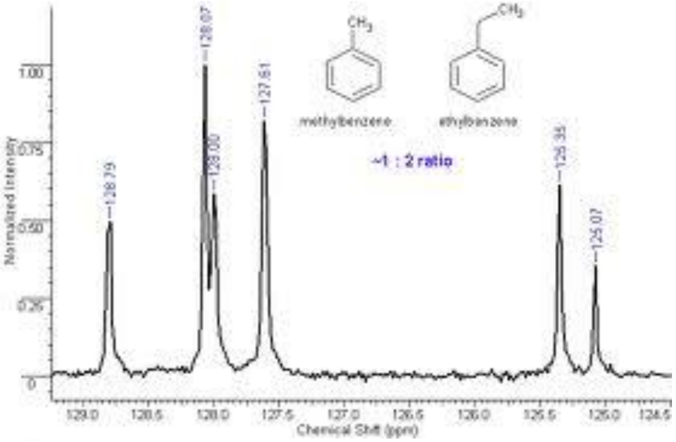
Basics of Natural Products

(PHG220)



Glycosides

(Part 1)

Definition

- Glycosides are non-reducing substances, which result from the establishment of a bond between a sugar (Monosaccharide or Oligosacchaide) and a non-sugar (aglycone or genin)

Classification

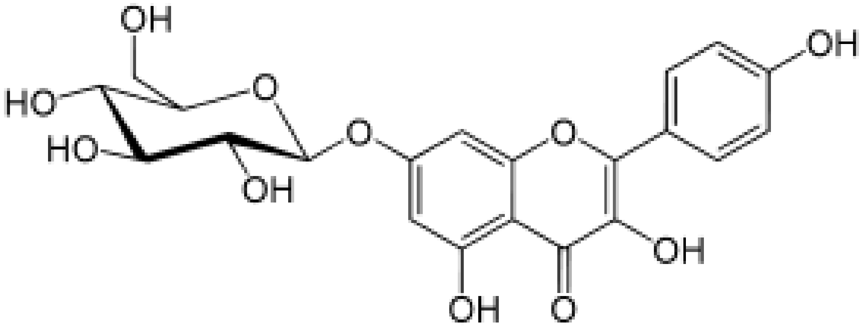
According to the glycosidic linkage, the following glycosides can be distinguished:

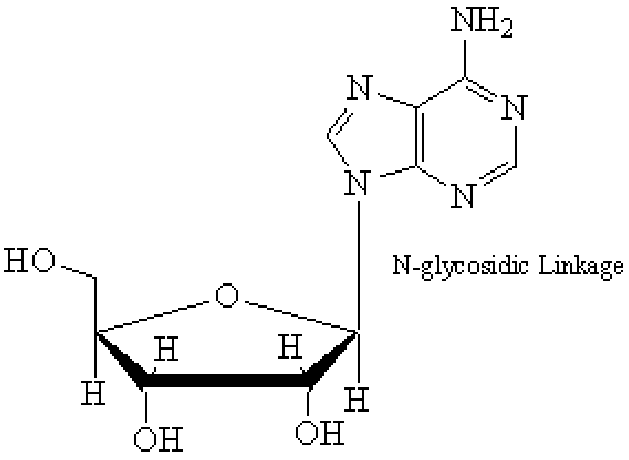
1- O-glycoside:

If this bond involves an alcoholic or phenolic hydroxyl group of the aglycone (such as the case of saponins, flavonoids among others)

2- N-glycoside:

If the bond involves a nitrogen-containing function in the aglycone such as the case of nucleosides





