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Wrocław University of Technology

Medicinal Chemistry

Jadwiga Sołoducho, Joanna Cabaj

# MEDICINAL NATURAL PRODUCTS

Wrocław 2011

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# I. INTRODUCTION

These lecture notes have been written primarily for medicinal chemistry students to provide a modern text to complement lectures dealing with phytochemistry, pharmacognosy and the use of natural products in medicine. The textbook is available on the web page of Wroclaw University of Technology and allows students to get background knowledge for the course. Nevertheless, it should be of value in most other courses where the study of natural products is included, although the examples chosen are predominantly those possessing pharmacological activity.

Phytochemistry in the strict sense of the word is the study of phytochemicals. These are chemicals derived from plants. In a narrower sense the terms are often used to describe the large number of secondary metabolic compounds found in plants. Many of these are known to provide protection against insect attacks and plant diseases. They also exhibit a number of protective functions for human consumers.

## II. METABOLISM

Metabolism is the set of chemical reactions that occur in living organisms to maintain life. Metabolism is usually divided into two categories:

- Catabolism breaks down organic matter, for example to harvest energy in cellular respiration.
- Anabolism, on the other hand, uses energy to construct components of cells such as proteins and nucleic acids.

The primary metabolism also called basic metabolism contains all pathways and products that are essential for the cell itself (Fig 1). Besides some specific pathways of plants (like photosynthesis) and micro-organisms, the reactions of the primary metabolism are nearly identical in all organisms. This fact can be regarded as a proof that their evolution was already largely accomplished before diversification into the different cells and organisms happened.

The secondary metabolism (Fig 2) produces molecules that are not that important for the survival of the cell itself but much more so for that of the whole organism. Especially in plants, such pathways play an important part. They lead to products like flower colours, scents and flavours, stabilizing elements, toxic components, etc.

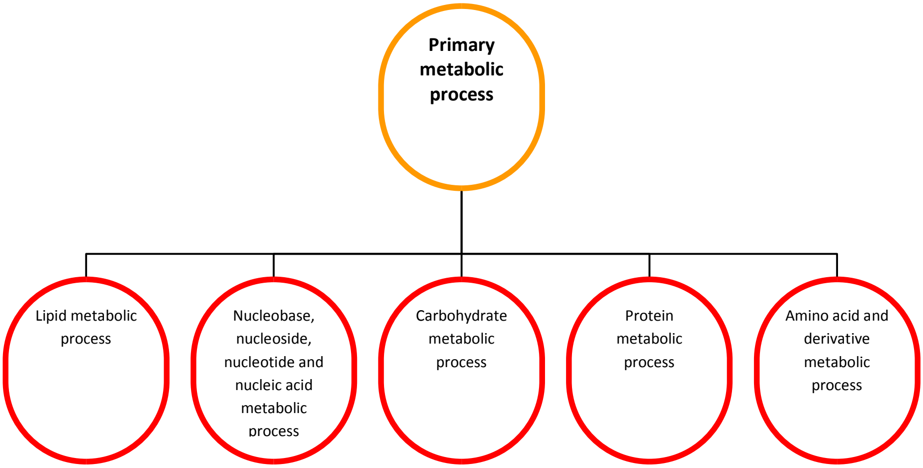
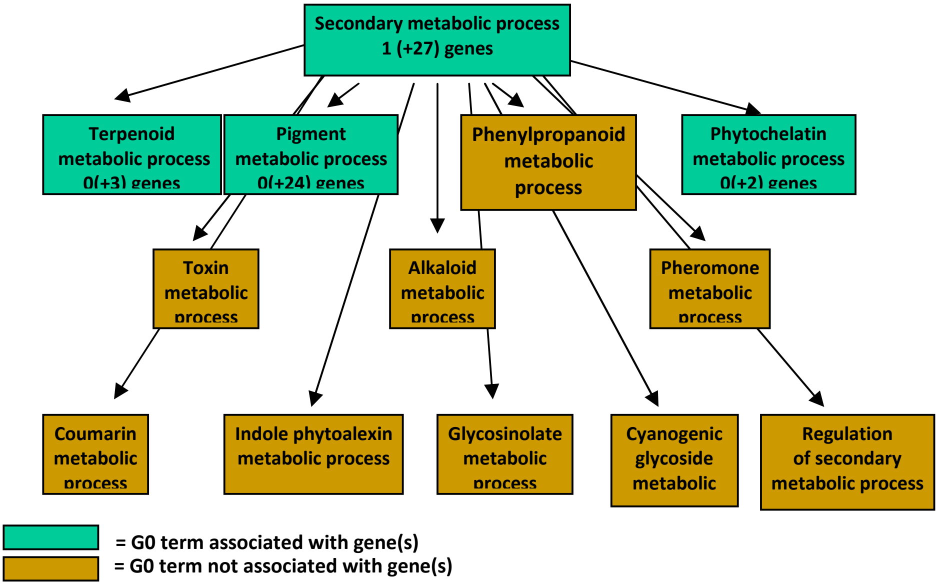


Fig 1. Primary metabolic process



**Each green box reports both the number of genes directly** annotated to that term, and combined total number of genes associated with G0 term's descendents. For example, 3(+64) indicates that 3 genes are directly annotated to that term, and combined total of 64 genes are annotated to that term's descendant terms

Fig 2. Secondary metabolic process

Secondary metabolites are those chemical compounds in organisms that are not directly involved in the normal growth, development or reproduction of organisms. Typically primary metabolites are found across all species within broad phylogenetic groupings, and are produced using the same pathway (or nearly the same pathway) in all these species. Secondary metabolites, by contrast, are often species-specific (or found in only a small set of species in a narrow phylogenetic group), and without these compounds the organism suffers from only a mild impairment, lowered survivability/fecundity, aesthetic differences, or else no change in phenotype at all.

Table 1. Terminology (II)

| *English* | *Polish* |
|---|---|
| diversification | zróżnicowanie |
| flavour | zapach |
| fecundity | rozrodczość |
| impairment | uszkodzenie |
| scent | zapach, woń |

# III. HERBAL METABOLITES – OVERVIEW

## 1. Slimes

A group of mixtures of compounds with polysaccharide character (monopolysaccharide and heteropolysaccharide). They are applied in pharmacology as coating, protecting and softening agents in treatment of alimentary canal and respiratory canal diseases.

Slimes as a mixture of polysaccharides are present in numerous plants:

- *Radix Althaeae (Marshmallow root)*
- *Semen Lini (Linsead)*
- *Folium Althaeae (Marshmallow leaf)*
- *Flos Malvae sylvestris (Common mallow flowers)*
- *Inflorescentia Tiliae (Linden flowers)*

Marshmallow (*Althaeae officinalis,* Fig 3) is a genus of 6-12 species of perennial herbs, including the *marshmallow* plant from whence the confection got its name, native to Europe and western Asia. They are found on the banks of rivers and in salt marshes, preferring moist, sandy soils. The stems grow to 1-2 m tall, and flower in mid summer. The leaves are palmately lobed with 3-7 lobes. *Althaea* species are used as food plants by the larvae of some Lepidoptera species including *Bucculatrix quadrigemina*.

Fig 3. *Althaeae officinalis* [F.E. Köhler , *Medizinal Pflanzen*, 1887]

The genus formerly included a number of additional species now treated in the genus *Alcea* (Hollyhocks). The root contains starch (37%), mucilage (11%), pectin (11%), flavonoids, phenolic acids, sucrose and asparagines.

2. Fats/Lipids

The basic classes of lipids:
a/ Fatty acids
- Saturated
- Unsaturated

b/ Glycerides or glycerolipids
- Monoglycerides
- Diglycerides
- Triglycerides (neutral fats)
- Phosphoglycerides or glycerophospholipides

b/ Nonglycerides
- Sphingolipids
- Sterol lipids (includes cholesterol and steroid hormones)
- Prenol lipids (includes terpenoids)
- Waxes
- Polyketides

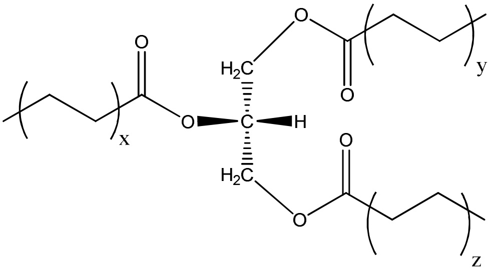


Fig 4. General structure of a triglyceride

Fats consist of a wide group of compounds that are generally soluble in organic solvents and largely insoluble in water. Fats may be either in the solid or the liquid form at normal room temperature, depending on their structure and composition. Although the words "oils", "fats" and "lipids" are all used to refer to fats, "oils" is usually used to refer to fats that are liquids at normal room temperature, while "fats" is usually used to refer to fats that are solids at normal room temperature. "Lipids" is used to refer to both liquid and solid fats.

Fats form a category of lipid, distinguished from other lipids by their chemical structure and physical properties. Fats are solid at room temperature as opposed to oils which are liquid. This category of molecules is important for many forms of life, serving both structural and metabolic functions. They are an important part of the diet of most heterotrophs (including humans)

There are many different kinds of fats, but each kind is a variation on the same chemical structure (Fig 4). All fats consist of fatty acids bonded to a backbone structure, often glycerol. Chemically, this is a triester of glycerol (Fig 5), an ester being the molecule formed from the reaction of an acid and an alcohol. Saturated and unsaturated fats differ in their energy content and melting point. Since an unsaturated fat contains fewer carbon-hydrogen bonds than a saturated fat with the same number of carbon atoms, unsaturated fats will yield slightly less energy during metabolism than saturated fats with the same number of carbon atoms. Saturated fats can stack themselves in a closely packed arrangement, so they can freeze easily and are typically solid at room temperature.

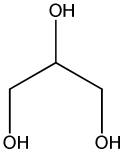


Fig 5. Glycerol

2.1. Palmitic acid

$CH_3(CH_2)_{14}COOH$ or hexadecanoic acid (Fig 6) is one of the most common saturated fatty acids found in animals and plants. Palmitic acid is a major component of the oil from palm trees; butter, cheese, milk and meat contain this fatty acid. Palmitic acid is the first fatty acid produced during lipogenesis (fatty acid synthesis) and from which longer fatty acids can be produced.

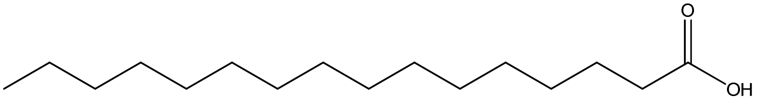


Fig 6. Palmitic acid

2.2. Oleic acid

$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$ – Fig 7 is a mono-unsaturated omega-9 fatty acid found in various animal and vegetable sources. The *trans*-isomer of oleic acid is called elaidic acid. Triglyceride esters of oleic acid comprise the majority of olive oil, though there may be less than 2.0% as actual free acid in the virgin olive oil. It also makes up 15-20% of grape seed oil. Oleic acid may be responsible for the hypotensive (blood pressure reducing) effects of olive oil.

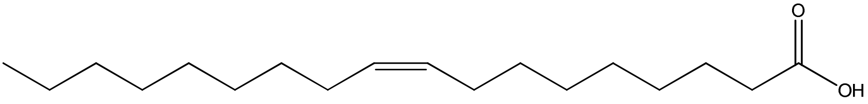


Fig 7. Oleic acid

## 2.3. Stearic acid

$C_{18}H_{36}O_2$ (Fig 8) is a saturated fatty acid it is a waxy solid. Its name comes from the Greek word *stéar* (genitive: *stéatos*), which means tallow. Stearic acid occurs in many animal and vegetable fats and oils. One important source is cocoa. Stearic acid is useful as an ingredient in making candles, plastics, dietary supplements, oil pastels and cosmetics, and for softening rubber. It is used as well to harden soaps, particularly those made with vegetable oil.

