes are responsible for the bitter taste that distinguishes reishi from most other mushrooms. These compounds inhibit histamine release, are antihepatotoxic and ACE-inhibiting. They also inhibit cholesterol synthesis (Komoda, *et al.* 1989) and some were proved to have cytotoxicity against hepatoma cells *in vitro* (Hirotani *et al.* 1985). Ten lanostane triterpenes have been found to be ACE inhibitors—these compounds were responsible for *in vivo* antihypertensive activity in mice (Morigiwa *et al.* 1986). Several of the terpenes inhibit HIV-1 *in vitro* (Kim *et al.* 2001).



ganoderic acid A

Poriatin, a low-molecular-weight triterpene from *Poria coccus*, has immunomodulating properties. It has demonstrated antiviral activity and increased production of macrophages and other immune cells. It has also demonstrated immunosuppressive activity, reducing the severity of induced autoimmune encephalitis in conjunction with a standard autoimmune drug. Poriatin is a known aldosterone antagonist (Hobbs 1995).

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## ESSENTIAL OILS AND RESINS



### Essential oils

Essential oils are odorous principles stored in special plant cells—glands, glandular hairs, oil ducts or resin ducts—situated in any part of a plant or its exudations. These oils are responsible for the distinctive aromas associated with individual plant species. They are soluble in alcohol and fats, but only slightly soluble in water. Most essential oils are colourless, apart from azulene, which is blue. On exposure to light and air they readily oxidise and resinify. They are also called volatile oils, since they evaporate when subjected to heat.

### Extraction of oils

Steam and steam/water distillation are the predominant extraction methods used. Other methods include solvent extraction, cold pressing, infusion, effleurage and water distillation. Distillation is a method that involves the evaporation and subsequent condensation of liquids in order to produce, refine and concentrate essential oils. High quality oils are distilled once only, while some commercial oils are ‘purified’ by double or triple distillation methods.

### The olfactory system

This is the structure that is responsible for our sense of smell. The olfactory nerves connect directly to the limbic system in the brain, and thereby influence sensory functions such as hunger, sex and emotions. Smelling involves the inhalation of microscopic chemicals such as those contained in essential oils which flow through our nostrils into the nasal cavity. Here they pass over moist bony structures called turbinates to reach the olfactory receptor cells, where

the chemical dissolves and comes in contact with a fine layer of hairs, which then stimulates the olfactory bulb of the brain (Wrigley and Fagg 1990). Research into the chemistry of plant odours shows there is a definite link between the shape of molecules and their smell. Compounds that occur as enantiomers produce odours that differ according to which isomer is present, so that compounds with the same chemical formula can have different odours and different biological actions (Pavia *et al.* 1982).

## Chemistry of essential oils

The total essential oil content of plants is generally very low (< 1%). However, many therapeutic oils are so potent that they are still active in herbal (Galenical) preparations. Upon isolation these oils are highly concentrated, and are widely used in this form by aromatherapists—mainly for external application but sometimes for internal consumption (in diluted forms). Most oils consist of complex mixtures of chemical compounds, and it is often the unique chemical combination rather than a single component that is responsible for any therapeutic activity. The composition can vary according to the season, time of day, growing conditions and genetic make-up of the plant. Many oils contain over 50 individual compounds—these can generally be identified using gas chromatography and mass spectrometry (GC/MS).

## Chemotypes of oils

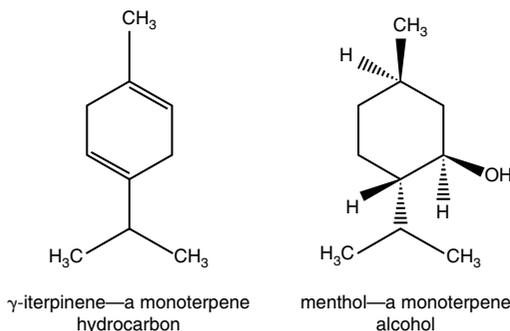
Essential oil composition can vary according to geographic and genetic factors, even though the same botanic species is involved—a phenomenon known as chemical polymorphism. When this occurs a terminology can be used where the Latin name is followed by the name of the chemical component most characteristic for that particular race of the plant, that is, its chemotype, for example *Thymus vulgaris* linalol, *Thymus vulgaris* thymol. Seven chemo types of thyme are known in the western Mediterranean area alone (Bruneton 1995).

## Major categories of aromatic oil compounds

### *Terpenoids*

These are constructed from a series of isoprene units linked together in head to tail fashion, as described in Chapter 5.

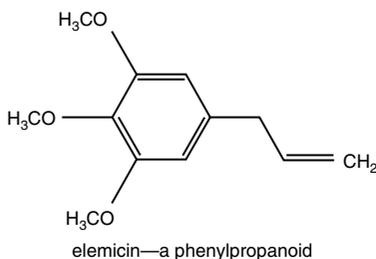
The most widely occurring terpenes are the smallest molecules, that is, the **monoterpenes**,  $C_{10}H_{16}$ , and their oxygenated derivatives such as ketones, aldehydes, alcohols, oxides, phenols, along with simple hydrocarbons. Their properties are determined by functional groups—oxygen-containing radicals attached to the carbon skeleton.



**Sesquiterpenes**,  $C_{15}H_{24}$ , and **diterpenes**,  $C_{20}H_{32}$ , also occur in essential oils.

### *Phenylpropanoids*

These compounds contain a benzene ring structure with an attached propane ( $C_3$ ) side chain (see Chapter 2). The most common precursor is cinnamic acid, a derivative of the shikimic acid pathway. They include some aldehydes, phenols and phenolic ethers.



Another major subclass consists of sulfur compounds whose linear structures are non-terpenoid.

The major subclasses or families of terpene essential oil constituents are listed in Table 7.1.

**Table 7.1 Classification of essential oil compounds**

| Compound         | Description  | Example                                 |
|------------------|--|---|
| Hydrocarbon      | Contains only carbon and hydrogen atoms                                | Pinene, limonene                        |
| Alcohol          | Contains a hydroxyl group (OH) attached to the terpene structure       | Menthol, terpenin-4-ol, geraniol        |
| Aldehyde         | Terpenoids with a carbonyl group (C=O) and hydrogen bonded to a carbon | Citral (geranial/neral), citronellal    |
| Cyclic aldehydes | Aldehyde group attached to a benzene ring                              | Cinnamic aldehyde, vanillin             |
| Ketone           | Contains a carbonyl group bonded to two carbon atoms.                  | Camphor, thujone                        |
| Phenol           | Hydroxyl group attached to a benzene ring                              | Thymol, eugenol, carvacrol              |
| Phenolic ether   | Contains an O between C and benzene ring                               | Safrol, anethole, myristicin            |
| Oxide            | Has an O bridging two or more carbons                                  | Cineole, ascaridole                     |
| Ester            | Condensation product of acid and alcohol                               | Methyl salicylate, allyl isothiocyanate |

### The influence of chemical structures on essential oil therapeutics

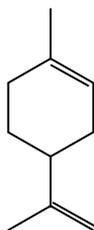
Essential oils are readily absorbed into the body and across the blood–brain barrier because of their small molecular size and strong lipophilic nature. Compared to other compounds the therapeutic action of essential oils can be anticipated by knowledge of their chemistry—based primarily on the functional groups. Hence oils in the same molecular class are likely to exhibit similar therapeutic activities (see Table 7.2).

### Monoterpene hydrocarbons

These are almost universal in essential oils, acting also as precursors of the more complex, oxidised terpenes. **Limonene**, for example, is the precursor of the main constituents of the monoterpenes in mints, *Mentha* spp. (Lamiaceae), including carvone and menthol

**Table 7.2 Properties of essential oil families**

| Compound               | Properties  |
|------------------------|---|
| Hydrocarbons           | Stimulant, decongestant, antiviral, antitumour    |
| Alcohols               | Antimicrobial, antiseptic, tonifying, spasmolytic |
| Sesquiterpene alcohols | Anti-inflammatory, antiallergenic                 |
| Phenols                | Antimicrobial, irritant, immune stimulating       |
| Aldehydes              | Spasmolytic, sedative, antiviral                  |
| Cyclic aldehydes       | Spasmolytic                                       |
| Ketones                | Mucolytic, cell regenerating, neurotoxic          |
| Esters                 | Spasmolytic, sedative, antifungal                 |
| Oxides                 | Expectorant, stimulant                            |
| Coumarins              | UV sensitising, antimicrobial                     |
| Sesquiterpenes         | Anti-inflammatory, antiviral                      |
| Phenylpropanes         | Carminative, anaesthetic                          |
| Sesquiterpene lactones | Mucolytic, immune stimulating                     |



limonene—a monoterpene hydrocarbon

(Croteau 1991). Limonene is also found in citrus oils and dill, *Anethum graveolens* (Apiaceae).

Limonene and other citrus oils have antitumour effects in mice, though the action may be lost or even reversed as the hydrocarbons gradually become oxidised. A study supported by the US National Cancer Institute found that hydrocarbons from dill and caraway oils (especially **carvone** and limonene) increased levels of the detoxifying enzyme glutathione S-transferase (GST) in mice tissues (Zheng *et al.* 1992). Limonene is active against a wide variety of tumour lines and is presently undergoing phase I trials in pancreatic and colorectal cancer patients (Boik 1995). Limonene, **terpenine** and other terpene

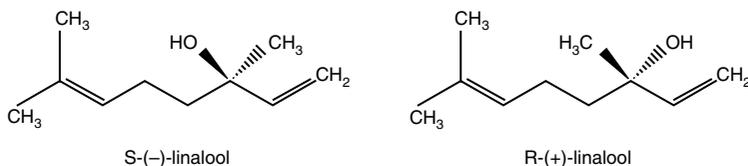
hydrocarbons have also been found to possess antiviral properties in low concentrations (Schnaubelt 1989). They are considered by aromatherapists to be tonics to the mucous membranes, being used widely as nasal decongestants (Battaglia 1995). The hydrocarbons in dill oil are thought to contribute to their diuretic action (Mahran *et al.* 1992).

$\alpha$ -pinene and  $\beta$ -pinene are widely distributed in plants, with high proportions in oil of turpentine (known also as terebinthina) from different species of *Pinus*. Turpentine oil is used as a rubifacient or linament in rheumatic disease. Pinene has a pleasant aromatic odour and is an important component of many culinary spices, including black pepper—*Piper nigrum* (Piperaceae). Other monoterpene hydrocarbons include  $\alpha$ -sabinene, *p*-cymene, myrcene and  $\alpha$ -phellandrene.

## Alcohols

Alcohols have a hydroxyl group attached to a C<sub>10</sub> hydrocarbon skeleton. Terpene alcohols are so highly valued for their fragrance, healing properties and gentle reaction on skin and membranes that they have been termed ‘friendly molecules’ (Schnaubelt 1989). Alcohols rank with phenols as being among the most potent antimicrobial essential oil compounds, but they do not contain the irritant properties of the latter.

**Linalool** (or linalol) is enantiomeric, existing in two isoforms. The (*R*)-form (licareol) is found in rose, neroli and lavender oils, and is a major component of *Mentha arvensis*. The (*S*)-form (coriandrol) is found in oil of coriander, and is the major component of *Cryptocarya moschata* (Lauraceae) (Connolly and Hill 1991). The presence of more than 5% of the S-form in lavender oil (*Lavandula angustifolia*) is a strong indicator of adulteration (Leach 2000).



enantiomeric forms of linalool

Linalool is widely distributed, contributing to the flavour and biological activity of grapevine leaves, lemon, basil, tea leaves, thyme and cardamom (Duke and Beckstrom-Sternberg 2001). It is also a major component of some Australian melaleuca oils, especially *Melaleuca ericifolia*.

Research into linalool-rich plants from Brazil demonstrates potent effects on the central nervous system *in vivo*, including sedative, spasmolytic and hypothermic activity. Linalool has been shown to modulate glutamate activation expression *in vivo* and *in vitro* and may also inhibit GABAergic transmission (Elizabetsky *et al.* 1999). Linalool has also been shown to produce an inhibitory effect on acetylcholine (Ach) release and on the channel opening time of the neuromuscular junction, as well as a local anaesthetic action (Re *et al.* 2000).

Tea tree oil is derived from leaves of *Melaleuca alternifolia* and *M. linearifolia* (Myrtaceae), native to the east coast of New South Wales. To meet the Australian standard for tea tree oil the **terpinen-4-ol** content must be at least 30% while that of the oxidised terpene **1,8 cineole** must not exceed 15% (Williams *et al.* 1988). The chemotypes of tea tree oil from natural stands is genetically determined, so that all commercial plantations are started from seed known to be of the right chemotype. Other terpene constituents of tea tree oil are the alcohol  $\alpha$ -**terpineol**, hydrocarbons  $\alpha$ -pinene and  $\beta$ -pinene, p-cymene and  $\gamma$ -terpinene, and sesquiterpenes including the unique compound viridiflorene (Penoel 1990). Terpinen-4-ol is also a major ingredient in marjoram—*Marjorana hortensis* (Lamiaceae).

While tea tree oil is not the most powerful antimicrobial available, it is considered by some to be the ideal skin disinfectant due to its activity against a wide range of microorganisms (both gram+ and gram- bacteria as well as fungi), its low incidence of irritation, and ease of penetration (Altman 1988). Tea tree oil can be applied to all afflictions of the skin and orifices. The broad antimicrobial activity makes it useful for vaginal irritations since these can result from a variety of pathogenic organisms including yeasts and bacteria (Williams and Home 1995). However, its action is not restricted to that of an antiseptic—it is revered by aromatherapists for its general harmonising attributes and immune stimulant effects (Penoel 1990).

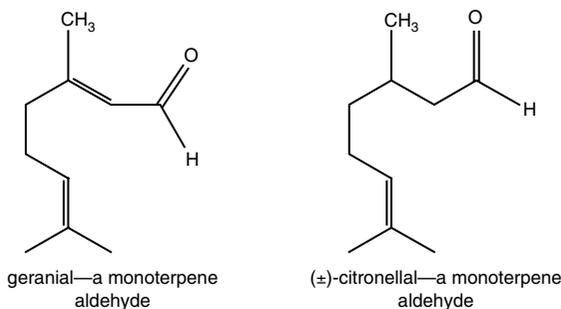
Peppermint oil is derived from the dried leaves and flowering tops of *Mentha piperita* (Lamiaceae). The oil consists of about 50% **menthol**. The taste and odour of peppermint oil are also influenced by some of its minor components, notably the menthol esters

**jasmone** and **menthofuran**. The latter compound has a disagreeable odour and is mainly concentrated in young peppermint plants (Samuelsson 1992). Peppermint is one of the best carminatives and the oil is sometimes administered in capsules for irritable bowel syndrome. Animal studies using peppermint oil demonstrated a significant spasmolytic effect, most likely as a result of the menthol content (Taddei *et al.* 1988). Menthol is an ingredient in several pharmaceutical preparations and inhalants for congestion of the respiratory tract.

