Introduction to the Different Classes of Natural Products

1

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Abstract Plants produce an enormous variety of natural products with highly diverse structures. These products are commonly termed "secondary metabolites" in contrast to the "primary metabolites" which are essential for plant growth and development. Secondary metabolites were formerly regarded as "waste products" without physiological function for the plant. With the emergence of the field of chemical ecology about 30 years ago, it became evident, however, that these natural products fulfill important functions in the interaction between plants and their biotic and abiotic environment. They can serve, for example, as defense compounds against herbivores and pathogens, as flower pigments that attract pollinators, or as hormones or signal molecules. In addition to their physiological function in plants, natural products also have a strong impact on human culture and have been used throughout human history as condiments, pigments, and pharmaceuticals.

This chapter provides an overview about the diversity of secondary metabolites in plants, their multiple biological functions and multifaceted cultural history. The compounds are classified into four different groups according to their biosynthetic origin: alkaloids, phenylpropanoids, polyketides, and terpenoids. Since more than 200,000 structures of natural products from plants are known, only selected groups and compounds are presented.

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Nitrogen-Containing Natural Products

The term alkaloid is derived from the Arabic word "al-qali" that refers to potassium carbonate-containing ashes from plant material. Traditionally, alkaloids are defined as heterocyclic nitrogen compounds biosynthesized from amino acids. Many other substances, however, that do not exactly match this rule are classified as alkaloids, either for historical reasons or due to their bioactivities. With currently more than 12,000 known structures, alkaloids represent one of the biggest groups of natural products. Due to this large number and the high structural diversity, it is impossible to give a comprehensive summary of all different types of alkaloids, and only some classes will be introduced. In addition to alkaloids, benzoxazinoids, glucosinolates, and cyanogenic glucosides will be presented. Like the alkaloids, these metabolites contain nitrogen and are derived from amino acids.

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Purine Alkaloids

Purine alkaloids are nitrogen containing compounds derived from nucleoside metabolism (Ashihara and Crozier, 2001). The purine backbone is synthesized from several small molecules of primary metabolism that include L-aspartic acid, L-glutamine, L-glycine, and formate. Cytokinins, plant hormones that control, e.g., stem growth and differentiation, apical dominance, and senescence, are derived from the same pathway. Purine alkaloids are produced in a variety of taxonomically unrelated plant species, e.g., coffee (*Coffea arabica* and other *Coffea* species, Rubiaceae), tea (*Camellia sinensis*, Theaceae), cacao (*Theobroma cacao*, Sterculiaceae), maté (*Ilex paraguariensis*, Aquifoliceae), guaraná (*Paullinia cupana*, Sapindaceae), and cola (*Cola nitida*, Sterculiaceae). The most abundant purine alkaloid is caffeine, followed by theobromine and some minor purines, e.g., theophylline and paraxanthine (Fig. 1). Coffee seeds ("beans") contain ca. 1% caffeine, young tea leaves 2-3% (Ashihara and Suzuki, 2004).

Since caffeine is accumulated in higher amounts than the other purines, its function in plants has been investigated. It may serve as defense against herbivores (Hollingsworth et al., 2002) and as autotoxin, because it inhibits the germination of coffee seedlings (Friedmann and Waller, 1985).

Caffeine is a central stimulant and widely consumed in beverages like coffee, tea, and sodas, but also in cold medicine and analgesics. The average daily caffeine consumption of adults is 280 mg; one cup of filter coffee contains ca. 140 mg caffeine, one cup of black tea ca. 80 mg (Lovett, 2005). Besides caffeine, theophylline is of interest, since it has found application in the therapy of asthma due to its bronchodilatory effect.

The predominant mode of action of caffeine and other purine alkaloids is the blockade of adenosine receptors resulting in the release of neurotransmitters (Benowitz, 1990). In higher concentrations, phosphodiesterase, the enzyme that hydrolyzes the second messenger cAMP, is inhibited. However, these blood concentrations are normally not reached by consumption of caffeine-containing beverages. More recently, the attention towards caffeine increased because coffee drinkers show a reduced risk for Parkinson's disease (Ascherio et al., 2004).

C. arabica originated from Ethiopia, where the fruits were first used as food by nomads. Roasted coffee seeds ("beans") were brewed in Arabia around AD 1000 to prepare a drink called "qahwah", and it was introduced into Europe as "kahveh" after AD 1600 coffee and coffee houses became soon popular in Europe. Johann Sebastian Bach's "Coffee Cantata" (BMV 211), which he composed for a text written by Picander in the beginning of the eighteenth century, reflects this growing popularity as well as the controversy on the assumed dangerous health effects of coffee at that time.

Tea is prepared from fermented (black tea) or unfermented (green tea), dried leaves of *C. sinensis*. The earliest records on tea drinking come from China in the first millennium BC. From there, it was introduced into Japan in the

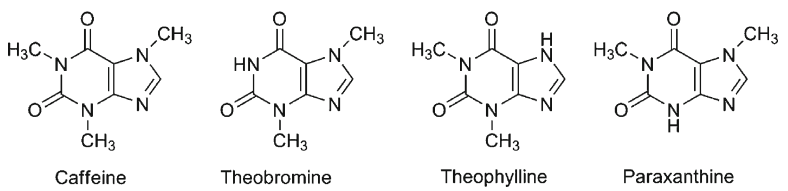

Fig. 1 Structures of the purine alkaloids caffeine, theobromine, theophylline, and paraxanthine

eighth century AD by Buddhist monks. Tea was first shipped to Europe by the Dutch East India Company in 1606.

The cacao tree (*T. cacao*, Sterculiaceae) originates from the Amazon Basin, but it was cultivated by the Mayas in Mesoamerica. Its seeds ("beans") contain theobromine and caffeine. Mayas and Azteks used roasted cacao seeds together with chili peppers and other spices to prepare a drink, which the Aztecs called "xocoatl". According to Aztec belief, cacao was given to humanity by the god Quetzalcoatl. The Swedish botanist Carl Linnaeus named the cacao tree after the Aztec tradition; *Theobroma* means "food of the gods" in Greek. The first cacao beans were brought to Europe by the Spanish Conquistador Hernán Cortés.

Tropane Alkaloids

Tropane alkaloids originate from the amino acids ornithine and/or arginine. They all have in common the bicyclic tropane skeleton that consists of a seven-membered ring with an *N*-bridge between C-1 and C-5, the nitrogen being methylated. Nortropanes lacking the *N*-methylation and *seco*-tropanes with a dissected *N*-bridge have been described, too (Griffin and Lin, 2000). Many tropane alkaloids are esters of the alcohols tropine (tropane-3α-ol) or pseudotropine (tropane-3β-ol) (Fig. 2) with aliphatic or aromatic acids. Tropane alkaloids were isolated first from the nightshade family (Solanaceae). Many structurally diverse tropanes, however, have been discovered in the related family Convolvulaceae, like the Solanaceae a member of the order Solanales, and in some species from the unrelated plant families Brassicaceae, Euphorbiaceae, Erythroxylaceae, Proteaeceae, and Rhizophoraceae (Griffin and Lin, 2000).

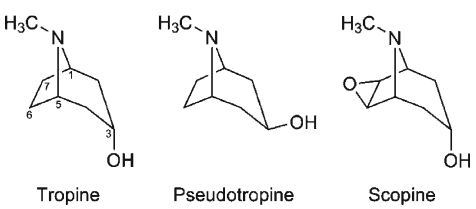

Fig. 2 Tropane amino alcohols

Hyoscyamine and Scopolamine

(*S*)-Hyoscyamine and (*S*)-scopolamine are esters of the amino alcohols tropine and scopine with (*S*)-tropic acid, which is derived from phenylalanine (Fig. 3). The two alkaloids occur exclusively in the Solanaceae family. They act as antagonists of muscarinic acetylcholine receptors (parasympatholytics) and lead to an increase in pulse rate, relaxation of smooth muscles, e.g., in the gastrointestine and the bronchial tract, reduction of salivary, bronchial, gastric, and sweat gland secretion. While hyoscyamine is a central stimulant, scopolamine depresses the central nervous system.

Atropine, the racemate of (*S*)- and (*R*)-hyoscyamine, is formed during the extraction of plant material. Although (*S*)-hyoscyamine is more effective than the (*R*)-enantiomer, atropine is more widely used for traditional reasons. In medicine, atropine is used against spasms during a biliary colic, as antidote against intoxication with organophosphorous insecticides, and as pre-medication before surgery to decrease salivation and respiratory secretion. (*S*)-Scopolamine

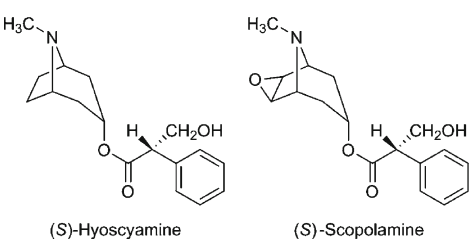

Fig. 3 The tropane alkaloids (*S*)-hyoscyamine and (*S*)-scopolamine occur only in the Solanaceae family

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is applied as treatment of motion sickness. Derivatives of hyoscyamine or scopolamine are used as mydriatics for eye examinations, as treatment for asthma and chronic obstructive bronchitis, and against gastrointestinal spasms.

Plants containing hyoscyamine and scopolamine have been used throughout history as psychoactive drugs, poisons, aphrodisiacs, and for the preparation of analgesic and sleeping potions. Famous examples include the deadly nightshade (*Atropa belladonna*), thorn-apple (*Datura* species), henbane (*Hyoscyamus niger*), and mandrake (*Mandragora officinarum*). All plants are toxic, and, for example, five to ten fruits of *A. belladonna* are lethal in an adult. This is reflected in the name "Atropa", the Greek goddess of destiny who cuts the thread of life. "Bella donna" (Italian for "beautiful woman") refers to the custom of Renaissance ladies who dilated their pupils with extracts of the deadly nightshade. Solanaceous plants with tropanes are often mentioned in literature, for example, in Homer's Odyssey and several pieces by William Shakespeare.

Atropine was first isolated from *A. belladonna* (Mein, 1833), and (*S*)-hyoscyamine was extracted from *H. niger* (Geiger and Hesse, 1833). In the late nineteenth century, (*S*)-scopolamine was detected by Ladenburg (1881) and Schmidt (1892). Today, (*S*)-hyoscyamine and (*S*)-scopolamine are obtained from *Duboisia leichhardtii* and *Duboisia myoporoides*, trees native to Australia, and hybrids of the two species.

Cocaine

Cocaine is the benzoic acid ester of the tropane base methylecgonine. Only *Erythroxylum coca* and *Erythroxylum novogranatense*, shrubs or small trees native to the Andes, contain substantial amounts of cocaine in their leaves, i.e., up to 1% of their dry mass (Plowman and Rivier, 1983). If the coca leaves are dried or stored improperly, the cocaine content decreases rapidly. The two *Erythroxylum* species contain also other ecgonine derivatives, e.g., *cis*- and *trans*-cinnamoylcocaine and the truxillins, esters of methylecgonine with dimeric cinnamic acid (Fig. 4) (Griffin and Lin, 2000).

Cocaine is a highly addictive central stimulant that inhibits the re-uptake of the neurotransmitters dopamine and norepinephrine at synapses,

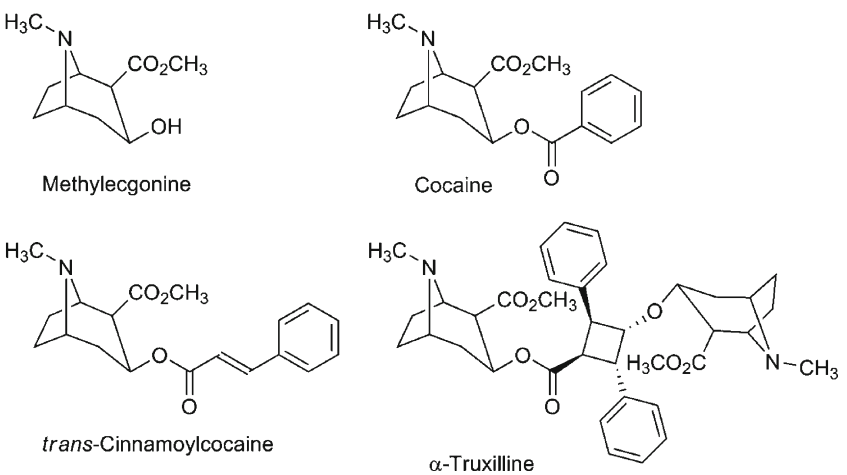


Fig. 4 *Erythroxylum* alkaloids

and inhibits monoamine oxidase, the enzyme that degrades dopamine, epinephrine, and norepinephrine. This leads to euphoria, hyperactivity, suppression of hunger and fatigue. Peripheral effects include increased heart rate and blood pressure, dilation of pupils, hyperglycaemia, and hyperthermia (White and Lambe, 2003). If cocaine is applied on mucous membranes, it blocks Na^+ channels leading to local anaesthesia. Therefore, cocaine is used as local anaesthetic in surgeries of the eye, ear, nose, and throat.

As an illegal drug, cocaine occurs in different forms. The hydrochloride is soluble in water and can be injected, sniffed, or chewed. "Freebase" is cocaine base, which is gained by extraction of cocaine from alkaline solutions with ether. It evaporates at high temperatures and can be inhaled by smoking. Another smokable form of the cocaine base is "crack", which is obtained by precipitating cocaine hydrochloride from solution with baking soda.

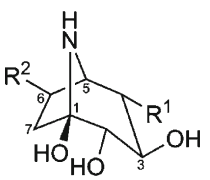
In South America, the chewing of coca leaves has a long tradition and dates back to 3000 B.C. It is used to overcome exhaustion, hunger, and thirst, and presumably does not have the addictive potential of cocaine. The leaves are chewed together with an alkaline agent like plant ash or sodium bicarbonate, which converts the alkaloids to their free bases. Only a small portion of the cocaine is hydrolyzed to methylecgonine (Rivier, 1981).

Coca leaves were brought to Europe by the Spanish conquistadores, and cocaine was isolated from the leaves in the 1860s. In 1863, the French chemist Angelo Mariani created the tonic "Vin Mariani", an extract of coca in Bordeaux wine. The non-alcoholic version "Coca-Cola" was invented in 1886 by the American Pharmacist John Pemberton, who mixed extracts of coca leaves and caffeine-containing cola nuts with soda. With the introduction of the first anti-drug laws in the USA in 1906, however, only decocainized leaves were used for the production of Coca-Cola.

Calystegines

Calystegines contain the nortropane skeleton with three to five hydroxyl groups. In contrast to most other tropane alkaloids, the hydroxyl groups are not esterified, but they can be glycosylated. The bridgehead C-1 of calystegines is hydroxylated, only in calystegine N_1 it is linked to an amino group instead (Dräger, 2004). The structures of the three most widespread calystegines are shown in Fig. 5. Calystegines were discovered in roots of *Calystegia sepium* (Tepfer et al., 1988), and the first structures were determined in 1990 (Goldmann et al., 1990). Since then, they have been isolated from numerous members of the Brassicaceae, Convolvulaceae, Erythroxylaceae, Solanaceae, and from two species of the Moraceae (Biastoff and Dräger, 2007). One important reason for their late discovery is their high hydrophily due to which they cannot be extracted with organic solvents like other alkaloids.

Calystegines are sugar-mimicking glycosidase inhibitors. Due to their structural similarity to sugars, they compete with polysaccharides for binding at the active site of the glycosidase. Therefore, one possible medicinal application for this group of metabolites is the prevention of post-prandial glucose peaks in patients with type II diabetes. In addition, calystegines might



	R^1	R^2
Calystegine A_3	H	H
Calystegine B_1	H	OH
Calystegine B_2	OH	H

Fig. 5 Structures of calystegines A_3, B_1, and B_2

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become useful for the therapy of Morbus Gaucher, a lysosomal storage disease that is caused by a mutation in the gene encoding glucocerebrosidase. Calystegines were reported to act as chaperones on the mutated enzyme thus preventing its misfolding and degradation. Nevertheless, it is still unclear whether these hydrophilic polyhydroxylated alkaloids can be absorbed in the intestines and transported to the lysosomes of target cells (reviewed by Biastoff and Dräger, 2007).

Pyrrolizidine Alkaloids

The backbone of pyrrolizidine alkaloids is composed of a hydroxymethylpyrrolizidine (necine base) that is mostly esterified with branched aliphatic mono- or dicarboxylic acids (necic acids). The necine base is biosynthesized from spermidine and putrescine, which in turn originates from arginine (Hartmann et al., 1988). The origin of the necic acids has been investigated only for pyrrolizidine alkaloids of the senecionine and lycopsamine type; they are derived from amino acid metabolism (Stirling et al., 1997; Weber et al., 1998). The major structural types of pyrrolizidine alkaloids are depicted in Fig. 6. In plants, these alkaloids are usually stored and transported as polar *N*-oxides. Pyrrolizidines occur mainly in the plant families Asteraceae, Boraginaceae, Fabaceae, and Orchidaceae, although scattered occurrences in other plant families have also been described (Hartmann and Ober, 2000).

Many pyrrolizidine alkaloids are hepatotoxic, mutagenic, and carcinogenic. They can cause veno-occlusive disease of the liver that may lead to cirrhosis and eventually liver failure. The main reasons for intoxications with pyrrolizidines are contamination of cereals with

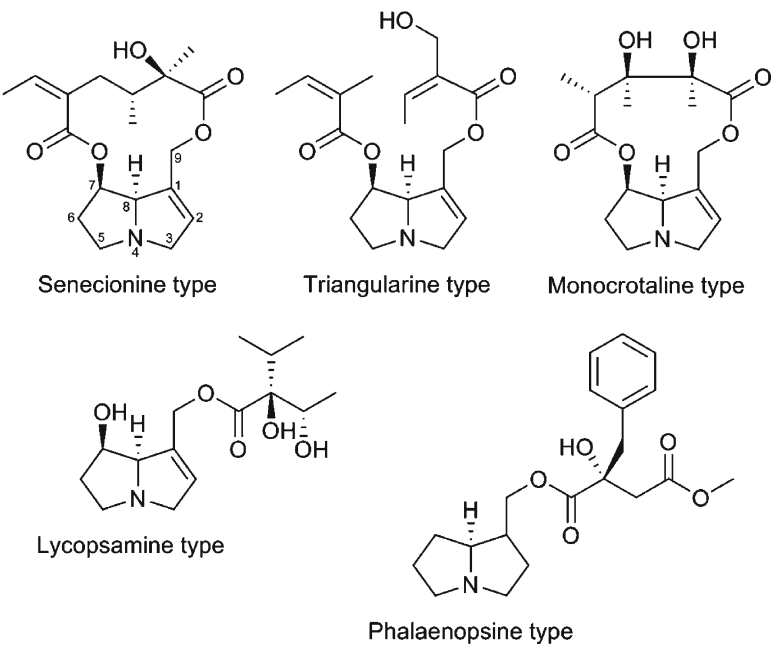

Fig. 6 The five major structural types of pyrrolizidine alkaloids. In plants, these alkaloids occur mostly in form of their *N*-oxides

pyrrolizidine-containing plants and the ingestion of herbal medicines containing these alkaloids.