Adenosine

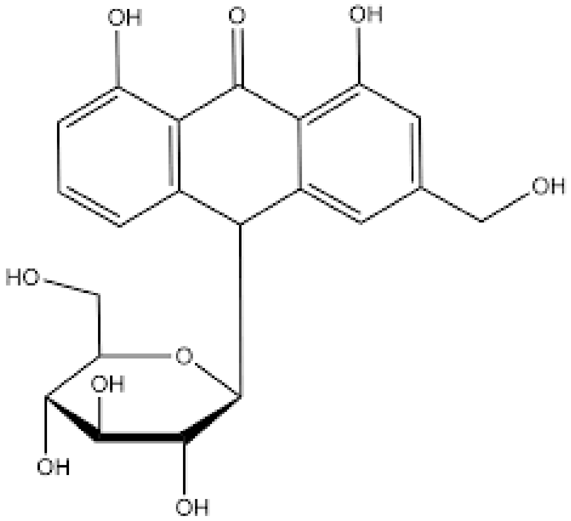
Classification

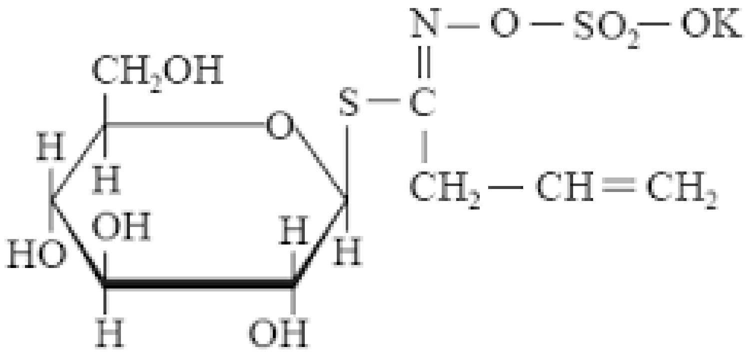
3- **C-glycoside:**

in which the saccharide-aglycone bond is established directly between two carbon atoms (For example aloin of aloe).

4- **S-glycoside:**

the sulfur-containing analogues of O-glycoside, and known as **glucosinolates.**





Sinigrin

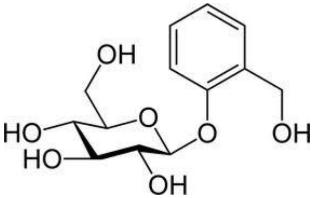
Classification

According to the nature of the aglycone (chemical structure of the aglycone), glycosides may conveniently be classified to the :

1- Steroidal glycosides
2- Antraquinone glycosides
3- Flavonoid glycosides
4- Saponine glycosides
5- Thioglycosides (Sulphur gly.)
6- Cyanogenitic glycosides
7- Phenolic glycosides
8- Alcoholic glycosides
9- Aldehydic glycoside**s**

Pharmacological activity

- The physiological action of glycosides is intimately associated with and due to the aglycone.
- Role of sugar: stabilization and solubility, modify pharmacodynamic properties of the aglycone.
- Some of them affect the heart e.g. digitoxin.
- Some are laxative e.g. sennosides.
- Others are analgesics e.g. salicin.
- some act against capillary fragility e.g. rutin, hesperidin.
- Others are antiinfalmmatory e.g. glyccerhezin.



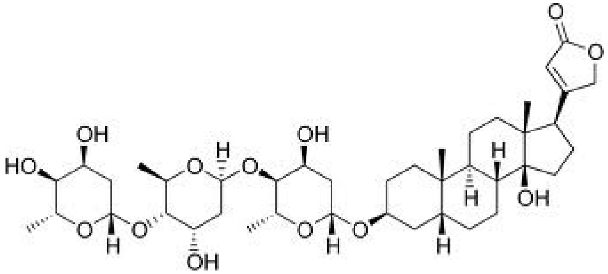
Salicin

Salix alba الصفصاف

Functions of glycosides in the plant

- They represent stored food reserve (sugar reserve).
- They play an important regulating roles in plants.
- They may serve as means of detoxifying many substances by transforming them to glycosides.
- Some glycosides have a role of defense against the invasion of the tissues by microorganisms subsequent to wounding. (many aglycones are antiseptic).

Steroidal Glycosides
(Cardiac glycosides)



What are Steroidal Glycosides ???

Definition:

- Cardiac glycosides are C23 or C24 steroid derivatives which exert on the failing heart a slowing and strengthening effect.

- They constitute a well-defined and highly homogeneous group from a structure, as well as pharmacological standpoint.