Other terpene alcohols include **geraniol**, **citronellol** from rose oil, *Rosa gallica* (Rosaceae), and scented geraniums *Pelargonium* spp. (Geraniaceae). **Nerol** is a stereoisomer of geraniol. **Borneol** is found in rosemary oil—*Rosmarinus officinalis* (Lamiaceae). **Santalol** from heartwood of sandalwood—*Santalum album*, *S. spicatum* (Santalaceae)—is a sesquiterpene alcohol.

## Aldehydes

Aldehydes are highly reactive compounds in which one hydrogen atom is bonded to a carbonyl group at the end of a hydrocarbon chain. Monoterpene aldehydes such as those found in citrus oils correspond to their respective alcohol; note their names end in ‘al’, hence: geraniol, citronellol (alcohols); **geranial**, **citronellal** (aldehydes).



Citrus essential oils are present in leaves, flowers and fruits of plants in the citrus family (Rutaceae); however, the main medicinal oils are found in the fruit peel. The best-quality oils come from the

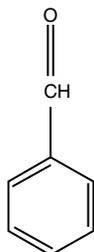
bitter orange, *Citrus aurantium*, and the lemon, *C. limon*. Although the hydrocarbon limonene is the major constituent, the aroma of the oils is determined by the presence of aldehydes, namely the isomers geranial ( $\alpha$ -citral) and neral ( $\beta$  citral)—together known as **citral**—and also citronellal. Citral features as the dominant constituent in other citrus-flavoured oils such as those from lemon grass (*Cymbopogon citratus*), lemon balm (*Melissa officinalis*), lemon verbena (*Aloysia triphylla*) and the Australian sweet verbena tree, *Backhousia citriodora*, which consists almost entirely of citral. The oil of the lemon-scented gum—*Eucalyptus citriodora* (Myrtaceae)—consists mainly of citronellal with a small amount of the alcohol citronellol, while that of lemon-scented tea tree (*Leptospermum citratum*) contains both citral and citronellal.

Apart from its pleasant aroma, citral is valued for its sedative, antiviral and antimicrobial properties. Citral-rich oils derived from lemon grass and lemon-scented tea tree were shown to inhibit *Candida albicans* at more than four times the rate (zone of inhibition) of tea tree oil (Williams and Home 1995). However, many aldehydes are irritants, causing skin sensitivity in some people thereby restricting their use in topical applications.

### *Cyclic aldehydes*

Also known as aromatic aldehydes, these are derived from phenylpropanoids and lack the terpene structure. They have characteristically sweet, pleasant odours and are found in some of our most well known culinary herbs and spices such as cinnamon and nutmeg.

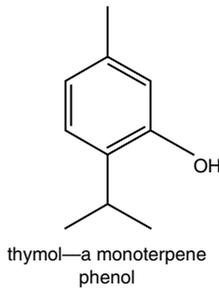
**Cinnamic aldehyde** is found in cinnamon and cassia barks—*Cinnamomum* spp. (Lauraceae). **Benzaldehyde** is the main constituent of bitter almond essential oil.



benzaldehyde—an  
aromatic aldehyde

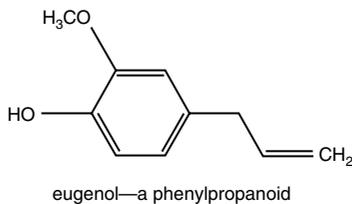
## Phenols

While present in only a relatively few aromatic herbs, phenolic volatile oils are among the most potent and potentially irritant compounds found in essential oils. Phenols are represented in both major classes of aromatic compounds—the monoterpenes and phenylpropanoids. The major monoterpene phenols, **thymol** and **carvacrol**, are found in thyme, *Thymus* spp., and oregano, *Origanum vulgare* (Lamiaceae).



Thyme oil consists entirely of terpenes, the most dominant being a mixture of the phenols thymol and carvacrol. Other compounds present are the alcohols linalool, geraniol and  $\alpha$ -terpineol (Stahl-Biskup 1991). Thymol is an expectorant, antimicrobial, anthelmintic and antispasmodic. It is a dermal and mucous membrane irritant and caution is required in its use. The tincture is a safer means of administration than the oil itself.

**Eugenol** is a phenylpropanoid with a free hydroxyl group. It is widely distributed in plants, one of the main sources being clove oil from flower buds of *Syzygium aromaticum* (Myrtaceae). It is a major constituent of bay leaf, nutmeg and allspice.



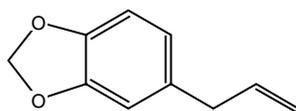
Eugenol has antimicrobial properties akin to thymol, which—coupled with its anaesthetic properties—make it an effective disinfectant and cauterising agent in dentistry (Valnet 1980). Clove oil is an effective topical remedy for toothache and is a powerful stimulant and aromatic. Clove powder is an essential ingredient in the ‘Composition Powder’ made famous by Samuel Thomson. Recent studies demonstrate potent inhibitory effects on lipid peroxidation (Toda *et al.* 1994) and dual inhibition of arachidonic acid and platelet-aggregating factor (PAF) for eugenol (Saeed *et al.* 1995). Recent investigations have also confirmed *in vivo* anticonvulsant (Sayyah *et al.* 2002) and anti-ulcerogenic activity (Capasso *et al.* 2000).

The Australian myrtle leaf (*Backhousia myrtifolia*) is a rich source of phenylpropanoid essential oils, particularly elemicin and methyl eugenol (Brophy *et al.* 1995).

## Phenolic ethers

The majority of these phenols are also **phenylpropane** derivatives—many are prominent constituents of common spices such as cloves, aniseed, celery seed, basil and tarragon.

The structures are characterised by a side group with two oxygen atoms attached to the phenylpropanoid ring as occurs in **safrole**.



safrole—a phenylpropanoid ether

Phenolic ethers when isolated are irritant and toxic, and the oils from which they derive must be used with great care. The spices themselves are generally considered to be safe.

Safrole is derived from the root bark of the sassafras tree, *Sassafras albidum*, and *Camphora* spp., both of the Lauraceae family. It is also found as a minor constituent in cocoa, nutmeg and pepper and was once the principle ingredients of ‘root beer’ (Hall 1973). Use of this oil is restricted due to suspected carcinogenic properties—demonstrated in rodents following administration of high doses.

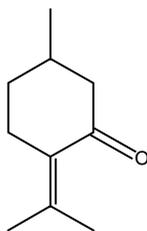
**Myristicin** is found in nutmeg and mace—*Myristica fragrans* (Myristicaceae). It also occurs in black pepper, carrot, parsley and dill. Myristicin is structurally related to safrol and is toxic in high doses. Nutmeg itself exhibits narcotic and intoxicating properties, though it does have medicinal uses in lower doses (Hall 1973).

**Methylchavicol** is the major constituent of oil of basil—*Ocimum basilicum* (Lamiaceae). As with other phenols this one is a skin irritant, though it is milder than eugenol—a component of the French basil varieties (Home and Williams 1990).

Other phenolic ethers in common herbs and spices include **anethol** from aniseed, star anise and fennel and **apiole** derived from parsley seed—*Petroselinum crispum* (Apiaceae).

## Ketones

Monoterpenoid ketones are cyclic compounds in which a carbonyl group is bonded to two carbon atoms. They are produced by oxidation of alcohols and are relatively stable molecules. Monocyclic ketones such as **pulegone** contain a single carbon ring while bicyclic ketones like **camphor** contain two fused rings. Most ketones have the suffix ‘one’.



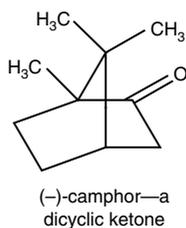
pulegone—a monoterpenoid ketone

Ketones have attained notoriety because of their alleged toxic and abortifacient properties; however, not all ketones are toxic (Tisserand and Balacs 1995). Ketones are present in some of the more benign essential oils such as those from spearmint and fennel. On the other hand, **thujone**, pulegone and related ketones are certainly toxic with potential for inducing convulsions in high doses, and they must never be used during pregnancy. On the positive side

ketone volatile oils are mucolytic and of benefit for respiratory congestion (Schnaubelt 1989).

The ketone **carvone** is optically isomeric—one isomer (+)-**carvone** is found in oil of caraway seed, *Carum carvi* (Apiaceae), whereas the other, (-)-**carvone**, is the main constituent of oil of spearmint, *Mentha spicata* (Lamiaceae).

Camphor is derived from the heartwood of the camphor laurel, *Cinnamomum camphora* (Lauraceae), in the (+) isomeric form. The (-) form occurs in feverfew, *Tanacetum parthenium* (Asteraceae), and in some lavender varieties. It is regarded as an undesirable constituent in lavender oil. Much of the camphor used in commerce is prepared synthetically from other monoterpenes. Camphor is a CNS stimulant, primarily used as a topical agent for its antipruritic, rubifacient and mucolytic properties. It is toxic in high doses.



Thujone was originally isolated from the Arbor Vitae, *Thuja occidentalis* (Cupressaceae); however, it also occurs in some unrelated plants, particularly those of the *Artemisia* genus (Asteraceae) including wormwood (*A. absinthium*) and mugwort (*A. vulgaris*). Other sources are tansy, *Tanacetum vulgare* (Asteraceae), sage (*Salvia officinalis*) and clary sage (*S. sclarea*) from the Lamiaceae family. Many of these herbs are steeped in folklore with reputations as stimulants, psychedelics, anthelmintics, abortifacients and as ingredients in intoxicating beverages such as vermouth and absinthe (Albert-Puleo 1978). The above herbs are all classed as emmenagogues and are contra-indicated for pregnancy.

Thujone exists in two isomeric forms— $\alpha$  and  $\beta$  ketone, with most of the toxicity residing in  $\alpha$  thujone. Sage oil is the least toxic of this group despite containing 50% thujone, being a mixture of the two isomers. Care is still necessary in its use (Tisserand 1988). Pulegone, a related ketone found in oil of pennyroyal, *Mentha pulegium*

(Lamiaceae), has similar properties, and the same precautions for its use apply as for thujone-containing oils.

**Isopinocampone** is the main constituent of oil of hyssop, *Hyssopus officinalis* (Lamiaceae), imparting the typical mucolytic properties of ketones, while muscle relaxant activity has been demonstrated *in vivo* (Lu *et al.* 2002). **Piperitone** is the main constituent of the leaf oils of the so-called ‘peppermint’ group of the genus *Eucalyptus*. An example is the broad-leaf peppermint, *Eucalyptus dives*, an excellent, non-irritant mucolytic agent for sinus congestion and bronchitis (Schnaubelt 1995).

## Oxides

Monoterpene oxides are relatively reactive, unstable molecules in which an oxygen atom is situated between two carbons. In most cases the oxygen atom substitutes a carbon in the ring of a monoterpenoid—usually an alcohol. An example is **bisabolol oxide** from chamomile (*Matricaria chamomilla*). However, in the two most significant oxides—**1,8-cineole** and **ascaridole**—found in essential oils, the oxygen atoms are attached outside the main hydrocarbon ring.



1,8-cineole—a monoterpene oxide

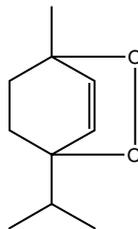
1,8-cineole (referred to also as cineole) is one of the most widely distributed compounds in the plant world, being an oxidised derivative of other monoterpene compounds. It is a monoterpene ether, in which a secondary ring (containing the O) is attached to the first ring at positions 1 and 8. Cineole is the major constituent of eucalyptus oil derived from numerous species of *Eucalyptus* (Myrtaceae)—hence the alternative name **eucalyptol**. It is also the major constituent of oil of cajuput—*Melaleuca cajuputi* (Myrtaceae). Cineole is an expectorant and mucolytic agent, and is a universal ingredient in cough

lozenges and other medications. In the past it had a reputation for being a skin irritant and hence an undesirable component in tea tree oil—many products for topical application having been formulated on oils with very low cineole content. This assertion has been challenged in recent years, and an occlusive patch test on human subjects has failed to demonstrate any skin irritancy for cineole (Southwell *et al.* 1997).

## Eucalyptus oil

Eucalyptus oils vary in aroma and quality according to the level of cineole, and of the minor constituents present in each oil. Cineole-rich oils (generally from *Eucalyptus globulus*) are preferred for medicinal use where their expectorant property is highly valued; however, other species with a different balance of compounds are sometimes preferred—especially by aromatherapists. These include *E. radiata* with the hydrocarbons  $\alpha$ -terpineol and pinene and *E. dives* containing phellandrene and the ketone piperitone. All eucalyptus oils are renowned for their antiseptic qualities, while some species have been shown to inhibit viruses as well. Oils high in cineole and terpene hydrocarbons are considered the most effective against influenza viruses (Schnaubelt 1988/89). The synergistic activity of using two or more essential oils together can result in an even stronger antimicrobial activity, as demonstrated in an experiment where the addition of basil oil to eucalyptus oil increased the bactericidal activity twenty-fold (Brud and Gora 1989).

**Ascaridole**, a peroxide, has two oxygen atoms between two carbons. It is considered to be the most highly toxic of all the essential oils, and is known to explode when mixed with organic acids (Tisserand and Balacs 1995). It is the main constituent of **wormseed**

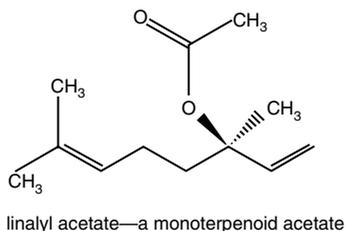


ascaridole—a monoterpene peroxide

oil—from *Chenopodium ambrosoides* (Chenopodiaceae)—and a lesser constituent of **oil of boldo**, from *Peumus boldo* (Monimaceae). Ascaridole is strongly anthelmintic though its use is limited by its toxic nature. Wormseed is sometimes used in a crude form, as a powder or extract where it is relatively safe to use in low doses.

## Esters

Most esters are formed by reaction of terpene alcohols with acetic acid. They are among the most widespread volatile oil compounds—being found mainly in flowers—however, they are generally present in small amounts. Their distinctively fragrant aromas characterise many of the oils in which they appear. Lavender oil contains the alcohol **linalool** along with its ester **linalyl acetate**; the relative abundance of these two constituents is considered to be an indicator of high quality.

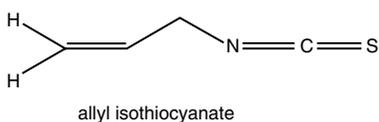


Most esters are gentle, non-irritant compounds, whose action is mainly sedative and antispasmodic. Examples of these are also found in oils of Roman chamomile, *Anthemis nobilis* (Asteraceae), clary sage, *Salvia sclarea* (Lamiaceae), and bergamot, *Citrus aurantium* (Rutaceae). Less benign esters are found in oils of wintergreen and mustard (see below).