The structural features responsible for the genotoxicity are a double bond in the necine base between C-1 and C-2, presence of hydroxy groups at C-7 and C-9, and esterification of at least one of these hydroxy groups with a branched carbon chain (Frei et al., 1992). In most vertebrates and insect herbivores, the alkaloid *N*-oxides are reduced in the gut to their free bases. The reduced alkaloids are then taken up and bioactivated by cytochrome P450-dependent monooxygenases of the liver to highly reactive dehydropyrrolizidine alkaloids that react with nucleophilic groups of proteins and DNA (Röder, 1995).

Although pyrrolizidines are toxic, many insects feed on pyrrolizidine-containing plants. Several butterflies and moths (Lepidoptera) and some Chrysomelid leaf beetles (Coleoptera) are even able to sequester pyrrolizidine alkaloids as defense compounds against predators. Adult members of the Lepidoptera selectively ingest plants with pyrrolizidines, a behaviour called pharmacophagy. In the gut of adapted Lepidoptera, the *N*-oxides are reduced and taken up as free bases. In the hemolymph, however, they are detoxified by oxidation to the water-soluble *N*-oxides, which do not serve as substrates for bioactivating cytochrome P450 enzymes. In addition to their function in chemical defense in adapted butterflies, pyrrolizidine alkaloids also play an important role in the mating process. Male moths utilize pyrrolizidines to synthesize the pheromone hydroxydanaidal in order to signal their alkaloid load to the females. During courtship, male moths of the species *Utetheisa ornatrix* transfer sequestered pyrrolizidine alkaloids as a nuptial gift to the female. The female moth transfers her own pyrrolizidines and the alkaloids acquired during mating to the egg mass to protect the offspring (Eisner and Meinwald, 1995).

Quinolizidine Alkaloids

Quinolizidine alkaloids are biosynthesized from lysine *via* cadaverine. Apart from the bicyclic lupinine, most other compounds of this group are tri- or tetracyclic. Some representative structures are shown in Fig. 7. Quinolizidine alkaloids occur abundantly in the Fabaceae, but also in several unrelated taxa, e.g., Berberidaceae, Chenopodiacae, Ranunculaceae, Rubiaceae, and Solanaceae (Wink, 2002). Traces of quinolizidines were found in elicited cell cultures of species that normally do not produce these metabolites (Wink and Witte, 1983). This finding, together with the occurrence of quinolizidines alkaloids in taxonomically unrelated species, has lead to the hypothesis that the genes for the biosynthesis of quinolizidines are widely distributed in the plant kingdom, but are actively transcribed only in a few species that use them as feeding deterrents against herbivores.

The function of quinolizidines as defense compounds can be observed in the example of sweet lupins, an alkaloid-free breeding form. In contrast to the alkaloid-containing wild form,

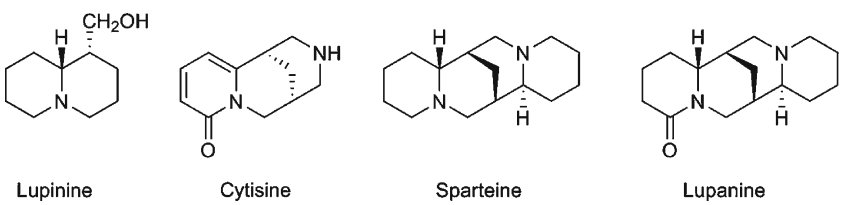

Fig. 7 Four representative structures of quinolizidine alkaloids

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the bitter lupin, sweet lupins are more susceptible to herbivores (Wink, 2003). In addition to their function as defense compounds, a minor function of quinolizidines is nitrogen transport in the phloem and probably storage of nitrogen in seeds (Wink and Witte, 1984, 1985).

Quinolizidines have antiarrhythmic, CNS-depressant, hypotensive, and hypoglycemic effects. Their toxicity and some of their pharmacological properties can be explained through inhibition of Na^+ and K^+ channels and interaction with nicotinic and muscarinic acetylcholine receptors. Sparteine from broom (*Cytisus scoparius*) is used as antiarrhythmic. However, its medicinal use is declining and restricted because about 10% of all patients are unable to metabolize this alkaloid and suffer from intoxication (Wink, 2003).

Only few insects have adapted to quinolizidine alkaloids and sequester them as defense compounds, e.g., some aphids and larvae of the pyralid moth *Uresiphita reversalis* (Wink and Witte, 1991; Montllor et al., 1990). This is in contrast to pyrrolizidines, which are utilized by a large number of butterflies and beetles.

Alkaloids Derived from Tyrosine

The amino acid tyrosine is a precursor of numerous alkaloids. The largest group is formed by the benzylisoquinoline alkaloids. In addition, several other alkaloid classes originate from tyrosine, for example, the Ipecac alkaloids and the Amaryllidaceae alkaloids. The benzylisoquinolines, Ipecac- and Amaryllidaceae alkaloids will be reviewed.

Benzylisoquinoline Alkaloids

Benzylisoquinoline alkaloids are derived from two molecules of tyrosine. The central intermediate in their biosynthesis, (*S*)-reticuline, can undergo various rearrangements and modifications to yield the different structural classes of benzylisoquinolines (Fig. 8). At present, this diverse group of alkaloids comprises about 2,500 known structures. Benzylisoquinolines occur mainly in basal angiosperms, e.g., in members of the Berberidaceae, Fumariaceae, Papaveraceae, Menispermaceae, and Ranunculaceae, but also in other taxa.

Some benzylisoquinoline alkaloids have powerful pharmacological activities and have therefore found application in medicine, e.g., the analgesic morphine, the antitussive and analgesic codeine, the muscle relaxant tubocurarine, and the antimicrobial and anti-inflammatory sanguinarine. As can be expected from their highly diverse structures, these compounds have different mechanisms of action. Morphine and codeine are agonists at the μ-, δ-, and κ- opioid receptors, which are normally targeted by endorphines, enkephalines and dynorphines as endogenous ligands (Schiff, 2002). The bisbenzylisoquinoline alkaloid tubocurarine is the active principle of arrow poison from the liana *Chondrodendron tomentosum*, which is native to the Amazon Basin. Tubocurarine is an antagonist at nicotinic acetylcholine receptors on the neuromuscular end plate of skeletal muscle and is used to induce complete muscle relaxation before surgeries (Howland et al., 2005). Due to its quaternary nitrogen it is absorbed poorly and has to be injected intravenously.

Like tubocurarine, the quarternary benzophenanthridine sanguinarine is absorbed badly. It reacts with negatively charged and nucleophilic groups of proteins and inhibits several enzymes, e.g., Na^+/K^+-ATPase (Straub and Carver, 1975). In addition, it intercalates DNA due to its planar structure (Nandi and Maiti, 1985).

The opium poppy (*Papaver somniferum*) is an important medicinal plant with a colorful history. Opium, the dried latex of unripe capsules of *P. somniferum*, contains more than 80 isoquinoline alkaloids. The main alkaloids in opium are morphine (4-21%), followed by codeine,

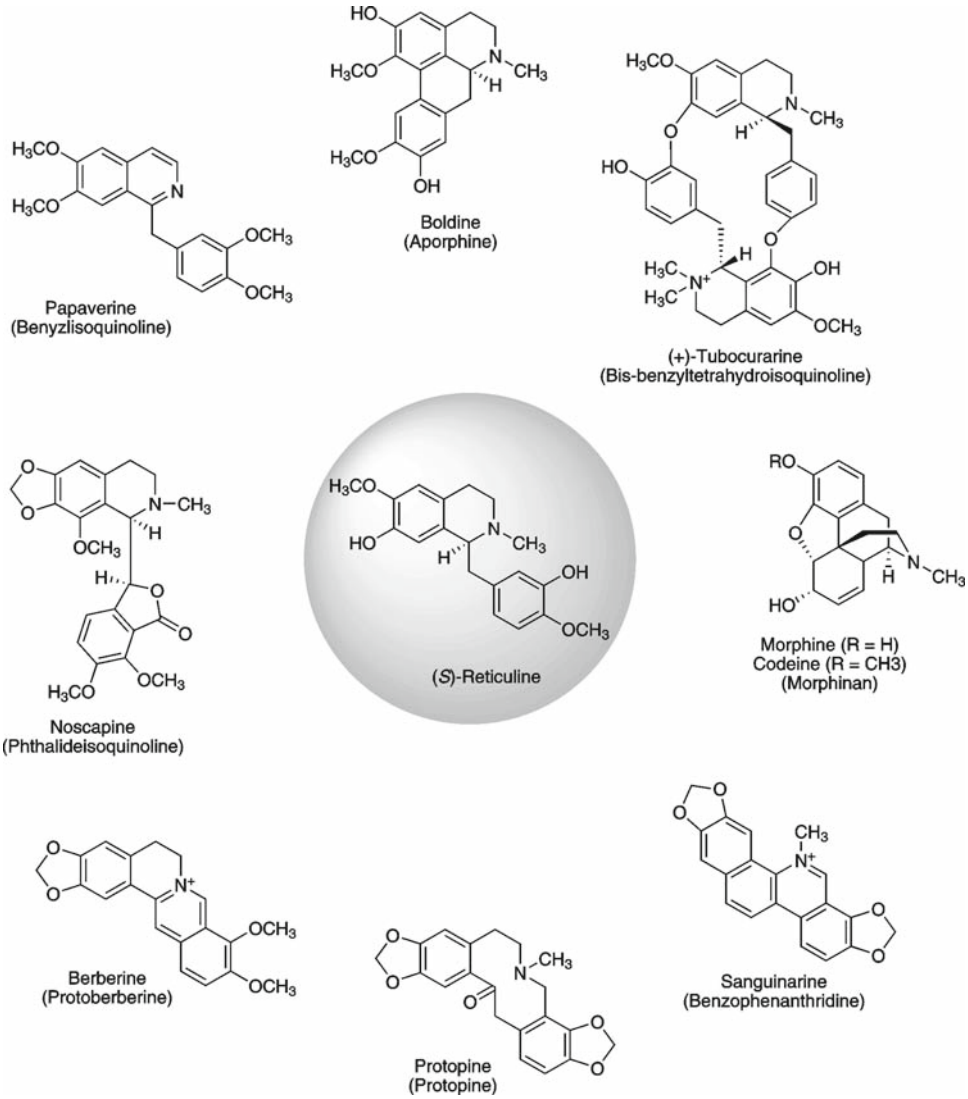

Fig. 8 (*S*)-Reticuline is the precursor for the various classes of benzylisoquinoline alkaloids

thebaine, papaverine, noscapine, and narceine (Dewick, 2002). The alkaloid concentrations vary strongly, and depending on the *P. somniferum* cultivar, also other alkaloids can occur in substantial amounts, e.g., oripavine in poppy from Tasmania (Frick et al., 2005). The only other plant species that accumulates the morphinans morphine and codeine is *Papaver setigerum*.

The opium poppy originated from the Mediterranean area. Earliest mention of the opium poppy, its cultivation, and the harvest of poppy latex are found on Sumerian clay tablets dating back to 3000 BC (Schiff, 2002). In

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ancient Greece, opium was used for medicinal and ritual purposes. The word "opium" is derived from the ancient Greek "opos" which means "milky juice of plants" (Askitopoulou et al., 2000). The twin brothers Hypnos and Thanatos, the Greek gods of sleep and death, are often depicted with opium poppies. Opium was mentioned by Homer in his "Iliad", and by the famous Greek physicians Hippocrates and Galen (Schiff, 2002). In the Roman empire, opium gained importance not only as medicine, but also as poison. Agrippina, emperor Claudius' wife, killed her stepson Brittannicus with an overdose of opium, so that her own son Nero could become emperor (Booth, 1998). Avicenna (980-1037), the famous Arab physician and scientist, recommended opium and plants of the nightshade family as analgesics and anaesthetics (Aziz et al., 2000). Arab traders brought opium to China, where it was first used only by the elite, but by the end of the seventeenth century by a large part of the Chinese population (Schiff, 2002). The high rate of addiction lead to a prohibition of opium by the Chinese government, but British merchants continued to smuggle opium into China. The conflict escalated in the Opium Wars (1839-1842 and 1856-1880), in which China was defeated and forced to allow the import of opium.

The sleep-inducing principle of opium was identified in 1806 by the German pharmacist Friedrich Sertürner. He succeeded in isolating crystalline morphine, which he named "morphium" after the Roman god of sleep "Morpheus" (Zenk and Jünger, 2007). It took more than 100 years, until the chemical structure of morphine was elucidated (1924-1925) by Gulland and Robinson. Total synthesis of morphine turned out to be extremely difficult due to its five stereo centers, and it was achieved by Gates and Tschudi (1952).

Since no cost-efficient synthesis of morphine and codeine has been developed, these alkaloids are isolated from "poppy straw", which consists of the entire plant tops (Dewick, 2002), and from opium. Legal cultivation of *P. somniferum* is carried out in India, Turkey, Russia, and Australia. Today, nearly all illegally produced opium (93%) originates from Afghanistan; smaller amounts are produced in South East Asia and South America (Sanderson, 2007; World Drug Report, 2007).

Ipecac Alkaloids

Ipecac alkaloids are derived from the amino acid tyrosine and the monoterpene secologanin and are therefore termed terpenoid-isoquinoline alkaloids. They occur in the eudicot families Alangiaceae and Rubiaceae. Two species, *Psychotria ipecacuanha* (Rubiaceae) and *Alangium lamarckii* (Alangiaceae), have been investigated in detail with respect to their metabolites and biosynthesis of their alkaloids (Fujii and Ohba, 1998). Roots and rhizomes of *P. ipecacuanha* are the source of cephaeline and emetine (Fig. 9), two compounds with emetic, expectorant, and amebicidal properties.

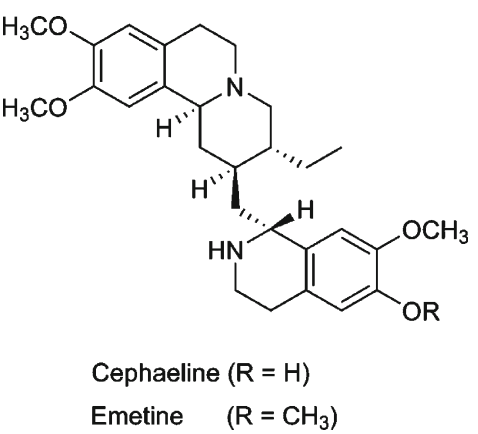


Fig. 9 Cephaeline and emetine, two alkaloids with emetic properties from roots of *Psychotria ipecacuanha*

The emetic effects are presumably mediated by 5-hydroxytryptamine 3 ($5HT_3$) receptors (Hasegawa et al., 2002). Ipecacuanha syrup is used to induce emesis after accidental ingestion of poisons. In lower doses, the extract of *P. ipecacuanha* roots is used as expectorant.

P. ipecacuanha occurs in the rainforests of Meso and South America. It was traditionally used in the Brazilian folk medicine. In the seventeenth century, the plant was brought by traders to France, and soon it found application in Europe as treatment against dysentery. The British physician Thomas Dover invented a special preparation *P. ipecacuanha* that was named Dover's powder after him. It consisted of Ipecacuanha root, opium, and potassium sulphate and was used as diaphoretic and medicine against cold and fever.

Amaryllidaceae Alkaloids

The Amaryllidaceae alkaloids are restricted to the monocot family that coined their name. They are derived from one molecule of tyrosine and protocatechuic aldehyde, which originates from phenylalanine. The central intermediate of their biosynthetic pathway is norbelladine. Nearly 500 structures of Amaryllidaceae alkaloids are known, and some of them possess significant pharmacological activities (Jin, 2007) (Fig. 10). For example, the isocarbostyrils pancratistatin from the spider lily (*Hymenocallis littoralis*) and narciclasine from *Narcissus* species show promising antineoplastic properties (Dumont et al., 2007; McLachlan et al., 2005). Lycorine that occurs, e.g., in *Clivia*, *Crinum* and *Galanthus*

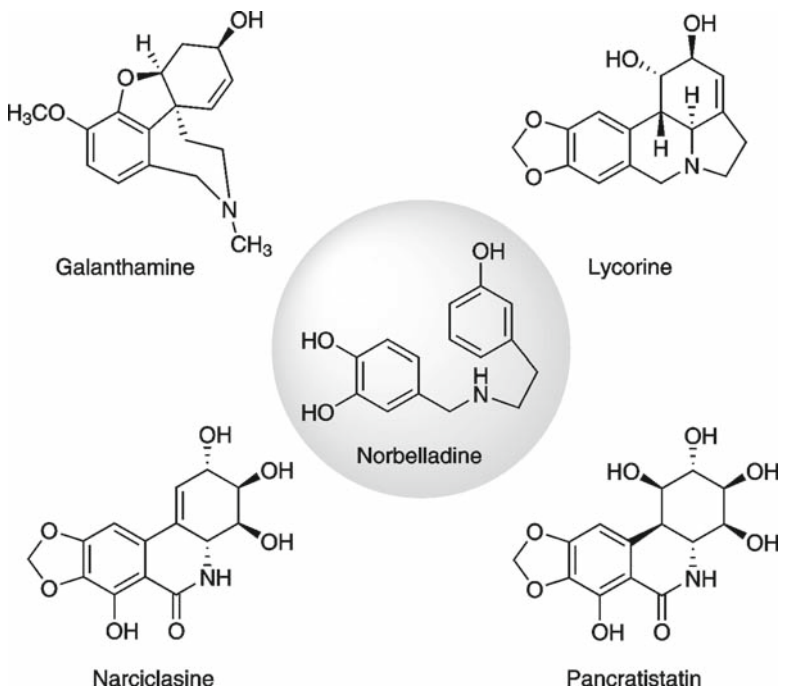


Fig. 10 Exemplary structures of Amaryllidaceae alkaloids

species exhibits antiviral activity (Ieven et al., 1983; Szlávik et al., 2004).