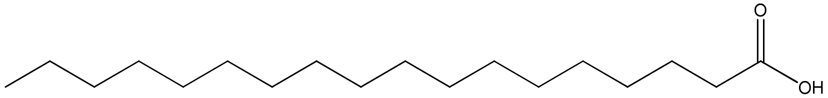


Fig 8. Stearic acid

## 2.4. Linoleic acid

$C_{18}H_{32}O_2$ (Fig 9) is an unsaturated acid. It is a colorless liquid. Linoleic acid (LA) is used in the biosynthesis of arachidonic acid and some prostaglandins. It is found in the lipids of cell membranes. LA is abundant in many vegetable oils, especially safflower and sunflower oils. Linoleic acid is a member of the group of essential fatty acids called omega-6 fatty acids, so called because they are an essential dietary requirement for all mammals.

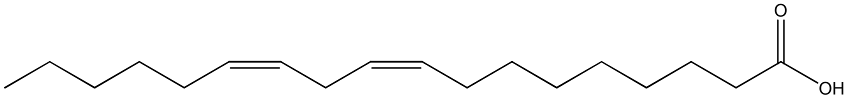


Fig 9. Linoleic acid

## 2.5. Fat-soluble vitamins

Vitamins A, D, E, and K are fat-soluble, meaning they can only be digested, absorbed, and transported in conjunction with fats. Fats are sources of essential fatty acids, an important dietary requirement.

### a/ Vitamin A

Vitamin A is also known as retinol (Fig 10). Good sources of vitamin A include cheese, eggs, oily fish (such as mackerel), milk, fortified margarine and yoghurt.

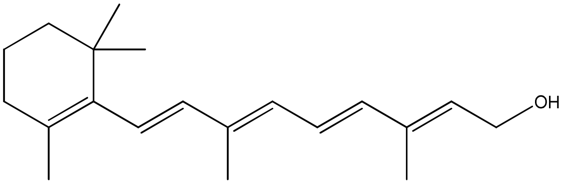


Fig 10. Retinol

b/ Vitamin D

Vitamin D (Calcitriol) plays an important role in the maintenance of organs. Calcitriol is a steroid hormone that has long been known for its important role in regulating body levels of calcium and phosphorus, and in mineralization of bone.

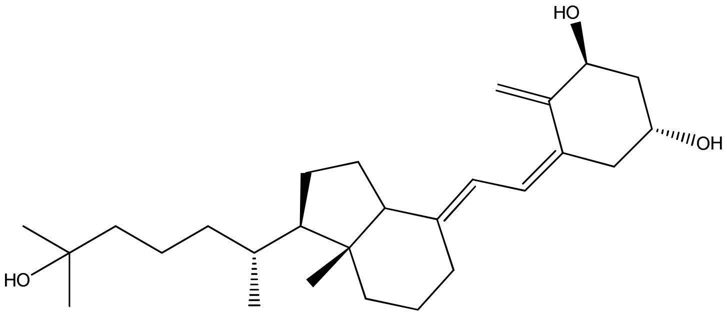


Fig 11. Calcitriol

c/ Vitamin K

Vitamin K is a group of lipophilic, hydrophobic vitamins that are needed for the posttranslational modification of certain proteins, mostly required for blood coagulation but also involved in metabolism pathways in bone and other tissue. They are 2-methyl-1,4-naphthoquinone derivatives.Vitamin K is found in nature in two forms - K1, also called **phylloquinone**, is found in plants and vitamin K2, also called **menaquinone**, which can be synthesized by many bacteria. Vitamin K3, **menadione**, is a synthetic form of this vitamin which is manmade.

- Vitamin K1 (phylloquinone, Fig 12) contains a functional naphthoquinone ring and an aliphatic side chain. Phylloquinone has a phytyl side chain.

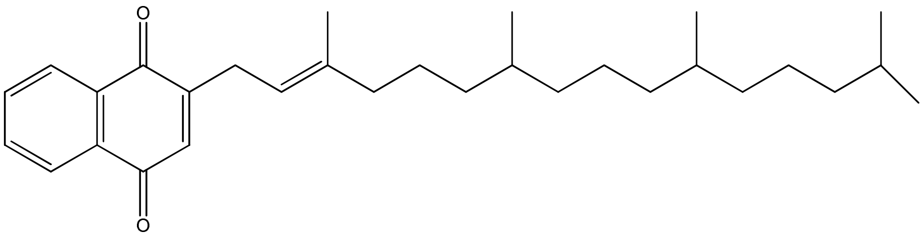


Fig 12. Phylloquinone

- Vitamin K2 (menaquinone) – Fig 13. In menaquinone the side chain is composed of a varying number of isoprenoid residues.

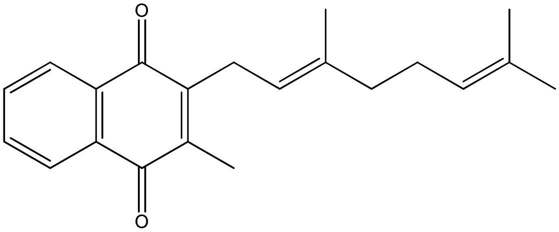


Fig 13. Menaquinone

## 2.6. Waxes

Waxes is a general term used to refer to the mixture of long-chain apolar lipids forming a protective coating (cutin in the cuticle) on plant leaves and fruits but also in animals (wax of honeybee, cuticular lipids of insects), algae, fungi and bacteria. The various materials named waxes do not form a chemically homogeneous group. All waxes are water-resistant materials made up of various substances including hydrocarbons (normal or branched alkanes and alkenes), ketones, diketones, primary and secondary alcohols, aldehydes, sterol esters, alkanoic acids, terpenes (squalene) and monoesters (wax esters), all with long or very long carbon chains (from 12 up to about 38 carbon atoms) and solid in a large range of temperature.

Examples of vegetable waxes:

- Candelilla wax - from the Mexican shrubs *Euphorbia cerifera* and *E. antisyphilitica*
- Carnauba wax - from the leaves of the *Carnauba Palm*
- Castor wax - catalytically hydrogenated castor oil
- Jojoba oil - pressed from the seeds of the jojoba bush, a replacement for spermaceti
- Ouricury wax - from the *Brasilian Feather Palm*
- Rice bran wax - obtained from rice bran.

### a/ Lanoline

Lanolin, also called *Adeps Lanae*, wool wax, wool fat, or wool grease, a greasy yellow substance from wool-bearing animals, acts as a skin ointment, water-proofing wax, and raw material (such as in shoe polish). Lanolin is "wool fat" or grease, chemically akin to wax. It is produced by wool-bearing animals such as sheep, and is secreted by their sebaceous glands. Most or all the lanolin is removed from wool when it is processed into textiles *e.g.* yarn or felt.

Lanolin is chiefly a mixture of cholesterol and the esters of several fatty acids. Crude (non-medical) grades of lanolin also contain wool alcohols, which are an allergen for some people. Lanolin is used commercially in many products ranging from rust-preventative coatings to cosmetics to lubricants.

## 2.7. Function of lipids

- Cell membrane structure
    1. Constitutes a cell barrier
    2. Controls the flow of material in and out of the cell
- Energy storage (for instance, fats stored in adipose tissue)
- Lipid hormones like steroids and eicosanoids - mediate communication between cells
- Signal transduction - function in the transmission of information in cells
- Lipid vitamins - required for metabolism, usually as co-enzymes.

## 5. Anthocyanins

Anthocyanins belong to the flavonoid group of secondary plant constituents. They are responsible for the characteristic dark violet color of berries. The darker a berry, the higher its anthocyanin content. Berries are the best food source of antioxidants also because of their high anthocyanin content. Anthocyanins are particularly effective free radical scavengers because they donate an electron to reactive oxygen species without themselves turning into one. Anthocyanins are much stronger antioxidants than vitamin C. Anthocyanins optimally boost body's immune defenses.

Examples of anthocyanins:

a/ Pelargonidin – one of the most popular anthocyanin, characteristic red colour

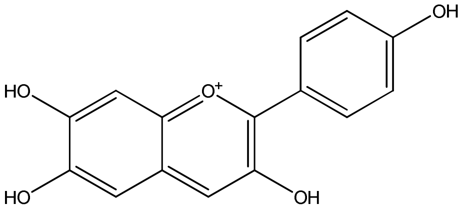


Fig 14. Pelargonidin

b/ Cyanidin – particularly popular as glycoside–cyane complex (dark blue colour).

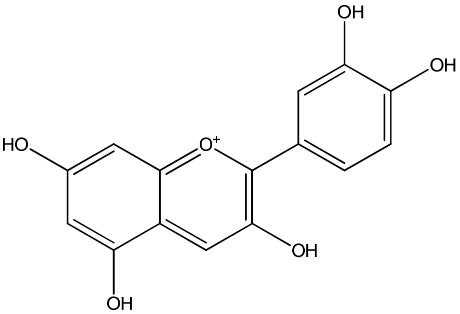


Fig 15. Cyanidin

c/ Delphinidin - present in the family of *Boraginaceae*

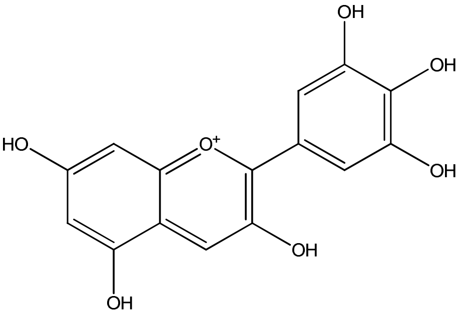
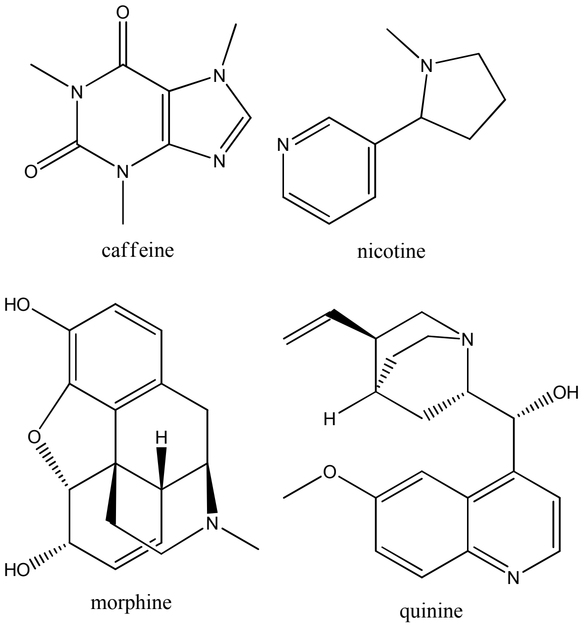


Fig 16. Delphinidin

6. Alkaloids

Alkaloids are naturally occurring chemical compounds containing basic nitrogen atoms. The name derives from the word *alkaline* and was used to describe any nitrogen-containing base. Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants, and animals and are part of the group of natural products (also called secondary metabolites). They often have pharmacological effects and are used as medicines, as recreational drugs, or in entheogenic rituals. Examples are the local anesthetic and stimulant cocaine, the stimulant caffeine, nicotine, the analgesic morphine, or the anti-malarial drug quinine (Fig 17). Some alkaloids have a bitter taste.



caffeine nicotine

morphine quinine

Fig 17. Alkaloids

Alkaloid groups:

- **Pyridine group**: piperine, coniine, trigonelline, arecoline, cytisine, lobeline, nicotine, anabasine, sparteine, .
- **Pyrrolidine group**: hygrine, cuscohygrine, nicotine
- **Tropane group**: atropine, cocaine, ecgonine, scopolamine, catuabine
- **Indozilidine group**: senecionine, swainsonine
- **Quinoline group**: quinine, quinidine, dihydroquinine, dihydroquinidine, strychnine, brucine, veratrine,
- **Isoquinoline group**: opium alkaloids (papaverine, narcotine), pancratistatin, sanguinarine, hydrastine, berberine, emetine, berbamine, oxyacanthine
- **Phenanthrene alkaloids**: opium alkaloids (morphine, codeine, thebaine, oripavine)
- **Phenethylamine group**: mescaline, ephedrine, dopamine
- **Indole group**:

a/ Tryptamines: serotonin, DMT, 5-MeO-DMT, bufotenine, psilocybin
b/ Ergolines (the ergot alkaloids): ergine, ergotamine, lysergic acid
c/ Beta-carbolines: harmine, harmaline, tetrahydroharmine
d/ Yohimbans: reserpine, yohimbine
e/ Vinca alkaloids: vinblastine, vincristine
f/ Kratom (*Mitragyna speciosa*) alkaloids: mitragynine, 7-hydroxymitragynine
g/ *Tabernanthe iboga* alkaloids: ibogaine, voacangine,
h/ *Strychnos nux-vomica* alkaloids: strychnine, brucine

- **Terpenoid group**:

a/ *Aconitum* alkaloids: aconitine

b/ Steroid alkaloids (containing a steroid skeleton in a nitrogen containing structure):

*Solanum* (*e.g.* potato and tomato) alkaloids (solanine, chaconine)

*Veratrum* alkaloids (cyclopamine, jervine)

Fire Salamander alkaloids (samandarin)

- **Others**

4.1. Pyridine alkaloids

a/ Nicotine

Nicotine (Fig 18) is an alkaloid found in the nightshade family of plants (*Solanaceae*), predominantly in tobacco, and in lower quantities in tomato, potato, eggplant (aubergine), and green pepper.