Structure:

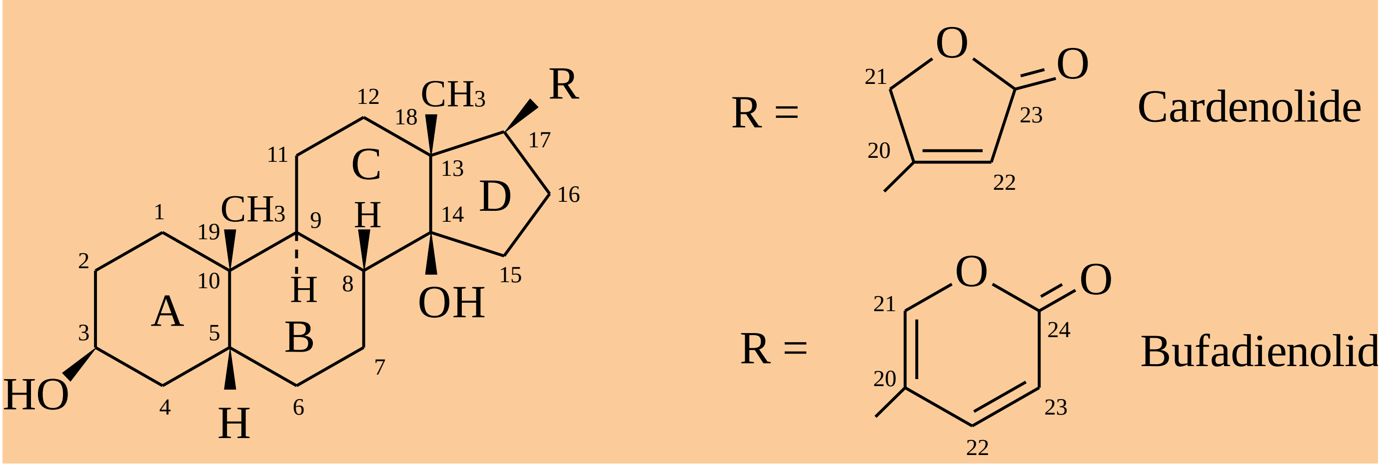
- The structures are remarkably homogenous, and comprise a **steroidal aglycone** of the **(C23) cardenolide** or of **the (C24) bufadienolide**, and a **sugar moiety**.

Structure of the aglycones:

- Have in common the classic, **tetracyclic, steroidal nucleus.**
- A, B, C, and D rings normally have a ***cis-trans-cis*** **configuration**
- All aglycones have **two hydroxyl groups**.
- Presence a β substituent (an **unsaturated lactone)** of at C-17**.**
- The size of the lactone ring distinguishes two groups of glycosides:

1- Cardenolides with an **α,β-unsaturated γ-lactone** (butenolide)

2- Bufadienolides with a **di-unsaturated δ-lactone** (pentadienolide)

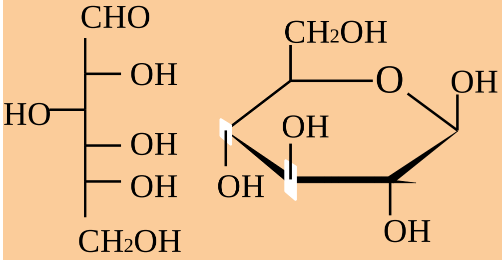


Structure of the Sugar Moiety:

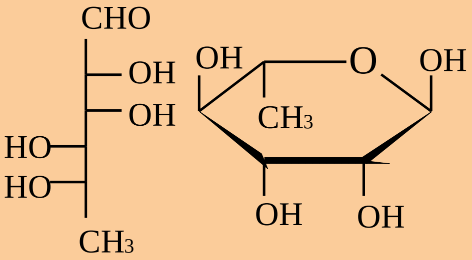
The majority of the saccharides found in cardiac glycosides are highly specific. They are:

1- **6-deoxyhexoses** (such **as L-rhamnose**, **D-fucose**)
2- **6-deoxy-3-methylhexoses** (such as **L-thevetose, D-digitalose**)
3- **2,6-dideoxyhexoses** (such as **D-digitoxose**)
4- **2,6-dideoxy-3-methylhexoses** (such as **L-oleandrose, D-cymarose**)
5- **Glucose may also be found in the glycosides**

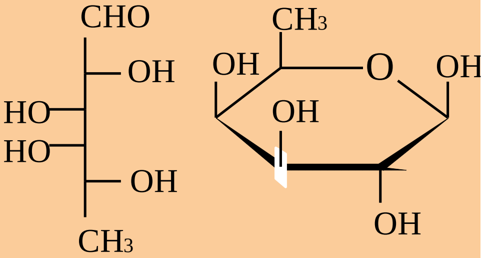
Note, that one hydroxyl group on a sugar can be acetylated.