Galanthamine is the only alkaloid of this class that has already found application in medicine. It is approved for the symptomatic treatment of Alzheimer's disease in Europe and the United States. Its mode of action consists in a competitive and reversible inhibition of acetylcholinesterase, which leads to an increased concentration of acetylcholine at neuronal synapses. In addition, galanthamine acts as an allosteric modulator on nicotinic acetylcholine receptors. Since a characteristic feature of Alzheimer's disease is the loss of acetylcholinergic neurons concomitant with decreased levels of acetylcholine, galanthamine can, at least partially, compensate the damage and thus enhance cognitive functions in Alzheimer's patients.

Galanthamine was isolated first from the Caucasian snowdrop (*Galanthus woronowii*) in the early 1950s. Most of the early research on galanthamine was carried out in Bulgaria and the USSR during the Cold War. Initially, galanthamine was used to reverse neuromuscular blockade induced by muscle relaxants and for the treatment of post-polio paralysis. After it was discovered that galanthamine passes the blood brain barrier, the interest in this drug increased, and it was eventually established as treatment for Alzheimer's disease (Heinrich, 2004).

Galanthamine occurs in the bulbs of *Galanthus*, *Narcissus*, and *Leucojum* species, where it accumulates in concentrations of 0.05-0.2% (Dewick, 2002). Initially, it was isolated from these plant species. In 1999, a feasible and economic protocol for the industrial synthesis of galanthamine was developed by the groups of Fröhlich and Jordis in collaboration with Sanochemia (Küenburg et al., 1999).

Monoterpene Indole Alkaloids

This class of alkaloids is biosynthesized from tryptophan and secologanin via the central intermediate 3α(*S*)-strictosidine. Over 2,000 structurally diverse monoterpene indole alkaloids are known, and among them are several pharmacologically valuable compounds (O'Connor and Maresh, 2006). Some representative structures of the major classes of monoterpene indole alkaloids are depicted in Fig. 11. These alkaloids are mainly found in the plant families Apocynaceae, Loganiaceae, Nyssaceae, and Rubiaceae. The following section will focus on some representative alkaloids with significant pharmacological activities.

Rauwolfia Alkaloids

The Indian snakeroot, *Rauwolfia serpentina* (Apocynaceae), is a shrub that grows in southern and southeast Asia. The root of this plant has been used traditionally in Ayurvedic medicine (Sanskrit name: "Sarpagandha") to treat hypertension and mental disorders. In the 1950s, the blood pressure lowering agent was identified as reserpine, a monoterpene indole alkaloid of the yohimbine class. Reserpine inhibits a proton pump that is responsible for maintaining a high concentration of protons in neuronal vesicles. If the proton pump is inhibited, neurotransmitters like dopamine and norepinephrine can no longer be stored in the vesicles. Thus, the neurons are depleted of their transmitters, which leads to a decrease in blood pressure and sedation. Due to serious negative side effects, in particular depression, reserpine has mainly been replaced by other drugs, but is still used in some combinations with other antihypertonics. In addition, extracts of *Rauwolfia* roots are used in herbal remedies against hypertension.

The roots of *R. serpentina* contain 0.7–2.4% monoterpene indole alkaloids (Dewick, 2002). In addition to their main alkaloid reserpine, they also produce other pharmacologically active alkaloids, e.g., the antihypertensive ajmalicine and the antiarrhythmic ajmaline. Ajmaline blocks Na^+ channels in the heart and thus prolongs intraventricular conduction times.

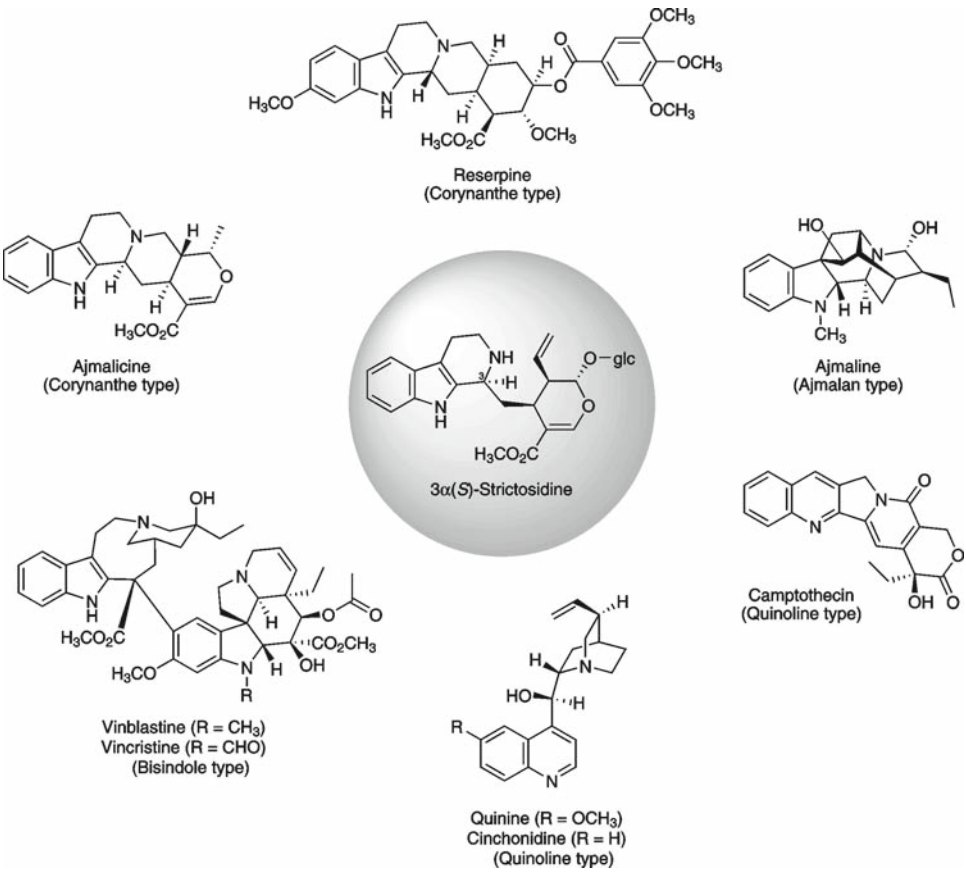


Fig. 11 Different classes of monoterpene indole alkaloids

Catharanthus Alkaloids

The Madagascar periwinkle (*Catharanthus roseus*, Apocynaceae, formerly known as *Vinca rosea*) is a small subshrub or herbaceous plant native to Madagascar. It contains about 130 monoterpene indole alkaloids of different subclasses (van der Heijden et al., 2004). Nowadays, *C. roseus* occurs worldwide in subtropical and tropical regions. It is cultivated as an ornamental plant, but it has also found application in the folk medicine of various countries. Because the plant was used as an antidiabetic in Jamaica, it was screened for hypoglycaemic activity by Eli-Lilly, USA, and the Cancer Research Center, Canada, in the late 1950s. Although plant extracts proved to be ineffective against diabetes, scientists of both institutes independently discovered the anticancer activity of several bisindole alkaloids, in particular, vinblastine and vincristine (reviewed by Noble, 1990). These compounds bind tubulin and inhibit its polymerization, thus hindering the formation of the mitotic spindle and causing cell cycle arrest at metaphase in dividing cells (Jordan et al., 1991). Vinblastine is used as therapy against Hodgkin's disease and non-Hodgkin's lymphomas. Its major side effect is a suppression of the bone marrow. Vincristine is more powerful but also more neurotoxic than vinblastine. It is used to

1

treat acute lymphatic leukaemia, non-Hodgkin's lymphomas, rhabdomyosarcoma, and Wilms tumor. Two semisynthetic analogs with less side effects than the two Vinca alkaloids, vinorelbine and vindesine, are used as to treat non-small cell lung cancer and breast cancer. Vindesine is also used as chemotherapeutic for lymphoma, acute leukaemia, and melanoma.

Initially, vincristine and vinblastine were isolated from leaves of the Madagaskar periwinkle, however, the yield was very low. The plant tissue contains only 0.0002% vinblastine (Noble, 1990), and the vincristine content is even lower. Therefore, a partial synthesis for the dimeric indole alkaloids was developed starting from the monomers vindoline and catharanthine (Dewick, 2002).

Camptothecin

Camptothecin (Fig. 11) belongs to the quinoline class of the monoterpene indole alkaloids. Although it lacks the indole ring, feeding studies proved that it originates from tryptamine and a monoterpene precursor, and the indole structure undergoes rearrangements to a quinoline heterocycle (Hutchinson et al., 1974; Sheriha and Rapoport, 1976). The alkaloid occurs in several unrelated eudicot species, e.g., *Camptotheca acuminata* (Nyssaceae), *Ophiorrhiza pumila* (Rubiaceae), *Ervatamia heyneana* (Apocynaceae), and *Nothapodytes foetida* (Icacinaceae).

Camptothecin is unique in its mechanism of action. It binds to the cleavable complex of topoisomerase I and covalently attached DNA and stabilizes it (Hsiang et al., 1985). This non-degradable DNA/topoisomerase I complex arrests the replication fork and thus kills cells by inhibition of DNA synthesis (Hsiang et al., 1989). Camptothecin and its derivatives are therefore also termed topoisomerase "poisons".

Camptothecin was isolated first in 1966 (Wall et al., 1966) from *Camptotheca acuminata*, a tree native to China and Tibet, also known as "Happy Tree" (chinese "xi shu"). Despite the promising anticancer activities, the poor solubility of the alkaloid presented a major obstacle to clinical application. Water-soluble derivatives were prepared by opening the lactone ring. During clinical trials, however, it became apparent that the anticancer activity of these analogs was greatly decreased, and the trials were abandoned. Only later it became known that the anticancer activity of camptothecin is dependent on the intact lactone ring. The interest in camptothecin returned in 1985 after its unique mechanism of action became known. This encouraged the synthesis of water-soluble analogs that retained the activity. At present, two derivatives of camptothecin are used in cancer chemotherapy. Irinotecan (syn. CPT-11) is used to treat colon cancer in combination with other chemotherapeutics; and topotecan is approved as therapy of ovarian and small-cell lung cancer. Several new camptothecin derivatives are currently tested in clinical trials (reviewed by Sirikantaramas et al., 2007).

Camptothecin derivatives are produced semisynthetically using the alkaloids extracted from intact plants of *C. acuminata* or *N. foetida*. Alternatives to this limited resource have been suggested. For example, young leaves of *C. acuminata* accumulate high levels of alkaloids (4-5 mg/g dry weight; López-Meyer et al., 1994) and can be harvested repeatedly without killing the trees. In addition, the clonal propagation of elite cultivars by shoot and bud culture of *C. acuminata* (Vincent et al., 1997) or hairy roots of *Ophiorrhiza pumila* (Sudo et al., 2002) might present a suitable solution to overcome the shortage in plant material. Recently, camptothecin production was detected in the endophytic fungi *Entrophospora infrequens* of *N. foetida* (Puri et al., 2005; Amna et al., 2006), and this may open a new source for the commercial production of the antineoplastic alkaloid.

Cinchona Alkaloids

The genus *Cinchona* (Rubiaceae) comprises about 25 species of tall, evergreen trees that grow in South America. The bark of these trees accumulates quinoline alkaloids that are, like camptothecin, derived from tryptophan and secologanin. Cinchona alkaloids are also found in the genus *Remijia* of the Rubiaceae family.

The *Cinchona* bark was called "Quina-Quina", which means "bark of barks", in the native Indian language Quechua. It was discovered by Spanish monks in Peru around 1630. They either learned to use the bark against fevers from the indigenous Indian population or discovered its application by themselves (Bruce-Chwatt, 1988). *Cinchona* bark was introduced to Europe by Jesuits, where it became known as "Jesuits' powder" and was used to cure malaria, which was then widespread in Europe. However, initially the use of *Cinchona* powder was controversial. Due to its approval by the Vatican, Protestants refused to take it. In addition, healing of malaria with a hot, bitter drink form a powdered bark contradicted the humoral theory of the antique Greek philosophers, which was at that time still the base for medicinal treatment. Moreover, often bark of bad quality or adulterated bark was sold that proved to be inefficient. *Cinchona* bark became only widely accepted after the English apothecary apprentice Robert Talbor applied it successfully as a secret formula to cure many members of European royalty from malaria, among them the English King Charles II and the son of the French King Louis XIV. After Robert Talbor's death it was disclosed that his secret remedy was based on *Cinchona bark* (Bruce-Chwatt, 1988; Kaufman and Rúveda, 2005). Quinine (Fig. 11) was isolated from the bark of *Cinchona* trees in 1820 by the French pharmacists Pelletier and Caventou, and its molecular formula was established in 1854 by Adolf Strecker.

For two centuries, *Cinchona* bark was obtained solely from South America. It was particularly valuable for the colonial powers because malaria was frequent in Asia and Africa. Due to the high demand for the drug and the dwindling natural resources, efforts were taken to cultivate the trees outside South America. In the middle of the eighteenth century, the Dutch and English succeeded in growing *Cinchona* trees in Java and India. Shortage of quinine in World Wars I and II due to trade embargos encouraged the development of synthetic analogs, e.g., the 4-aminoquinolines chloroquine and mefloquine, and the 8-aminoquinoline primaquine. A formal synthesis of quinine was achieved by Woodward and Doering (1944), however, due to the four stereocenters in the quinine molecule it is a very complex synthesis and commercially not feasible.

Today, three *Cinchona* species are cultivated for the production of quinine. *C. succirubra* yields the "red bark", *C. legderiana* the "brown bark", and *C. calisaya* the "yellow bark" (Dewick, 2002). In addition to quinine, the barks contain significant amounts of three other quinoline alkaloids: quinidine, the diastereomer of quinine, which is used as an antiarrhythmic, and 6-demethoxy analogs of the two alkaloids, cinchonine and cinchonidine.

Quinine and its analogs act on erythrocytic stages of *Plasmodium falciparum*, the causative agent of malaria. It is assumed that these antimalarial agents inhibit the polymerization of haematine, which is released upon the degradation of haemoglobin and is toxic for the parasite, into non-toxic hemozoin (Chou et al., 1980; Sullivan et al., 1996).

Since quinine is extremely bitter, gin was added to make it easier to drink, giving rise to the cocktail "gin and tonic" that nowadays contains only minute amounts of the alkaloid. In addition to tonic water, quinine is also an ingredient of other beverages, e.g., bitter lemon or vermouth.

Benzoxazinones

Benzoxazinones are derived from indole-3-glycerol phosphate, a molecule that is also the direct precursor of tryptophan. In the literature, acronyms derived from the substitution pattern of the benzoxazinone ring are often used to distinguish individual members of this class. For example, DIMBOA is 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one. Benzoxazinones occur mainly in the monocot Poaceae family, but also in some families of eudicot plants, e.g., Ranunculaceae, Acanthaceae, and Plantaginaceae. At present, it is still being investigated whether the pathway developed only once or several times independently after the divergence of moncots and dicots (Sicker et al., 2000).

Two characteristic structural features are found in all benzoxazinones: a cyclic hemiacetal in combination with a cyclic hydroxamic acid or a cyclic lactam (Fig. 12); the hydroxy function of the hemiacetal is usually glucosylated. In the intact plant tissue, these benzoxazinone glucosides are stored in the vacuole, whereas a specific glucosidase is located in plastids. Only after injury of the plant tissue, glucosides and glucosidases are released, and free aglucones are formed. Those benzoxazinone aglucones that contain a hydroxamic acid function are chemically instable, and their tautomeric open-ring form can be converted to benzoxazolinones under loss of one carbon as formic acid (Fig. 12).

Benzoxazinones act as pre-formed defense and possess antibacterial, antifungal, and antialgal properties (Bravo and Lazo, 1993, 1996). In addition, they serve as feeding deterrents and reduce the vitality of pests. In particular, these metabolites confer resistance to one of the major corn pests, the European corn borer (*Ostrinia nubialis*) (Grombacher et al., 1989). Only benzoxazinones with hydroxamic acid function show these bioactivities. An electron-donating hydroxy or methoxy group at C-7 increases the reactivity. The mode of action of benzoxazinones can be explained by modification of amino and thiol groups of biomolecules. The aldehyde function of the tautomeric open-ring form can react as an electrophile with NH_2 groups and form Schiff bases (Pérez and Niemeyer, 1989). Thiol groups can be oxidized by the cyclic hydroxamic acid form, which is in turn reduced to a lactam. Structural prerequisite for this oxidation is an electron-donating substitution at C-7 of the benzoxazinone skeleton (Atkinson et al, 1991). Benzoxazinoids that have been bio-activated by *N*-acetylation may act as alkylating agents towards nucleic acids and proteins (Hashimoto and Shudo, 1996).

Due to their toxicity, benzoxazinones can also function as allelochemicals (Sicker et al., 2000) and are therefore discussed as natural herbicides.