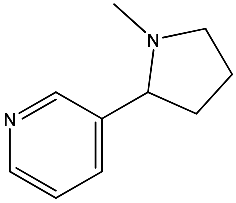
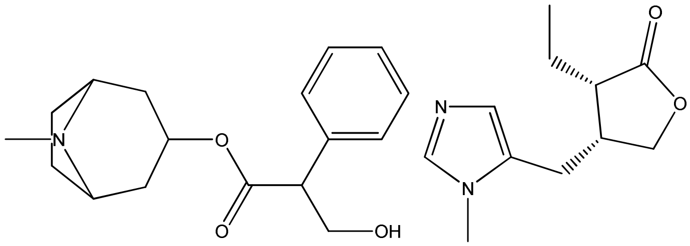


Fig 18. Nicotine

4.2. Tropane alkaloids

Belladonna is one of the most toxic plants found in the Western hemisphere. All parts of the plant contain tropane alkaloids. Symptoms of belladonna poisoning are the same as those for atropine (the most well known of the tropane alkaloids, Fig 19), and include dilated pupils, tachycardia, hallucinations, blurred vision, loss of balance, a feeling of flight, staggering, a sense of suffocation, paleness followed by a red rash, flushing, husky voice, extremely dry throat, constipation, urinary retention, and confusion. The skin can completely dry out and slough off. Fatal cases have a rapid pulse that turns feeble. The antidote is physostigmine or pilocarpine, the same as for atropine.



atropine pilocarpine

Fig 19. Tropane alkaloids

a/ Atropine - *Atropa belladonna* (Fig 20) in modern medicine:

- The plant is an important source of atropine, which is an effective antidote to the effects of poisoning by cholinesterase inhibitors such as Parathion and Malathion.
- Atropine will also reverse the effects of poisoning by nerve agents designed for chemical warfare. In Europe, the plant is specifically cultivated for this purpose
- Optometrists and ophthalmologists use atropine for pupil dilation in eye examinations, though the dose used is extremely small
- It can be used in homeopathic remedies as a treatment for pinkeye.

Fig 20. *Atropa belladonna* [From Jackson: *Experimental Pharmacology and Materia Medica*, plate XVII, 1940]

b/ Cocaine

Cocaine (Fig 21) is a crystalline tropane alkaloid, that is obtained from the leaves of the coca plant (*Erythroxylum coca*). It is a stimulant of the central nervous system. Cocaine was found in **very small amounts** in the original *Coca-Cola* formula.

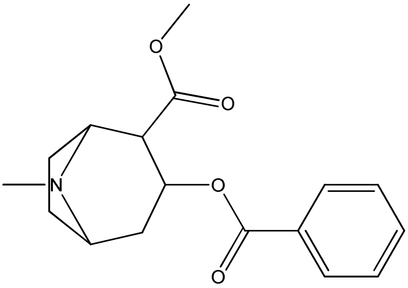


Fig 21. Cocaine

4.3. Quinoline alkaloids

a/ Quinnie

Quinine (Fig 22) is a natural white crystalline alkaloid having antipyretic (fever-reducing), anti-smallpox, analgesic (painkilling), and anti-inflammatory properties and a bitter taste, isolated from *Cinchona succirubra*. Quinine is one of 31 alkaloids with related structures, and the principal anti-malarial compound, in the plant.

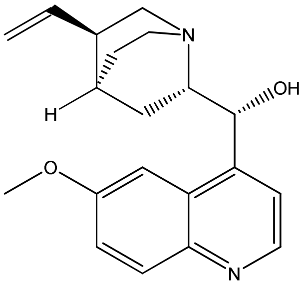


Fig 22. Quinnie

### 4.4. Isoquinoline alkaloids

a/ Narcotine

Narcotine (Fig 23) alkaloid found in opium, and extracted as a white crystalline substance, tasteless and less poisonous than morphine.

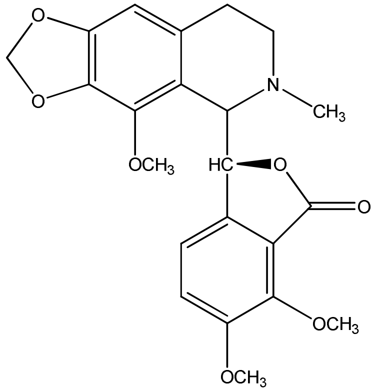


Fig 23. Narcotine

### 4.1. Phenanthrene alkaloids

a/ Morphine

The morphine alkaloids, derived from the opium poppy, *Papaver somniferum*, are powerful pain relievers and narcotics. Morphine (Fig 24) is the principal alkaloid and was first isolated between 1803 and 1806. Other derivatives of morphine have been developed as opiate antagonists or as animal tranquilizers.

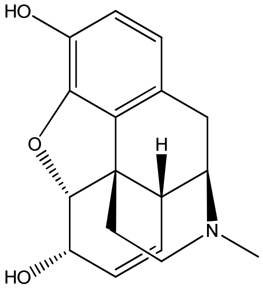


Fig 24. Morphine

## 4.2. Phenethylamine alkaloids

### a/ Mescaline

Mescaline (Fig 25) is a psychedelic alkaloid of the phenethylamine class. It is mainly used as a recreational drug, an entheogen, and a tool used to supplement various types of practices for transcendence, including in meditation, psychonautics, and psychedelic psychotherapy whether self administered or not.

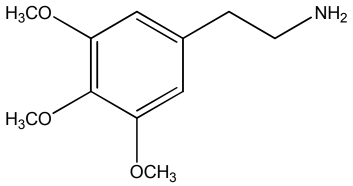


Fig 25. Mescaline

## 4.3. Indole alkaloids

### 4.3.1. Tryptamines

### a/ Psilocybin

Psilocybin (also known as psilocybine, Fig 26) is a psychedelic alkaloid of the tryptamine family, found in psilocybin mushrooms.

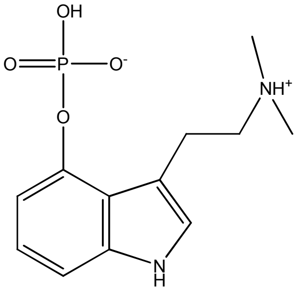


Fig 26. Psilocybin

### 4.3.2. Ergolines

### a/ Ergotamine

Ergotamine (Fig 27) is an ergopeptine and part of the ergot family of alkaloids; it is structurally and biochemically closely related to ergoline.

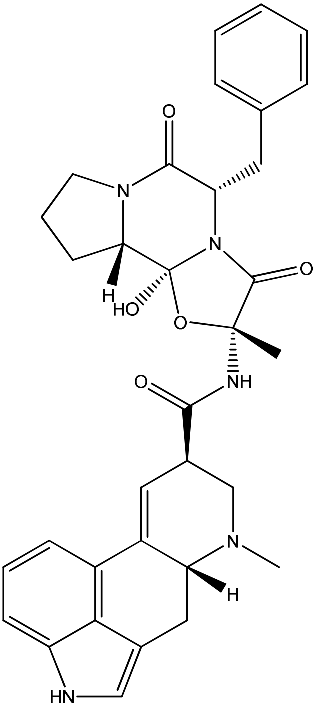


Fig 27. Ergotamine

b/ Lysergic acid

The most famous of these alkaloids is lysergic acid diethylamide, LSD (Fig 28) a powerful hallucinogen that is a synthetic derivative of the natural products. Similar alkaloids, particularly ergine, are also found in Mexican morning glories, such as *Ipomeoa tricolor.*

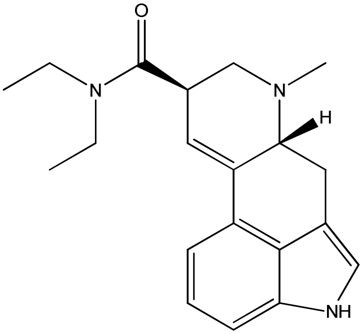


Fig 28. LSD

### 4.3.3. Vinca alkaloids

#### a/ Vincristine

Vincristine (Fig 29) one of the most potent anti-leukemic drugs today in use. It was isolated in a search for diabetes treatments from *Vinca rosea* (now *Catharanthus roseus*) in the 1950's along with vinblastine, a homologue in which the *N*-methyl group is oxidized to an aldehyde moiety.

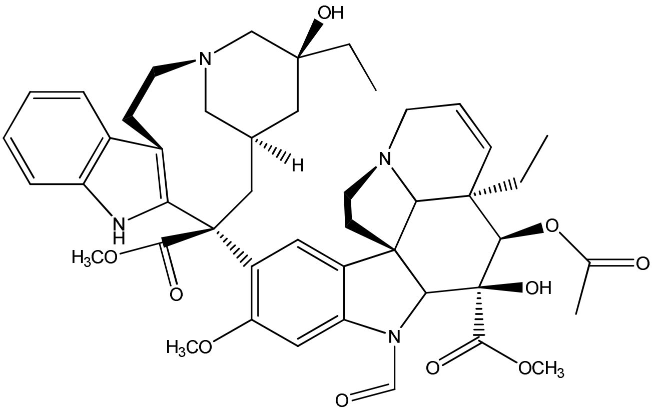


Fig 29. Vincristine

Table 2. Terminology (III)

| *English* | *Polish* |
|---|---|
| anti-leukemic | przeciwbiałaczkowy |
| cutin | kutyna |
| entheogen | psychoaktywna substancja |
| ergine | alkaloid ergina |
| hypotensive | obniżający ciśnienie |
| ingredient | składnik |
| mackerel | makrela |
| mucilage | śluzy |
| perennial | wieloletni |
| rice bran | otręby ryżowe |
| starch | skrobia |
| sucrose | sacharoza |
| tallow | tłuszcz, łój |
| tranquilizer | środek uspokojający |
| wax | wosk |
| yarn | włókno |

## IV. MAIN BIOGENETIC GROUPS

1. C1: The simplest of the building blocks is composed of a single carbon atom, usually in the form of a methyl group, and most frequently it is attached to oxygen or nitrogen, but occasionally to carbon. It is derived from the *S* – methyl of L-methionine.

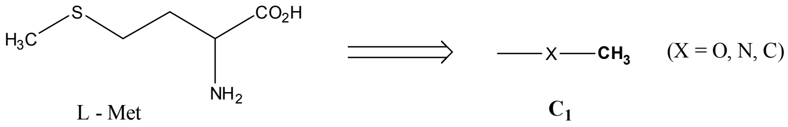


Fig 30. C1 building block

2. C2: A two-carbon unit may be supplied by acetyl-CoA. This could be a simple acetyl group, as in an ester, but more frequently it forms part of a long alkyl chain (as in a fatty acid) or may be part of an aromatic system (*e.g.* phenols). Of particular relevance is that in the latter examples, acetyl-CoA is first converted into the more reactive malonyl-CoA before its incorporation.