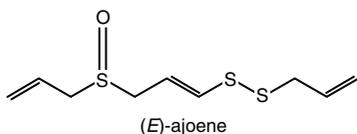
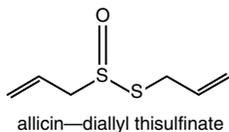
**Methyl salicylate** is derived from oil of wintergreen—*Gaultheria procumbens* (Ericaceae). It is an aromatic ester derived from salicylic acid and methanol, though it can now be produced synthetically. Methyl salicylate is mainly used in topical applications and liniments as a counter-irritant and antirheumatic. Internal administration is not recommended since it is quite toxic in large doses.

## Sulfur compounds

These are linear molecules containing one or more sulfur substituents. They are quite reactive. Most are based on the ‘allyl’ group structure ( $\text{CH}_2=\text{CHCH}_2$ ). They occur mainly as aglycones to glucosinolates, covered in Chapter 4. **Allyl isothiocyanate** contains both nitrogen and sulfur and it is derived from oils of mustard, *Brassica nigra* and spp., and horseradish, *Cochlearia armoracia* (Brassicaceae). Allyl isothiocyanate and similar compounds from the *Allium* genus are known to have antimicrobial and antitumour properties.



**Allyl sulfides** are a group of sulfur compounds based on the allyl structure, and found in **garlic**, *Allium sativa*, **onion**, *A. cepa*, and other members of the *Allium* genus (Liliaceae). Their common precursor is the sulfur-containing amino acid **cysteine**. The complex chemistry of garlic and onions is best reviewed by Eric Block (1985) and more recently by Sendl (1995). Extraction techniques using different solvents have assisted in identification of oxidation and decomposition products of garlic and onions. These include: **diallyl disulfide**—product of steam distillation of garlic; **allicin**—the oxide of diallyl disulfide, and source of garlic odour; **ajoene**—formed from decomposition of allicin; and **lachrymatory factor**—converted from precursor by enzymic action when slicing onion (Block 1995).



Apart from the antimicrobial properties noted above, allyl derivatives such as ajoene have demonstrated activity against platelet aggregation, inhibition of pro-inflammatory prostaglandins, anti-tumour and hypoglycaemic effects (Reuter 1995).

## Resins

Resins are solid, brittle substances secreted by plants into special ducts, often as a response to damage to the plant by wounding, wind damage, etc. Their main role appears to be protection of the plant from attack by fungi and insects. Resins are difficult to classify because of their amorphous nature; they are complex mixtures that include lignans, resin acids, resin alcohols, resinotannols, esters and resenes (see Table 7.3).

Resins are insoluble in water but soluble in alcohol and fixed oils. They are heavier than water and volatile oils, and have high boiling points. They are translucent and burn with a characteristic smoky flame—hence their use in incense. They have fixative actions, making them useful ingredients in crafts and industry.

While classifying individual resins is difficult, they are sometimes classified as mixtures with other plant constituents, for example gum-resins, oleo-gum-resins, glycoresins. One of the most well known resins comes from the *Pinus* genus (Pinaceae) and is known as **rosin**. This amber-coloured resin is mainly used in varnishes and other industrial products.

## Balsams

These are resinous mixtures that contain cinnamic and/or benzoic acid or their esters. **Benzoin** is a balsamic resin derived from the bark of *Styrax benzoin* (Styraceae) trees in Southeast Asia. Benzoin contains cinnamic, benzoic and triterpene acids. Its action is antiseptic, stimulant, expectorant, diuretic and antifungal. It is used as a food preservative and also as an ingredient in pharmaceutical preparations such as Whitfield's Ointment (with salicylic acid) for ringworm and athlete's foot (Tyler *et al.* 1988).

**Podophyllin** is derived from dried rhizomes and roots of *Podophyllum peltatum* (Berberidaceae), a plant originating in the forests of central and eastern United States.

The plant contains 3.5–6% **podophyllin** resin consisting of the

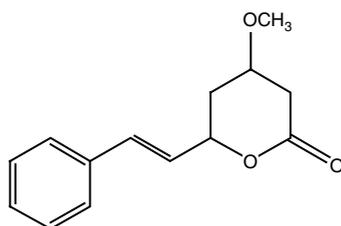
**Table 7.3 Classification of resins**

| <b>Class</b>    | <b>Composition</b>                        | <b>Examples</b>   |
|-----------------|---|---|
| Pure resins     | Solid complexes                           | Guaiac— <i>Guaiacum officinale</i><br>Hashish— <i>Cannabis sativa</i>   |
| Oleoresins      | Mixture of resins and volatile oils       | Capsaicin— <i>Capsicum frutescens</i><br>Gingerols— <i>Zingiber officinale</i><br>Mastic— <i>Pistacia lentiscus</i><br>Turpentine— <i>Pinus palustris</i><br>Aspidinol— <i>Dryopteris filix-mas</i><br>Balm of Gilead— <i>Populus balsamifera</i> |
| Oleo-gum-resins | Mixture of resins, volatile oils and gums | Frankincense— <i>Boswellia carterii</i><br>Asafoetida— <i>Ferula assa-foetida</i>   |
| Balsams         | Cinnamic or benzoic acids or their esters | Benzoin— <i>Styrax benzoin</i><br>Balsam of Tolu— <i>Myroxylon balsamum</i><br>Storax— <i>Liquidambar styraciflua</i> ,<br><i>L. orientalis</i>   |
| Resin acids     | Diterpenoid acids                         | Myrrh— <i>Commiphora molmol</i>   |
| Resinotanninols | Complex alcohols                          | Asaresinatannols— <i>Ferula assa-foetida</i>  |
| Glycoresins     | Sugars, resin acids                       | Podophyllin— <i>Podophyllum peltatum</i><br>Jalap— <i>Exogonium purga</i>   |

lignans **podophyllotoxin** 20%;  $\alpha$  and  $\beta$  **peltatin** 15%—purgative principle; and lignan glycosides (lost during preparation of resins).

Podophyllin powder has a peculiar bitter taste and is highly irritating to mucous membranes, especially of the eyes. Its caustic nature is utilised in the form of topical applications for warts and condylomas. Internally it acts as a drastic though slow-acting purgative. It is also antimitotic; it stops cell divisions and is sometimes used in leukaemia, but problems with side effects limits its use.

**Kava kava**, *Piper methysticum* (Piperaceae), is a large shrub widely cultivated in Oceania. The dried rhizome and root are used in preparation of an intoxicating beverage. Kava contains 5–10% resin, made up of lactones known as kava pyrones—mainly **kavain** and **methysticin**.

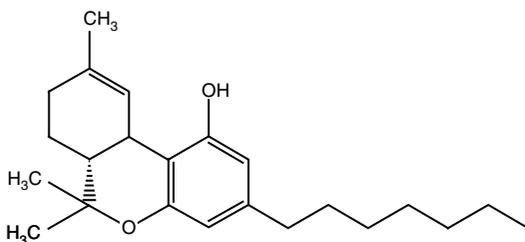


kavain—a kava pyrone

Kava pyrones are potent, centrally acting skeletal muscle relaxants. They act as hypnotics, antipyretics, sedatives, local anaesthetics, smooth muscle relaxants and antifungal agents. No interaction with benzodiazepine drugs or with moderate consumption of alcohol occurs, nor does kava impair mental alertness. However, continually chewing the root can destroy tooth enamel and eventually becomes habit forming (Bone 1994).

## Cannabis

Cannabis resin, or Indian hemp, is derived from the dried flowering tops of pistillate plants of *Cannabis sativa* and *C. indica* (Cannabidaceae). The plants contain 15–20% resin consisting mainly of  $\Delta^9$ -tetrahydrocannabinol, or THC. THC is technically a benzotetrahydropyran and its structure derives from both phenolic and terpenic precursors (Bruneton 1995). It is in a molecular class of its own—the cannabinoids.

 $\Delta^9$ -tetrahydrocannabinol

THC is a lipophilic compound—quickly absorbed but slowly excreted—and responsible for most of the pharmacologic actions of cannabis. Therapeutically it is euphoric, sedative, anti-nauseant, appetite stimulant, bronchodilator and reduces intraocular pressure in glaucoma. However, legal restrictions mean that most use of the herb is illicit. The euphoric effects of the herb are well documented, as are the psychological dependence and disruptive effects on memory and cognitive processes. Its use has also been linked to infertility (Sethi *et al.* 1991). However, acute toxicity is very low and there are few if any documented cases of fatalities from cannabis use (Bruneton 1995).

THC acts at both spinal and supraspinal levels to produce analgesia. As with opioids (opium derivatives), cannabinoids inhibit GABAergic synaptic transmission, while opioids also inhibit post-synaptic neurones. In this way THC and opioids have synergistic analgesic effects. Endogenous cannabinoids (**anandamide**) produce analgesia, but anandamide is less potent than THC and synthetic cannabinoids (Vaughan and Christie 2002).

## Major resin- and oleo-gum-resin-containing herbs

### *Myrrh*

Oleo-gum-resin exudes from incisions made in bark of myrrh trees (family Burseraceae) in North Africa and the Arabian Peninsula—*Commiphora molmol*—and India—*C. mukul*—where it is known as guggul. The main constituents are resin 25–40%, gum 60%, volatile oil 2.5–8% along with a bitter principle. Its actions are antiseptic, antimicrobial, astringent and stimulant.

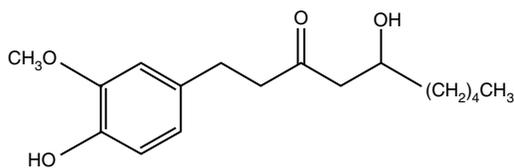
### *Capsicum*

**Capsaicin** is the pungent principle derived from fruits of cayenne pepper—*Capsicum annum*, *C. frutescens* (Solanaceae). Capsaicin, a phenolic amide, is present in the fruit at a level of only 0.02%, yet its taste is detectable even in minute doses. The compound acts as a local anaesthetic and pain reliever through a complex mechanism (see Chapter 8).

### *Ginger*

The oleoresin from the rhizome of ginger, *Zingiber officinalis* (Zingiberaceae), contains phenolic arylalkanones which are related to the

pigment curcumin, from turmeric. These are known as **gingerols** and **shogaols**, and are the compounds responsible for the familiar pungent taste of ginger. They are derived from phenylpropanes, but with extended linear hydrocarbon chains. They have cholagogue and hepatoprotective effects in rats (Bruneton 1995). Recently, related compounds (diarylheptenones) with antifungal properties were identified in ginger and named **gingerenone A, B and C** (Endo *et al.* 1990).



6-gingerol—from ginger oleoresin

### *Asafoetida*

Asafoetida, one of the most pungent of all spices, is obtained from the rhizomes and roots of the shrub *Ferula assa-foetida* (Apiaceae), native to the southwest Asian region. It is rich in an oleo-gum-resin made up of 6–17% volatile oils, 40–64% resin and 7–25% gum. The volatile oil contains disulfide compounds similar to those in garlic. The resin consists of farnesiferols—sesquiterpenoid coumarins—along with ferulic acid and asaresinatannols (Bradley 1992).

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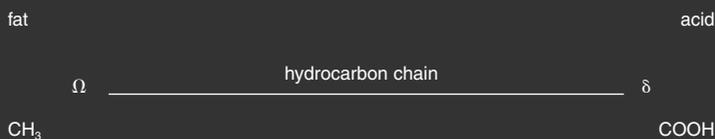
## FIXED OILS AND ALKAMIDES



### Introduction

Fixed oils are lipids, classified as primary metabolites, and therefore essential for life. Unlike secondary metabolites, which are the main compounds of relevance to the medical herbalist, fixed oils are universally present in plants—particularly their seeds—varying only in their abundance and chemical composition. Apart from their nutritional value, these oils are widely used for specific therapeutic purposes, associated with cardiovascular, autoimmune and numerous other chronic diseases.

Fixed oils are composed of fatty acids, hydrocarbon chains with a methyl ( $\text{CH}_3$ ) group at one end ( $\Omega$  end), and a carboxyl group ( $\text{COOH}$ ) at the other ( $\delta$  end). The hydrocarbon chains may be up to 24 carbon atoms long.

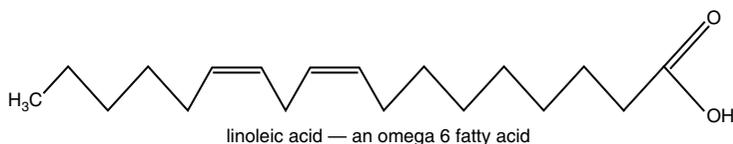


A simplified fatty acid structure

### Carbon bonding

Fatty acids are classified according to their number of double bonds, and which end of the carbon chain the double bonds are nearest to.

1. Saturated fatty acids—no double bonds, e.g. stearic acid
2. Monounsaturated fatty acids—one double bond, e.g. oleic acid
3. Polyunsaturated fatty acids—two or more double bonds, e.g. linoleic acid



## Structure of a polyunsaturated acid

The more double bonds a lipid contains, the greater the fluidity. Conversely the saturated fatty acids without double bonds tend to be solid. Plants and animals from cold regions (e.g. fish from the deep oceans) contain high levels of polyunsaturated acids whereas those from tropical regions (e.g. pigs, coconut and palm oils) contain more saturated fatty acids.

## Nomenclature of fatty acids

Shorthand conventions are widely used to represent the various fatty acids. Carbon atoms may be counted from either end of the hydrocarbon chain; however, in this chapter they are all counted from the methyl end. **Linoleic acid** has 18 carbons with two double bonds, the first of which occurs at the sixth carbon from the  $\Omega$  (omega, or methyl) end. Hence it is represented as **18:2  $\Omega$ 6** (or 18:2 n6), one of the family of  $\Omega$ 6 fatty acids.

## Omega 3 and 6 essential fatty acids

While fatty acids in general are essential for human growth and survival, there are two specific compounds the body is unable to synthesise—therefore they must be obtained through the diet. The two essential fatty acids (EFAs) are linoleic acid and  **$\alpha$ -linolenic acid** (18:3  $\Omega$ 3).

EFAs are present in all the body's cells, and especially concentrated in the brain and central nervous system. Properties attributed to EFAs include regulation of cholesterol metabolism and inflammatory processes. Table 8.1 lists some of the main dietary sources of EFAs. The quality of these dietary sources depends not only on the levels of the essential fatty acids, but also on their ratios. Many vegetable oils contain moderate levels of saturated fatty acids such as **palmitic acid**—they too provide therapeutic benefits.