Cyanogenic Glycosides

Cyanogenic glucosides are β-glucosides of α-hydroxynitriles (syn. cyanohydrins), which

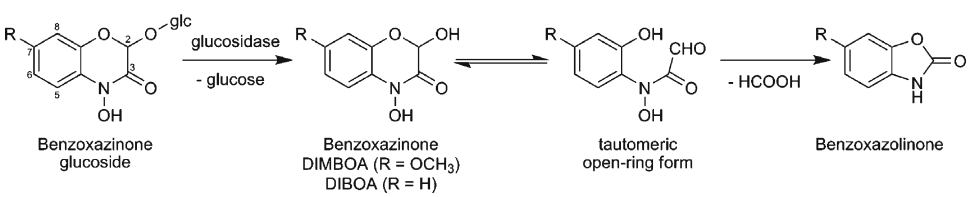


Fig. 12 Enzymatic and chemical degradation of benzoxazines with hydroxamic acid function (Sicker et al., 2000)

are derived from the five proteinogenic amino acids phenylalanine, tyrosine, valine, isoleucine, leucine and the non-proteinogenic amino acid cyclopentenyl-glycine. Because of the stereo-center in the α-hydroxynitrile function, (*R*)- and (*S*)-forms of several cyanogenic glucosides exist. About 2,500 different plant species including ferns, gymnosperms, and angiosperms produce cyanogenic glucosides (Hegnauer, 1986; Seigler, 1991). Despite their widespread occurrence, these natural products are found predominantly in the families Araceae, Asteraceae, Euphorbiaceae, Fabaceae, Passifloraceae, Poaceae, and Rosaceae (Dewick, 2002). Some of the most abundant molecules are amygdalin (Rosaceae), linamarin and lotaustralin (Fabaceae), and the epimers dhurrin and taxiphyllin in the genus *Sorghum* (Seigler, 1991).

Like the benzoxazinones, cyanogenic glucosides belong to the preformed defense of the plant and are stored in the vacuole. Upon disruption of the plant tissue, they are degraded by β-glucosidases to the corresponding α-hydroxynitriles, which are hydrolyzed by α-hydroxynitrile lyases to aldehydes or ketones and toxic hydrogen cyanide (HCN) (Fig. 13). Since the α-hydroxynitriles are unstable, they can also decompose spontaneously, but the enzyme catalyzed reaction proceeds up to 20 times faster (Selmar, 1999). In the gut of herbivores, the β-glucosidic bond can also be hydrolyzed by intestinal bacteria. The toxicity of hydrogen cyanide can be explained by its affinity to metal ions. Cyanide ions complex iron (III) in the active site of cytochrome oxidase and thus inhibit the respiratory chain. Mammals can consume small amounts of cyanogenic glucosides and detoxify them, mainly *via* the liver enzyme rhodanese that converts cyanide to thiocyanate. Chronic intake of non-lethal amounts, however, can result in paralysis of legs (Konzo) or neurological disorders due to cyanide intoxication or iodine deficiency caused by accumulation of the iodine antagonist thiocyanate (Selmar, 1999). Intoxications by cyanogenic glucosides are often observed in populations that live on a diet poor in protein with insufficient supply of sulfur-containing amino acids, which are required for the detoxification of cyanide.

Cyanogenic glucosides act as feeding deterrents. Herbivores are probably rejected by the keto or aldehyde compound that arises after cleavage rather than by the cyanide (Jones, 1988). By transferring all genes required for the

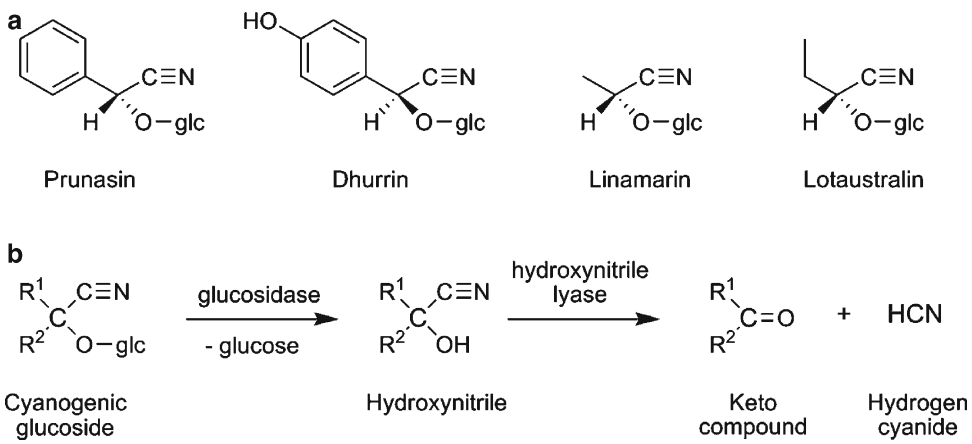


Fig. 13 Representative structures of cyanogenic glucosides (**a**) and degradation of cyanogenic glucosides with concomitant release of toxic hydrogen cyanide (**b**)

formation of the cyanogenic glucoside dhurrin from *Sorghum bicolor* into *Arabidopsis*, Tattersall et al. (2001) proved that cyanogenic glucosides play a role in plant defense. In comparison with wild-type leaves, leaves of transgenic *Arabidopsis* plants producing dhurrin were hardly consumed by the yellow-striped flea beetle (*Phyllotreta nemorum*). Despite the toxicity of the cyanogenic glucosides, several herbivores, especially insects, are able to feed on plants containing these natural products, and in this case the toxic compounds may act as phagostimulants. Some species of beetles, centipedes, and millipedes, but particularly many moths and butterflies sequester cyanogenic glucosides as defense compounds. The compounds are either taken up by feeding on cyanogenic plants or synthesized *de novo* by endogenous enzymes. In contrast to vertebrates, these arthropod species detoxify cyanide not by rhodanese, but mostly *via* β-cyanoalanine synthesis, a mechanism that is also used by plants (reviewed by Zagrobelny et al., 2008).

It has been postulated that cyanogenic glucosides also serve as storage compounds for reduced nitrogen and sugar (Selmar et al., 1988; Sánchez-Pérez et al., 2008). This has been deduced from the observation that cyanogenic glucosides are degraded during seed development or germination.

Interestingly, many important food crops accumulate cyanogenic glucosides (Jones, 1998), but usually not in the portion of the plant that is consumed. Some plants, however, contain high levels of these toxic constituents in the parts that are eaten, e.g., bamboo, cassava, lima beans, and sorghum. This problem is particularly serious in the case of cassava (*Manihot esculenta*), which is a major crop in many tropical countries. Cassava roots contain between 10 and 500 mg of cyanide equivalents per kg fresh weight (O'Brien et al., 1991) and have to be processed carefully to remove the toxic metabolites. Unfortunately, this treatment usually results in loss of protein, minerals, and vitamins. Various approaches to produce transgenic cassava with reduced content of cyanogenic glucosides in roots are currently underway (Jørgensen et al., 2005; Siritunga and Sayre, 2007).

Glucosinolates

Glucosinlates are β-thioglucosides of (Z)-*N*-hydroximinosulfate esters (Fig. 14). They are derived from the aliphatic amino acids alanine, isoleucine, leucine, methionine, and valine or from the aromatic amino acids phenylalanine, tryptophan, and tyrosine and share the first steps of cyanogenic glucoside biosynthesis. About 120 different structures of glucosinolates are known (Fahey et al., 2001). They occur exclusively in sixteen eudicot families, the majority belonging to the order Brassicales. Many of these plants are cultivated and consumed as vegetables or spices, e.g., cabbage (*Brassica oleraceae*, Brassicaeae), capers (*Capparis spinosa*, Capparidaeae), mustard (*Sinapis alba*, Brassicaeae), and wasabi (*Wasabia japonica*, Brassicaeae). The strong or pungent flavor of these plants can be explained by the presence of glucosinolates. If the plant tissue is damaged, the glucosinolates are hydrolyzed by myrosinase, a thioglucosidase that is spatially separated in the undamaged tissue. The resulting unstable thiohydroximate-*O*-sulfate intermediates undergo non-enzymatic loss of sulfate and spontaneous rearrangement to various bioactive products like isothiocyanates, nitriles, oxazolidine-2-thiones, epithionitriles, and thiocyanates (Halkier and Gershenzon, 2006) (Fig. 14). Hydrolysis of glucosinolates can also occur in the intestine of humans by myrosinases of the gut microflora.

The main product of the "mustard bomb" consisting of glucosinolates and myrosinase are isothiocyanates. These compounds are also responsible for many of the biological effects of glucosinolates, e.g., antibacterial, antifungal,

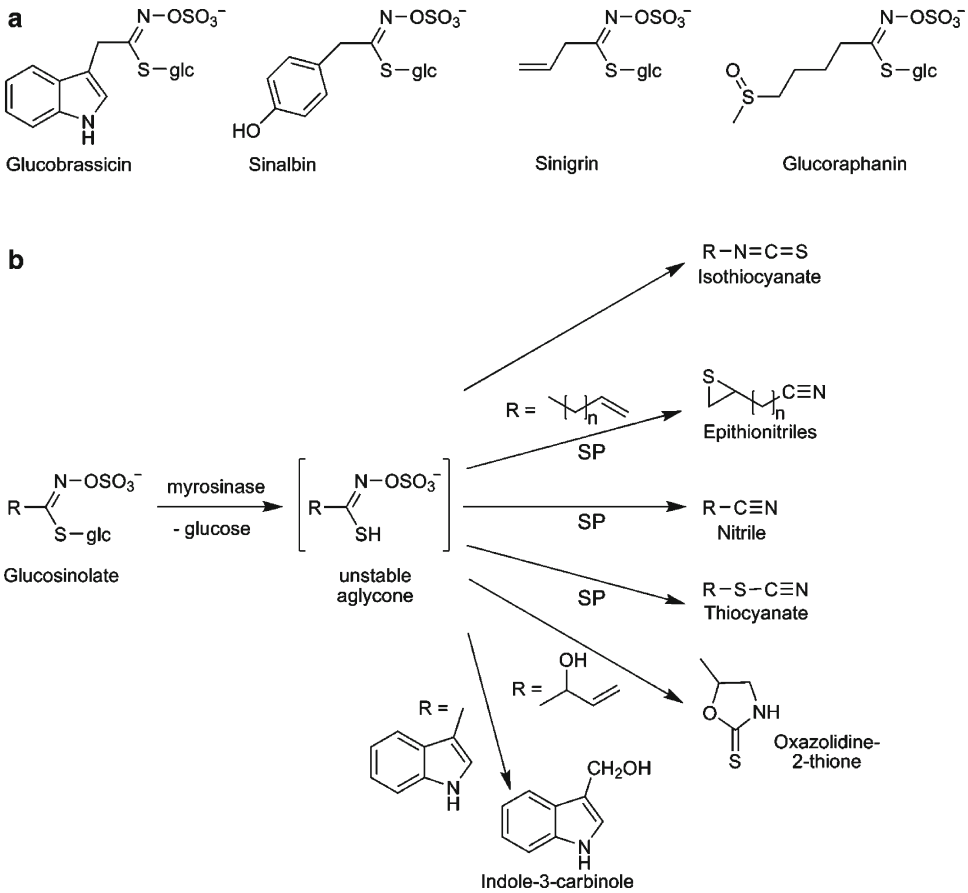


Fig. 14 Exemplary structures of glucosinolates (**a**) and hydrolysis of glucosinolates by myrosinase and rearrangement to various products (**b**) Isothiocyanates are the predominant degradation products. For the formation of epithionitriles, nitriles, and thiocyanates, specifier proteins (SP) are required

nematicidal, and feeding deterrent activities (Fahey et al., 2001). The formation of hydrolysis products distinct from thiocyanates depends on the structure of the glucosinolates, pH, and the presence or absence of Fe^{2+} ions or specifier proteins. Specifier proteins do probably not possess catalytic activity, but may modulate myrosinase activity allosterically to yield nitriles, epithionitriles, or thiocyanates as degradation products instead of thiocyanates (Wittstock and Burow, 2007). Epithionitriles are produced only from glucosinolates with a terminal double bond. Indolyl glucosinolates are hydrolyzed to unstable indole isothiocyanates that give rise to the alcohol indole-3-carbinol and a variety of other products. Hydrolysis of β-hydroxyalkenyl glucosinolates yields oxazolidine-2-thiones that can cause goitre by inhibiting the incorporation of iodine into thyroid hormones. A crop particularly rich in goitrogenic glucosinolates is rape (*Brassica napus*), an important source of vegetable oil. To make the protein rich seed cake that

remains after extraction of the oil suitable as animal foodstuff, rape plants with low levels of glucosinolates have been developed by breeding efforts (Fahey et al, 2001).

Glucosinolates from Brassicaceae vegetables (e.g., broccoli, cauliflower, Chinese cabbage, kale, kohlrabi, mustard) are discussed as cancer preventive agents. In particular, sulforaphane and indole-3-carbinol, the degradation products of glucoraphanin and glucobrassicin, respectively, show promising activities, e.g., stimulation of apoptosis. Sulforaphane enhances the excretion of cancerogenous compounds by inducing phase II detoxification enzymes like glutathione-*S*-transferase, UDP-glucuronosyl transferase, and NADPH quinone oxidoreductase. Indole-3-carbinol may prevent estrogen-sensitive cancers by increasing the ratio of weak to strong estrogens, but it may also possess cancer-promoting activities. Although some epidemiological studies suggest that a diet rich in glucosinolates can reduce the risk of cancer, it has not yet been unambiguously proven. In addition, the bioavailability of glucosinolates may be influenced by genetic polymorphisms that lead to a slower excretion of these compounds (Higdon et al., 2007).

Although glucosinolates act as feeding deterrents, many insect herbivores feed on plants containing these natural products. Two very different mechanisms for the detoxification of glucosinolates are known from two insect species. The diamond-black moth (*Plutella xylostella*) produces a sulfatase that cleaves the sulfate from glucosinolates and converts them to compounds that cannot be degraded by myrosinases (Ratzka et al., 2002). The cabbage white butterfly (*Pieris rapae*) contains a specifier protein that transforms glucosinolates in the presence of myrosinase to nontoxic nitriles that are excreted with the feces (Wittstock et al., 2004). Both detoxifying enzymes are expressed in the gut of the insects, the organ in which the glucosinolates would normally be degraded to isothiocyanates. Other insect herbivores sequester glucosinolates and use them for their own defense. This requires either an endogenous myrosinase that is spatially separated from the glucosinolates in the insects or myrosinases from the gut microflora of their enemies (Halkier and Gershenzon, 2006).

Natural Products Derived from the Shikimate Pathway and Phenylpropanoids

The shikimate pathway provides the precursors for benzoic acid derivatives and phenylpropanoid compounds in plants (Fig. 15). Shikimate is biosynthesized from D-erythrose-4-phosphate and phosphoenolpyruvate, two metabolites derived from the pentose phosphate cycle and glycolysis, respectively. Shikimate is further converted to chorismate by addition of a C_3 unit from phosphoenolpyruvate; and chorismate serves as precursor of the aromatic amino acids L-phenylalanine, L-tyrosine, and L-tryptophan.

An intermediate of the shikimate pathway, most likely 5-dehydroshikimate, is the precursor of gallic acid and the gallotannins (Werner et al., 1997), which are esters of glucose with several molecules of gallic acid. Gallotannins have been used for centuries for the tanning of hides and for the preparation of ink from ferrous sulfate and oak gall extract.

Since the shikimate pathway occurs only in plants and microorganisms, L-phenylalanine, L-tyrosine, and L-tryptophan are essential for animals and have to be taken up with food. L-Phenylalanine, and in monocots also L-tyrosine, are the precursors of the phenylpropanoids. This class comprises cinnamic acid derivatives, lignin, lignans, phenylpropenes, and coumarins, which all share the basic C_6-C_3 skeleton. Phenylpropanoids are aromatic compounds, often with a hydroxy group in the *para* position. If more than one hydroxy group is present at the aromatic ring, the new hydroxy function is usually positioned next to the first hydroxy group (*ortho* position).

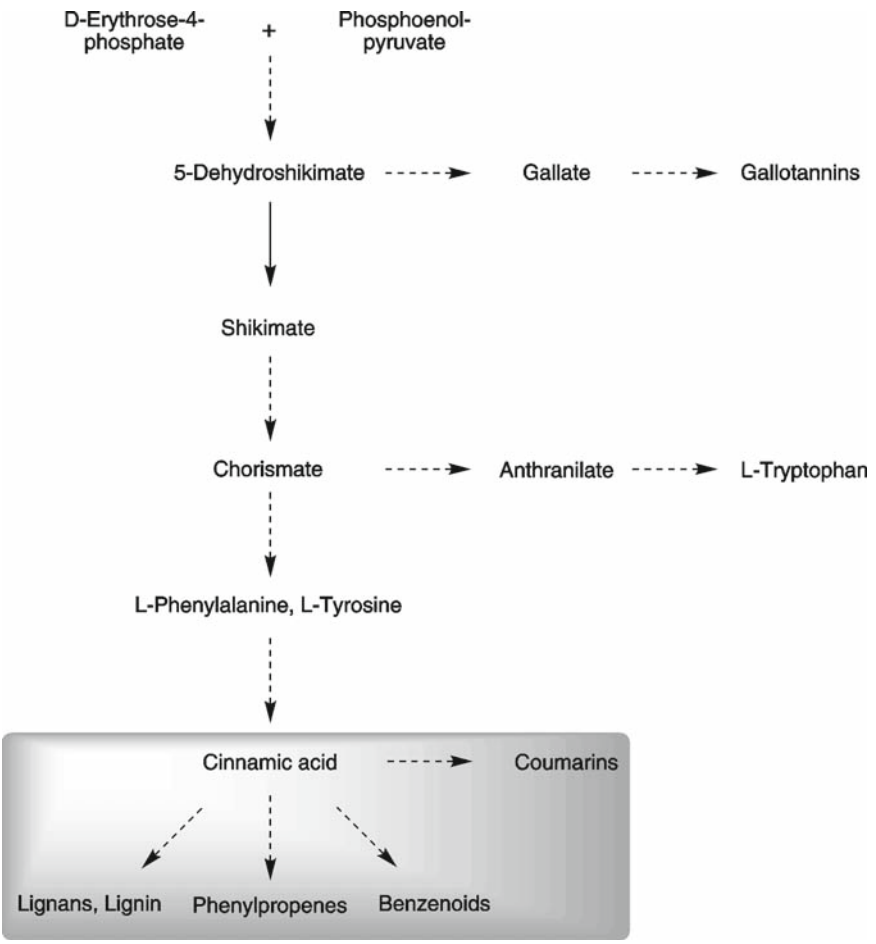


Fig. 15 Schematic overview of shikimate and phenylpropanoid biosynthesis. *Arrows* with dashed lines indicate multiple biosynthetic reactions. Boxed compounds are phenylpropanoids

Phenylpropanoids with additional carbons derived from acetate units, e.g., the flavonoids, will be discussed together with the polyketides.