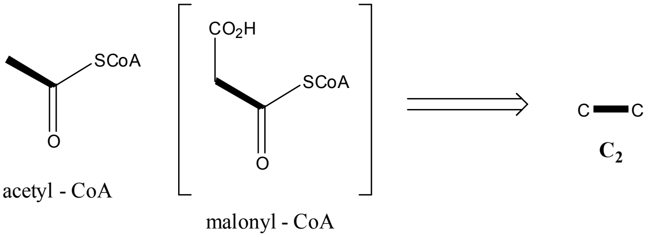


Fig 31. C2 building block

3. C5: The branched-chain C5 ‘isoprene’ unit is a feature of compounds formed from mevalonate or deoxyxylulose phosphate. Mevalonate itself is the product formed from three acetyl-CoA molecules, but only five of mevalonate’s six carbons are used, the carboxyl group being lost. The alternative precursor deoxyxylulose phosphate, a straight-chain sugar derivative, undergoes a skeletal rearrangement to form the branched chain.

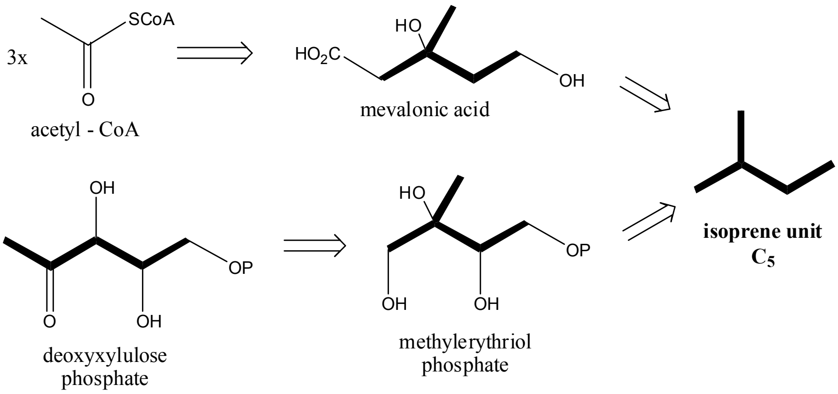


Fig 32. C5 building block

4. C6C3: This refers to a phenylpropyl unit and is obtained from the carbon skeleton of either L-phenylalanine or L-tyrosine, two of the shikimate-derived aromatic amino acids. This, of course, requires loss of the amino group. The C3 side-chain may be saturated or unsaturated, and may be oxygenated. Sometimes the side chain is cleaved, removing one or two carbons. Thus, C6C2 and C6C1 units represent modified shortened forms of the C6C3 system.

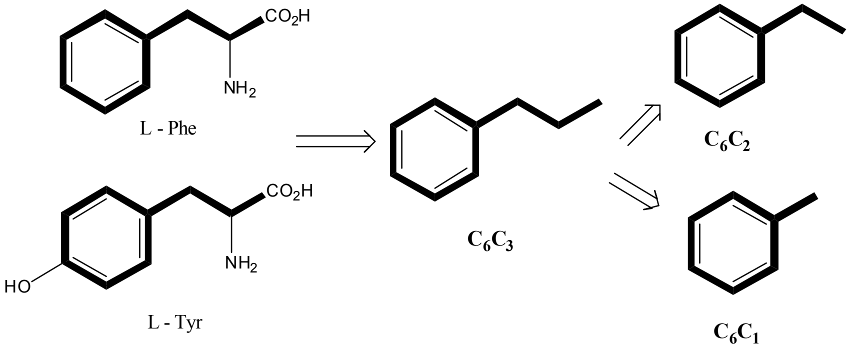


Fig 33. C6C3 building block

5. C6C2N: Again, this building block is formed from either L-phenylalanine or L-tyrosine, L-tyrosine being by far the more common. In the elaboration of this unit, the carboxyl carbon of the amino acid is removed.

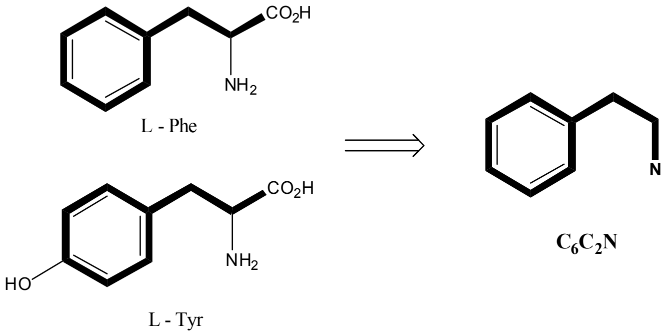


Fig 34. C6C2N building block

6. Indole.C2N: The third of the aromatic amino acids is L-tryptophan. This indole-containing system can undergo decarboxylation in a similar way to L-phenylalanine and L-tyrosine, so providing the remainder of the skeleton as an indole, C2N unit.

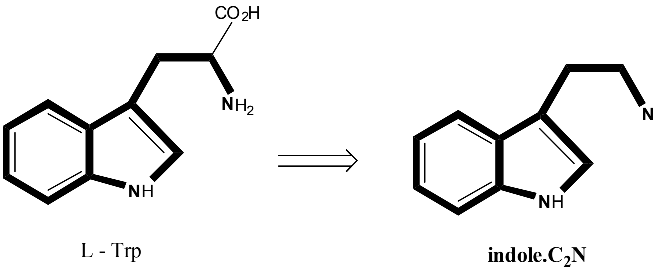


Fig 35. Indole.C2N building block

7. C4N: The C4N unit is usually found as a heterocyclic pyrrolidine system and is produced from the non-protein amino acid L-ornithine. In marked contrast to the C6C2N and indole.C2N units described above, ornithine supplies not its α-amino nitrogen, but the δ-amino nitrogen. The carboxylic acid function and the α-amino nitrogen are both lost.

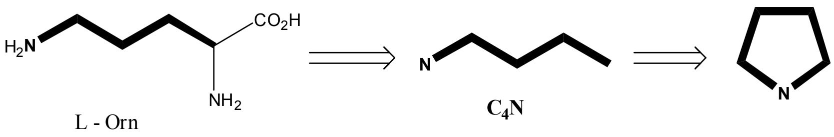


Fig 36. C4N building block

Table 3. Terminology (IV)

| *English* | *Polish* |
|---|---|
| fatty acid | kwas tłuszczowy |
| rearrangement | przegrupowanie |

# V. BIOGENETIC PATHWAYS

## 1. Biogenetic pathway of acetate

The active acetyl-CoA (Fig 37) is the precursor of fatty acids (saturated and unsaturated), esters (lipids and similar compounds), polyacetylenes, triphenols, poliketoacids, lichen acids, bitter acids, derivatives of pyridine, alkaloids, antibiotics.

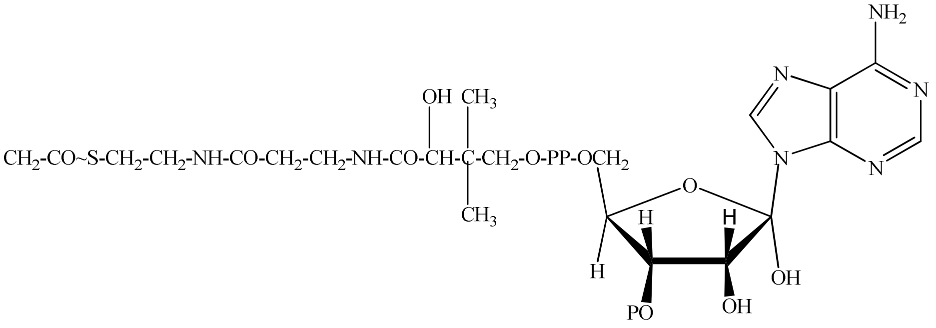


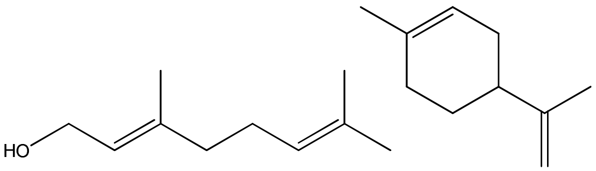
Fig 37. Acetyl-CoA

## 2. Biogenetic pathway of isoprenoids

Active isoprene, isopren unit (isopenthylphosphate, IPP), is achieved more often from acetyl–CoA.

Biogenetic groups of isoprenoids:

- Monoterpenes (Fig 38)



geraniol limonen

Fig 38. Monoterpenes (acyclic – geraniol, monocyclic – limonen)

- Sesquiterpenes (Fig 39)

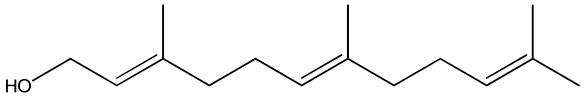


Fig 39. Farnesol

- Di-, tri-, tetra- and polyterpenes (Fig 40)

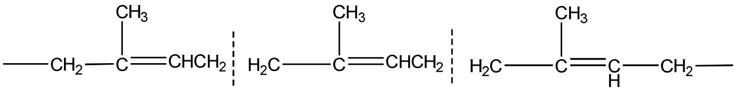


Fig 40. Rubber

- Steroids, and other terpenoids for example: terpenoid alkaloids.

3. Biogenetic derivatives of shikimic acid

Shikimic acid (Fig 41) is produced from a combination of phosphoenolpyruvate, a glycolytic pathway intermediate, and erythrose 4-phosphate from the pentose phosphate pathway. The reactions of the pentose phosphate cycle may be employed for the degradation of glucose, but they also feature in the synthesis of sugars by photosynthesis. The shikimate pathway leads to a variety of phenols, cinnamic acid derivatives, lignans, coumarins, and alkaloids.

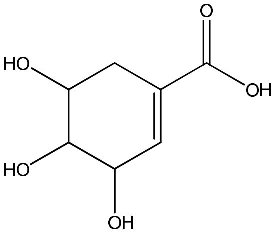


Fig 41. Shikimic acid

4. Biogenetic derivatives of amino acids

Peptides, proteins, alkaloids, and many antibiotics are derived from amino acids. Intermediates from the glycolytic pathway and the Krebs cycle are used in constructing many of them, but the aromatic amino acids phenylalanine, tyrosine, and tryptophan are themselves products from the shikimate pathway. Ornithine (Fig 42), a non-protein amino acid, along with its homologue lysine, are important alkaloid precursors having their origins in Krebs cycle intermediates.

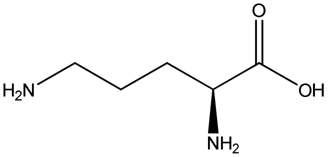


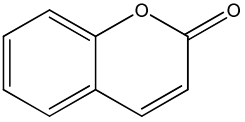
Fig 42. Ornithine

Table 4. Terminology (V)

| *English* | *Polish* |
|---|---|
| intermediate | półprodukt |
| lichen | porost |
| psoriasis | łuszczyca |

## VI. COUMARINS

Coumarins owe their class name to *coumarou*, the vernacular name of the tonka bean – *Dipteryx odorata* of the *Fabaceae* family. Coumarins, which are also C6-C3 derivatives, belong to a group of compounds known as the benzo-α-pyrone (Fig 43).



benzo-2-pyrone

Fig 43. Coumarin (benzo-2-pyrone)

This group of phenolic compounds can be found free in nature or in combined form with sugars as heterosides and glycosides in many dicotyledonous families, including the *Asteraceae*, *Rosaceae*, *Rubiaceae* and *Solanaceae*. Although mainly synthesised in the leaves, coumarins occur in high levels in fruits, roots and stems.