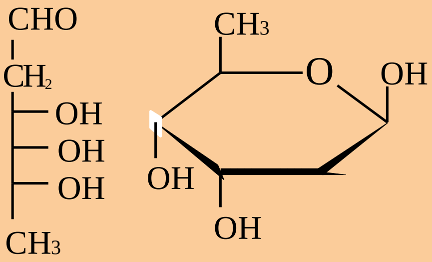
D-Glucose



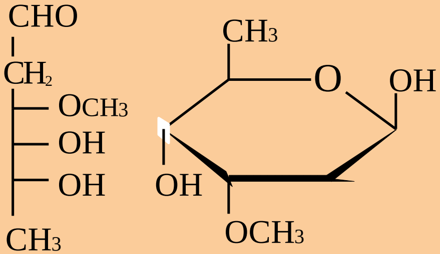
L-Rhamnose



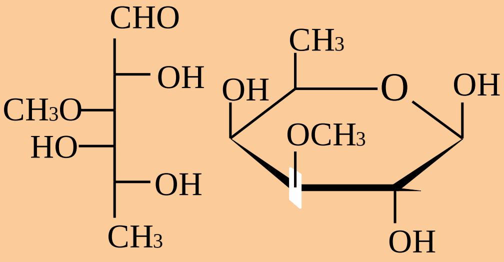
D-Fucose



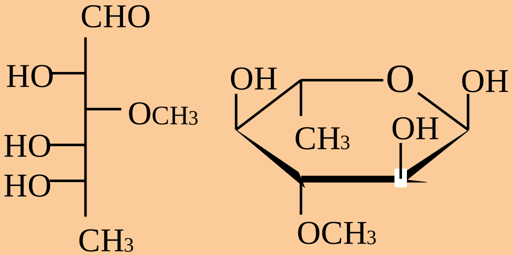
D-Digitoxose



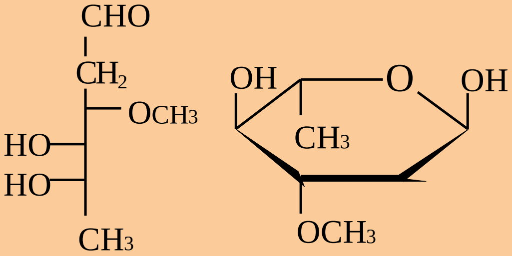
D-Cymarose



D-Digitalose



L-Thevetose



L-Oleandrose

Structure-activity Relationships

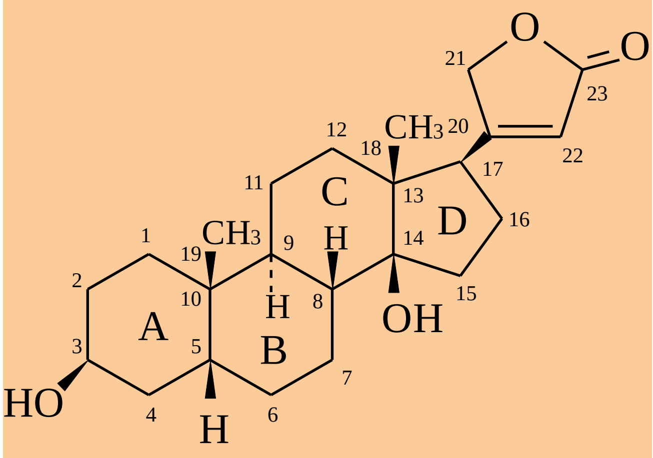
The presense of a certain number of structural elements is required for the activity:

1- The lacton ring

- unsaturated lacton ring at C-17
- The lacton must be in the β configuration

2- The configuration of the cycles

- The activity is maximized with the *cis-trans-cis* configuration.
- The activity is diminished when the A and B rings are trans fused (uzarigenin)
- The C and D rings must be *cis* fused.