Lignans and Lignins

Lignans and lignins are both composed of the hydroxy cinnamic alcohols (monolignols) *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol (Fig. 16). Lignans are formed by stereoselective coupling of two hydroxy cinnamic alcohols units and lignins are polymers of monolignols.

After incorporation into the polymer lignin, the monolignols *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol are also referred to as H (*p*-hydroxyphenyl), G (guaiacyl), and S (syringyl) units, respectively.

Lignin from gymnosperms consists mainly of G units and low levels of H units. Eudicots

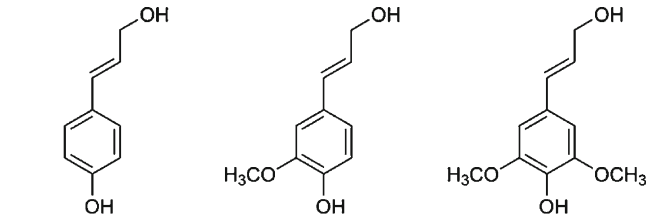


Fig. 16 *p*-Coumaryl alchol, coniferyl alcohol, and sinapyl alcohol are the building blocks of lignins and lignans

and monocots utilize all three monolignols, although lignin from eudicots consist mainly of G and S units (Boerjan et al., 2003). Recently, it became evident that also other phenolic monomers, in particular acylated monolignols, are incorporated into lignin. In the lignin polymer, the alcohols are connected by various bonds comprising ether and carbon-to-carbon linkages. In addition, lignin can be interconnected with hemicelluloses of the cell wall (Sun et al., 2005). Although the monolignol composition of lignins can be determined, their exact structure has not yet been elucidated due to the large size and complexity of the polymers (Davin and Lewis, 2005). The function of lignin is to reinforce the cell walls together with the sugar polymers cellulose and hemicellulose. Lignification of cell walls is required to strengthen the vascular tissue and evolved ca. 400 million years ago in the Silurian with the emergence of the first vascular plants. After cellulose, lignin is the second most abundant biopolymer on earth. From an economic point of view, lignin is important for the quality of wood, but it is an undesirable component for the paper industry, because its oxidation leads to yellowing of paper. Lignin cannot be digested by ruminants and therefore decreases the digestibility of forage and the absorption of nutritients (Boerjan et al., 2003; Rouhi et al., 2000). In addition, lignin has to be removed from lignocellulose-containing plant material prior to the production of biofuels, because it hinders the degradation and extraction of cellulose. Possible strategies to improve biofuel production from lignocellulose are the generation of genetically modified crops with altered lignin content or composition and the use of lignin degrading enzymes from fungi or bacteria (Weng et al., 2008).

Lignans are formed by stereoselectively linking two monolignols at the central atoms of their side chains. If the monolignols are produced by other types of coupling, the dimers are termed neolignans (Dewick, 2002). In norlignans, the last carbon of one side chain of a monolignol is missing in the dimer. Lignans were found in more than 70 plant families, and because of their antiviral, antibacterial, and antifungal properties they presumably act as defense against herbivores and pathogens (Saleem et al., 2005). In addition, they occur in many plant foods like oil seeds, whole cereals, fruits and vegetables. A particular rich source of lignans with more than 0.3 g/100 g are flaxseed and sesame seed with secoisolariciresinol (Fig. 17) and sesamine as main constituents, respectively (Adlercreutz, 2007; Milder et al., 2005). These latter and several other lignans can be converted by the intestinal microflora to the mammalian lignans enterodiol and enterolactone (Fig. 17). The two enterolignans are weak phytoestrogens; they increase the concentrations of sex hormone binding globulin in the plasma and modulate steroid hormone concentrations by competing for their metabolizing enzymes (Adlercreutz, 2007). It is assumed that consumption of a diet

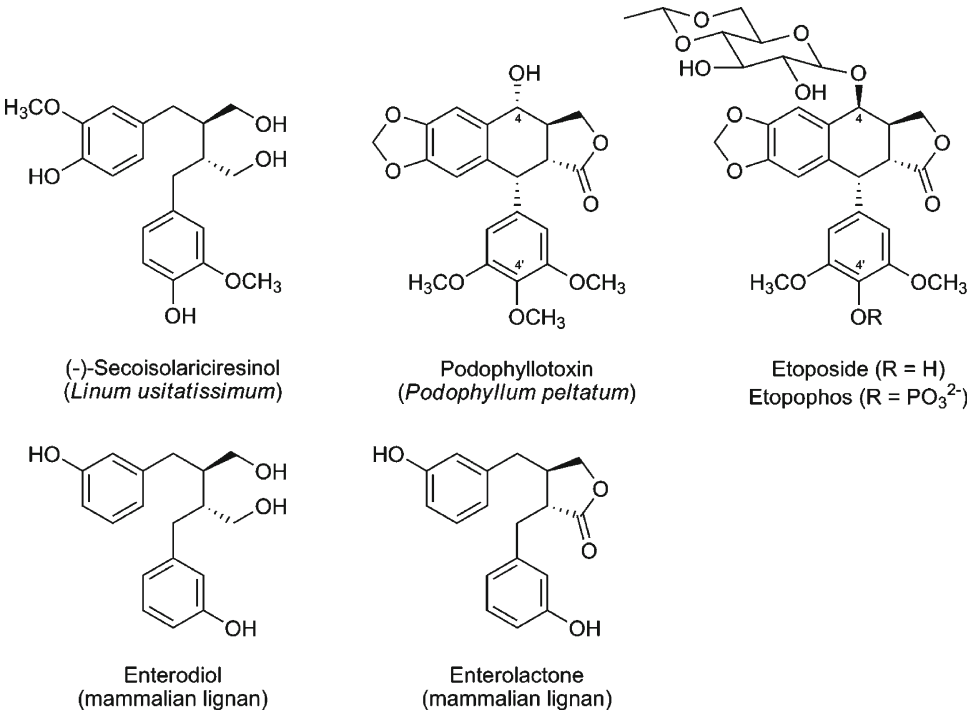


Fig. 17 Lignans of various origin

rich in lignans benefits health and reduces the risk for colon and breast cancer. Since lignan-rich food usually contains other health-promoting ingredients like fibers or other polyphenols, it is difficult, however, to attribute the beneficial effects solely to lignans.

A strong cytotoxic lignan is podophyllotoxin (Fig. 17) from *Podophyllum peltatum* or *P. hexandrum* (Berberidaceae). Podophyllotoxin has the same mechanism of action as the terpene indole alkaloids vinblastine and vincristine; it inhibits cell division by binding to tubulin and preventing its polymerization. This lignan is used as treatment for warts, but is too toxic for systemic application. Derivatives with reduced toxicity are etoposide, etopophos, and teniposide. They are prepared semi-synthetically from 4'-demethylpodophyllotoxin and have an inverted stereochemistry at C-4. These changes lead to a new anticancer mechanism, the stabilization of topoisomerase-DNA complexes, which is similar to that of camptothecin. Unlike camptothecin, however, the podophyllotoxin analogues attack topoisomerase II, not topoisomerase I. Etoposide and its prodrug teniposide are used in combination with other drugs to treat small cell lung cancer, testicular cancer, and certain lymphomas. Teniposide is used as therapy for childhood acute lymphocytic leukemia.

Phenylpropenes and Benzenoids

Phenylpropenes are derived from cinnamic acid and share the first steps of lignin/lignan biosynthesis. Shortening of the cinnamic acid side chain by two carbons leads to compounds with a C_6-C_1 skeleton called benzenoids. Other volatile

phenylpropanoid-related compounds are phenylacetaldehyde and 2-phenylethanol. They originate from phenylalanine which is shortened by one carbon (Pichersky and Dudareva, 2007). Phenylpropene and benzenoid volatiles are lipophilic compounds with a characteristic scent. They constitute the second largest group of plant volatiles after terpenoids. In many plants, phenylpropanoid/benzenoid and terpenoid volatiles occur as mixture, although usually one group accumulates predominantly. In addition to these two large groups of natural products, many other volatiles of plant origin are derivatives of amino acids and fatty acids. Each plant has its own cocktail of volatiles that is used for the attraction of pollinators and seed dispersers or as defense compounds. The defense function can be fulfilled either by directly deterring or intoxicating herbivores, or indirectly by attracting insect predators in case of tritrophic interactions or by communicating the danger to other plants in the neighborhood (Dudareva et al., 2006). In addition, many volatiles have antibacterial and antifungal properties (Kalemba and Kunicka, 2003).

Essential oils with phenylpropenes are found, e.g., in the Apiaceae, Lauraceae and Myrtaceae families. Many of these phenylpropene-containing plants have been employed by humans since antiquity as condiments and herbal remedies. Cloves, the unopened flower buds of the evergreen clove tree (*Syzygium aromaticum*, Myrtaceae) native to the Maluku islands, are used as spice, but also as anaesthetic and antiseptic in dentistry. The active ingredient and major component of essential oil from cloves is the phenylpropene eugenol (Fig. 18). Another evergreen tree of the tropics, *Cinnamomum ceylanicum* (Lauraceae) from Sri Lanka, is the source of cinnamon bark with *trans*-cinnamaldehyde as main flavor component. Cinnamon was highly priced in the antique world. The roman emperor Nero is said to have spent a year's supply of cinnamon for the funeral of his wife Poppaea Sabina (Klein, 1987). Some phenylpropenes are potentially carcinogenic, e.g., safrole, methyleugenol, and estragole. They require bioactivation including hydroxylation and sulfation at the side chain to become toxic (Zhou et al., 2007).

Benzenoids contribute to characteristic fragrance of many flowers. Methyl benzoate, for example, is a major scent constituent of *Petunia* flowers. Other benzenoids that frequently contribute to floral scents are benzaldehyde, benzyl alcohol, benzyl acetate, and methyl salicylate (Fig. 18) (Knudsen et al., 1993). The latter compound is responsible for the characteristic smell and the analgesic effect of wintergreen (*Gaultheria procumbens*, Ericaceae) (Dewick, 2002).

Polyketides

Polyketides are synthesized from two-carbon units derived from activated acetate in the form of acetyl-CoA and malonyl-CoA. Unlike fatty acids, which also originate from these precursors, polyketides retain all or most of their oxygen

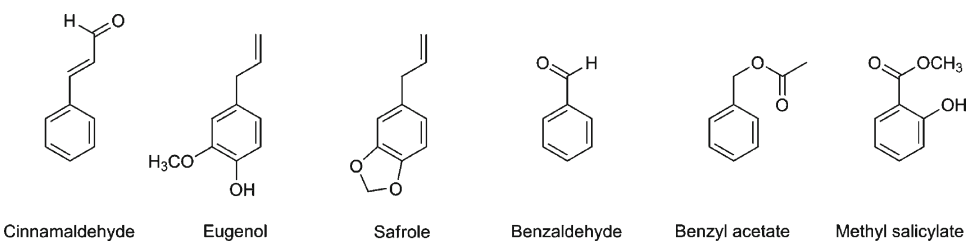


Fig. 18 Phenylpropanoid and benzenoid volatiles

functions. In the course of polyketide biosynthesis, highly reactive poly-β-keto intermediates are formed, which often undergo cyclization to six-membered aromatic or 2-pyrone rings. Many polyketides are phenolics like the phenylpropanoids, but the two groups can be distinguished by the substitution pattern of the aromatic ring. While polyketides usually contain oxygen functions on alternate carbons (*meta* position), phenolics derived from the phenylpropanoid pathway show an *ortho* oxygenation pattern. Many polyketides are glycosylated and may carry acyl substitutents on the sugar unit.

Polyketides occuring in plants are not always exclusively synthesized from acetate units, but often are of mixed biosynthetic origin. Phenylpropanoid or terpenoid building blocks or sometimes both can be connected with the acetate-derived backbone. In addition, parts of the carbon skeleton can be derived from fatty acids or amino acids. This mixed assembly principle results in a plethora of structurally diverse compounds. Polyketide alkaloids obtained when nitrogen or nitrogen-containing precursors are incorporated into the polyketide backbone will also be discussed.

Polyketides Derived Exclusively from Acetate Units

Naphthoquinones of polyketide origin occur in a few taxonomically related families of the order Caryophyllales (Heubl et al., 2006), e.g., the Droseraceae, Nepenthaceae, Plumbaginaceae, and Polygonaceae, but also in the unrelated genus *Diospyros* (Ebenaceae) (Thomson, 1987). These compounds are built from six acetate units, and one carbon is lost in the course ot their biosynthesis, thus yielding an eleven carbon skeleton with two six-membered rings (Fig. 19). Plants that accumulate naphthoquinones often also contain naphthohydroquinone glycosides and dimeric naphthoquinones. Naphthoquinones,

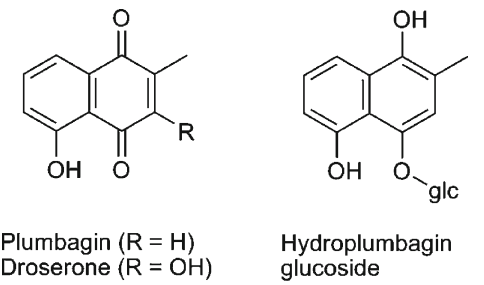
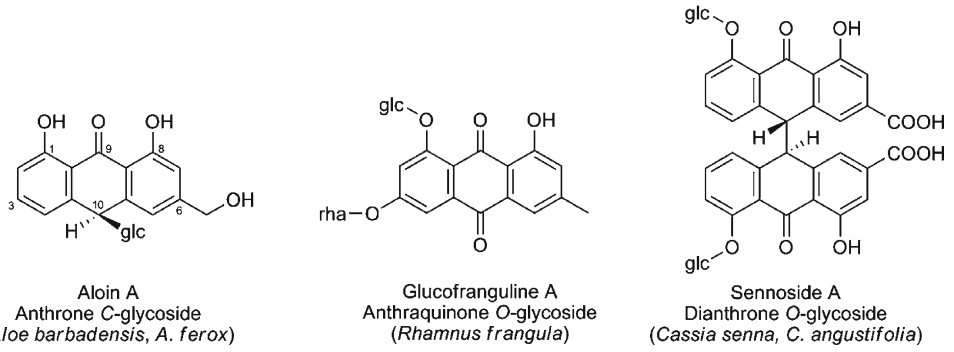


Fig. 19 Naphthoquinones and a naphthohydroquinone glucoside

e.g., plumbagin and droserone, are strongly colored and lipophilic substances. Plumbagin is accumulated predominantly in roots and acts as an allelopathic compound. It has also antifeedant effects on insects (Tokunaga et al., 2004) and antimicrobial properties (Didry et al., 1994). Due to their structural similarity to ubiquinone, naphthoquinones may interfere with mitochondrial electron transport.

Structurally related to the naphthoquinones are the anthraquinones, which originate from eight acetate units and are composed of three six-membered rings. As in the case of the naphthoquinones, one of the sixteen carbons is lost by decarboxylation. Anthrones are reduced anthraquinones and their biosynthetic precursors. Dimeric anthrones are called dianthrones. All three groups of acetate-derived anthranoids in plants have two hydroxy groups at C-1 and C-8, a third hydroxy goup can occur at C-3. They are conjugated with sugar, mostly glucose, as *O*- and *C*-glycosides (Fig. 20). The presence of a carbonyl group in conjugation with an aryl is a strong chromophore, and consequently, anthranoids show yellow, orange or red pigmentation. In contrast to naphthoquinones of polyketide origin, anthranoids occur in several unrelated plant families, e.g., the eudicot Fabaceae (*Cassia*), Rhamnaceae (*Rhamnus*), Polygonaceae (*Rheum*), and the monocot Asphodelaceae (*Aloe*). Anthranoids have antibacterial and antifungal properties (Srinivas et al., 2007) and are therefore probably used as defense compounds.

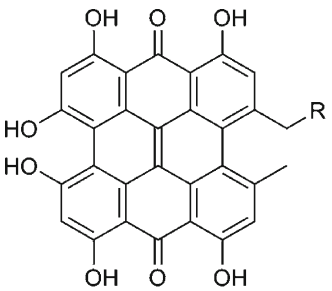


Aloin A
Anthrone *C*-glycoside
(*Aloe barbadensis*, *A. ferox*)

Glucofranguline A
Anthraquinone *O*-glycoside
(*Rhamnus frangula*)

Sennoside A
Dianthrone *O*-glycoside
(*Cassia senna, C. angustifolia*)

Fig. 20 Anthranoid glycosides from various plant species. Abbreviations for sugars: glc, glucose; rha; rhamnose



Hypericin (R = H)
Pseudohypericin (R = OH)

Fig. 21 Naphthodianthrones of *Hypericum perforatum*

Plants containing anthranoids are used as laxatives in case of habitual constipation. After ingestion, anthraquinones and dianthrones are converted to anthrones, the active metabolites, by bacteria of the large intestine. Anthrones stimulate the movement of the large intestine and increase secretion of water and electrolytes into the intestinal lumen. Frequent use of athranoid laxatives can lead to dehydration, depletion of minerals, and reversible pigmentation of the intestinal mucosa (*pseudomelanosis coli*). Emodin, a 1,3,8-trihydroxy-6-methylanthraquinone, proved to be mutagenic in *in vitro* assays. However, more recent *in vitro* studies suggest that it has also anti-tumor activities, e.g., by induction of apoptosis, inhibition of cell cycle and angiogenesis (Srinivas et al., 2007).

Hypericin and pseudohypericin (Fig. 21) are naphthodianthrones and occur in St. John's wort (*Hypericum perforatum*, Clusiaceae). These dark-red compounds are accumulated in glands on the margin of *H. perforatum* leaves and petals. It was assumed for a long time that they represent the antidepressant principle in extracts of St. John's wort. Recently, however, it became evident that the prenylated acylphloroglucinols hyperforin and adhyperforin are responsible for most of the pharmacological effects.

Anthraquinones and naphthoquinones are not exclusively formed via the polyketide biosynthetic route. They can also be derived from the shikimate pathway, e.g., the allelopathic naphthoquinone juglone from the walnut tree (*Juglans regia*) and the anthraquinone alizarin from madder root (*Rubia tinctorium*), which was used as purple dye.