1. Coumarins groups

a/**Hydroxycoumarins**, the most common ones being umbelliferone, (a)esculetin (Fig 44) and scopoletin.

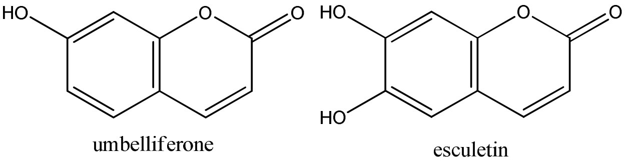


Fig 44. Hydroxycoumarins

b/**Furocoumarins** and members of this group consist of a 5-membered furan ring attached to the coumarin core (Fig 45).

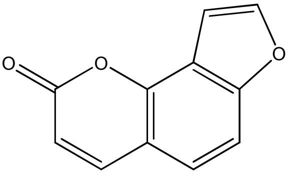


Fig 45. Furocoumarin - angelicin

c/**Pyrocoumarins** are analogous to **furocoumarins**, but contain a six-membered pyran ring (Fig 46).

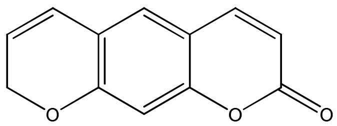


Fig 46. Pyrocoumarins – xanthyletin

Coumarins act as vasculoprotectors, coronary vasodilators and umbelliferone for example shows antibacterial activities against *Brucella*. Some furano-coumarins are used in the treatment against psoriasis.

Important sources of coumarins are: *Citrus bergamia, Dipteryx odorata* and members of the *Umbelliferae* family. Umbelliferone, (a)esculetin and scopoletin are the most widespread coumarins in nature.

## 2. Biosynthesis of coumarins

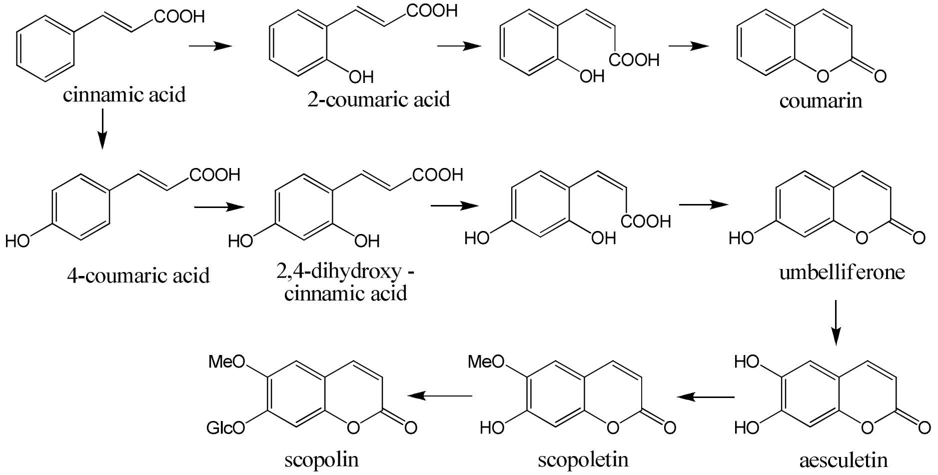


Fig 47. Biosynthesis of coumarins

## 3. Furocoumarins

The most important types of furocoumarines can be regarded as derivatives of psoralen or angelicin (isomer of psoralen), Fig 48. Some important psoralen derivatives are imperatorin, xanthotoxin, bergapten and nodakenetin.

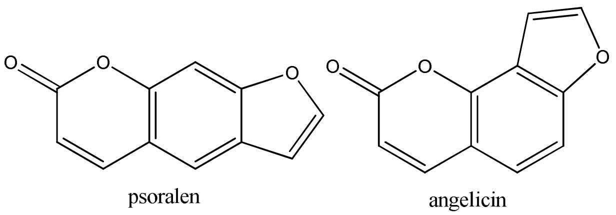


Fig 48. Furocoumarins

### 3.1. Psoralen

It is **structurally related to coumarin** by the addition of a fused furan ring, and may be considered as a derivative of umbelliferone.

## 4. Pyranocumarins

These compounds have pyran ring condensed in C-6, C-7 position – type of xanthyletin, or C-7, C-8 – type of seselin (Fig 49).

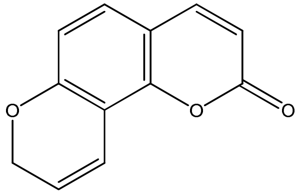


Fig 49. Seselin

### 4.1. Dicoumarol

Dicoumarol (INN) – Fig 50 or dicumarol (USAN) is an anticoagulant that functions as a Vitamin K antagonist (similar to warfarin). It is also used in biochemical experiments as an inhibitor of reductases. Dicoumarol interferes with the body's ability to produce Vitamin K. Vitamin K is essential to blood clotting. Thus, dicoumarol acts as an anticoagulant.

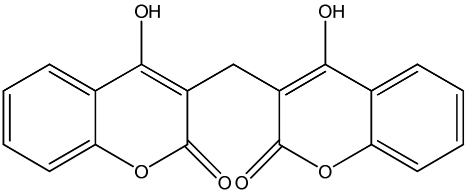


Fig 50. Dicoumarol

## 4.2. Biosynthesis of dicoumarol

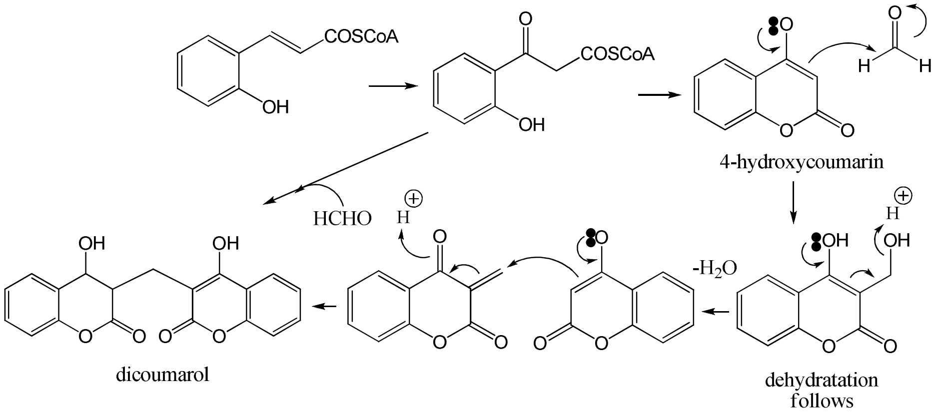


Fig 51. Biosynthesis of dicoumarol

## VII. QUINONES

Quinone is a class of organic compounds which are not aromatic, and are characterized by fully conjugated cyclic **dione** structure (quinones are conjugated but not aromatic!). This type of structures possesses the ketone-like carbonyl groups. The prototypical member of the class are 1,4-benzoquinone or cyclohexadienedione, often called simply **quinone** (whence the name of the class). Other important examples are 1,2-benzoquinone (***ortho*-quinone**) – Fig 52, 1,4-naphthoquinone and 9,10-anthraquinone.

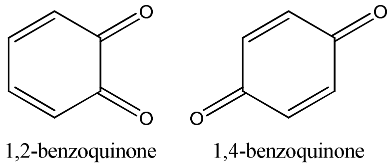


Fig 52. Structure of quinones

*para*-Benzoquinone is the oxidized form of hydroquinone, whereas *ortho*-benzoquinone is the oxidized form of catechol (1,2-dihydroxybenzene), Fig 53.

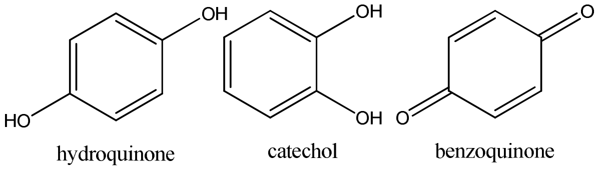


Fig 53. Quinones

Many of quinones play an important biochemical role as electron transport systems in respiration process or photosynthesis. Derivatives of quinones are common constituents of biologically relevant molecules (*i.e.* Vitamin K1).

### 1. Ubiquinones

Ubiquinones (*i.e.* coenzyme Q) - Fig 54, are found in almost all organisms and function as electron carriers for the electron transport chain in mitochondria. The length of the terpenoid chain is varied (n=1−12) and depends on species, but most organisms synthesize a terpenoid chain n=7−10 long. The human redox carrier is **coenzyme Q10**. Ubiquinones are derived from 4-hydroxybenzoic acid.

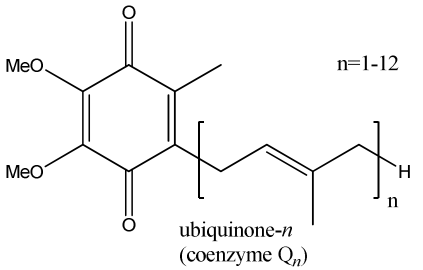


Fig 54. Ubiquinones

Coenzyme Q10

Coenzyme Q10 (Fig 55, also known as **ubiquinone**, **ubidecarenone**, **coenzyme Q**, and abbreviated at times to **CoQ10** – pronounced *ko-cue-ten* –, **CoQ**, **Q10**, or simply **Q**) is a 1,4-benzoquinone, where Q refers to the quinone chemical group, and 10 refers to the isoprenyl chemical subunits.

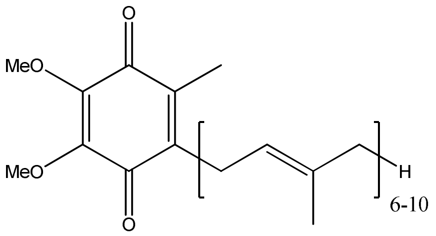


Fig 55. Coenzyme Q10

Chorismic acid

Chorismic acid (Fig 56), more commonly known as its anionic form chorismate, is an important biochemical intermediate in plants and microorganisms.
It is a precursor of:

- aromatic amino acids phenylalanine and tyrosine
- indole, indole derivatives and tryptophan
- 2,3-dihydroxybenzoic acid (DHB) used for enterobactin biosynthesis
- plant hormone - salicylic acid
- many alkaloids and other aromatic metabolites.

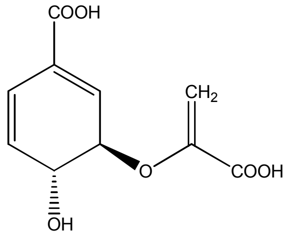


Fig 56. Chorismic acid

2. Vitamin $B_{12}$ (cobalamin)

Vitamin $B_{12}$ is the only known biomolecule with a stable carbon-metal bond - it is an organometallic compound. It contains the biochemically rare element cobalt in its core (Fig 57).

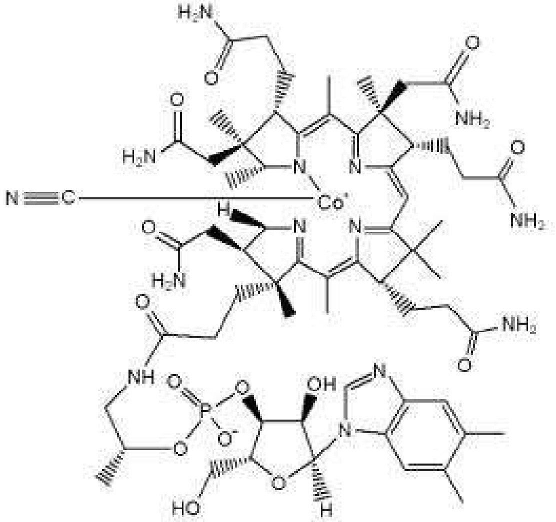


Fig 57. Cobalamin

3. Porphyrins

Porphyrins (Fig 58) are a group of organic compounds of which many occur in nature. One of the best-known porphyrins is heme, the pigment in red blood cells. Heme is a cofactor of the protein hemoglobin. They are heterocyclic macrocycles composed of four modified pyrrole subunits interconnected at their α carbon atoms *via* methine bridges (=CH-). Porphyrins are aromatic.