Digitoxigenin (H-5 beta)
Uzarigenin (H-5 alpha)

3- The substituents

- The OH groups at C-3 and C-14 must be in the β configuration
- The inversion of the configuration at C-3 or at C-14 diminishes the activity, but 3- or 14-deoxy compounds are not completely inactive.

Distribution

Cardenolides

They are the more common and are particularly in the **Apocynaceae** (e.g. Adenium, Strophanthus) and **Asclepiadaceae** (e.g. Calotropis), but are also found in some **Liliaceae** (e.g. Convallaria), **Scrophulariaceae** (e.g. Digitalis), **Ranunculaceae** (e.g. Adonis and Helleborus) and in the **Moraceae** and **Tiliaceae**.

Bufadienolides

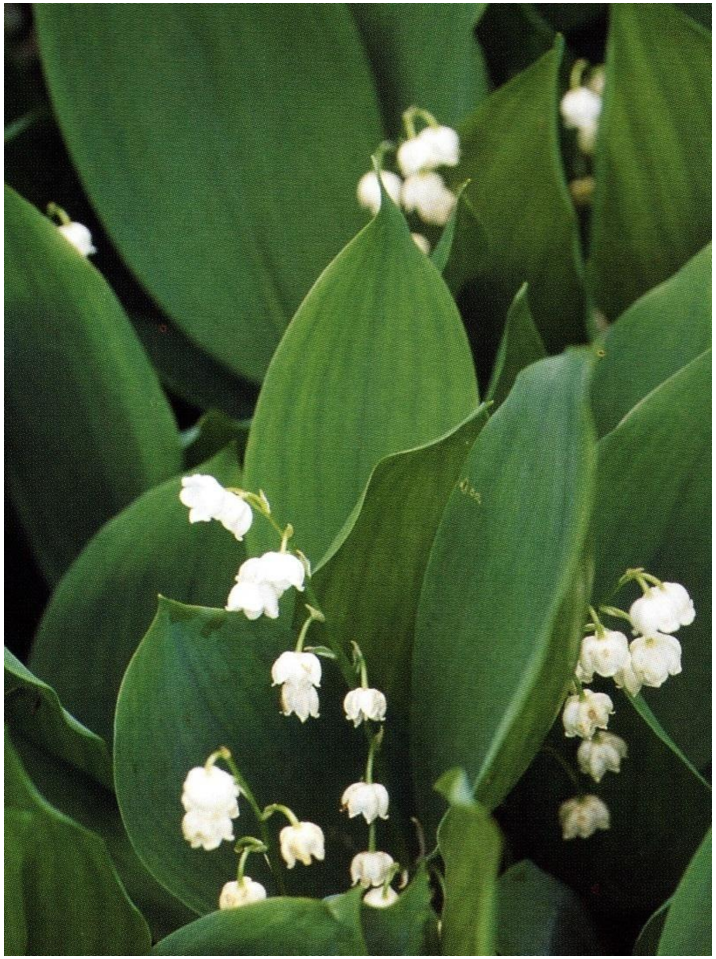
They occur in some **Liliaceae** (e.g. Urginea), in some **Ranunculaceae** (e.g. Helleborus), and in some **toad venoms.**

Digitalis sp.

Urginia maritima

Strophanthus sp.

Adonis vernalis



Convaleria majalis


Photo: Jamil.F.Jaber

Calotropis procera

Adenum obesum

Pharmacological activities and Indications

Pharmacological properties:

The cardiac effects are:

1- Positive inotropic effect.

- increase the force and speed of contraction of the heart.

2- Negative chronotropic effect.

- decrease the heart rate by the affecting the autonomic nervous system.

3- Negative dromotropic effect.

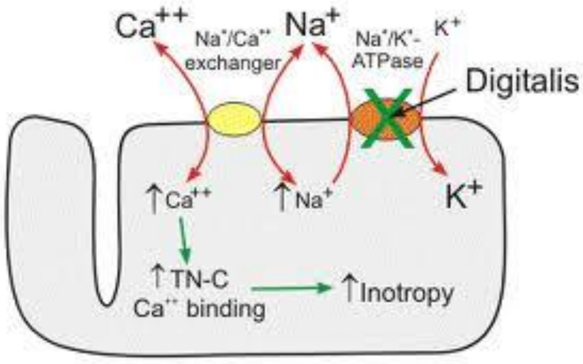
-decrease in the conduction velocity at the atrium-ventricle (A-V) junction and by an increase in the refractory period of the A-V node.