**Table 8.1 Dietary sources of essential fatty acids**

| <b>Linoleic acid 18:2 <math>\Omega</math>6</b> | <b><math>\alpha</math>-linolenic acid 18:3 <math>\Omega</math>3</b> |
|--|---|
| Sunflower seed                                 | Deep ocean fish, e.g. salmon, mackerel                              |
| Safflower seed                                 | Cod liver oil   |
| Evening primrose                               | Flax seed   |
| Borage seed                                    | Walnuts   |
| Hemp seed                                      | Hemp seed   |
| Blackcurrant seed                              | Blackcurrant seed   |
| Corn   | Green vegetables  |
| Legumes, e.g. soy oil                          |   |
| Lean meat especially wild game                 |   |

### Saw Palmetto—*Serenoa repens* (Palmae)

Fruits obtained from this species of palm are very rich in fats, including **oleic, lauric, myristic, capric**, palmitic, **stearic** (all saturated) and linoleic **fatty acids** as well as ethyl esters of these fatty acids. The lipophilic constituents also include numerous sterols, diterpenes, sesquiterpenes, triterpenes, carotenoids and high-molecular-weight alcohols (Winston 1999). Water-soluble polysaccharides with high molecular weights are also found in the seed, but not in the widely used liposterolic extracts.

The lipophilic compounds from this herb, most notably lauric acid, inhibit the enzyme ( $5\alpha$ -reductase) responsible for converting the male hormone testosterone to  $5\alpha$ -dihydrotestosterone, the metabolite associated with prostate enlargement. Clinical trials support the use of saw palmetto extracts in the treatment of benign prostatic hypertrophy (BPH) while its anti-androgenic properties may also assist in acne, female hirsutism and even baldness. *Serenoa* improves urine flow values, residual urine values and all other symptoms of BPH to a similar degree to standard drugs such as finasteride, without side effects such as decreased libido or modification of PSA values—the marker antigen for prostate cancer (Cristoni *et al.* 2000).

Investigations show that inhibition of  $5\alpha$ -reductase corresponds with degree of saturation of the fatty acids, the length of the carbon chain and absence of esterification—esters of lauric acid showed no inhibition (Niederprum *et al.* 1994).

## Evening primrose oil

The oil is derived from seed of *Oenothera biennis* (Onagraceae). Evening primrose oil is rich in the  $\Omega 6$  fatty acids linoleic acid and  $\gamma$ -linolenic acid. While linoleic acid is easily obtained as a dietary oil,  $\gamma$ -linolenic acid (GLA) is relatively rare in foods and is usually converted to it in the body from dietary linoleic acid. However, there are many factors that may be responsible for blocking the enzymic process responsible for this, and atopic individuals with inherent susceptibility to allergic disorders, eczema and asthma included, are usually deficient in GLA (Willard 1992). Therapeutically, evening primrose oil and other preparations containing GLA are used for atopic eczema, PMS and mastalgia, rheumatoid arthritis, endometriosis and schizophrenia (Horrobin and Manku 1987; Vaddadi 1981; Wright and Burton 1982). GLA is also present in oil of borage seed (*Borago officinalis*) and other plants in the Boraginaceae, as well as species in the blackcurrant family—Saxifragaceae (see Table 8.2).

**Table 8.2 Botanical sources of GLAs**

| Botanical name                  | Common name            | % GLA |
|---------------------------------|------------------------|-------|
| <i>Alkanna orientalis</i>       |                        | 12.4  |
| <i>Borago officinalis</i>       | Borage                 | 20–26 |
| <i>Pectocarya platycarpa</i>    |                        | 15    |
| <i>Oenothera biennis</i>        | Evening primrose       | 8–12  |
| <i>Oenothera grandiflora</i>    | Large evening primrose | 9.3   |
| <i>Scrophularia marilandica</i> | American figwort       | 9.6   |
| <i>Ribes nigrum</i>             | Blackcurrant           | 14–19 |
| <i>Ribes uva-crispa</i>         | Gooseberry             | 10–12 |

Source: D. J. McKenna, K. Jones and K. Hughes 2002, *Botanical Medicines*, 2nd edn, The Haworth Press, New York.

While it is obvious from Table 8.2 that evening primrose oil is by no means the highest source of GLAs, it is often preferred due to the corresponding high levels of linoleic acid. However, it contains virtually no  $\alpha$ -linolenic acid, whereas seeds from species of *Ribes* contain relatively high amounts (McKenna *et al.* 2002). These factors must be considered when prescribing essential fatty acids for therapeutic use—often a combination of evening primrose oil with a fish oil or  $\Omega 3$  supplement is preferred (see below).

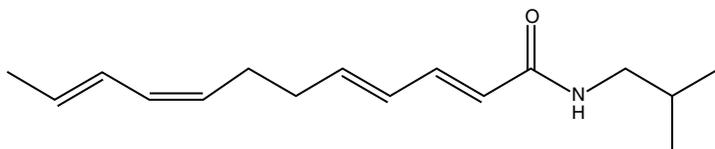
EPA is an  $\Omega 3$  fatty acid metabolised in the body from  $\alpha$ -linolenic acid. EPA can also be obtained from fish oils. This long-chain (20-carbon) polyunsaturated fatty acid inhibits pro-inflammatory prostaglandins including leukotriene—responsible for bronchospasms that occur in asthma. High levels of dietary EPAs reduce thrombosis by activation of a blood-clotting inhibitor prostaglandin and partial inactivation of the platelet aggregation factor. The resulting decrease in blood viscosity leads to prolonged bleeding time and thus EPAs should be taken with caution by those on antithrombotic therapy. Other effects recorded are decreases in cholesterol, VLDL and triglyceride levels—indicating that EPAs are generally protective against diseases of the vascular system (Marderosian and Liberti 1988).

## Alkamides

**Amides** are compounds derived from carboxylic acids and amines, involving elimination of water (similar to ester formation from acids and alcohol). Amide functional groups are quite resistant to hydrolysis, and amide linkages between amino acids and peptides are essential to the stability of proteins. **Acetaminophen**, a well-known anti-inflammatory drug, is a simple amide formed from 4-hydroxyphenylamine and acetic acid.

In **alkamides**, amines are combined with unsaturated fatty acids by amide linkages, forming unbranched chains with one or more double and/or triple bonds.

Alkamides are responsible for the sharp, burning or tingling taste associated with herbs and spices such as prickly ash bark (*Zanthoxylum* spp.), black pepper (*Piper nigrum*), *Echinacea angustifolia*, *E. purpurea* and cayenne (*Capsicum* spp.). *Capsicum* oleoresin contains several phenolic amides including capsaicin.



alkamide from *Echinacea purpurea*

**Isobutylamides** are a subclass of alkamides based on the amine group 2-methylpropyl. They first aroused the interest of researchers for their insecticidal activities, being toxic to numerous classes of insects including the ubiquitous housefly and mosquito. Upon further investigation, it was obvious the most active insecticidal compounds were the ones that produced the most potent sialagogue (stimulating saliva flow) effects in humans (Brinker 1991/92). Isobutylamides so far investigated are derived from four plant families—Asteraceae, Rutaceae, Piperaceae and Aristolochiaceae (see Table 8.3).

**Table 8.3 Medicinal plants containing isobutylamides**

| Asteraceae family                                  | Others                                 |
|--|--|
| <i>Echinacea angustifolia</i> , <i>E. purpurea</i> | <i>Piper nigrum</i> , <i>P. longum</i> |
| <i>Spilanthes oleracea</i>                         | <i>Zanthoxylum clava-herculis</i>      |
| <i>Achillea millefolium</i>                        | <i>Zanthoxylum americanum</i>          |
| <i>Chamaemelum nobile</i>                          |  |

Differences in the chemical structures and relative abundance of isobutylamides in the roots have been used as a means of assessing the correct identity of the three medicinal species of *Echinacea*. The subgroup known as (2E,4E,8Z,10E/Z)-tetraeonic acid isobutylamides contains the key constituents. They are C<sub>11</sub>–C<sub>16</sub> straight-chain fatty acids with olefinic (double) and/or acetylenic (triple) bonds. According to Bauer and Wagner's 1991 investigations, the relative content of these compounds is as follows (in Bergner 1997):

|                        |              |
|------------------------|--------------|
| <i>E. angustifolia</i> | 0.009–0.151% |
| <i>E. purpurea</i>     | 0.004–0.039% |
| <i>E. pallida</i>      | negligible   |

*E. pallida* also lacks the distinctive sharp taste of the other two species, hence it is considered by many to be inferior. It does, however, contain its own chemical fingerprint in the form of another group of alcohol-soluble constituents—polyacetylenes.

In a survey of 32 manufactured *Echinacea* products in the Australian marketplace, isobutylamides and cichoric acid (a caffeic acid derivative) were used as chemical markers to assess the quality and consistency of the products in the marketplace. The survey

revealed a high level of variability in levels of the marker compounds, implying a need to strengthen quality assurance and improve the labelling system by the local herb industry (Wills and Stuart 1998).

### Pharmacological actions

Alkamides can be readily detected by organoleptic means, by placing a very small quantity on the tongue. The initial sharp sensation and saliva production is followed by a local anaesthetic or numbing effect. Not surprisingly many are associated with management of toothache—*Spilanthes* and *Zanthoxylum* spp. are both known in their respective regions as ‘toothache plant’.

The most significant actions of alkamides are analgesic, anti-inflammatory, counter-irritant, sialagogue, vermifuge, digestive and circulatory stimulation. Other likely effects are spasmolytic, carminative and immune stimulation.

### Anti-inflammatory activity

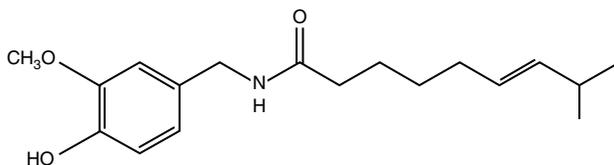
In an *in vitro* study involving alkamides from *Echinacea angustifolia* and several *Achillea* species, 20 compounds tested were relatively potent inhibitors of cyclooxygenase, while a few also inhibited 5-lipoxygenase (Muller-Jakic *et al.* 1994). The two enzymes are involved in the metabolism of arachidonic acid, the major pathway to inflammation. Considering the structural similarities to arachidonic acid, the authors propose the alkamides act as analogues, competitively inhibiting the enzymes.

In a later study, *E. purpurea* alkamides were also found to inhibit both isoforms of cyclooxygenase; however, inhibition of COX-1 was greater than for COX-2 (Clifford *et al.* 2002). Mosquitocidal activity of the alkamides was also confirmed in this study.

### Capsaicinoids

These compounds are responsible for the hotness in chillis (hot peppers), the degree of pungency being related to the length of the acid side chain. Total capsaicinoid content is around 1% of the dried fruit, the majority of which is usually **capsaicin**. Structurally, capsaicinoids are vanillyl-acyl amide analogues (Tucker and Debaggio 2000).

Capsaicinoids stimulate receptors (known as vanillinoid receptors)



capsaicin—an aromatic amide

on cutaneous sensory neurons, resulting in a massive release of neuropeptides including so-called ‘substance P’ molecules responsible for pain transmission to the brain and modulation of local inflammatory responses. Topical applications of medications containing capsaicinoids deplete the neuropeptides, therefore preventing transmission of pain signals to the brain (Warber 1999). Hence the successful use of capsicum-based preparations for treatment of neuralgias, diabetic neuropathy and joint inflammation.

### Stability

Alkamide are known to be subject to degradation over time. Studies on *Echinacea purpurea* alkamides showed that, while drying had no effect, most of the compounds were lost after the dried roots had been stored for a little over a year (Perry and van Klink 2000). Loss of alkamides was rather less when the roots were stored at subzero temperatures. Preservation in ethanolic tincture form is an effective method of retaining these compounds. Chopping the root produces only minimal losses.

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## POLYSACCHARIDES



### Introduction

Polysaccharides or glycans are high-molecular-weight polymers consisting of chains of sugars (monosaccharides or oligosaccharides) with chemical linkages. The simplest polysaccharides are cellulose and starch, which are polymers of glucose only. Polysaccharides are difficult to represent in the usual structural formulas as they are so big—and often the identity and number of all the sugars present is unknown. Usually the chemical structures are represented by a section of the molecule, or by a series of named sugars with indications of the bonding arrangement and branching patterns—if any.

Polysaccharides of some kind are universal in the plant kingdom, and also occur in algae and fungi. Their functions include food storage, protection of membranes, and maintaining rigidity of cell walls in plants, except for seaweeds where they help maintain the flexibility required for life in the ocean (Bruneton 1995).

### Gums

Many plants (especially those growing in semi-arid conditions) produce gummy exudates when the bark is damaged which serve to heal the wound. The exudate often dries to a hard amorphous mass, and is produced in sufficient abundance by some species of trees and shrubs to warrant collection and commercial utilisation. Gum exudates are readily obtainable in relatively pure, undegraded form though in some cases purification is still required. These polysaccharides often occur in association with a protein.

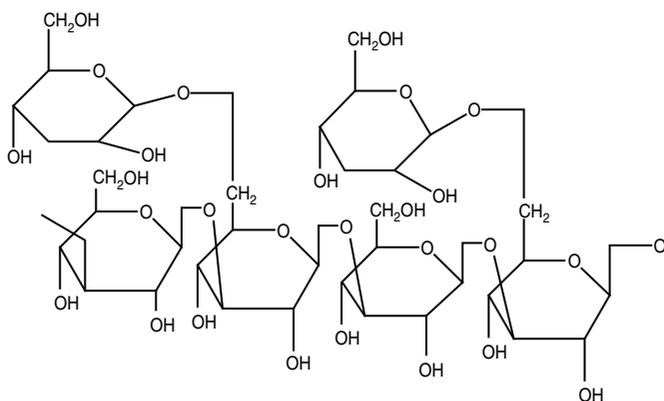
**Gums** are made up of branching chains of chemically linked sugars (monosaccharides) or their salts, and uronic acid derivatives (uronic

acids are oxidation products of sugars). They may have acidic, basic or neutral characteristics.

They are usually heterogenous—composed of various monosaccharide residues and uronic acids.

Gums are water soluble and tend to be sticky or tacky in texture. Examples include **gum arabic** from *Acacia* spp. (Mimosaceae), **gum tragacanth**, *Astragalus* spp. (Fabaceae), and **prunus gums**, *Prunus* spp. (Rosaceae).

Seed gums are obtained from certain types of seed endosperms. They are common in the legume (Fabaceae) family, for example locust bean gum and tamarind gum.



astragaloglucan—branch-chained polysaccharide from *Astragalus* spp.

## Acacia gums

Although wattle bark (*Acacia* spp.) was used medicinally by indigenous Australians for coughs and colds, and to varying degrees for other ailments, it was popular among white settlers as a domestic medicine mainly for gastrointestinal complaints. The bark is astringent due to its tannin content, and a large number of species were used; some, however, were unsuitable due to the presence of poisonous saponins. In general the extract of bark was prepared as either an infusion or a decoction. It was taken especially for cases of dysentery and diarrhoea, but was also used for other minor ailments such as perspiring feet.