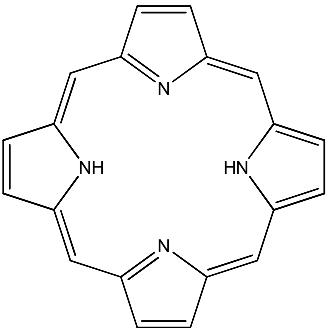


Fig 58. Porphyrin

4. Phthalocyanines

Phthalocyanine (Fig 59) is a macrocyclic compound having an alternating nitrogen atom-carbon atom ring structure, widely used in dyeing.

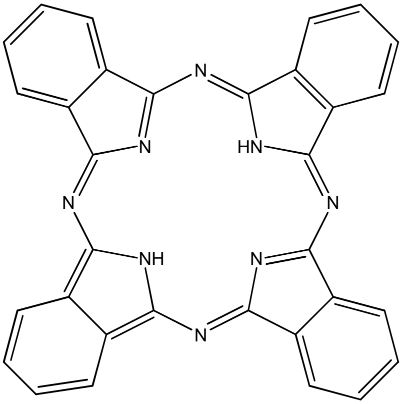


Fig 59. Phthalocyanine

5. Plastoquinones

Plastoquinones bear considerable structural similarity to ubiquinones, but they are not derived from 4-hydroxybenzoic acid. Instead, they are produced from homogentisic acid, a phenylacetic acid derivative formed from 4-hydroxyphenylpyruvic acid by a complex reaction involving decarboxylation, $O_2$-dependent hydroxylation, and subsequent migration of the $-CH_2CO_2H$ sidechain to the adjacent position on the aromatic ring.

Plastoquinone, (often abbreviated **PQ**), - Fig 60 is a quinone molecule involved in the electron transport chain in the light-dependent reactions of photosynthesis.

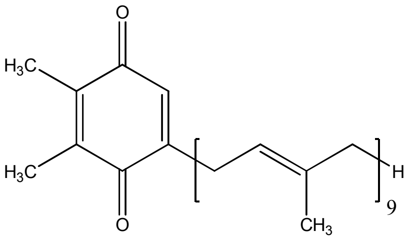


Fig 60. Plastoquinone (PQ)

## 6. Tocopherols

Tocopherols are also frequently found in the chloroplasts and are members of the vitamin E(x) group. Their biosynthesis shares many of the features of plastoquinone biosynthesis, with an additional cyclization reaction involving the *p*-quinol and the terpenoid side-chain to give a chroman ring. Thus, the tocopherols, *e.g.* α-tocopherol (Fig 61) and γ-tocopherol, are not in fact quinones, but are indeed structurally related to plastoquinones. The added isoprenoid side-chain, from phytyl diphosphate, contains only four isoprene units, and three of the expected double bonds have suffered reduction.

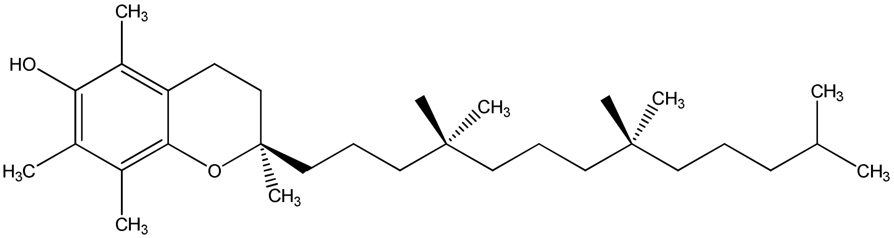


Fig 61. α-Tocopherol

## 7. Antraquinones

The anthraquinones occur widely in plants but in only a few animals. These brilliantly coloured compounds have found wide application as dyes and as chemical indicators of acidity or alkalinity.

### Alizarin

Alizarin (Fig 62) is the main colorant found in the madder plant *Rubia tinctorum* (Fig 63). Alizarin is a unique pigment in that it is a lake. This term is a bit confusing for those unfamiliar with painting terminology. A lake is a pigment made by precipitation of a soluble dye with a metallic salt or acid complex with a base.

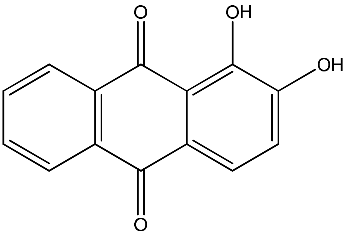


Fig 62. Alizarin

Fig 63. *Rubia tinctorum* [F.E. Köhler , *Medizinal Pflanzen*, 1887]

## VIII. FLAVONOIDS

The flavonoids are polyphenolic compounds possessing 15 carbon atoms; two benzene rings joined by a linear three carbon chain. The skeleton can be represented as the C6 - C3 - C6 system. Flavonoids constitute one of the most characteristic classes of compounds in higher plants. Many flavonoids are easily recognized as flower pigments in most angiosperm families (flowering plants). However, their occurrence is not restricted to flowers and they can appear in all parts of the plant.

The term flavonoid refers to a class of plant secondary metabolites based around a phenylbenzopyrone structure (Fig 64). Flavonoids are most commonly known for their antioxidant activity.

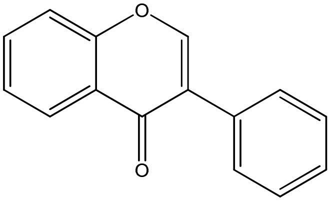


Fig 64. Phenylbenzopyrone

Flavonoids are also commonly referred to as **bioflavonoids** in the media – these terms are equivalent and interchangeable, since all flavonoids are biological in origin.

The term flavonoid (or bioflavonoid) refers to a class of plant secondary metabolites. According to the IUPAC nomenclature, they can be classified into:

*a*/ ***flavonoids***, derived from 2-phenylchromen-4-one (2-phenyl-1,4-benzopyrone) structure

b/ ***isoflavonoids***, derived from 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone) structure

c/ ***neoflavonoids***, derived from 4-phenylcoumarine (4-phenyl-1,2-benzopyrone) structure.

There are five subclasses of flavonoids:

- **FLAVONOLS**: Quercetin, Kaempferol, Myricetin, Isorhamnetin
- **FLAVONES**: Luteolin, Apigenin
- **FLAVANONES**: Hesperetin, Naringenin, Eriodictyol
- **FLAVAN-3-OLS**: (+)-Catechin, (+)-Gallocatechin, (-)-Epicatechin, (-)-Epigallocatechin, (-)-Epicatechin 3-gallate, (-)-Epigallocatechin 3-gallate, Theaflavin, Theaflavin 3-gallate, Theaflavin 3'-gallate, Theaflavin 3,3' digallate, Thearubigins

- **ANTHOCYANIDINS**: Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin

1. Flavonols

Flavonols are polyphenolic secondary plant metabolites that are present in varying levels in commonly consumed fruits, vegetables and beverages. Flavonols that have the 2-phenylbenzopyrone backbone with a hydroxyl group at the 3 position (Fig 65). Examples: Quercetin, Kaempferol, Myricetin, Isorhamnetin, Pachypodol, Rhamnazin.

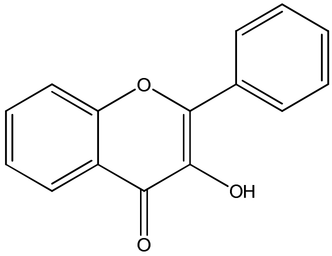


Fig 65. Flavonol

Good sources of flavonols in the diet are onion, kale, broccoli, lettuce, tomato, apple, grape, berries, tea, red wine. The greener the leaf is, the more it contains flavonols.

Quercetin

Quercetin (Fig 66) is a flavonoid that forms the "backbone" for many other flavonoids, like rutin. In studies, quercetin is found to be the most active of the flavonoids, and many medicinal plants owe much of their activity to their high quercetin content. Quercetin has demonstrated significant anti-inflammatory activity because of direct inhibition of several initial processes of inflammation. In addition, it exerts potent antioxidant activity and vitamin C-sparing action.

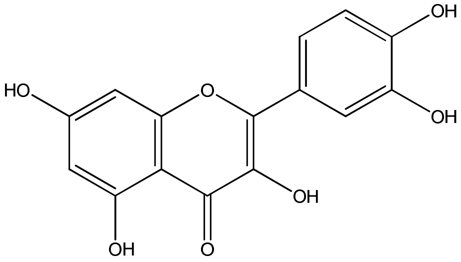


Fig 66. Quercetin

## 2. Flavones

Flavones (Fig 67) are a class of flavonoids based on the backbone of 2-phenylchromen-4-one skeleton. Flavones are mainly found in cereals and herbs. Examples: Luteolin, Apigenin, Tangeritin.

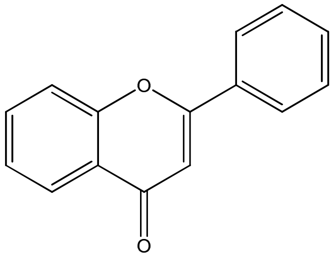


Fig 67. Flavone

### 2.1. Apigenin

Apigenin (Fig 68) is a flavone (citrus bioflavonoid) that is the aglycone of several glycosides. It is a yellow crystalline solid that has been used to dye wool. Apigenin is found in high amounts also in several herbs including parsley, thyme, and peppermint. Apigenin is a potent inhibitor of CYP2C9, an enzyme responsible for the metabolism of many pharmaceutical drugs in the body.

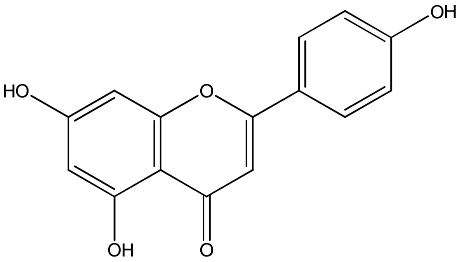


Fig 68. Apigenin

## 3. Flavanones

Flavanones are a type of flavonoids, the dominant flavonoid class in the genus citrus. A flavanone structure is obtained (Fig 69) by taking away the double bond between carbons 2 and 3 of the flavone. Notice the "o" has changed back to an "a," which indicates that the **flavanones** have a single bond between carbons 2 and 3, like the basic flavan nucleus. The heterocyclic ring of flavanones is easily opened and that is why flavanones converse into chalcones. Examples: Hesperetin, Naringenin, Eriodictyol.

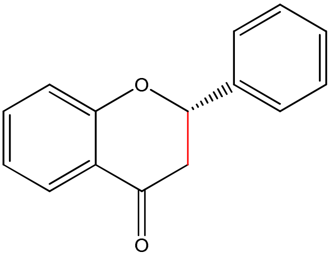


Fig 69. Flavanone

3.1. Naringenin

Naringenin – Fig 70 (not to be confused with naringin) is a flavanone that is considered to have a bioactive effect on human health as antioxidant, free radical scavenger anti-inflammatory, carbohydrate metabolism promoter, and immune system modulator. Source of naringenin - grapefruit, oranges, and tomato (skin).

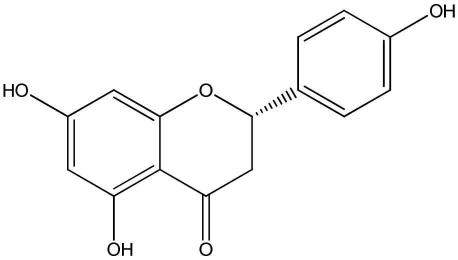


Fig 70. Naringenin

3.2. Chalcones

Chalcone – Fig 71 (and related compounds chalconoids) is an aromatic ketone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones. They show antibacterial, antifungal, antitumor and anti-inflammatory properties. Some chalcones demonstrated the ability to block voltage-dependent potassium channels.