Therapeutic indications:

Cardiac glycosides are indicated for:

1- cardiac insufficiency with low output

2- Supraventricular rhythm abnormalities: to slow down or decrease atrial fibrillation or flutter.



Identification of cardiac glycosides

I- Color reactions of the Sugars.

1- Reaction with a xanthydrol

(Xanthydrol in concentratrd acetic acid, development red color).

2- Keller-Kilani-Reaction

(conc. acetic acid containing two drops of 5% $FeCl_3$ solution and conc. H_2SO_4, blue color)

II- Color reaction of the Aglycones

1- Baljet reaction (uses picric acid and yields an orangy color)

2- Kedde reaction (3,5-dinitrobenzeoic acid and yields a reddish-violet color)

3- Raymond reaction (m-dinitrobenzene yields a blue color)

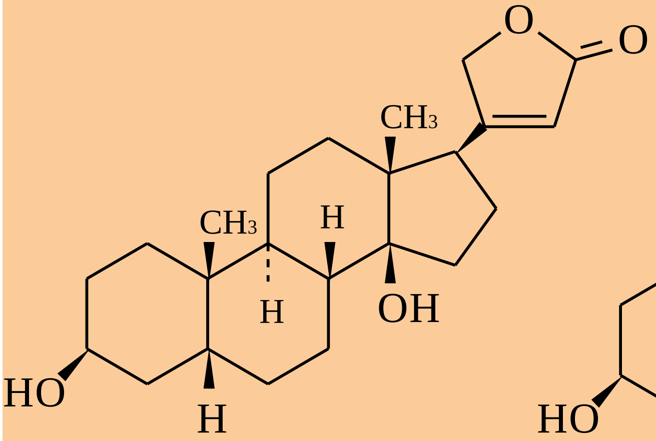
Drugs containing cardenolides

1- *Digitalis purpurea*

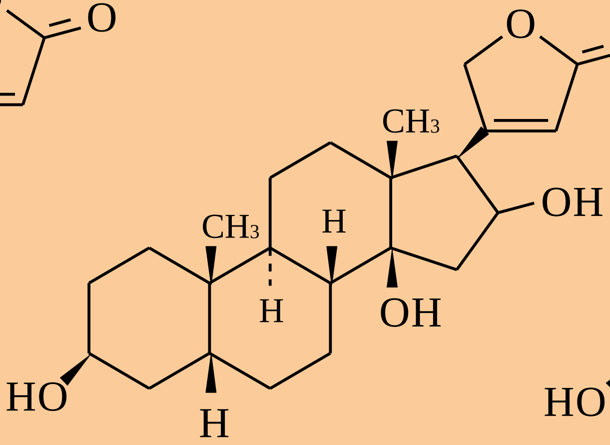
- The concentration of cardenolides in the leaves is about 0.2-0.5%
- The chief cardenolides of the leaf of *D. purpurea* fall into **three series** defined by the structure of their aglycone:

Sugar components (attched at C-3)	(Aglycone)		
	Series A (Digitoxigenin)	Series B (Gitoxigenin)	Series E (Gitaloxigenin)
-Dx-Dx-Dx-Glu	Purpurea glycoside A	Purpurea glycoside B	Glucogitaloxin
-Dx-Dx-Dx	Digitoxin	Gitoxin	Gitaloxin
-Dtl-Glu	Gluco-odoroside H	Digitalinum verum	Glucoverodoxin
-Dtl	Odoroside H	Strospeside	Verodoxin