Probably the most widely used was *Acacia decurrens*—black wattle. Bark of this species was exported to Britain and was at one

time included in the *British Pharmacopoeia*. The bark was collected from trees seven or more years old and then allowed to mature for a year before use.

The gum, which exudes from small injuries in the bark of the acacia, has also been used medicinally, although the Australian product is regarded as inferior to that from Africa. Dissolved in water, the insipid gum makes a soothing syrup for inflamed mucous membranes. Several species in Western Australia are noted as having been used to make cough medicine—bark or roots were infused or soaked to produce a liquid drunk for treating cough and colds. A report from the mid-nineteenth century states that all common ailments among the indigenous Australians of the southern state of Victoria were effectively treated with lotions and decoctions of wattle bark and gum. This suggests that the medicinal use of *Acacia* was probably much more widespread than the specific records show (Cribb and Cribb 1981).

Acacia trees usually attain heights of from 4.5 to 6 metres (15–20 feet) with exudation of gum in appreciable amounts commencing when trees become 6–7 years old. Most of the exudation occurs during the dry season following leaf drop. The gum forms in response to breaks or infections in the bark of the tree and may be induced by ‘tapping’ in which a narrow strip of bark is removed. The gum is collected by hand, sorted and dried to yield the crude gum. Purified samples are obtained by dissolving the crude gum in water, then recovering the polysaccharide by alcohol precipitation.

Acacia gums are very soluble in water, yielding solutions of comparatively low viscosity in relation to those of most other polysaccharide gums. Gum arabic is an effective emulsifying agent for oil–water systems and is used for this purpose in many food products. When present in the diet at levels of less than 10% the gum is completely digested and absorbed, and is without toxicity when ingested or when administered intravenously in humans (Miller 1973).

### Seaweed gums

These are found in the leaves of several groups of algae, for example agar agar—red algae; kelp—brown algae; Irish moss (carrageenan)—red algae. Alginic acid found in bladderwrack, *Fucus vesiculosus* (Fucaceae), is a linear polymer yielding mannuronic and glucuronic acid residues.

## Pectins

Pectins are complex galactouronic acid-based carbohydrates found in the plant cell wall of many fruits, for example apples, citrus. During fruit ripening an insoluble precursor is converted to soluble pectin and becomes gelatinous. It is used as setting agents for jams. Pectin has similar properties to gums—it adsorbs toxins, cholesterol and acts as a bulk laxative agent.

## Mucilages

**Mucilages** are long-chain polysaccharides that combine with water to form a slimy, semi-solid mass. They are not confined to specific plant parts, but may occur in:

- Roots: comfrey—*Symphytum officinalis* (Boraginaceae); marsh-mallow—*Althaea officinalis* (Malvaceae)
- Leaves: coltsfoot—*Tussilago farfara* (Asteraceae)
- Bark: slippery elm—*Ulmus fulva* (Ulmaceae)
- Seeds: psyllium—*Plantago ovata*, *P. psyllium* (Plantaginaceae)

Their properties are similar to those of seaweed gums and the term is often applied to aqueous suspensions or solutions of gums and gelatinised starches.

## Properties of gums and mucilages

In physical terms they are hydrophilic (they attract water). In energetic terms they are cooling and sweet or bland.

Since they are more or less indigestible, their physical properties are of more significance than their chemical properties. Even if some polysaccharides were broken down in the digestive tract, the breakdown products—sugars and uronic acids—have little pharmacological effect (Mills 1994). Therefore these compounds are sometimes regarded as inert. They are often considered undesirable and omitted from pharmaceutical preparations, except where ‘gummy’ properties are required, for example in tablets and lozenges.

## Solubility

Polysaccharides are insoluble in organic solvents—they precipitate in alcohol. Tinctures, which are made using alcoholic solvents of 45% strength or higher, are therefore of little use where demulcent or emollient effects are required.

The degree of water solubility depends on the polysaccharide structure. Linear polymers (mucilages) are less water soluble, they tend to precipitate at high temperatures and form viscous solutions. They may be referred to as ‘slimy’. Branched polymers (gums) are more water soluble, forming gels. These can be referred to as ‘tacky’ (Mills 1994).

## Local effects

The primary action is local, by direct contact with the surface of mucous membranes or skin. Here they produce a coating of slime that acts to soothe and protect exposed or irritated surfaces of the gastrointestinal tract—a **demulcent** action. When this effect occurs on the skin it is referred to as an **emollient** action.

Mucilaginous herbs tend to be ideal for topical application for a wide variety of conditions ranging from bruises and swellings to irritable dermatological lesions. When applied topically, mucilaginous agents are soothing and emollient. Mucilages retain heat due to their hydrophilic properties, a characteristic often utilised in herbal preparations such as warm compresses, as they allow heat to penetrate the tissues progressively. Several herbs, including comfrey, slippery elm bark, marshmallow and linseed, are used in this way.

Gums and mucilages are invaluable aids in the management of irritable digestive disorders, especially where ulceration is a feature. Their relative indigestibility and hydrophilic properties create an influence on bowel behaviour, acting as:

- Laxative agents—the bulk effect results in increased peristalsis, drawing moisture into the colon producing a mild aperient effect
- Antidiarrhoeal agents—small quantities absorb excess water in the colon. Tannins if present have a binding effect, e.g. slippery elm powder

Demulcents—especially psyllium hulls—are ideal for treatment of irritable bowel disorders. **Alginates** from seaweeds are used in

pharmaceutical gastric antacids for relief of gastric reflux, oesophagitis and hiatal hernias. Slippery elm powder is also effective for these disorders.

Gums and mucilages also check fermentation and bacterial growth, adsorb toxins and wastes helping their elimination from the body. Cholesterol is also lowered through this mechanism—a general property of water-soluble fibres such as those in oat bran. The hydrophilic effect produces a sensation of ‘fullness’ in the stomach without providing calories, hence the use of guar gum and others for appetite suppression. There is also a blood sugar lowering effect, observed in both diabetics and normal subjects.

### **Reflex effects**

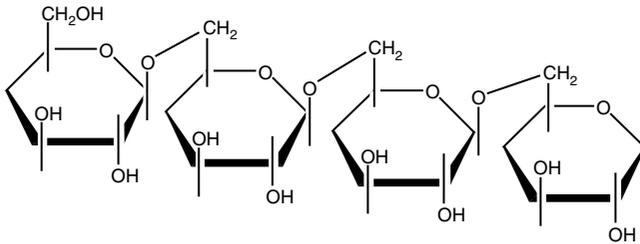
The soothing, demulcent effects of gums and mucilages also benefit irritable states of the urinary and respiratory tract. Take, for example, the widespread use of marshmallow or Irish moss for bronchitis, and soothing preparations such as barley water for cystitis. While there is little difficulty in comprehending the strictly localised demulcent effect on the lining of the digestive tract, the mode of operation on organs with which the mucilage doesn’t come into contact—respiratory tract, genitourinary tract and uterus—is believed to occur via reflex associations with the digestive tract, through an embryonic link in the nervous system (Mills 1994).

### **Immunostimulating polysaccharides**

Polysaccharides are generally indigestible to humans, so their effects are not manifested in the bloodstream. However, their physical movement through the colon appears to trigger certain physiological reactions in humans, possibly due to an immune reaction via the Peyer’s patches. Immunostimulatory polysaccharides are large, insoluble, extensively branched molecules often occurring in triple helix formation (Turner 1998).

Many polysaccharides, especially  $\beta$ -(1/3)-glucans, have been shown to have immunomodulatory effects by cytokine-stimulating activities. Cytokines can increase proliferation and differentiation of macrophages, T and B cells, and enhance cellular mechanisms of antitumour activity and antibody production. The polysaccharides are sometimes linked to a protein peptide. The so-called ‘D-fraction’,

a  $\beta$ -D-glucan from maitake mushroom (*Grifola frondosa*), has been extensively studied on animals and demonstrated enhanced macrophage, T cell and natural killer cell activity, increased interleukin-1 production and activation of the alternate complement pathway (Turner 1998).



section of beta-1,6'D-glucan

When polysaccharides are ingested as foods or in standardised capsules (guaranteed to carry specific polysaccharides) they are more likely to produce immune-stimulating effects than when taken as tinctures or in other liquid preparations. Polysaccharides from reishi mushroom (*Ganoderma lucidum*)—especially the  $\beta$ -glucan fraction—have been found to have broad stimulatory effects on white blood cells, for example leukocytes, monocytes, macrophages, natural killer cells, which in turn lead to release of cytokines and lymphokines (IL, interferon, etc.). These are responsible for antitumour, anti-inflammatory, bactericidal and immunomodulatory effects—useful in the treatment of autoimmune disorders, HIV-AIDS and cancer (Chang 1994). *In vitro* and *in vivo* activity against a number of malignant tumour lines by hot water extracts of *Ganoderma lucidum* was demonstrated by Taiwanese researchers (Lee 2001). The effects were attributed to the presence of high-molecular-weight polysaccharides.

Two polysaccharides from shiitake can suppress tumours in experimental trials. Lentinan is a high  $M_r$  (1 000 000)  $\beta$ -1,3 glucan, with no peptide. It has pronounced antitumour activities in animals and is a potent interferon inducer in animals when administered intravenously; however, oral administration did not suppress tumour growth in animals. KS-2, containing mannose as the main component and a small amount of peptide, demonstrated effective suppression of tumour growth *in vivo* by oral or intraperitoneal administration. Studies indicate strong macrophage activation—this is associated with induction of interferon (Fuji *et al.* 1978).

Immunomodulating polysaccharides are not confined to the fungal kingdom—they are also present in many plant-based medicines. While their significance in the immune-enhancing properties of *Echinacea* species is controversial, they have been shown to play significant roles in the activity of numerous herbs used in traditional Chinese (TCM) and Japanese (Kampo) medicines, as Table 9.1 demonstrates.

**Table 9.1 TCM and Kampo herbs containing bioactive polysaccharides**

|                            |                            |
|----------------------------|----------------------------|
| <i>Aloe</i> spp.           | <i>Bupleurum</i> root      |
| <i>Actractylodes</i> spp.  | <i>Glycyrrhiza</i> root    |
| <i>Cinnamomum</i> bark     | <i>Panax pseudoginseng</i> |
| <i>Codonopsis pilosula</i> | <i>Rehmannia</i> root      |
| <i>Curcuma zedoaria</i>    | <i>Salvia miltiorrhiza</i> |
| <i>Isatis indigotica</i>   | <i>Zizyphus</i> fruit      |
| <i>Panax notoginseng</i>   |                            |

*Source:* Based on a table in R. Chang 2002, ‘Bioactive polysaccharides from traditional Chinese medicine herbs as anticancer adjuvants’, *Journal of Alternative and Complementary Therapies* 8: 561.

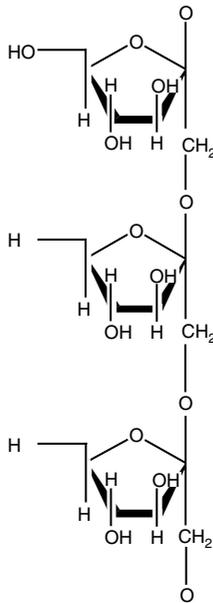
There are also numerous examples linking polysaccharides from Chinese herbs with protective effects on the digestive system. In one study ginseng—*Panax ginseng* (Araliaceae)—showed anti-ulcerogenic activity against induced ulcers (Sun, Matsumoto and Yamada 1991). The pectin-like **bupleuran 2II** from *Bupleurum falcatum* (Apiaceae) also exhibited significant anti-ulcer activity (Yamada *et al.* 1991). Polysaccharides from dang gui—*Angelica sinensis* (Apiaceae)—demonstrated protection of the gastrointestinal mucosa against ethanol and indomethacin (Cho *et al.* 2000), while polysaccharide-rich fractions of hot water extract of *Actractylodes lancea* stimulated proliferation of bone marrow cells mediated by Peyer’s patch cells (Yu *et al.* 1998).

The latter study demonstrates the relationship of the gut-associated lymphoreticular tissue (GALT) and the intestinal immune system to the immunomodulating actions of polysaccharides.

## Fructans

Fructans are polymers of fructose stored in some plants as reserve material instead of starch. They have much lower molecular weight than starch, and are water soluble. The branched fructans are found mainly in the grass (Poaceae) and lily (Liliaceae) families while linear fructans (specifically inulin) are particularly common in the Asteraceae. Fructans are composed almost entirely of fructosyl–fructose linkages, and in some cases glucose molecules are present in the chain (Cseke and Kaufman 1999).

**Inulin** contains 35 fructose residues with the possible addition of a terminal glucose. Inulin helps stabilise blood sugar in hypoglycaemia, and also acts as a diuretic. There is also evidence of immunostimulating activity. It is found in significant quantities in the following herbs: elecampane—*Inula helenium*; burdock—*Arctium lappa*; globe artichoke—*Cynara scolymus*; *Echinacea* spp. Other sources are the tubers of dahlias and Jerusalem artichoke (*Helianthus tuberosus*); the latter may be used as a potato substitute. Studies indicate that fructans from foods such as rye, onions, garlic and artichoke tubers are digested in the large intestine by *Bifidobacterium*, acting as a source of energy and providing other benefits noted above (Cseke and Kaufman 1999).



inulin—part of polysaccharide chain

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## ALKALOIDS



### Introduction

Typical alkaloids are alkaline organic compounds containing one or more nitrogen atoms, each connected to at least two carbon atoms within a heterocyclic ring system. They have limited distribution in plants, so that vitamins and hormones are excluded even though they may structurally comply with the definition. Most alkaloids are derived at least partly from various amino acids as their direct precursors, while a few are derived from isoprene units (terpenoids).

The isolation of morphine by Seturner in 1806 led to the discovery of several more alkaloids over the next 15 years, including emetine, piperine, caffeine and quinine. The term alkaloid was first applied by Meissner, a German pharmacist, and originally referred to all plant alkalis.

Alkaloids are found in 15–30% of all flowering plants and are particularly common in certain families, such as Fabaceae, Liliaceae, Ranunculaceae, Apocynaceae, Solanaceae and Papaveraceae. The most widely occurring alkaloids are caffeine and berberine.

While the higher plants are the major source of alkaloids, they are also known to occur in lower plants such as horsetails, in algae, fungi, microorganisms, insects and even the organs of mammals (Kapoor 1995). Over 10 000 different alkaloids have been isolated from over 300 plant families (Raffauf 1996). They may be found in roots, rhizomes, leaves, bark, fruit or seeds. Over 40 alkaloids may occur in a single plant, for example *Vinca major*.

### Properties of alkaloids

Alkaloids are generally white or colourless crystalline solids containing oxygen. A minority of alkaloids are oxygen free, existing

as liquids. These include **nicotine**, **conine**, **sparteine** and **lobeline**. Very few coloured alkaloids exist—exceptions are **sanguinarine** (red) and **chelidone** (yellow).