Polyketides with Phenylpropanoid Moieties

In plants, phenylpropanoid and shikimate derived compounds can be combined with one to three C_2 units derived from malonyl-CoA to yield

polyketides of various structures. The largest group of these compounds are the flavonoids with more than 6,000 known compounds (Harborne and Baxter, 1999). Other polyketides of phenylpropanoid origin are less widely distributed, e.g., stilbenes, styrylpyrones, and curcuminoids.

In the structure of flavonoids, the phenylpropanoid C_6-C_3 backbone is extended with three C_2 units that form a second aromatic ring. This basic C_6-C_3-C_6 skeleton of flavonoids can be modified by hydroxylations, methylations, prenylation and, in the case of isoflavonoids, by aryl migration. Flavonoids occur mostly in glycosylated form and are often accumulated in the vacuole. The central intermediates in flavonoid biosynthesis are chalcones, which serve as precursors of all other subgroups (Fig. 22). Flavones, flavonols, flavan-3,4-diols (leucoanthocyanidins), anthocyanins, and proanthocyanidins (polymerized flavan-3-ols, condensed tannins) occur nearly ubiquitously in higher plants. Other subgroups of flavonoids are restricted to certain taxa. Isoflavonoids are produced mainly in leguminous plants (Fabaceae). Aurones are yellow pigments with widespread occurrence, e.g., in snapdragon (*Antirrhinum majus*), dahlia (*Dahlia variabilis*), and tickseed (*Coreopsis* species). Flavan-4-ols or 3-deoxyanthocyanidins are precursors of the phlobaphene polymers, which are red pigments and occur in

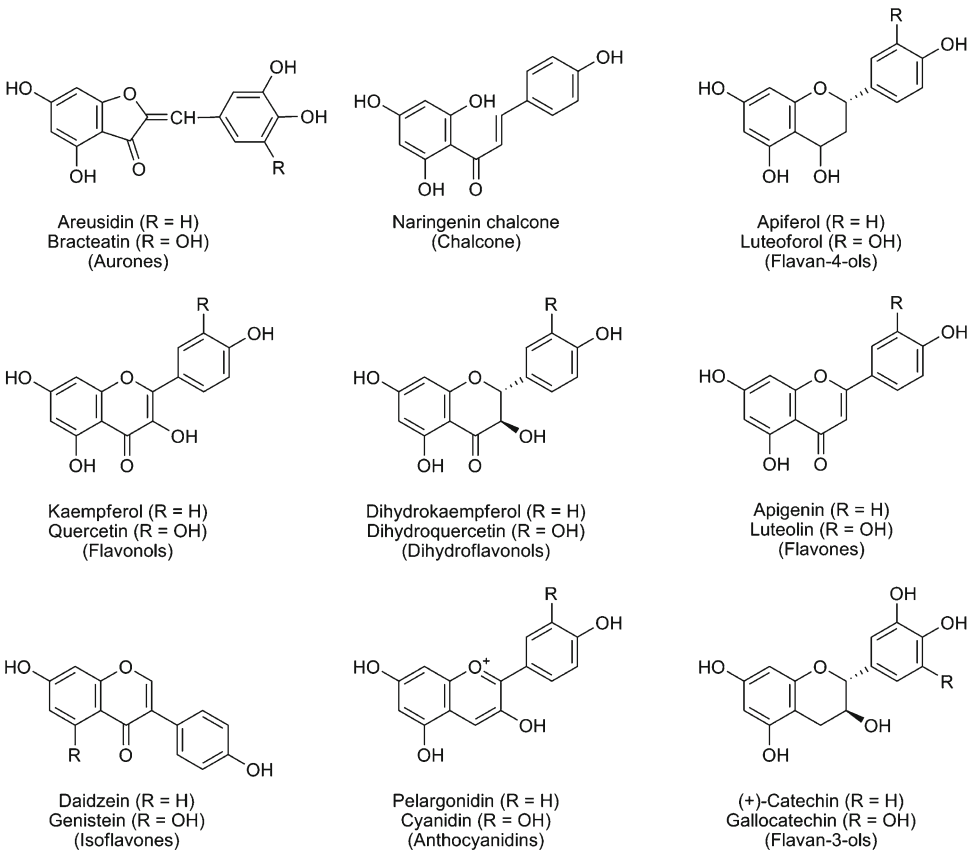


Fig. 22 Diverse classes of flavonoids

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some Poaceae (*Sorghum bicolor*, *Zea mays*) and gloxinia (*Sinningia cardinalis*) (Winkel-Shirley, 2001).

Flavonoids fulfill several physiological functions in plants. Anthocyanins serve as pigments to attract pollinators and seed dispersers. They are responsible for the red, pink, purple, and blue coloration of many flowers, fruits, and leaves. Different hues and shades are achieved by glycosylation and acylation as well as by complexation with flavones or metal ions and by variation of vacuolar pH. Flavonoids have two absorption maxima in the ultraviolet (UV) range and therefore protect plant tissue from damage by UV radiation (Harborne and Williams, 2000). Anthocyanins absorb also light in the visible range and may provide protection for chlorophyll in senescing leaves from photooxidative damage (Feild et al., 2001). In addition, flavonoids serve as radical scavengers, signaling molecules in symbiotic relationships with rhizobia, and as defense compounds (Dixon and Paiva, 1995). They are important for male fertility (Mo et al., 1992) and modulate the transport of the phytohormone indole-3-acetic acid (Peer and Murphy, 2007). Many naturally occuring flavonoids carry one or two prenyl moieties. This modification renders them more lipophilic than other flavonoids, and consequently, they show higher affinities to biological membranes and often possess antibacterial and antifungal properties (Botta et al., 2005). These phytochemicals are of limited distribution in the plant kingdom and occur in several unrelated families, e.g., in the Fabaceae, Moraceae, Asteraceae, and Rutaceae. While prenylated isoflavonoids of the Fabaceae are phytoalexins and produced upon fungal attack or elicitation, other prenylated flavonoids are accumulated constitutively (Barron and Ibrahim, 1996).

Flavonoids are part of the human diet, and high levels occur in fruits, vegetables, wine, tea, and cocoa. It is suggested that dietary intake of flavonoids has beneficial health effects due to their antioxidant and radical-scavenging properties (Heim et al., 2002). By inhibiting the oxidation of low density lipoprotein (LDL), flavonoids may prevent coronary heart disease. This mechanism has been postulated for the cardio-protective effect of red wine polyphenolics including resveratrol. Two prenylflavonoids from hops (*Humulus lupulus*) with interesting bioactivities are 8-prenylnaringenin, the strongest phytoestrogen known so far, and the promising cancer chemopreventive agent xanthohumol (Stevens and Page, 2004). Xanthohumol *in vitro* inhibits phase I enzymes that activate procarcinogens and induces detoxifying phase II enzymes. Moreover, it has radical scavenging activities and inhibits cyclooxygenases 1 and 2, which participate in the biosynthesis of prostaglandins, inflammation mediators that promote carcinogenesis (Gerhäuser et al., 2002). Like 8-prenylnaringenin, many isoflavonoids are phytoestrogens, though much weaker. Food rich in isoflavonoids, especially soy products, may be beneficial for the chemoprevention of hormone-related breast cancer if consumed during adolescence. However, intake of purified genistein, the major isoflavonoid in soy together with daidzein, cannot be regarded as safe, because it increases breast cancer cell growth in animal models (Duffy et al., 2007). A more promising chemopreventive agent against cancer is (-)-epigallocatechin 3-gallate, the most abundant polyphenol in green tea (Nagle et al., 2006). Various mechanisms are discussed, e.g., induction of apoptosis, cell cycle arrest, inhibition of angiogenesis.

Stilbenes originate from the same biosynthetic precursors as flavonoids, but have a different structure, since the polyketide portion undergoes a different type of cyclization including loss of one carbon by decarboxylation. Stilbenes occur in several unrelated plants such as peanut (*Arachis hypogaea*), grapevine (*Vitis vinifera*), rhubarb (*Rheum*), false hellebores (*Veratrum*) and pine (*Pinus*) species. These compounds have antifungal properties. They are induced upon stress, injury, and fungal infection and can therefore be classified as phytoalexins.

Stilbene production can be conferred to a plant by transformation with a single gene, stilbene synthase. Several transgenic plants producing stilbenes or stilbene glucosides were described, and some showed enhanced resistance against fungal pathogens (Hain et al., 1993; Thomzik et al., 1997; Zhu et al., 2004).

Resveratrol (Fig. 23), a stilbene found in many food sources, e.g., peanuts and red wine, is assumed to have multiple benefits on human health. Most attention has been received by the so-called "French paradox", the low occurrence of cardiovacular disease in populations living on a diet high in saturated fats, but consuming red wine. The protective effect of red wine is attributed to its proanthocyanidin and resveratrol contents. Possible mechanisms disscussed are the inhibition of oxidation of LDL cholesterol and platelet aggregation. Resveratrol may also increase longevity by activation of sirtuins, NAD^+-dependent protein deacetylases involved in aging, which respond to oxidative stress and are induced by a low-calory diet. Resveratrol mimics the effects of a low-calory diet and extends the lifespans of baker's yeast (*Saccharomyces cerevisiae*), fruit flies (*Drosophila melanogaster*), and roundworms (*Caenorhabditis elegans*) (Howitz et al., 2003; Wood et al., 2004). In addition, resveratrol increases the survival of mice fed on a high-calory diet (Baur et al., 2006). Whether similar beneficial effects can be reproduced in humans will depend on the pharmacokinetics and long-term toxicity of resveratrol in humans.

In styrylpyrones, the phenylpropanoid is extended by two C_2 units derived from malonyl-CoA, and a lactone heterocycle is formed that contains four carbons of polyketide origin and one carbon of the phenylpropanoid side chain. These natural products occur, e.g., in horsetail (*Equisetum*) and kava (*Piper methysticum*). Kava grows on the Pacific islands of Melanesia, Micronesia, and Polynesia, and its roots and rhizomes were used to prepare an intoxicating drink named "Kava-Kava" (Briskin, 2000). An extract from the rhizomes of kava is used as medication against anxiety and tension, the styrylpyrones, also called kavapyrones, being the active ingredients (Fig. 23). Kavapyrones interact

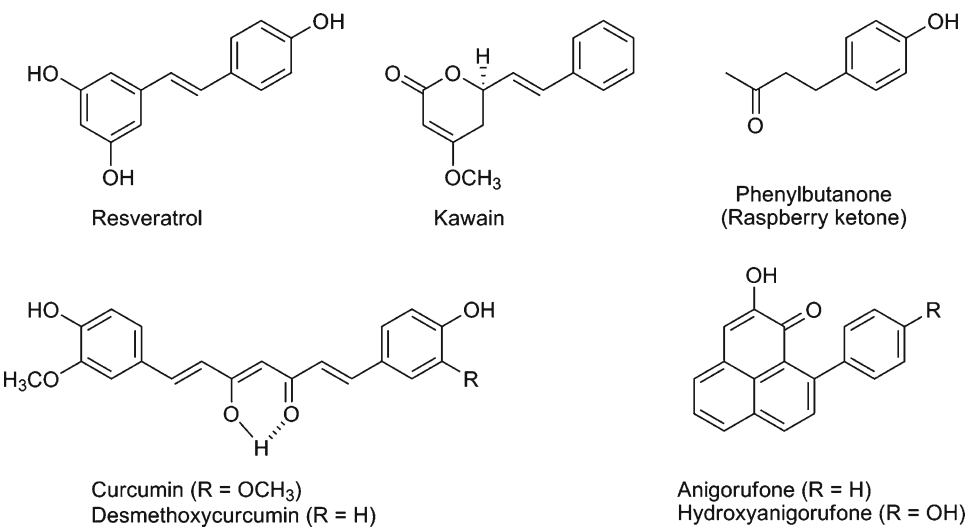

Fig. 23 Various polyketides containing one or two phenylpropanoid units

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with the gamma-aminobutyric acid (GABA) receptor (Boonen and Häberlein, 1998), which mediates mainly inhibitory effects in vertebrates. Due to the liver toxicity of kava preparations, this phytomedicine was banned from the European market.

Polyketides with one or two phenylpropanoid moieties and only one carbon derived from malonyl-CoA are the raspberry aroma *p*-hydroxyphenylbutan-2-one, the curcuminoids of turmeric (*Curcuma*), and phenylphenalenones from *Musa* and *Anigozanthos* species (Fig. 23). Curcuminoids and phenylphenalenones contain two phenylpropanoid moieties on both sides of the acetate-derived carbon and are therefore classified as diarylheptanoids. These two groups of natural products are pigments due to their conjugated system of π-electrons. Curcuminoids are widely used as spices and also have antiinflammatory, antioxidative, and anti-cancer properties (Joe et al., 2004).

Polyketides with Terpenoid Building Blocks

This group of natural products comprises the prenylated acylphloroglucinols, e.g., bitter acids from the hop plant (*Humulus lupulus*) and hyperforin from St. John's wort (*Hypericum perforatum*), as well as cannabinoids from Indian hemp (*Cannabis sativa*) (Fig. 24). These compounds are lipophilic due to their terpenoid moiety and are often produced or stored in special glands or glandular trichomes.

Hop bitter acids and hyperforin are both derived from three different building blocks: a branched short-chain CoA ester derived from amino acid metabolism and three C_2 units derived from malonyl-CoA constitute the acyl phloroglucinol core, which carries two to several isopentenyl side chains that originate from terpenoid metabolism (Adam et al., 2002; Drawert and Beier, 1976; Goese et al., 1999; Karppinen et al., 2007).

Hyperforin accumulates in translucent glands of leaves of St. John's wort (Soelberg et al., 2007) and represents the major antidepressive principle of this plant. It inhibits the re-uptake of the neurotransmitters serotonin, noradrenaline, dopamine, and GABA, thus increasing their concentrations at the synapses of the brain. This is achieved by an unprecedented mechanism. By elevating the intracellular sodium concentration, hyperforin inhibits the sodium-driven proton gradient required for the transport of neurotransmitters from the synaptic gap into the axoplasm of the neuron (Müller, 2003).

Female inflorescences (cones) of hop carry glandular trichomes that contain volatiles derived from terpenes and fatty acids and a

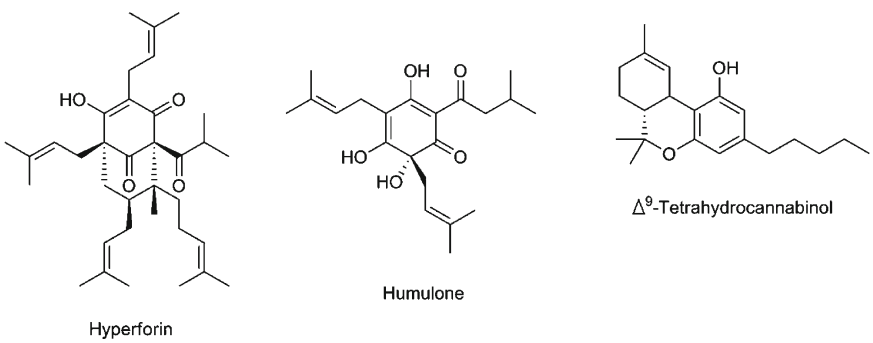

Fig. 24 Polyketides with terpenoid components

resin consisting of the hop bitter acids with humulone (α-resin) and lupulone (β-resin) as lead compounds. Hop cones are an important ingredient for beer production and contribute to its flavor, in particular its bitter taste. In addition, the hop bitter acids act as foam stabilizers and prevent the growth of bacteria due to their antimicrobial properties. Extracts of hop cones are also used as a mild sedative and sleep inducer.

Cannabinoids are derived from hexanoyl-CoA, three molecules of malonyl-CoA and the C_{10} terpenoid geranyldiphosphate. They occur only in Indian hemp, which belongs to the Cannabaceae family like hop. *C. sativa* plants accumulate a resin in glandular trichomes that are more abundant on female inflorescences than on male. The glandular resin contains more than sixty cannabinoids, e.g., δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Turner et al., 1980). Cannabis has been used as psychoactive drug since prehistoric times. Its use is nowadays prohibited in most parts of the world, but cultivation of *C. sativa* plants with low THC contents is permitted for production of fibers and oil-rich seeds in serveral countries, though not in the USA. The dried flowering parts of female hemp plants are termed marihuana, while hashish (Arabic for "grass") is their concentrated resin. These cannabis preparations are usually smoked, but they can also be ingested orally, e.g., as cakes or cookies. THC, the major psychoactive compound in cannabis, binds to cannabinoid receptors that occur in brain, spinal cord and immune cells. The consumption of cannabis products leads to a feeling of euphoria and relaxation, but repeated use may cause addiction (Dewick, 2002). Nevertheless, THC has also useful medicinal properties, e.g., antiemetic, analgesic, and appetite-inducing. It is used for the prevention of nausea during radiotherapy and chemotherapy and as treatment of the wasting syndrome in AIDS patients.

Polyketide Alkaloids

The most famous compounds of this group are probably the piperidine alkaloids of poison hemlock (*Conium maculatum*), which were used to execute the Greek philosopher Socrates. While piperidine alkaloids are usually synthesized from the amino acid L-lysine, the carbon skeleton of the piperidine alkaloids in *C. maculatum* originates from four acetate units (Leete, 1963, 1964). Only the nitrogen is derived from L-alanine by transamination (Roberts, 1971). Hemlock alkaloids are accumulated in all plant parts, however, highest levels are found in unripe fruits (1.6%) (Dewick, 2002). The two major hemlock alkaloids are γ-coniceine and coniine (Fig. 25). Piperidine alkaloids like coniine occur

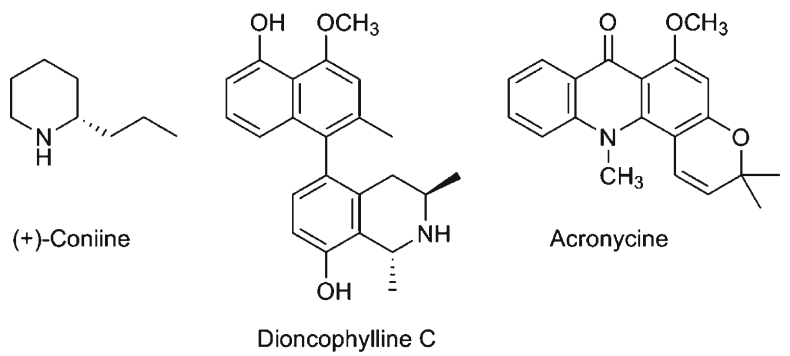

Fig. 25 Different types of polyketide alkaloids

not only in *C. maculatum*, but also in several *Aloe* species (Reynolds, 2005). These compounds are neurotoxic and cause paralysis, muscular tremor and death by respiratory paralysis.