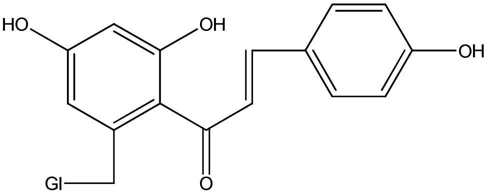


Fig 71. Isosalipurpuroside

## 4. Flavan-3-ols

Flavan-3-ols (referred to as **flavanols**, Fig 72) are a class of flavonoids that use the 2-phenyl-3,4-dihydro-2H-chromen-3-ol skeleton. These compounds include the *catechins* and the catechin gallates. Flavanols possess two chiral carbons. Examples: (+)-Catechin, (-)-Epicatechin.

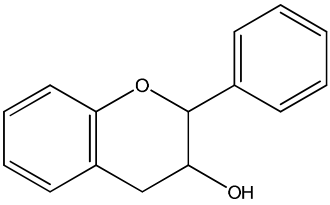
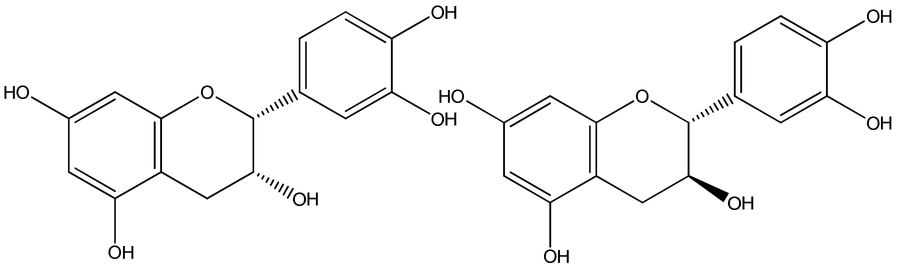


Fig 72. Flavan-3-ol

### 4.1. Catechins

Catechin (Fig 73) is a polyphenolic antioxidant. The term *catechins* is also commonly used to refer to the related family of flavonoids and the subgroup flavan-3-ols (flavanols). Catechins appear predominantly in green tea, in smaller amounts in black tea, grapes, wine, and chocolate.



(-)-epicatechin

(+)-catechin

Fig 73. Catechins

## 5. Anthocyanidins

Anthocyanidins are very similar to the flavans. One difference is that the oxygen atom has a positive charge on it (Fig 74, flavylium cation); there are also two double bonds in the C ring. They are common plant pigments. There are many different kinds of anthocyanidins and anthocyanins, varying in the number and position of -OH groups, sugar groups, and other functional groups attached. Some are quite complicated, with parts of other flavonoid molecules attached to them. This class of flavonoids contains the pigments that give certain fruits, vegetables and herbs their dark red, blue, and purple colors. Many of them are antioxidants. Examples: Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin

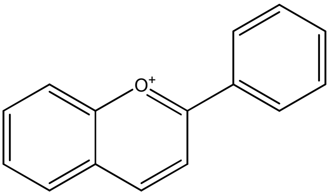
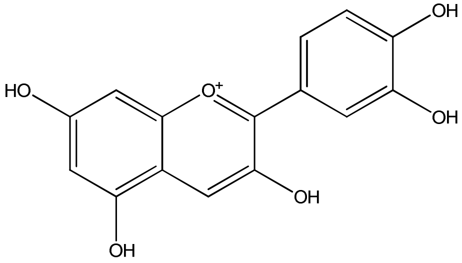


Fig 74. Flavylium cation



cyanidin

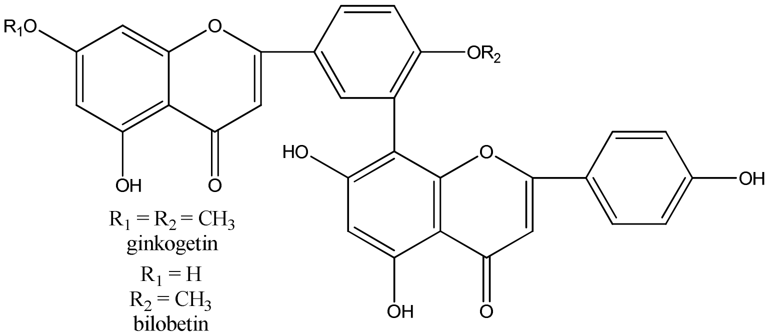
Fig 75. Anthocyanidins

6. Biflavonoids

Biflavonoids are flavonoid dimers connected with a C–C or C–O–C bond. Biflavonoids were isolated from *Ginkgo biloba L. and Cephalotaxus harringtonia.* Biflavonoids are a series of naturally occurring with a variety of biological activities.

There are two types of dimmeric flavon connections:

- Arylic type is the ginkogetin connection of two flavonoids by two aromatic carbons, Fig 76



$R_1 = R_2 = CH_3$
ginkogetin
$R_1 = H$
$R_2 = CH_3$
bilobetin

Fig 76. Biflavonoids

- Arylether type is the connection of two flavonoids by means of an oxygen.

7. Glycoside of flavonoids

Rutin

The flavonoid rutin (Fig 77) is a flavonol glycoside comprised of the flavonol quercetin and the disaccharide rutinose. Rutin is found in many plants, especially the buckwheat plant *Fagopyrum esculentum* Moench, the flour of which is used to make pancakes. Other rich dietary sources of rutin include black tea and apple peels. Rutin may have antioxidant, anti-inflammatory, anti-carcinogenic, cytoprotective and vasoprotective activities.

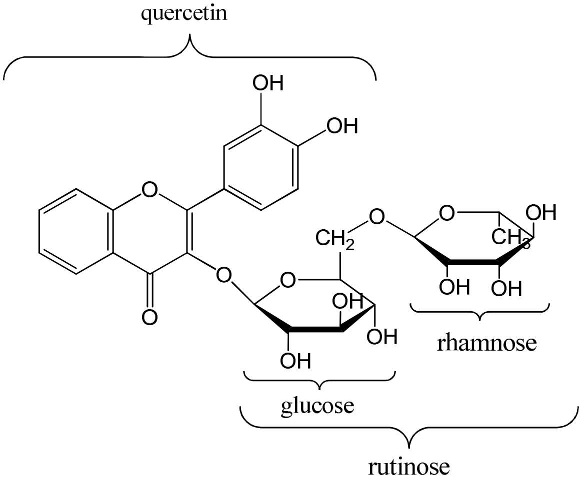
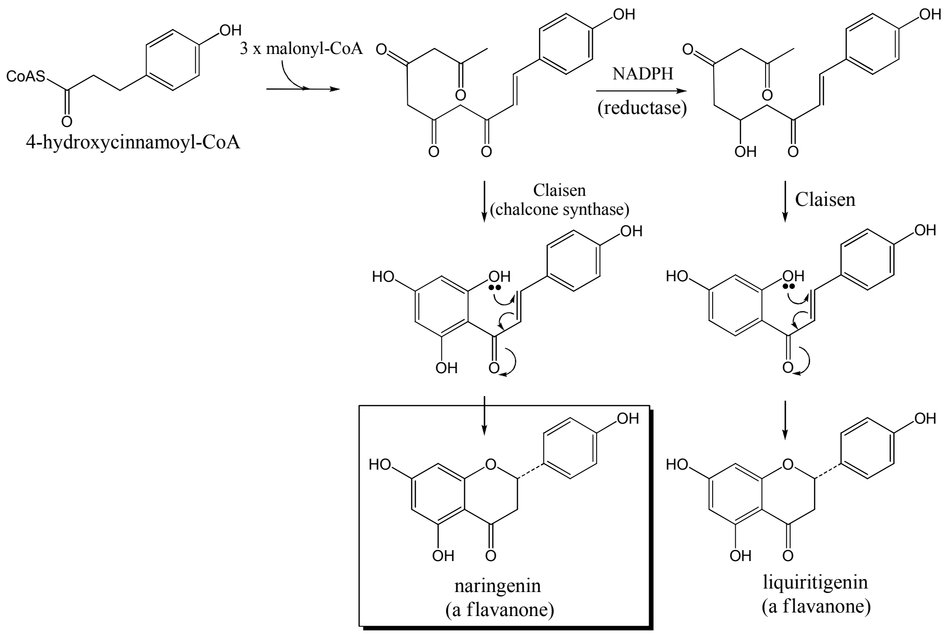
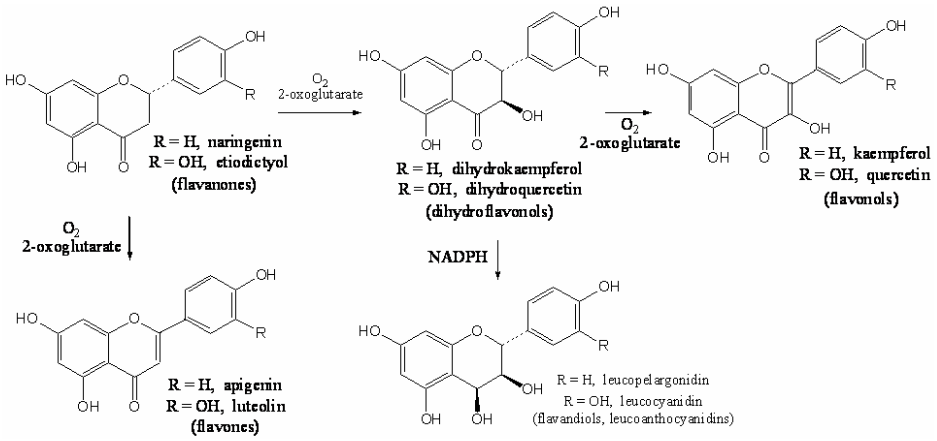


Fig 77. Rutin

## 8. Biosynthesis of flavonoids





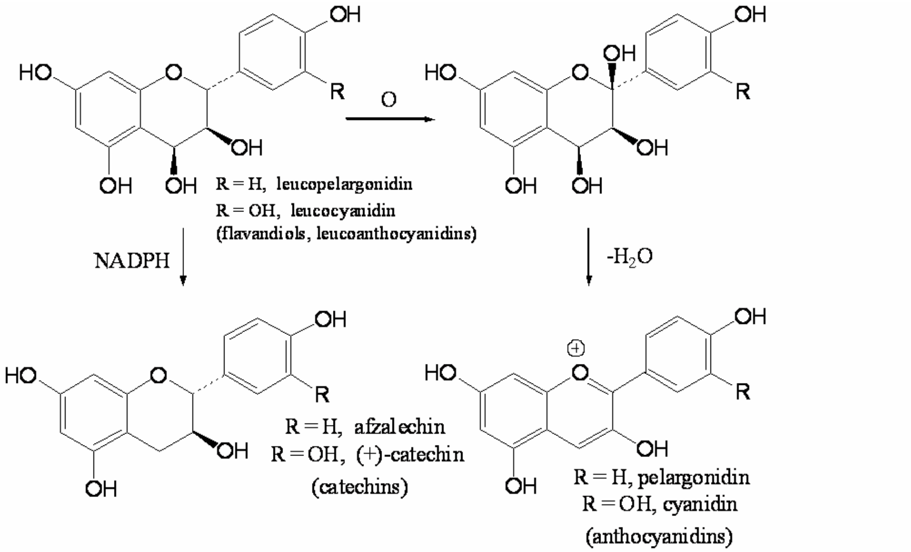


Fig 78. biosynthesis of flavonoids

9. Properties of flavonoids

Properties of selected flavonoids:

- witexin – in *Fructus Crataegi*, vasodilating effect in coronary vessels biflavonoids – isolated from *Gingo biloba*, anti-thrombotic effect pinocembrin – in *Pinus Cembra* (stone pine), anti-mycotic effect
- flavonoids of *Anthodium Chamomillae,* anti-allergic effect, anti-inflammatory effect
- flavonoids of *Radix Glycyrrhizae* anti-ulcer effect
- flavonoids of *Inflorescentia Helichrisi* and *Herba Hyperyci,* diastolic effect on smooth muscles of bloodvessels and cholangioles
- flavonoids of *Herba Equiseti*, *Folium Betulae, Herba Solidaginis* –diuretic effect
- flavonoids of *Inflorescentia tiliae,* anti-inflammatory effect.