With few exceptions (**colchicine**, **berberine**) alkaloids are bases, turning red litmus paper blue. Many are precipitated by various reagents, for example Meyers (mercuric chloride and potassium iodide). Some give more or less characteristic colour reactions with certain reagents. Most are susceptible to destruction by heat, some by exposure to air and light.

Most alkaloids are soluble in organic solvents such as chloroform, ether and alcohol, but are practically water insoluble. Water-soluble alkaloids include **ephedrine** and **colchicine**. Alkaloidal salts are generally soluble in water and alcohol.

## Nomenclature

All alkaloid names end in 'ine'. Otherwise their names have a number of origins:

1. From generic name of plant—hydrastine
2. From specific name of plant—cocaine
3. From common name of plant—ergotamine
4. From physiological activity—emetine
5. From discoverer's name—lobeline (after L'Obel)

Where two or more similar alkaloids are present in a plant, prefixes and suffixes may be added; for example **quinidine**, **hydroquinine** are present along with **quinine** in *Cinchona* spp.

## Pharmacological actions

Plant alkaloids usually have profound physiological actions in humans with nervous system effects being the most prominent. There are several good reviews published on this subject (e.g. Marini Bettolo 1986; Robinson 1986, 1981). Examples of some of the more dramatic actions of alkaloids are:

- Analgesics/ narcotics—morphine
- Mydriatics—atropine
- Miotics—pilocarpine
- Hypertensives—ephedrine

- Hypotensives—reserpine
- Bronchodilator—lobeline
- Stimulants—strychnine
- Antimicrobials—berberine
- Antileukemic—vinblastine

Because they are so reactive, even at small doses, most alkaloid-rich plants are used sparingly, if at all, in Western herbalism. Indeed, use of many of the alkaloidal species is restricted by law, or listed on poison schedules. However, alkaloids—either as isolated compounds or their semi-synthetic derivatives—are widely used in pharmaceutical medicines. Much of our understanding of the mechanisms of neurotransmitters and receptor sites comes from research into the pharmacodynamics of alkaloids. The widespread use of terms such as nicotinic and muscarinic receptors supports this idea.

## Classification of alkaloids

Alkaloids are a large and diverse group of chemical compounds that defy easy classification. They are commonly grouped together according to their ring structures. Two major divisions can be made:

1. **Heterocyclic alkaloids**—regarded as most typical
2. **Non-heterocyclic alkaloids**—also known as protoalkaloids or biological amines, e.g. ephedrine, colchicine

## Pyridine-piperidine alkaloids

These alkaloids have their nitrogen atoms in typical six-membered rings, which in the case of pyridine is a benzene ring. The precursors are generally ornithine and nicotinic acid although lobeline has a unique biosynthesis (see below).

**Coniine**,  $\alpha$ -propylpiperidine, is found in spotted hemlock—*Conium maculatum* (Apiaceae). It is a piperidine structure with a short aliphatic side chain, and is a volatile oily compound. Coniine is very toxic and causes death by paralysis.

**Nicotine**, 1-methyl-2 (3-pyridyl) pyrrolidine, is found in tobacco derived from *Nicotiana tabacum* and other plants of the Solanaceae, including the Australian pituri (*Duboisia hopwoodii*), whose properties were exploited by the indigenous Australians of the central desert

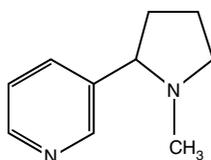
**Table 10.1 Major alkaloidal groups, with examples and actions**

| Class                   | Examples    | Plant species                             | Pharmacological actions                        |
|-------------------------|-------------|---|--|
| Pyridine/<br>piperidine | Nicotine    | <i>Nicotiana tabacum</i>                  | Adrenergic, CNS stimulant                      |
|                         | Lobeline    | <i>Lobelia inflata</i>                    | Expectorant,<br>bronchodilator                 |
|                         | Piperine    | <i>Piper nigrum</i> ,<br><i>P. longum</i> | Stimulant,<br>hepatoprotective                 |
| Tropane                 | Arecoline   | <i>Areca catechu</i>                      | Vermicide, taenifuge                           |
|                         | Hyoscyamine | <i>Atropa belladonna</i>                  | Anticholinergic,<br>antisialagogue             |
|                         | Cocaine     | <i>Erythroxylon coca</i>                  | CNS stimulant,<br>anaesthetic, narcotic        |
| Quinoline               | Scopolamine | <i>Datura metel</i>                       | Anticholinergic, CNS<br>depressant             |
|                         | Quinine     | <i>Cinchona</i> spp.                      | Antimalarial,<br>antiarrhythmia                |
| Isoquinoline            | Quinidine   |   | Cardioactive                                   |
|                         | Berberine   | <i>Berberis</i> spp.                      | Antimicrobial,<br>antiprotozoal,<br>cholagogue |
| Quino-<br>lizidine      | Morphine    | <i>Papaver somniferum</i>                 | Sedative, analgesic,<br>narcotic               |
|                         | Chelidonine | <i>Chelidonium majus</i>                  | Spasmolytic, cholagogue                        |
|                         | Boldine     | <i>Pneumus boldo</i>                      | Spasmolytic, choleric                          |
|                         | Emetine     | <i>Cephaelis<br/>ipecacuanha</i>          | Emetic   |
| Pyrrrolizidine          | Sparteine   | <i>Sarothamnus<br/>scoparius</i>          | Oxytocic, cardiotonic,<br>diuretic             |
| Indole                  | Sececionine | <i>Senecio jacobeeae</i>                  | Hepatotoxin                                    |
|                         | Symphytine  | <i>Symphytum</i> spp.                     |  |
| Indole                  | Reserpine   | <i>Rauwolfia<br/>serpentina</i>           | Sedative,<br>antihypertensive                  |
|                         | Ergotamine  | <i>Claviceps purpurea</i>                 | Vasoconstrictor,<br>hypertensive               |
|                         | Strychnine  | <i>Strychnos<br/>nux-vomica</i>           | CNS stimulant, deadly<br>toxin                 |
|                         | Yohimbine   | <i>Aspidosperma<br/>quebracho</i>         | Aphrodisiac, stimulant                         |

Table 10.1 (continued)

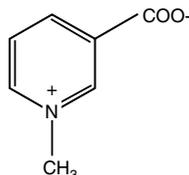
| Class               | Examples     | Plant species                | Pharmacological actions                |
|---------------------|--------------|------------------------------|--|
| Imidazole           | Pilocarpine  | <i>Pilocarpus jaborandi</i>  | Miotic, cholinergic                    |
| Alkaloidal amines   | Colchicine   | <i>Colchicum autumnale</i>   | Antimitotic, uric acid solvent         |
|                     | Ephedrine    | <i>Ephedra sinica</i>        | Sympathetic stimulant, bronchodilator  |
|                     | Mescaline    | <i>Lophophora williamsii</i> | Hallucinogenic                         |
| Purine alkaloids    | Caffeine     | <i>Coffea arabica</i>        | CNS and sympathetic stimulant          |
|                     | Theophylline | <i>Thea sinensis</i>         | Bronchodilator, diuretic               |
|                     | Guaranine    | <i>Paullinia cupana</i>      | CNS and sympathetic stimulant          |
| Steroidal alkaloids | Solanine     | <i>Solanum</i> spp.          | Steroid precursors, anti-inflammatory  |
|                     | Veratrine    | <i>Veratrum album</i>        | Cardiac depressants, antihypertensives |

(Watson *et al.* 1983). Nicotine also occurs in many remotely related plants such as club mosses. This is possible since the precursor nicotinic acid (vitamin B3) is of widespread distribution in the plant family. Pure nicotine is a colourless oily alkaloid, while salts of nicotine are readily water soluble. The prime pharmacological alkaloid in tobacco is **L-nicotine** (0.5–10%), along with **nornicotine**, **anabasine** and **nicotyrine**. Structurally nicotine consists of a simple linking of pyridine and pyrrolidine rings.



nicotine

Another nicotinic acid derivative is **trigonelline**, found in fenugreek seed (*Trigonella foecum-graecum*) and unroasted coffee beans.

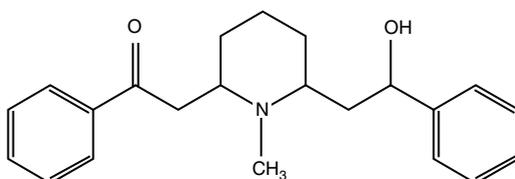


trigonelline—a pyridine alkaloid

**Piperine**, 1-piperoylpiperidine, is found in *Piper* spp.—*Piper nigrum* (black pepper) and *P. longum* (long pepper). Both peppers are of major importance in Ayurvedic medicine. Piperine has been shown to have hepatoprotective effects though is less potent than silymarin (Koul and Kapil 1993). The amide side chain imparts high lipophilic (fat-soluble) properties, ensuring the compound is readily absorbed in the small intestine. Piperine has also been shown to influence the bioavailability of other compounds, be they herbal or pharmaceutical. This interaction is thought to occur via an increased absorptive surface of the small intestine linked to alterations in membrane dynamics and permeation characteristics following ingestion of piperine (Khajuria *et al.* 2002).

**Arecoline** arecaidine methyl ester, found in betel nut derived from the palm *Areca catechu*, is widely used in many countries as a masticant. *Areca* also contains about 15% tannins.

**Lobeline** is found in *Lobelia inflata* along with **lobelanine** and **lobelanidine**. The main ring in lobeline is derived from lysine via piperidine, while the two benzene rings it contains derive from phenylalanine via the shikimic acid pathway (Samuelsson 1992).



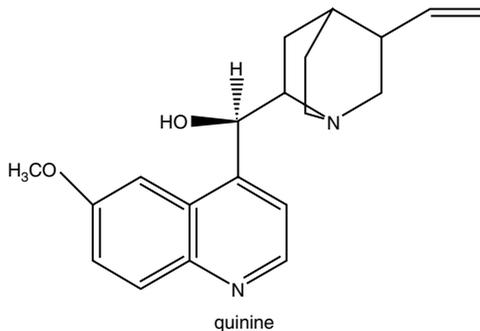
lobeline—a piperidine alkaloid

*Lobelia* is a relaxant and bronchodilator originally made famous by Thomson and the Physiomedical School of herbalists; however, its use in Australia is now restricted to medical practitioners.

## Quinoline alkaloids

This is an example of a bicyclic ring system with the fusion of benzene and pyridine rings. Biosynthetically they are related to indole alkaloids since both groups are derived from the same two precursors, tryptophan and loganin—a monoterpene iridoid (Samuelsson 1992).

**Quinine**, 6-methoxycinchonine  $C_{20}H_{24}N_2O_2$ , is found in Peruvian bark, *Cinchona* spp. (Rubiaceae), a tree that originates in the Andes mountains. The major species used are *Cinchona succirubra* and *C. ledgeriana*. **Quinidine** is isomeric to quinine.



*Cinchona* bark contains 25 closely related alkaloids, including the main therapeutic alkaloids in this category. The average yield is 6–7% (25% quinine, 5% quinidine). The bark also contains cinchotannic acid (2–4%).

Quinine is used as the basis for anti-malarial drugs, as a skeletal muscle relaxant (treatment of nocturnal cramps) and traditionally as a febrifuge for influenza and other acute infectious disorders. Quinine is very bitter and is the main flavour component of tonic water.

Quinidine is a medical drug—indicated for cardiac complications, namely arrhythmias, atrial flutter and fibrillation. It depresses myocardial excitability, conduction, velocity and contractility. It is used in the form of quinidine sulfate.

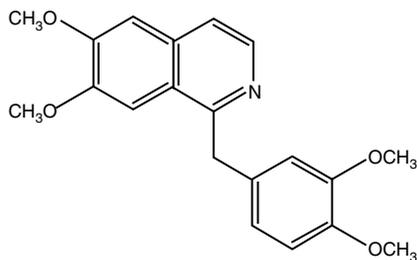
Side effects of quinine drugs include tinnitus ('cinchonism'); skin rash; vertigo; unusual bleeding/bruising; visual disturbances.

Quinoline alkaloids are particularly common among plants of the Rutaceae family. *Ruta graveolens*, or common rue, contains 30 known alkaloids of the quinoline type (Harborne and Baxter 1993). These include **arborinine** and  $\gamma$ -**fagarine**.

Another Rutaceous plant with a similar alkaloidal spectrum to rue is prickly ash bark—*Zanthoxylum* spp. Two new quinoline alkaloids isolated from *Zanthoxylum simulans* were shown to have cytotoxic and antiplatelet activities (Chen *et al.* 1994).

## Isoquinoline alkaloids

These alkaloids result from the condensation of a phenylethylamine derivative with a phenylacetaldehyde derivative. Both moieties are derived from the same precursors. The precursors are phenylalanine or tyrosine. The prototype alkaloid of this class is papaverine, found in several species of the poppy family (Papaveraceae).



papaverine

Isoquinoline alkaloids are most frequently found in the Papaveraceae, Berberidaceae and Ranunculaceae families. This is a very large class of medicinally active alkaloids, which for convenience can be divided into the following subclassifications:

- **Morphinane alkaloids**—morphine, codeine, thebaine (phenanthrene derivatives)
- **Benzylisoquinolines**—papaverine, oxyacanthine, tubocurarine
- **Protoberberines**—berberine, hydrastine, palmatine
- **Protopines**—cryptopine, protopine
- **Benzophenanthradine**—chelidone, sanguinarine

- **Ipecac alkaloids**—emetine, cephaeline
- **Aporphine alkaloids**—boldine

The properties of the various alkaloids in this class are extremely variable. Reported pharmacological properties include the following:

- Antispasmodic (papaverine) (Martin *et al.* 1993)
- Antimicrobial, antitumour (Wu *et al.* 1989)
- Antifungal (jatrorrhizine) (Grayer and Harborne 1994)
- Anti-inflammatory, cholagogue and hepatoprotective, antiviral, amoebicidal (De Silva 1983), antioxidant (oxyacanthine) (Muller and Ziereis 1994)
- Enzyme inhibitors (Robinson 1986)

**Opium** is the dried latex obtained from incisions made in unripe fruits of the opium poppy—*Papaver somniferum* (Papaveraceae). The official opium drug is standardised to contain 10% morphine. Opium contains over 40 alkaloids, usually combined with meconic acid—a signature compound for identifying opium. Some major opium alkaloids are listed below (Kapoor 1995):

- **Morphine** (8–14%) narcotic, analgesic and hypnotic
- **Noscapine** (4–8%) antitussive; no narcosis
- **Codeine** (2.5%–3.5%) antitussive; mild narcotic and analgesic
- **Papaverine** (0.5–1%) smooth muscle relaxant; antitussive
- **Thebaine** (0.1–2%) alternative source for synthesis of codeine

**Heroin** is diacetylmorphine—a synthetic derivative—and is more toxic and habit forming than morphine.

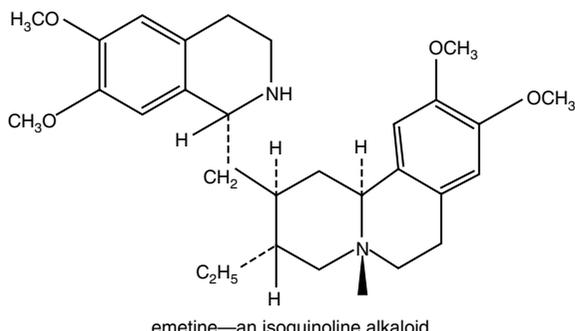
**Morphine**,  $C_{17}H_{19}NO_3$ , is a complex phenolic compound whose pentacyclic structure is derived from tyrosine. It is analgesic, narcotic and a powerful respiratory depressant which was previously used in cough elixirs. Morphine induces euphoria and dependency in some people, anxiety and nausea in others. The central nervous system effects occur through stimulation of specific receptors. Opiate receptors are widely distributed in animals; they respond to both endogenous transmitters (peptides) and ingested plant alkaloids. The main receptor types are:  $\delta$  emotional;  $\lambda$  sedative;  $\mu$  analgesic;  $\sigma$  psychotomimetic (Robinson 1986).