Although the carbon skeleton of naphthylisoquinoline alkaloids is much more complex than that of the coniine alkaloids, it is composed of the same building blocks, C_2 units derived from acetyl-CoA and malonyl-CoA. Each part the the naphthylisoquinoline skeleton, naphthalene and isoquinoline moiety, are derived from six acetate units. Nitrogen is incorporated only in the isoquinoline part and most likely derived from amino acid metabolism (Bringmann and Feineis, 2001). Naphthylisoquinoline alkaloids occur only in the plant families Ancistrocladaceae and Dioncophyllaceae that comprise lianas from southeast Asia and Africa. They were shown to possess fungicidal activities and antifeedant properties towards insects, which might relate to their physiological function. Michellamine B, a dimeric naphthylisoquinoline from the liana *Ancistrocladus korupensis*, was discovered during a screening by the U.S. National Cancer Institute. It showed promising anti-HIV acitivity by inhibiting the viral reverse transcriptase and by blocking the fusion of virus particles with the human cell membrane (McMahon et al., 1995). Other alkaloids of this group, e.g., dioncophylline C (Fig. 25) and ancistrocladinium A and B, have antiplasmodial and antileishmanial properties, respectively (François et al.,1997; Ponte-Sucre et al., 2007).

In contrast to the previous two groups of alkaloids, the nitrogen in the backbone of acridone alkaloids is not acquired by transamination from an amino acid. Instead, the nitrogen and part of the carbon skeleton of acridones originate from *N*-methylanthraniloyl-CoA, which is derived from the shikimate pathway. In addition, three C_2 units derived from malonyl-CoA are incorporated. The basic acridone skeleton can be modified by prenylation with dimethylallyldiphosphate (DMAPP), which can be followed by the formation of an additional heterocyclic five- or six-membered ring. In plants, acridone alkaloids occur abundantly in the Rutaceae family. Due to their planar aromatic structure, acridones can intercalate DNA. Acronycine (Fig. 25) from *Acronychia baueri* showed promising anticancer activity, but did not yield convincing results in clinical studies. Its new derivative S23609-2, a benzoacronycine, is a potent DNA-alkylating agent and currently undergoes phase I clinical trials (Léonce et al., 2006).

Terpenoids

Terpenoids, also named isoprenoids, are the largest class of natural products in plants and comprise more than 40,000 different structures. They are derived from five-carbon isoprene units, and according to the number of isoprene molecules incorporated, they can be classified into hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), triterpenes (C_{30}), tetraterpenes (C_{40}), and polyterpenes such as rubber (Dewick, 2002). In plants, terpenoids originate from two different biosynthetic routes: the cytosolic mevalonic acid (MVA) pathway and the plastid-located desoxyxylulose phosphate (DXP) pathway (also called methylerythritol phosphate or MEP pathway). Both biosynthetic routes yield the activated isoprene units dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP), which are joined by head-to-tail or tail-to-tail linkage and subsequently can undergo cyclization and other modifications, e.g., oxidations or rearrangements. While hemiterpenes, monoterpenes, diterpenes, and tetraterpenes are derived from the DXP pathway, triterpenes, steroids, and certain sesquiterpenes originate from mevalonic acid (Fig. 26). Although MVA and DXP pathway are located in different compartments, there is an exchange between the two biosynthetic routes, especially from the plastidial to the cytosolic pathway

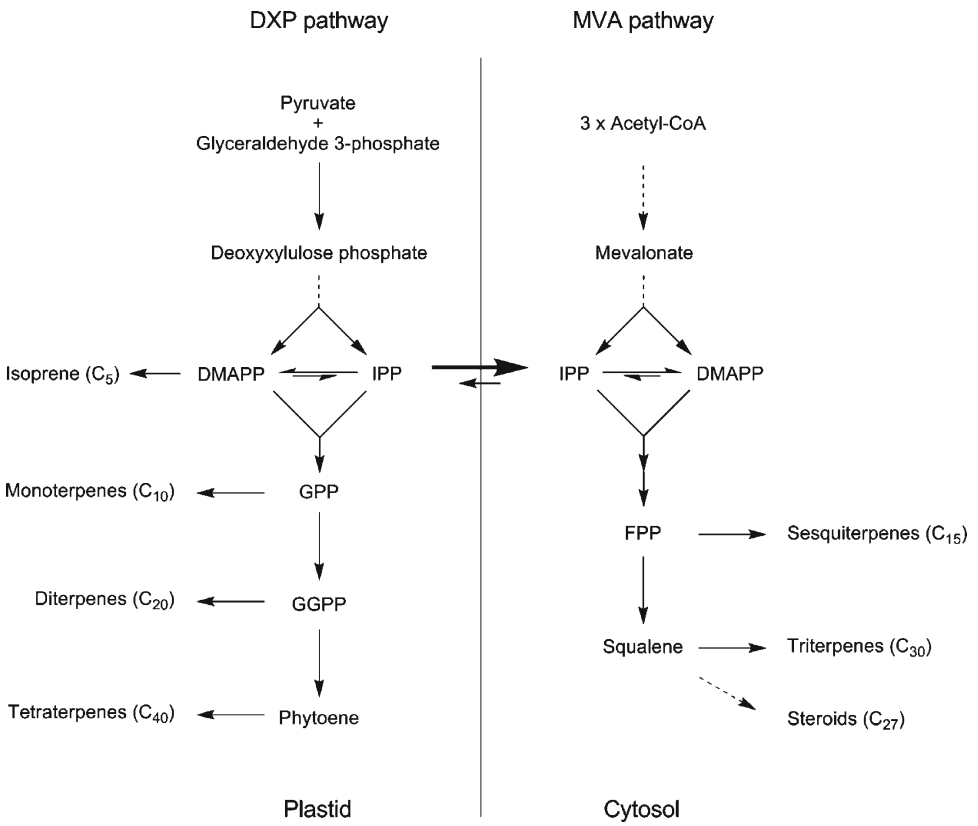

Fig. 26 Schematic overview of terpene biosynthesis in plants. DMAPP, dimethylallyl diphosphate; DXP, desoxyxylulose phosphate; FPP, farnesyl diphosphate; GGPP, geranylgeranyl diphosphate; GPP, geranyl diphosphate; IPP, isopentenyl diphosphate; MVA, mevalonate

(Laule et al., 2003; Schuhr et al., 2003). This has become particularly evident in the case of several sesquiterpenes, which are synthesized from DMAPP and IPP units provided by the DXP pathway, but not from MVA (Dudareva et al., 2005; Piel et al., 1998).

Hemiterpenes

The most abundant true hemiterpene from plants is isoprene (Fig. 27), a volatile compound synthesized from DMAPP. Production and emission of isoprene is distributed very widely in the plant kingdom, and species that synthesize this compound are found among mosses, ferns, gymnosperms, and angiosperms. Many isoprene-emitting species are trees, particularly poplar and aspen, and plants from the humid tropics. Isoprene is emitted into the atmosphere

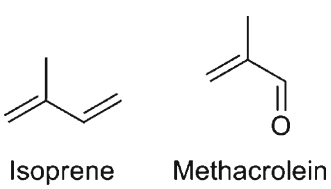

Fig. 27 Hemiterpenes

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and protects leaves to survive short periods of high temperature. Moreover, it increases the plant's tolerance towards ozone and reactive oxygen species. (Sharkey et al., 2008).

Hemiterpenes may also act as signaling molecules. Leaves of sagebrush (*Artemisia tridentata*) emit the highly volatile hemiterpene methacrolein (Fig. 27) in addition to other volatile compounds like hexenal, monoterpenes, and methyljasmonate when the plant is damaged. This is perceived by plants in its close neighborhood and enables them to react faster to a possible attack. A plant that is prepared in this manner, is less likely to be damaged by herbivores (Baldwin et al., 2006).

In addition, C_5 units derived from DMAPP are found in natural products of mixed biosynthetic origin, e.g., prenylated flavonoids, hop bitter acids, and hyperforins.

Monoterpenes

Monoterpenes originate from one molecule DMAPP and one molecule IPP that are joined in most cases head-to-tail, yielding all-*trans* geranyldiphosphate (GPP) (Fig. 28). GPP can be folded into mono-, bi- and tricyclic structures and may undergo other modifications to yield more than 1,000 different monoterpenes. Monoterpenes are lipophilic volatile compounds that occur in defensive resins of conifers, essential oils, and floral scents and contribute to the characteristic flavor or aroma of many plants. Since monoterpenes are volatile, large amounts can only be accumulated in specialized structures. Several plant families, e.g., the Lamiaceae and Asterace, have glandular trichomes with secretory cells that produce terpenes and secrete them into a shared subcuticular storage cavity (Croteau et al., 2005). Similarly, conifers accumulate oleoresin, a complex mixture of mono-, sesqui-, and diterpenes, in resin blisters or ducts, which are covered by a layer of epithelial cells that synthesize and secrete the terpenes into the lumen (Trapp and Croteau, 2001). As in the case of the conifers, many other plants accumulate monoterpenes in mixtures containing the larger sesqui- and diterpenes, rather than monterpenes alone.

The physiological function of monoterpenes is defense, attraction of pollinators, and plant-plant communication (Mahmoud and Croteau, 2002). The role of terpenes in plant-insect-interactions has been particularly well-studied in the example of conifers and the bark beetle. Upon tissue damage by the beetle, oleoresin is secreted from the ducts or produced newly. The volatile turpentine fraction of oleoresin consisting of biologically active mono- and sesquiterpenes, e.g., limonene and pinene, kills the beetles and associated pathogenic fungi. After evaporation of turpentine, the remaining non-volatile rosin fraction consisting of diterpene resin acids solidifies, thus trapping the predators and sealing the wound (Philipps and Croteau, 1999). Despite their toxicity, monoterpenes in oleoresin serve as olfactory signals that help the bark beetles to find their host. Ingested monoterpenes

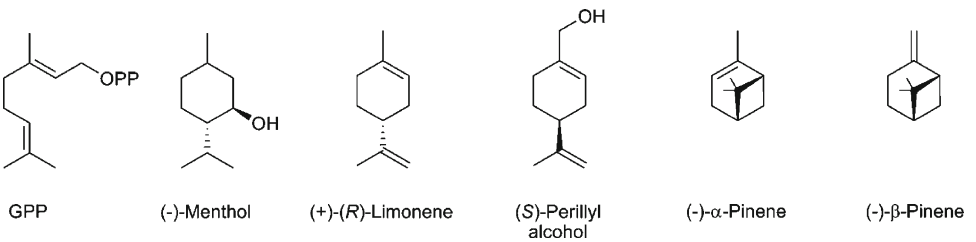

Fig. 28 Mono- and bicyclic monoterpenes derived from geranyldiphosphate (GPP)

are converted by the beetles to pheromones that either attract more beetles or serve as anti-aggregation signals. In addition, conifer monoterpenes take part in tritrophic interactions and attract insect predators that feed on bark beetles (Trapp and Croteau, 2001).

Many monoterpenes have found application in perfumery, aromatherapy, as cosmetics and insecticides. Menthol, a constituent of essential oils from *Mentha* species, is the most widely used monoterpene. It is contained in pharmaceuticals, oral health care products, chewing gums, and tobacco products (Croteau et al., 2005). More than 7,000 t of menthol are produced every year either by total synthesis or from the steam-distilled essential oil of cornmint (*Mentha arvensis* var. *piperascens*). The cooling sensation stimulated by menthol is caused by excitation of cation channels that serve as thermal receptors (Jordt et al, 2003).

Two monoterpenes with promising anticancer effects are perrillyl alcohol and (+)-(*R*)-limonene (Mo and Elson, 2004). The two compounds induce apoptosis and suppress translation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, an enzyme of the MVA pathway. This enzyme is a promising target for anti-tumor compounds, because many proteins involved in cell growth are prenylated, and tumor cells have elevated HMG-CoA reductase levels. Suppression of HMG-CoA reductase is sufficient to decrease terpene biosynthesis in humans, since animals lack the alternative DXP pathway.

Iridoids are monoterpenes with a six-membered oxygen heterocycle annealed to a cycplopentane ring. The hydroxy group of the oxygen containing heterocycle (dihydropyrane) is glucosylated, thus converting the enol-hemiacetal into an acetal (Fig. 29). Cleavage of the cyclopentane ring of the iridoid skeleton yields the secoiridoids, which are biosynthetic building units of the Ipecac alkaloids and the monoterpene indole alkaloids. Iridoids are named after ants of the genus *Iridomyrmex* that produce these metabolites as defense compounds. In plants, iridoids are chemotaxonomic markers of the genera *Plantago* (Plantaginaceae), *Galium*

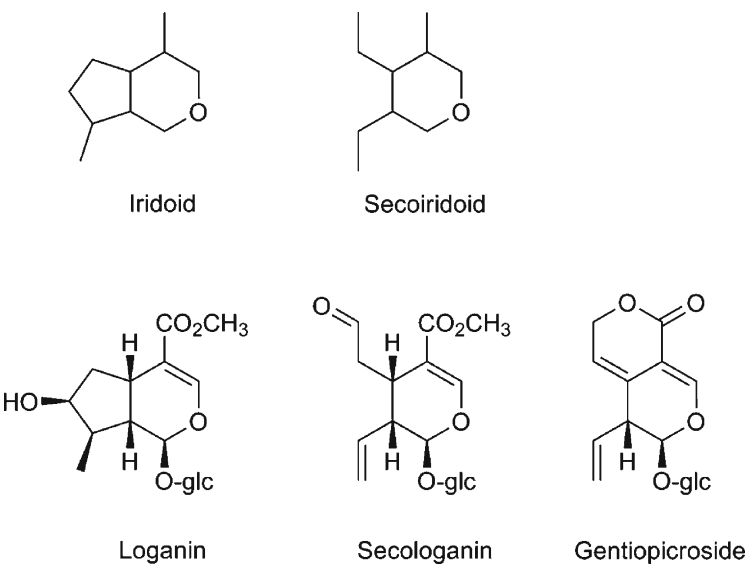

Fig. 29 Iridoids

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(Rubiaceae), and *Scrophularia* (Scrophulariaceae) and also occur frequently in the Gentianaceae, Oleaceae, and Verbenaceae (Dinda et al., 2007a, b). Many iridoids have an intense bitter taste and therefore act as feeding deterrents (Seigler, 1998). On the other hand, plants with bitter tasting iridoids, e.g., gentian (*Gentiana lutea*) with its bitter principle gentiopicroside and amarogentine, are used for the preparation of tonics against anorexia and dyspepsia.

Sesquiterpenes

Sesquiterpenes contain three isoprene units and are formed by condensation of DMAPP with two molecules IPP. The central C_{15} intermediate farnesyldiphosphate (FPP) can be folded into mono-, bi- or tricyclic systems. In general, sesquiterpenes are less volatile than monoterpenes (Dewick, 2002). Initially, it was assumed that all sesquiterpenes are produced via cytosolic MVA pathway. Recent studies, however, revealed that certain sesquiterpenes originate from isoprene units provided by the DXP pathway (Dudareva et al., 2005; Piel et al., 1998) or by both biosynthetic routes (Adam and Zapp, 1998). This can be explained by transport of isoprenoid precursors from the plastids to the cytosol (Bick and Lange, 2003).

Abscisic acid is a sequiterpene phytohormone that is induced by drought and promotes stomatal closure and seed dormancy. Other sesquiterpenes take part in tritrophic plant-herbivore-parasite interactions (reviewed by Dudareva et al., 2006). In maize infested with lepidopteran larvae, the sesquiterpenes (*E*)-β-farnesene and the (*E*)-α-bergamotene (Fig. 30) attract the parasitic wasp *Cotesia marginiventris* (Schnee et al., 2006). Maize roots release (*E*)-β-caryophyllene (Fig. 30) upon attack of larvae of the beetle *Diabrotica virgifera* to attract the parasitic nematode *Heterorhabditis megidis* (Rasmann et al., 2005).

Many sesquiterpenes contain a pentacyclic lactone group and are therefore referred to as sesquiterpene lactones. These compounds occur abundantly in the family Asteraceae. Because of their bitter taste sesquiterpene lactones presumably serve as feeding deterrents of herbivores (Heinrich et al., 1998). Pharmacologically active sesquiterpene lactones often show anti-inflammatory effects due to inhibition of the transcription factor NF-κB that mediates immunological responses and inflammation (Lyß et al., 1998). Sesquiterpenes with such activities occur, for example, in chamomile (*Matricaria recutita*), one of the most popular medicinal plants. Antimigraine action of some sesquiterpene lactones, e.g., parthenolide from feverfew (*Tanacetum parthenium*), is mediated by inhibition of platelet aggregation

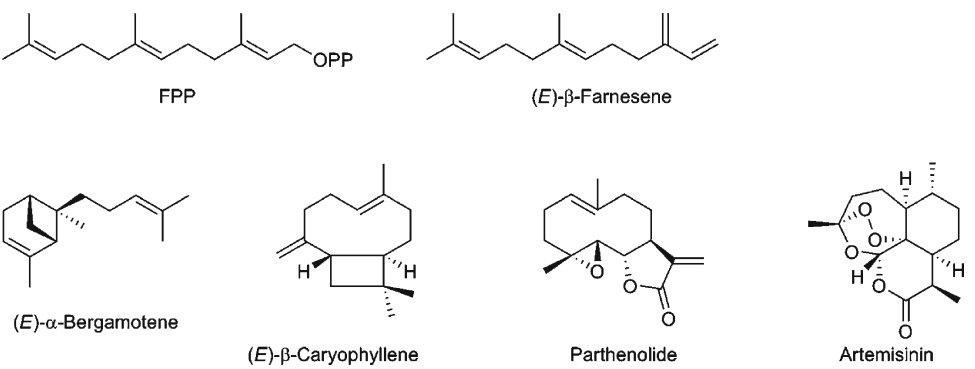

Fig. 30 Linear and cyclic sesquiterpenes

and serotonin secretion (Dewick, 2002). Structural prerequisite for the biological activities of sesquiterpene lactones is an α,β-unsaturated lactone that acts as nucleophile and alkylates proteins, particularly at their thiol groups. On the other hand, alkylation of proteins is the reason for the allergenicity and cytotoxicity of sesquiterpene lactones with an α,β-unsaturated lactone.