Table 4. Terminology (VIII)

| *English* | *Polish* |
|---|---|
| anti - allergic | przeciwalergiczny |
| anti - inflammatory | przeciwzapalny |
| anti - mycotic | przeciwgrzybiczy |
| anti - thrombotic | przecizakrzepowy |
| beverage | napój |
| cereal | płatki zbożowe |
| cholangioles | przewody żółciowe |
| stone pine | limba |

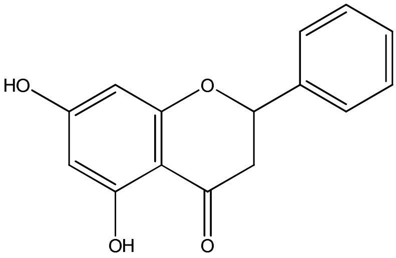


Fig 79. Pinocembrin

## IX. TERPENOIDS

Terpenoids, sometimes referred to as isoprenoids, are a large and diverse class of naturally occurring organic chemicals similar to terpenes, derived from five-carbon isoprene units assembled and modified in thousands of ways.

Most of them are multicyclic structures which differ from one another not only in functional groups, but also in their basic carbon skeletons. Terpenes and terpenoids are the primary constituents of the essential oils of many types of plants and flowers.

Terpenoids can be classified according to the number of isoprene units:

- **Monoterpenoids**, 2 isoprene units
- **Sesquiterpenoids**, 3 isoprene units
- **Diterpenoids**, 4 isoprene units
- **Sesterterpenoids**, 5 isoprene units
- **Triterpenoids**, 6 isoprene units
- **Tetraterpenoids**, 8 isoprene units
- **Polyterpenoids** with a larger number of isoprene units

Terpenoids can also be classified according to the number of cyclic structures they contain.

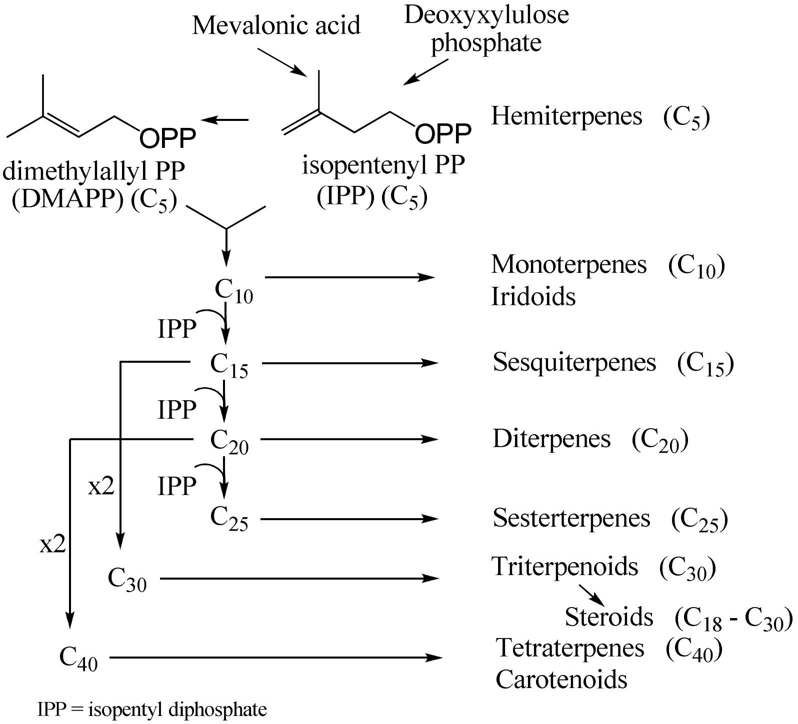


Fig 80. Classification of terpenoids [P. M. Dewick, *Medicinal Natural Products*, 2003, Wiley, Chichester]

1. Monoterpenes

Monoterpenes are a class of terpenes that consist of two isoprene units and have the molecular formula $C_{10}H_{16}$. Monoterpenes may be linear (acyclic) or contain rings. Biochemical modifications such as oxidation produce the related monoterpenoids.
Classification of monoterpenes:

- acyclic
- monocyclic
- bicyclic.

Acyclic monoterpenes

Isopentenyl pyrophosphate and dimethylallyl pyrophosphate are combined to form geranyl pyrophosphate (Fig 81) in a biosynthetic way.

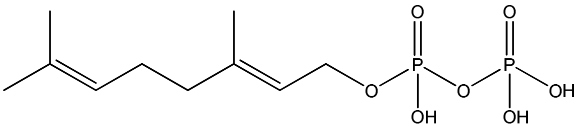
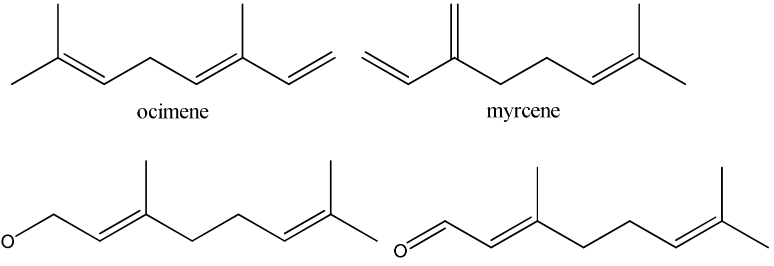


Fig 81. Geranyl pyrophosphate

Elimination of the pyrophosphate group of geranyl pyrophosphate leads to the formation of acyclic ocimene and the myrcenes (Fig 82). Hydrolysis of the phosphate groups leads to the prototypical acyclic monoterpenoid - geraniol. Additional rearrangements and oxidations provide compounds such as citral, citronellal, citronellol, linalool, and many others.



ocimene

myrcene

geraniol

citral

Fig 82. Acyclic monoterpenes

a/ Linalool

Linalool (Fig 83) is a naturally-occurring terpene alcohol found in many flowers and spice plants with many commercial applications, the majority of which are based on its pleasant scent (floral, with a touch of spiciness).

It is also known as β-linalool, linalyl alcohol, linaloyl oxide, *p*-linalool, allo-ocimenol and 2,6-dimethyl-2,7-octadien-6-ol.

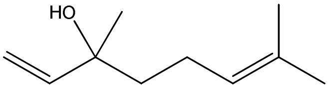


Fig 83. Linalol

Monocyclic monoterpenes

The isoprene units are able to form rings in connection with terpenoids structures. The most common ring size in monoterpenes is a six-membered ring - a classic example is the cyclization of geranyl pyrophosphate to form limonene (Fig 84).

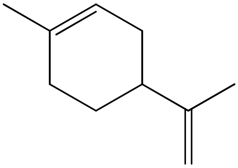


Fig 84. Limonene

Examples of monocyclic terpenes (Fig 85):

- **Hydrocarbons** – limonen, felandren, terpinen (alfa, beta, gamma)
- **Alcohole** – terpineol, mentol
- **Ketone** – carvone, pulegone
- **Oxide** – 1,8-cineole, ascaridol.

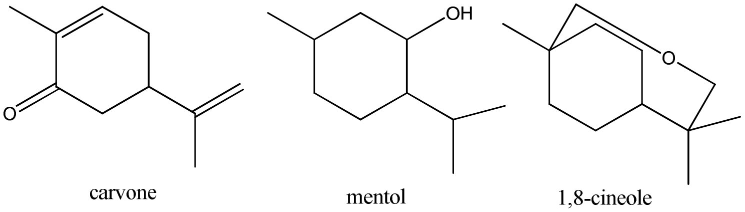


Fig 85. Monocyclic terpenem

Bicyclic monoterpenes

Geranyl pyrophosphate can also undergo two sequential cyclization reactions to form bicyclic monoterpenes, such as pinene (Fig 86) which is the primary constituent of pine resin.

Other bicyclic monoterpenes include carene, sabinene, camphene, and thujene.

Camphor, borneol and eucalyptol are examples of bicyclic monoterpenoids containing ketone, alcohol, and ether functional groups (Fig 86), respectively.

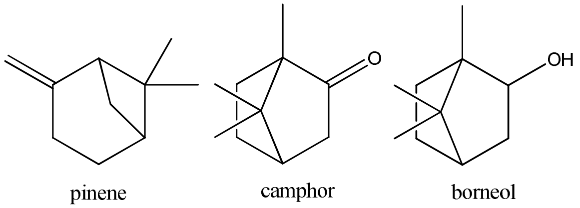
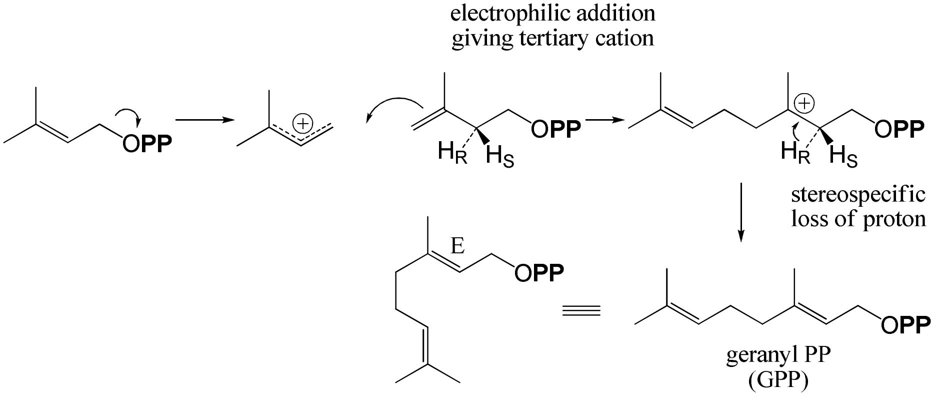


Fig 86. Bicyclic terpenes

### Biosynthesis of monoterpenes

Monoterpenes are biosynthesized by plants from the condensation of two active isoprene units C5 (Fig 87).



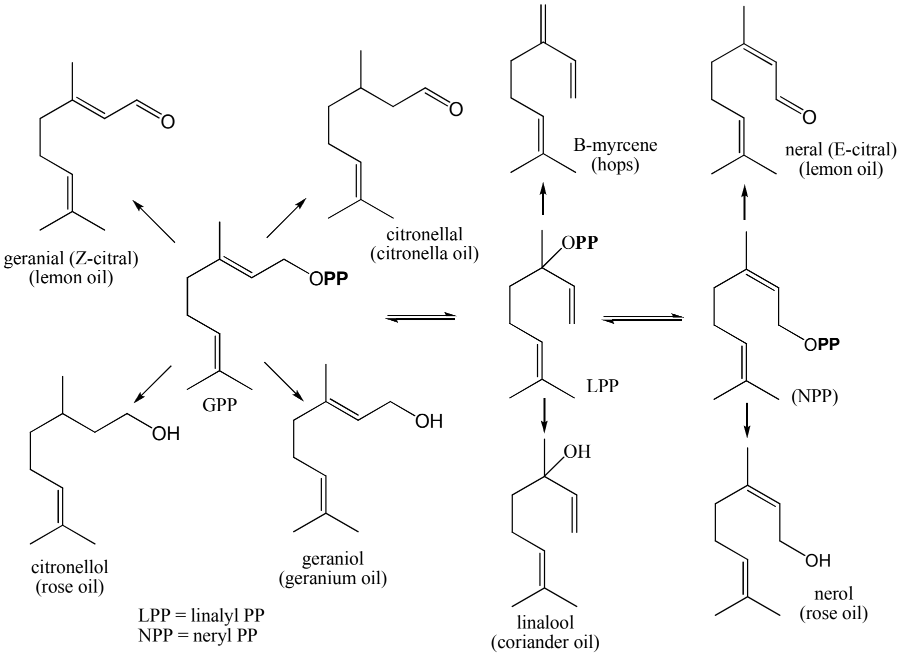


Fig 87. Biosynthesis of monoterpenes

Table 5. Terminology (IX)

| *English* | *Polish* |
|---|---|
| pine resin | kalafonia |
| spiciness | pikantność |

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