Other effects of morphine include decrease in pupillary size, reduced hydrochloric acid secretion in the stomach and constipation.

Overdose of morphine can cause death through respiratory arrest (Kapoor 1995).

Ipecac is obtained from the dried rhizome and roots of *Cephaelis ipecacuanha* (Rubiaceae), a low bush indigenous to Brazil. Ipecac contains five isoquinoline alkaloids, including **emetine**, **cephaline** and **psychotrine**. Emetine hydrochloride is used as an antiprotozoal agent. Syrup of ipecac is an emetic and poison antidote.

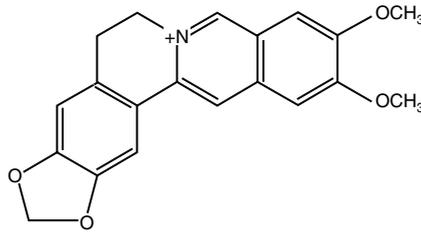
Emetine is a gastrointestinal tract irritant causing reflex increase in respiratory secretions. It acts as an emetic in higher doses, and is indicated in chronic bronchitis and whooping cough.



**Curare** is a muscle relaxant drug, originally used as an arrow poison by Amazonian Indians. The traditional curare is prepared by a secret recipe thought to involve a number of plant species (Plotkin 1993). Plant sources of curare include *Strychnos castelnaei* and species in the Loganiaceae family and *Chondodendron tomentosum* in the Menispermaceae family. **Tubocurarine**, a benzyloisoquinoline dimer, is the major alkaloid in the curare plants. It exhibits paralyzing effects on skeletal muscles, and is used as a muscle relaxant in surgical procedures. It controls convulsions caused by the toxic alkaloid strychnine.

**Chelidonium** is a yellow alkaloid derived from *Chelidonium majus*. It has an analgesic action similar to though milder than morphine—its action lasts from 4 to 48 hours (Huang 1993).

**Berberine** is a protoberberine alkaloid whose salts form yellow crystals. It is found along with related alkaloids in: *Hydrastis canadensis*, **goldenseal**, (family Ranunculaceae); *Berberis* spp. (family



berberine—a protoberberine isoquinoline alkaloid

Berberidaceae)—*B. vulgaris*, **common barberry**, *B. aquifolium* or *Mahonia aquifolium*, **Oregon grape root** and *B. aristata*, **Indian barberry**.

Actions of berberine include amoebicidal; antibacterial; antifungal; cholagogue; hepatoprotective-tyramine inhibitor; elastase inhibitor—helps repair tissues and reduce inflammation; antitumour (Pizzorno and Murray 1986). Berberine has been shown to have a negative inotropic effect on the heart; it markedly reduces atrial rate. It also has an antiarrhythmic action (Huang 1993). Recent studies indicate berberine and sanguinarine are potent inhibitors of DNA synthesis (repair and replication)—the likely mechanism for their antiviral effects. Adding this to a variety of known effects such as inhibition of protein biosynthesis and uncoupling of oxidative phosphorylation, berberine along with palmatine and sanguinarine can be regarded as potent allelochemicals that are toxic to bacteria and fungi, as well as other plants, insects and animals (Schmeller *et al.* 1997).

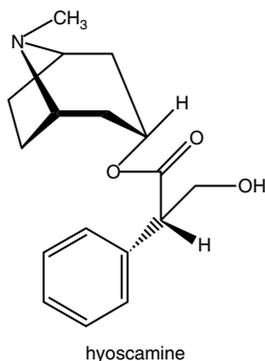
**Boldine**, (S)-2,9-dihydroxy-1,10-dimethoxyaporphine, is found in the leaves and bark of *Peumus boldo* (Monimiaceae), an evergreen tree native to Chile. Boldine imparts choleric, cholagogue, antioxidant and smooth muscle relaxant properties to the herb (Speisky *et al.* 1991). It is used primarily in the treatment of gallstones.

## Tropane alkaloids

These are complex molecules containing pyrrolidine and piperidine ring structures, derived from the precursors ornithine and phenylalanine. Isoleucine and acetate also play a role in the biosynthesis of tropane structures. Alkaloids used in medicine are restricted largely

to the Solanaceae family, apart from cocaine which comes from the coca plant in the Erythroxylaceae family.

Esterification of the nitrogenous moiety with tropic acid is a structural type thought to be unique to the Solanaceae family (Evans 1990; Roddick 1991). The major alkaloids are **hyoscamine** and **hyoscine (= scopolamine)**. **Atropine**, the racemic form of hyoscamine, generally occurs in trace amounts only.



These alkaloids and their near relatives are found in varying concentrations in 22 genera of the Solanaceae. Some of the best sources are:

- *Atropa belladonna*—deadly nightshade
- *Datura stramonium*—thornapple
- *Hyoscyamus niger*—henbane
- *Mandragora officinarum*—mandrake
- *Duboisia myoporoides*, *D. leichhardtii*—corkwood

### Pharmacological actions of hyoscamine and atropine

Hyoscamine acts on tissue cells innervated by post-ganglionic cholinergic fibres of the parasympathetic nervous system; it is antimuscarinic and a parasympathetic depressant.

Hyoscamine has a spasmolytic effect on bronchial and intestinal smooth muscles. The mydriatic effect (inhibits contraction of iris muscle) is more pronounced than that of atropine. It reduces salivary and sweat gland secretions, controls excess motor activity in the gastrointestinal tract, producing an antidiarrhoeal effect, and

reduces rigidity and tremors in Parkinsonism. Scopolamine is a CNS depressant, used for motion sickness ‘patches’, whereas hyoscamine and atropine are CNS stimulants (Roddick 1991). Atropine has been used as an antidote in cases of poisoning by cholinesterase inhibitors, for example phytostigmine, organophosphates.

### Toxicity of tropane solanaceous alkaloids

Symptoms of poisoning by tropane solanaceous alkaloids include dilated pupils, impaired vision, dryness of skin and secretions, extreme thirst, hallucinations and loss of consciousness.

### Datura

This includes *Datura stramonium* and other species, also known as stramonium or thornapple.

*Datura* contains over 30 tropane alkaloids, mainly hyoscamine and hyoscine, as well as nitrogen oxides of hyoscamine and hyoscine, tigloylmeteloidine and nicotine. It is indicated for asthma, pertussis, muscular spasm and excess salivation in Parkinsonism (Bradley 1992).

Stramonium is listed in Schedule 1—dangerous poisons and Schedule 2—medicinal poisons (containing 0.25% or less of alkaloids calculated as hyoscamine) of the New South Wales Poisons List in Australia. Exceptions are made in preparations for smoking or burning.

### Duboisia

Unlike the pituri, *Duboisia hopwoodii*, the nicotine-containing species that inhabits the central and western regions of Australia, the two trees/shrubs *Duboisia myoporoides* and *D. leichhardtii*, also known as corkwood, are restricted in their distribution to the east coast of Australia and adjacent areas. Corkwood leaves contain the highest levels of atropine and tropane alkaloids in the world, and since World War II have replaced *Atropa belladonna* and *Hyoscyamus niger* as the leading source of these alkaloids (Barnard 1952; Roddick 1991).

*D. myoporoides* exists naturally in distinct chemical races, some of which have higher levels of tropane alkaloids. In commercial cultivation a hybrid form of the species has been utilised whose leaves contain up to 7% alkaloids (Evans 1990; Roddick 1991).

## Cocaine

**Cocaine** is obtained from the leaves of the coca shrub, *Erythroxylon coca* (Erythroxylaceae), which is indigenous to South America. Alkaloids present include cocaine, cinnamylcocaine, tropacocaine and valerine.

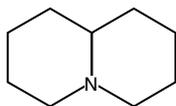
Cocaine is the methyl ester of benzoylecgonine, and can be semi-synthetically produced from ecgonine (Tyler *et al.* 1988).

Cocaine is relatively unstable and is more often administered as cocaine hydrochloride—a more stable form. Cocaine blocks nerve conduction upon local application, hence its employment as an anaesthetic (e.g. Novacaine). In large doses it is a cerebral stimulant and narcotic. Its adrenergic action is due to inhibition of reuptake of noradrenaline, creating an amphetamine-like effect, though only of very short duration.

Cocaine is quickly absorbed into the lungs, heart and brain with almost instant effects, leading to psychic dependence and tolerance. It causes destruction of mucous membranes such as those of the nose. Coca leaf is chewed by the native South Americans, and appears to be relatively harmless in this form.

## Quinolizidine alkaloids

These are also referred to as ‘lupin’ alkaloids since they were first discovered in *Lupinus* spp. They occur primarily in the Papilionaceae family. The quinolizidine structure consists of two carbon rings with a shared nitrogen atom. Their precursor is lysine.

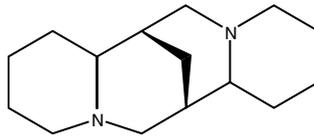


quinolizidine structure

The major quinolizidine alkaloids are **sparteine** found in *Sarothamnus scoparius* (Scotch broom) and greater celandine (*Chelidonium majus*), and **cytisine** from lupins. **Myrine** comes from bilberry (*Vaccinium myrtillus*) in the Ericaceae family.

Sparteine is a tetracyclic, oxygen-free alkaloid. It is oxytocic, a

cardiac stimulant and diuretic. It binds strongly to muscarinic receptors and (less strongly) to nicotinic receptors (Schmeller *et al.* 1994). It is a peripheral vasoconstrictor.



sparteine

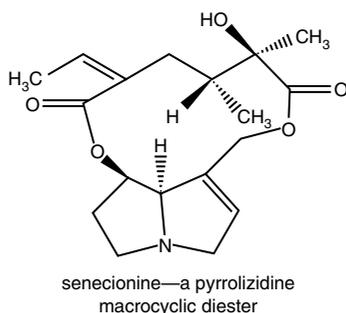
Sparteine has a similar cardiac action to quinidine (Samuelsson 1992). The action of broom in this regard is modified by the presence of flavonoids. It has an ergot-like action on the uterus and has been used as a substitute for ergot drugs. Some sources claim broom is narcotic and it has been used in smoking mixtures, although this practice is considered dangerous. Sparteine-containing herbs are contra-indicated during pregnancy.

## Pyrrolizidine alkaloids

Pyrrolizidine alkaloids (PAs) contain two fused five-membered rings in which a nitrogen atom is common to both rings. The precursor is ornithine. A hydrogen atom usually occurs opposite the nitrogen atom in the  $\alpha$  position, with a hydroxymethyl substitute at the adjacent C-1 position. Most pyrrolizidines have diester groups at C-1 and C-7—these may be non-cyclic, for example **echimidine**, or macrocyclic, for example **senecionine**. Toxicity (see below) appears to be mainly linked to the macrocyclic diester type (Denham 1996). The alkaloids also occur as water-soluble nitrogen oxides.

These alkaloids are widespread in the Boraginaceae, Asteraceae and Papilionaceae families, the majority occurring in the mega-genus *Senecio*. All 1500 species of the mega-genus are believed to contain them, including the common ragwort (*S. jacobaeae*) (Harborne and Baxter 1993).

PAs have been associated with veno-occlusive disease and virtually all herbs that contain them are scheduled and unavailable to herbalists in Australia. This includes comfrey (*Symphytum* spp.), borage (*Borago officinalis*), coltsfoot (*Tussilago farfara*), liferoot (*Senecio*



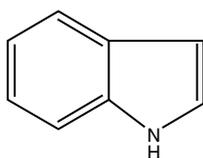
*aureus*) and lungwort (*Pulmonaria officinalis*). PAs from comfrey include **symphytine**, **intermedidine** and **symlandine**—these do not contain the macrocyclic diesters.

Few therapeutic effects have been postulated for PAs. The main interest has been in their toxicity; this is dealt with in numerous other publications (e.g. Bruneton 1995).

## Indole alkaloids

This is a very large group of alkaloids whose basic structure contains a pyrrole ring fused to a benzene ring. Biosynthesis of pure indoles involves the amino acid tryptophan as precursor, while that of a major subgroup of the indoles, including the *Catharanthus* and *Rauwolfia* alkaloids, involves a second precursor—the monoterpene iridoid loganin.

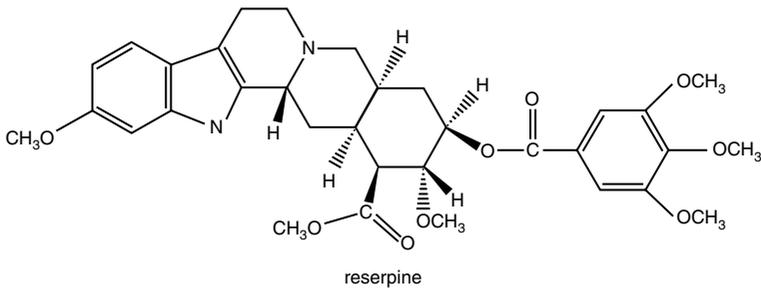
The indole alkaloid structures typically involve multiple ring



systems, often complex in character. They form the basis of several pharmaceutical drugs as well as some of the most potent hallucinogenic drugs, and include poisonous compounds such as strychnine. Of the indole alkaloids used in medicine and pharmacy, the majority

are found in members of the family Apocynaceae (e.g. *Rauwolfia*, *Vinca*, *Catharanthus* and *Alstonia* spp.). Other families in which they occur are the Loganaceae, Rubiaceae and Convovulaceae. Indole alkaloids are represented in the fungal kingdom by the ergot alkaloids and the *Psilocybin* mushrooms.