Artemisinin is a novel promising agent against malaria. Structurally, it is a tetracyclic sesquiterpene with a six-membered lactone ring and an unusual 1,2,4-trioxane ring (Fig. 30). It occurs in *Artemisia annua* (*qinghao*), which has been used for centuries in Traditional Chinese Medicine to treat fevers including malaria. The starting point of the discovery of artemisinin was a request of Ho Chi Minh, the president of North Vietnam, to the Chinese government for a cure against malaria to support his troops in the malaria-infested jungles during the American/Vietnamese war (Hsu, 2006). A screening of plants used in Traditional Chinese medicine revealed the antimalarial activity of an ether extract from *A. annua* in 1971, and artemisinin (*qinghaosu*) was isolated as the active principle in the late 1970s. The mode of action of artemisinin is still being investigated. Most likely, it interferes with a sarco-endoplasmic reticulum calcium ATPase (SERCA) of *Plasmodium falciparum*, but other mechanisms, e.g., alkylation of biological macromolecules or the production of reactive oxygen species are discussed as well (White, 2008). The peroxide bridge is a necessary structural feature required for antimalarial activity. In contrast to quinine, artemisinin kills already young erythrocytic forms of the parasite *Plasmodium*, thus curing malaria at an early stage. Two semisynthetic analogs, artemether and artesunate, with superior efficiency in comparison to artemisinin were developed and are now used as first-line therapy against malaria in combination with other antimalarial drugs like the quinine analogs mefloquine and lumefantrine. This combination of two drugs tends to prevent resistances of *Plasmodium*. The success of artemisinin and its analogs has triggered a huge demand that cannot be covered at low cost by extraction of the sesquiterpene from the plant, because *A. annua* contains only 0.01-1.5% of artemisinin (Covello et al., 2007). Approaches to provide the powerful drug at affordable price for the people in malaria-endemic areas are either breeding of *A. annua* plants with elevated artemisinin levels or biotechnological production of the artemisinin precursor artemisic acid by cloning the biosynthetic genes from *A. annua* (Covello et al., 2007) and engineering the pathway into the bacterium *Escherichia coli* or yeast (Chang et al., 2007; Ro et al., 2006).

Diterpenes

Diterpenes originate from the plastdic DXP pathway and are synthesized from DMAPP and three molecules IPP yielding the C_{20} metabolite geranylgeranyl diphosphate (GGPP). GGPP is the precursor of the lipophilic phytyl side chain of chlorophyll and plastoquinone. Like the smaller terpenes, GGPP can also undergo cyclization and rearrangements to many different structures.

Gibberellins are tetracyclic diterpenes that act as phytohormones and promote shoot elongation, flowering and seed germination (Bishopp et al., 2006). Diterpenes like abietic- and levopimaric acid (Fig. 31) are constitutents of conifer oleoresin and function as defense against herbivores and pathogens. After removal of mono- and sesquiterpenes (turpentine) from oleoresin by distillation, the solid diterpene fraction (rosin) is called colophonium and used on the bows of string instruments. The mono- and sesquiterpene containing distillate is used as oil of turpentine for the thinning of paints and varnishes.

The powerful cytostatic compound paclitaxel (Taxol®) is a diterpene with an *N*-benzoyl

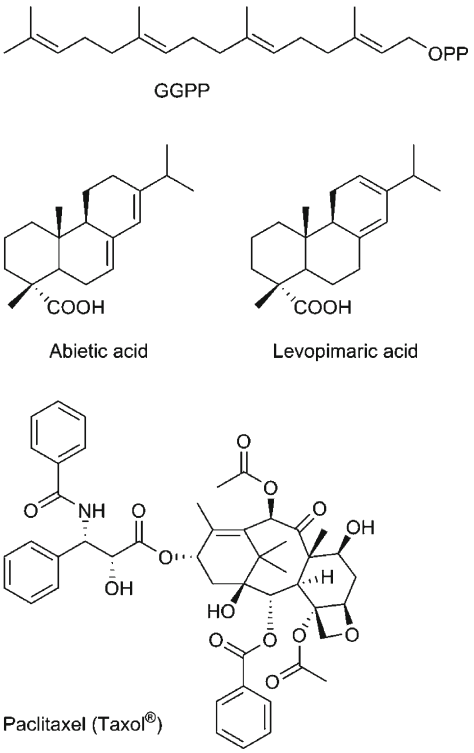

Fig. 31 Diterpenes

phenylisoserinoyl side chain derived from two molecules phenylalanine (Fig. 31). Paclitaxel was first isolated from the bark of the Pacific yew (*Taxus brevifolia*) by bioactivity-directed fractionation in 1966, and its structure was elucidated 5 years later (Wani et al., 1971). Its anti-cancer activity is based on a unique mechanism. Paclitaxel binds to microtubules, stabilizes them against depolymerisation and thus blocks cell proliferation (Schiff and Horwitz, 1980). Paclitaxel is used in the therapy of breast, ovarian and lung cancers, cancers of head and neck and Kaposi's sarcoma. Since paclitaxel occurs only in relatively low amounts in the bark of *T. brevifolia* (0.01-0.02%) and the trees grow slowly, other sources had to be found to supply enough of the diterpene for industrial production. Today, paclitaxel is obtained either from tissue cultures of various *Taxus* species or by semisynthesis from baccatin III and 10-deacetylbaccatin III, which can be extracted in sufficient amounts from leaves and twigs of the common yew (*T. baccata*), a tree that grows much faster than *T. brevifolia*.

Triterpenes and Steroids

Triterpenes are synthesized via the MVA pathway from two molecules of FPP that are joined by tail-to-tail condensation to squalene. Cyclization of its metabolite 2,3-oxidosqualene followed by rearrangements and methyl shifts yields various structures, mostly tetra- or pentacyclic. 2,3-Oxidosqualene is also the precursor of plant steroids. In this case, it is cyclized to the triterpene cycloartenol, which is then converted to the C_{27} compound cholesterol with the loss of three methyl groups. The oxygen of 2,3-oxidosqualene is usually retained as hydroxy group at C-3 in both triterpenes and steroids.

In contrast to animals, where cholesterol is the major sterol, many plant sterols are methylated or ethylated at C-24 of the side chain, e.g., campesterol and stigmasterol (Fig. 32). These phytosterols are constituents of biomembranes in plants and influence their permeability. Phytosterols inhibit the absorption of cholesterol in animals. Since they are more lipophilic than cholesterol, they are more readily incorporated into the micelles involved in fat digestion. Esters of phytosterols are therefore used as cholesterol-lowering food additives (Dewick, 2002). Brassinosteroids are a group of plant hormones that derive from campesterol. They regulate various biological processes, e.g., stem elongation, leaf expansion, seed germination, and xylem differentiation (Bishopp et al., 2006).

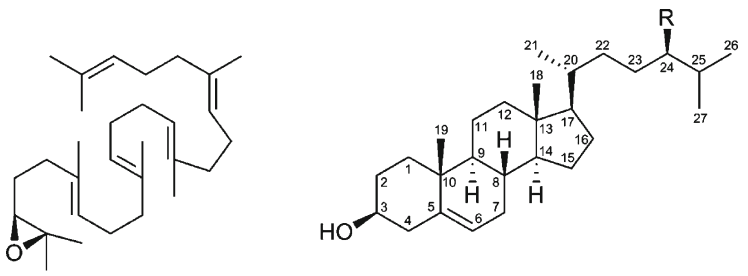

Fig. 32 Sterols derived from 2,3-oxidosqualene

Saponins

Triterpene saponins are widely distributed among eudicot plants, for example, in the Araliaceae, Caryophyllaceae, Fabaceae, and Primulaceae families. Monocots, instead, preferably accumulate steroidal saponins, which are abundant in the Agavaceae, Dioscoraceae, and Yuccaceae. Triterpenoid saponins often contain the pentacyclic α-amyrin (ursane), β-amyrin (oleanane) or lupane skeleton or the tetracyclic dammarane backbone as aglycone. This aglycone is linked with one to three carbohydrate chains containing up to six sugar molecules or uronic acids (Dewick, 2002; Hostettmann and Marston, 1995). The first sugar chain is attached to the hydroxy group at C-3 of the triterpene backbone. If two or more carbohydrate chains are present, they are usually connected with hydroxy or carboxy groups at C-28 or C-30.

Steroid saponins can be classified into two groups, spirostanols and furostanols. In furostanols, the side chain of cholesterol is used to form a tetrahydrofuran ring, and the hydroxy group at C-26 is glycosylated. Upon cleavage of this sugar moiety, a second oxygen-containing heterocycle is formed, thus yielding a spirostanol (Fig. 33). Steroidal glycoalkaloids have the same structure like spirostanol saponins, except that the oxygen in the six-membered heterocycle of the spiro function is replaced by nitrogen. As in the case of the triterpene saponins, steroidal saponins carry a sugar chain at the C-3 hydroxy group.

The name saponin is derived from the Latin word “sapo”, soap. This refers to the properties of saponins, which consist like soaps of a lipophilic moiety (triterpenoid or steroid aglycone, also called sapogenin) and a hydrophilic moiety (sugars) and produce foam when shaken in aqueous solution. Plants like soapwort (*Saponaria officinalis*) and soapbark tree (*Quillaia saponaria*) were therefore used as detergents. Today, extracts of saponin-containing plants or isolated saponins are used in cosmetics, as detergents and as foaming agents in soft drinks (Güçlü-Üstündag and Mazza, 2007). Saponins lyse red blood cells, a process called hemolysis, because they complex sterols of the plasma membrane and thus increase membrane permeability. This membrane-permeabilizing effect is also responsible for the antimicrobial and antifungal activities of saponins and their function as defence compounds in plants. In general, saponins with only one sugar chain (monodesmosides) show stronger hemolytic and antifungal effects than saponins with two oligosaccharide chains (bisdesmosides). Like cyanogenic glucosides or glucosinolates, bisdesmosidic saponins

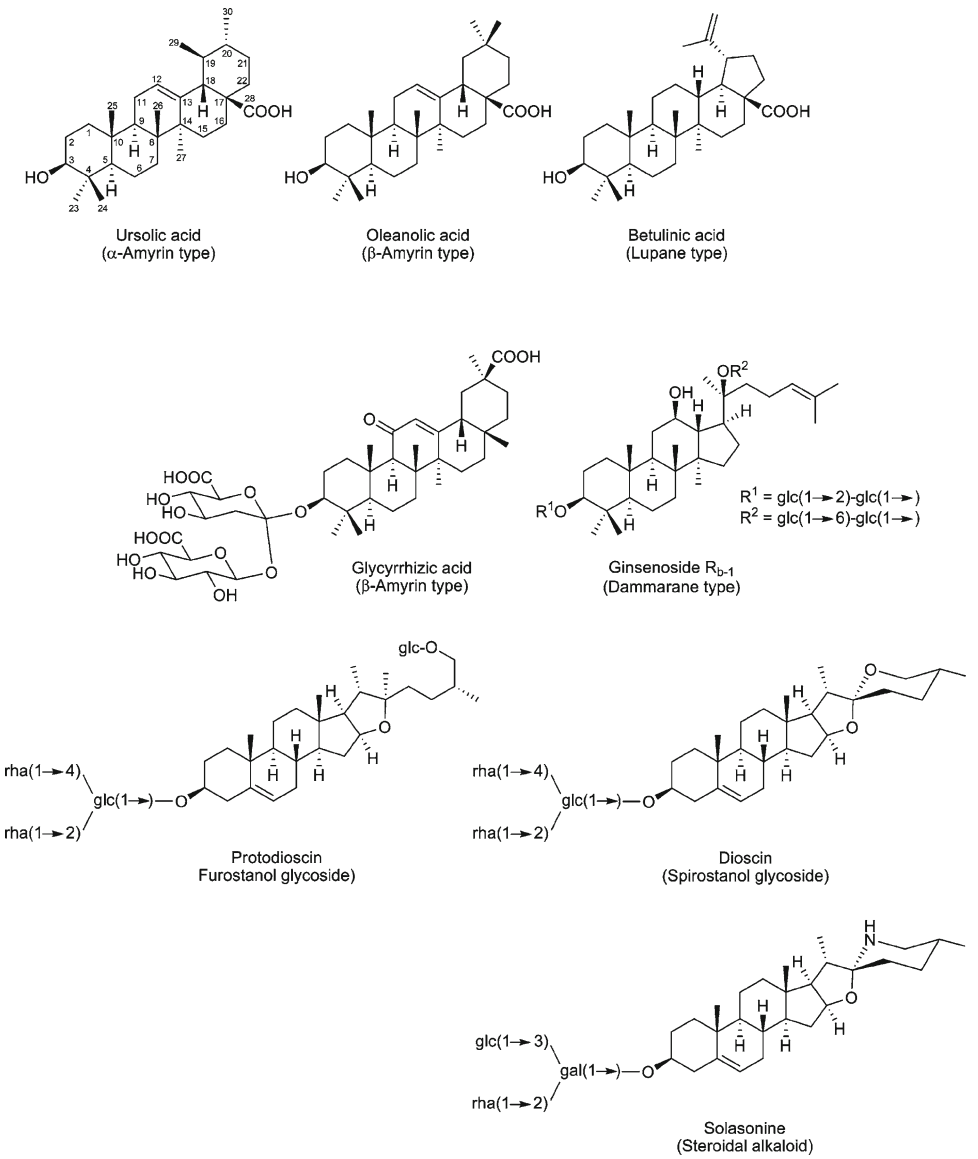

Fig. 33 Triterpene and steroid saponins

can be thought of as prodrugs that are cleaved in case of wounding by a specific hydrolase normally located in a different compartment and converted into active defence compounds (Osbourn, 1996). However, one sugar chain is required for the biological activity of saponins, whereas other natural products usually lose their activity when glycosylated.

Taken orally, saponins are not toxic because they are poorly absorbed and the sugar chain important for their hemolytic properties is hydrolyzed. In contrast, saponins are toxic to

fish, since they damage the membranes of the gills (Hostettmann and Marston, 1995). Plant material rich in saponins has therefore been used to poison and stupefy fish. The fish can then be caught without difficulty and are not toxic to humans.

Most saponins have a bitter taste, but some sweet saponins are known as well. Glycyrrhizic acid from licorice root (*Glycyrrhiza glabra*), a β-amyrine type triterpene linked to two molecules of glucuronic acid (Fig. 33), is 50 times sweeter than sucrose (table sugar). Licorice extracts are used to prepare candies (licorice) and as a sweetener. They are also used as mild expectorant and as anti-inflammatory agent. The anti-inflammatory effect is caused by inhibition of an enzyme that inactivates cortisol. On the other hand, this may also lead to side effects such as sodium retention, excretion of potassium, water retention and increased blood pressure.

The roots of ginseng (*Panax ginseng*) have been used in the traditional medicine of Korea, China and Japan for several thousand years. It is used as adaptogen to help the body to cope with stress, to improve performance and during convalescence (Radad et al., 2006). Active ingredients are saponins, mainly of the dammarane type, containing two or three sugar side chains (Fig. 33) (Dewick, 2002). The ginseng aglycones protopanaxadiol and protopanaxatriol show promising anticancer activities (Güçlü-Üstündag and Mazza, 2007), and a preparation containing ginseng aglycones has been given conditional approval in China for the therapy of various tumors as single agent or in combination with paclitaxel.

The triterpene sapogenins betulinic acid, oleanolic acid and ursolic acid show cytotoxic and anti-inflammatory effects, and based on their structures novel chemopreventive and anticancer agents are being developed (Liby et al., 2007). A derivative of betulinic acid, bevirimat, is the first member of a new class of anti HIV therapeutics, maturase inhibitors. These compounds inhibit the processing of the HIV Gag protein, the precursor of the capsid, and lead to defective and non-infectious virus particles (Li et al., 2003).

Tetraterpenes

Tetraterpenes comprise only one group of compounds, the carotenoids. They are synthesized from two molecules GGPP by tail-to-tail addition. Double bonds are inserted to yield an extended conjugated system with all-*trans* configuration that is responsible for the yellow, orange and red color of the carotenoids. Either one or both ends of the tetraterpene chain are cyclized to a six-membered ring. Carotenoids with hydroxy or epoxy functions are classified as xanthophylls (Dewick, 2002).

Carotenoids fulfill important physiological functions in plants, since they are part of the light harvesting complex and act as accessory pigments of chlorophyll. In addition, they quench triplet chlorophyll and singlet oxygen in case of excess light energy and thus protect the plant from photo-oxidative damage. As pigments of flowers and fruits, carotenoids attract pollinators and seed dispersers (Howitt and Pogson, 2006).

Carotenoids are essential for human health. α-carotene, β-carotene (Fig. 34), and β-cryptoxanthine are precursors of vitamin A. They are taken up with food, cleaved in the intestinal mucosa and converted in the liver to vitamin A, which serves as pigment of the light receptors of human eyes. To overcome vitamin A deficiency

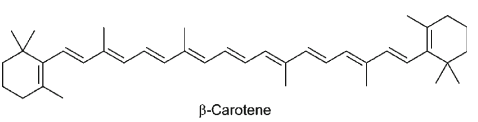

Fig. 34 β-Carotene

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in areas with malnutrition, a transgenic rice termed, golden rice "was developed that expresses high levels of carotenoid biosynthetic enzymes in the endosperm and accumulates elevated levels of carotenoids (Ye et al., 2000). Due to their anti-oxidant and radical scavenging properties, a diet with fruits and vegetables rich in carotenoids is assumed to decrease the risk of cardiovascular disease or cancer. However, the intake of carotenoids as supplement probably has no health promoting effects (Riccioni et al., 2007; U.S. Preventive Service Task Force, 2003).

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