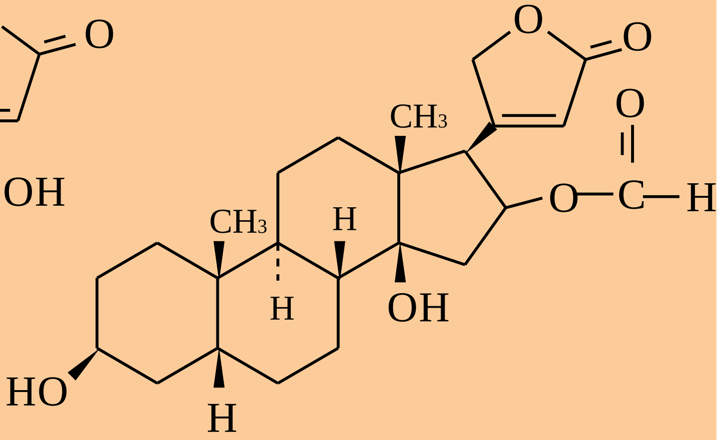
Dx = Digitoxose, Glu = Glucose, Dtl = Digitalose



Digitoxigenin
(Series A)



Gitoxigenin
(Series B)

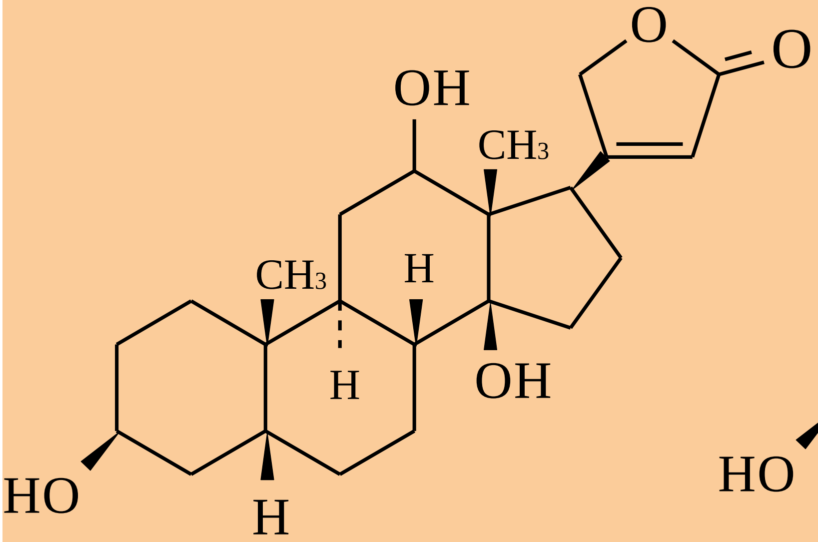


Gitaloxigenin
(Series E)

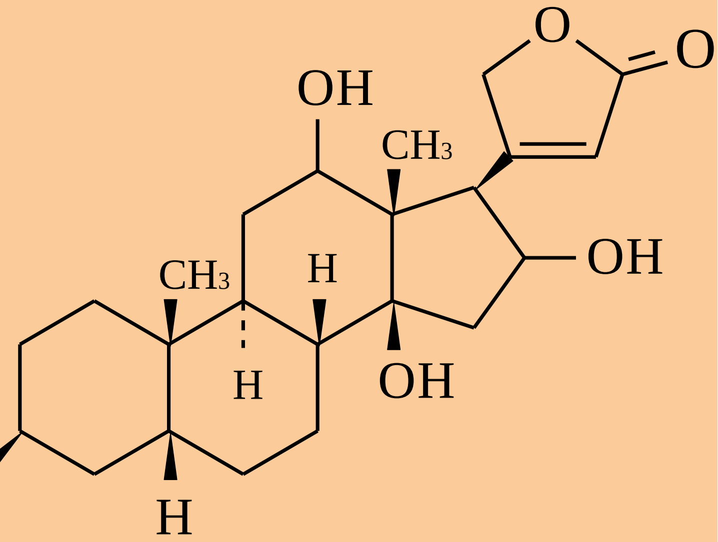
2- *Digitalis lanata*

Glycoside	Aglycone	Sugar moieties
Lanatoside A	Digitoxigenin	-Dx-Dx-Dx(Ac)-Glu
Lanatoside B	Gitoxigenin	-Dx-Dx-Dx(Ac)-Glu
Lanatoside C	**Digoxigenin**	-Dx-Dx-Dx(Ac)-Glu
Digoxin	Digoxigenin	-Dx-Dx-Dx
Lanatoside D	**Diginatigenin**	-Dx-Dx-Dx(Ac)-Glu
Lanatoside E	Gitalioxigenin	-Dx-Dx-Dx(Ac)-Glu