**Reserpine** is found in the roots of *Rauwolfia serpentina* (Apocynaceae) along with the related alkaloids **resiccinnamine**, **deserpidine** and **ajmaline**. The main actions are hypotensive, sedative and tranquillising. Ajmaline is of benefit for heart arrhythmias (Samuelsson 1992).



The primary actions of reserpine alkaloids are caused by inhibition of noradrenaline and depletion of amines in the central nervous system. While the hypotensive effects have a slow onset their duration is long, and the effective dose is sufficiently low to limit any side effects. It was previously used as a tranquilliser; however, the much higher doses required often resulted in depression and Parkinson disease-like symptoms (Huang 1993). As a result *Rauwolfia* has become a restricted herb in Australia and has no place in current herbal prescribing.

### *Alstonia constricta*—Australian bitter bark

This is one of the best of the bitter tonics and febrifuge remedies to come from Australia. It is a uterine stimulant and should be avoided during pregnancy. It contains several antihypertensive alkaloids of the indole class—**alstonine**, **alstonidine** and small amounts of reserpine.

## Periwinkles

According to Samuelsson (1992) over 100 alkaloids have been isolated from *Cantharanthus roseus*—the rose or Madagascar periwinkle, a popular garden plant—including some with hypoglycaemic properties. However, the alkaloids occur naturally in very small quantities. **Vinblastine** and **vincristine** are antineoplastic, used as chemotherapy treatment in childhood leukaemia and Hodgkin's disease. They are dimeric indole alkaloids.

*Vinca minor*, *V. major*—the common periwinkles—contain numerous indole alkaloids including **vincamine**, **majdine**, **majoridine**. Their actions are antihæmorrhagic and astringent. *Vinca* spp. do not contain the antineoplastic alkaloids found in *Cantharanthus* (Wren 1988).

## Ergot alkaloids

Ergot (*Claviceps purpurea*) is a fungus with a sclerotina (fruiting body) that produces over 20 indole alkaloids. It grows on rye and other cereal plants. Ergotism is a toxic response to ingesting ergot-contaminated grain, and manifests either as painful spasms of the limb muscles leading to epileptic-like convulsions ('St Anthony's fire'), or as vomiting and diarrhoea leading to gangrene of the toes and fingers. Both syndromes can lead to fatalities.

**Ergotamine** constricts peripheral blood vessels and raises blood pressure. It is used in treatment of migraine headaches. **Ergonavine** is oxytocic and vasoconstrictive and is used as treatment or a preventative for post-partum hæmorrhage. **LSD (lysergic acid)** is a semi-synthetic derivative of ergot; similar natural compounds are found in *Ipomoea* spp. (morning glory).

**Strychnine** comes from the seed of *Strychnos nux-vomica* (Loganiaceae); it is also known as nux vomica. It is a powerful stimulant to the central nervous system in low doses, but becomes deadly poisonous in larger doses (60–90 mg), causing an exaggeration of reflexes and tonic convulsions (Tyler *et al.* 1988). Brucine is a related but less toxic alkaloid in *Strychnos* spp.

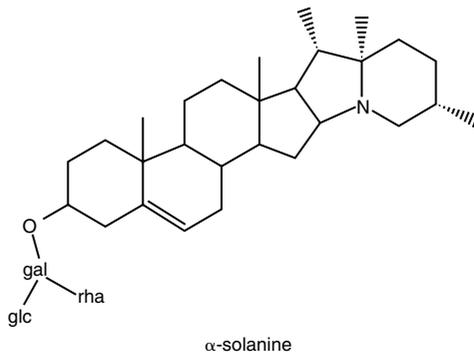
**Yohimbine** is derived from the bark of *Aspidosperma quebracho* (Apocynaceae) and *Pausinystalia yohimba* (Rubiaceae). These plants are reputedly aphrodisiacs. Yohimbine blocks  $\alpha$ -adrenergic transmissions but stimulates  $\beta$ -adrenergic sites (Robinson 1981). Yohimbine and strychnine are sometimes combined in pharmaceutical preparations for use as aphrodisiacs and nerve tonics.

## Steroidal alkaloids

Steroidal alkaloids are derived from triterpenoids, being distinguished from other compounds in that class by the presence of a nitrogen atom. The main subgroups in this class are found in the Liliaceae and Solanaceae. The Solanaceae group occur as glycosides and some are used as the basis for synthesis of steroid drugs.

**Solasodine**, the glycoalkaloid used in production of contraceptives, is obtained from the Australian species *Solanum laciniatum* and *S. aviculare*, which are now cultivated in several countries for this purpose (Bradley *et al.* 1978).

In unripe potatoes (*Solanum tuberosum*) the glycoalkaloids  $\alpha$ -**solanine** and  $\alpha$ -**chaconine** are derived from the widely occurring aglycone solanidine. Glycoalkaloids are mainly concentrated in unripe fruits and green potatoes and disappear in the ripening process. These alkaloids are toxic so that avoidance of sprouting potatoes and unripe tomatoes is recommended, particularly for pregnant women since there is evidence of teratogenicity. Supplementation with ascorbic acid has been shown to protect against toxicity from these alkaloids (Renwick 1986).



The *Veratrum* genus (Liliaceae) is also rich in steroidal alkaloids. They are derived from the white hellebore (*Veratrum album*) and the green hellebore (*V. viridis*). These alkaloids have steroid skeletons though some are highly oxygenated—the **protoveratrines A and B** contain up to nine oxygen atoms.

Veratrine alkaloids are cardiac depressants, and are used in medicine in the treatment of severe hypertension. Their action is mediated through inhibition of Na-K ATPase, the enzyme required for transport of mineral ions across cell membranes—an action they

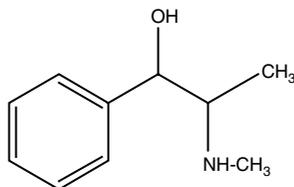
share with the cardiac glycosides (Robinson 1981). Owing to their high toxicity the *Veratrum* species are not used in herbal medicine.

## Alkaloidal amines

Amines are simple compounds derived from ammonia ( $\text{NH}_3$ ) in which one or more hydrogen atoms is replaced by carbon. Replacement of one, two or three hydrogen atoms results in primary, secondary and tertiary amines respectively. Amino acids and alkaloids are derived from amines; however, in one group of alkaloids the only nitrogen atoms occur in the amino side group attached to a benzene ring—they are not heterocyclic. Hence alkaloidal amines are often regarded as ‘pseudo alkaloids’. The precursors for alkaloidal amines are aromatic amino acids—phenylalanine, tyrosine and tryptophan.

**Ephedrine** and **pseudoephedrine** are derived from the aerial parts of *Ephedra* spp. (Ephedraceae). The major source is the Chinese species known as ‘ma huang’—*Ephedra sinica*—for centuries one of the most important medicines in the Chinese Materia Medica. In the West its use is clouded in controversy and, in the case of Australia, restricted to registered practitioners. The two major alkaloids in *Ephedra* form the basis of several proprietary prescription medicines, as well as the illicit amphetamine drugs. Issues of safety concerns and legal status, as well as uses both ancient and modern, have been reviewed in *Herbalgram* (Blumenthal and King 1995).

Ephedrine is structurally simple, its aromatic skeleton deriving from phenylalanine, while an extra methyl group ( $\text{CH}_3$ ) derives from methionine (Samuelsson 1992). The basic structure occurs in several isomeric forms, one of which (a diastereoisomer) is pseudoephedrine.



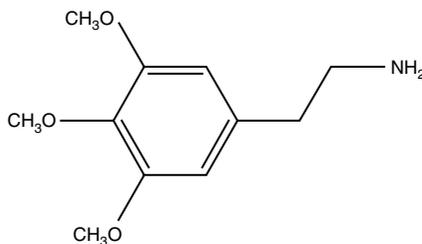
ephedrine—an alkaloidal amine

Ephedrine is a sympathomimetic or central nervous system stimulant. It is a potent stimulator of  $\alpha$ ,  $\beta_1$  and  $\beta_2$  adrenergic receptors. The effects include vasoconstriction, raised blood pressure and pulse, bronchodilation and diuresis. Ephedrine-based drugs are used as nasal decongestants, bronchodilators and in anaphylactic shock. In excess they cause insomnia, tachycardia and dizziness.

In herbal medicine *Ephedra* is valued highly as a reliable treatment for asthma and allergic conditions of all types. Being both bronchodilatory and nasal decongestant (due to constriction of blood vessels), *Ephedra* is useful also in bronchitis, emphysema, rhinitis, as well as common colds and influenza. It is contra-indicated for hypertension, angina pectoris, hyperthyroidism, during pregnancy and where monoamine oxidase inhibitors are being used.

Other alkaloidal amines include:

- **Colchicine**—from *Colchicum autumnale* (Liliaceae), the autumn crocus. Both the alkaloid and the herb are beneficial in the treatment of gout. Because of its ability to inhibit cell division, colchicine is used in plant breeding and genetic research.
- **Muscarine**—from *Amanita muscaria* (Agaricaceae), the fly agaric mushroom. Muscarine is a toxic constituent found in several mushroom species. It is a parasympathetic agent that binds to cholinergic receptors. Owing to its toxicity it is not used therapeutically.
- **Mescaline**—from *Lophophora williamsii* (Cactaceae)—peyote, mescal buttons. This plant is used as a hallucinogen by some native North Americans.
- **Psilocybin**—from *Psilocybe* spp. and other hallucinogenic fungi.
- **Hordeanine**—from barley, *Hordeum vulgare* (Poaceae).

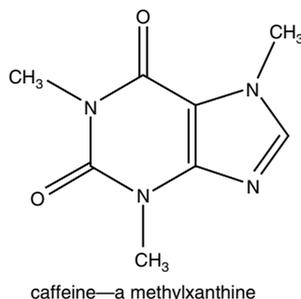


mescaline

## Purine alkaloids

Purine bases are a group of compounds found in plants and animals—they include nucleic acids. Their biosynthesis is complex with numerous non-amino-acid precursors (Samuelsson 1992). **Xanthine**, an oxidised purine that occurs as a breakdown product of nucleic acid metabolism, is itself oxidised in the body to uric acid. Xanthine consists of two fused ring systems each containing two nitrogen atoms.

Alkaloidal amines are methylated xanthines forming weak bases that are pharmacologically active. There are three methylxanthines and all are present in our most popular stimulant beverages—coffee and tea.



**Caffeine** is found in a number of botanically unrelated species, including *Coffea arabica* (Rubiaceae), *Camellia sinensis* (Theaceae), or tea, *Cola nitida* (Sterculiaceae), or kola nut, and *Paullinia cupana* (Sapindaceae), or guarana. Caffeine is bound to chlorogenic acid in raw coffee beans, the roasting process liberating the caffeine and other compounds that contribute to the aroma of coffee (Samuelsson 1992).

Caffeine is a central nervous system stimulant, enhancing alertness and overcoming fatigue, while high doses lead to insomnia and tremors. It also stimulates cardiac output and heart rate, and acts as a mild diuretic. Caffeine raises metabolism, influences blood sugar and is habit forming. It is sometimes used in formulations for treating migraine.

Structurally **theophylline** resembles caffeine; however, it lacks the methyl group in the five-carbon ring. It occurs naturally in the tea plant, but it is synthesised from caffeine for use in medicine. The

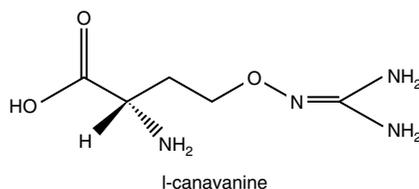
effects on the central nervous system and cardiovascular system are similar to those of caffeine though milder, while the diuretic activity is more pronounced. However, the main use for theophylline is as a bronchial smooth muscle relaxant for treatment of bronchial asthma and emphysema. It forms the basis of the drug aminophylline, used as a diuretic and asthma medicine.

**Theobromine** is found mainly in the cocoa plant *Theobroma cacao* (Sterculiaceae). It is isomeric with theophylline; however, it lacks the potent central nervous system effects of the other two alkaloids in this class. It is used mainly as a diuretic and bronchial muscle relaxant.

## Amino acids

Amino acids are nitrogenous compounds whose main role is the synthesis of proteins necessary for growth and maintenance of healthy tissues. They also act as precursors to alkaloids (see above). Apart from their nutritional and biosynthetic roles, amino acids are increasingly being utilised as therapeutic agents for a wide range of conditions (Marshall 1994). While most emphasis is on the essential amino acids—not covered in this text—some lesser known compounds have also proven to be of interest.

**L-canavanine** is a non-protein amino acid, an L-arginine antagonist and therefore an antimetabolite. It is found in the seeds of many legumes, being particularly high in alfalfa seeds. Lower levels are found in the South African leguminous plant *Sutherlandia frutescens*.



L-canavanine is a documented antiviral, antibacterial, antifungal and antineoplastic agent. Antiviral activity has been demonstrated for influenza and retroviruses. It is a selective inhibitor of inducible nitric oxide synthetase. The antitumour mechanism involves incorporation

of canavanine into the protein of cancer cells where it replaces arginine (Rosenthal and Nkomo 2000).

## Lectins

Lectins are high-molecular-weight polypeptides, known to interact with glycoproteins bearing polysaccharide side chains on cell membranes of animals, causing agglutination *in vivo* and inducing cytotoxicity. They are also known as phytohaemagglutinins. Lectins can also act as mitogens, stimulating B and T lymphocytes to divide and mature. B cells are able to produce immunoglobulins. Their large complex structures do not lend themselves to diagrammatic representation.

Lectins are of widespread occurrence in legumes (e.g. soybeans, lentils, kidney beans, jack beans). They are potentially toxic as they can impair tissue functions, but the body can usually replace any damaged cells faster than they are destroyed (Johns 1990). Lectins are responsible for toxicity in the notorious garden plant rosary pea—*Abrus precatorius*. Lectins in foods are readily destroyed by processing and cooking.

Medicinal species containing lectins include *Phytolacca decandra*, *Viscum album*, *Urtica dioica* and *Juglans nigra* (Lewis and Elvin-Lewis 1977). Mistletoe (*Viscum album*) contains lectins, viscotoxins (low-molecular-weight polypeptides), amines, polysaccharides, alkaloids, flavonoids, triterpenes, sterols, fatty acids and phenylpropanoids. Mistletoe lectins have been found to bind to erythrocytes, lymphocytes, leucocytes, macrophages, glycoproteins and plasma proteins. Cytotoxic activity has been demonstrated for the glycoprotein fraction, alkaloid fraction and Iscador™ (plant juice preparation)—positive *in vitro* and *in vivo*. Human studies with Iscador™ have shown slight improvement over controls, with best results for colon cancer. In Europe it is often used as adjunct treatment to surgery and radiotherapy (Newall *et al.* 1996).

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