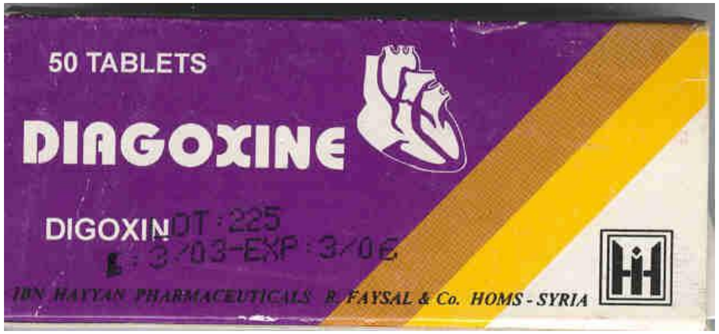
Dx = Digitoxose, Glu = Glucose,



Digoxigenin
(Serie C)

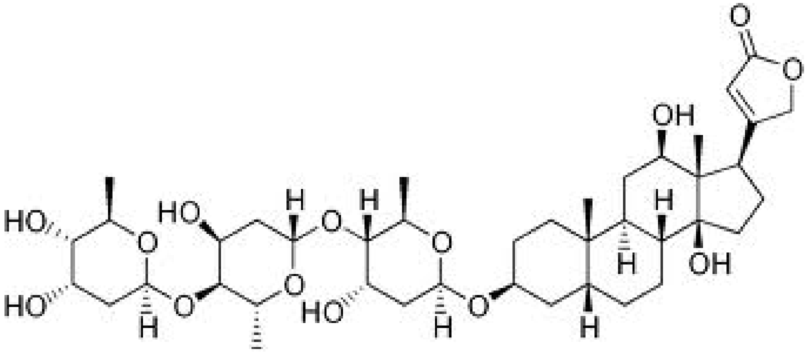


Diginatigenin
(Serie D)



Digitalis lanata

Digitalis purpurea

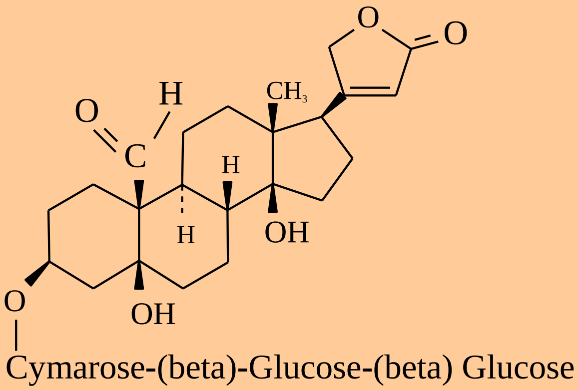


Digoxin

D. lanata

3- *Strophanths kombe*

- The seeds contain 7-10% cardenolides.
- The principal glycosides are K-strophanthoside, K-strophanthin-β and cymarin, all based on the genin strophanthidin.
- They are **used intravenously in emergency** for its cardiac effects.
- It is absorbed too poorly to be used orally.



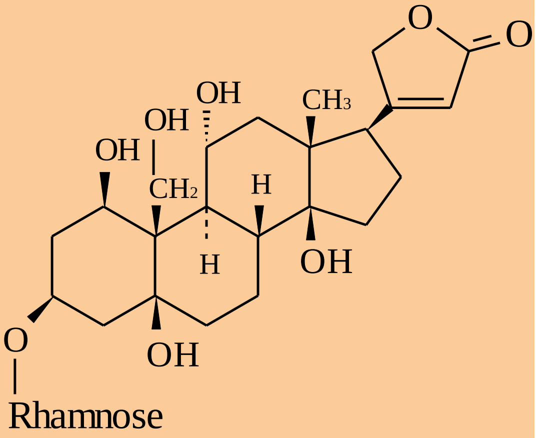
Cymarin

k-Strophanthin (beta)

k_Strophanthosid

4- *Strophanthus gratus*

- The seeds contain 4-8 % of ouabain (g-strophanthin).
- This compound is very polar, practically not absorbed orally.
- It is a heart tonic with a rapid onset and short duration of action.



g-Strophanthin (Ouabain)

Strophanthus gratus

Strophanthus kombe


© Harustak 2007

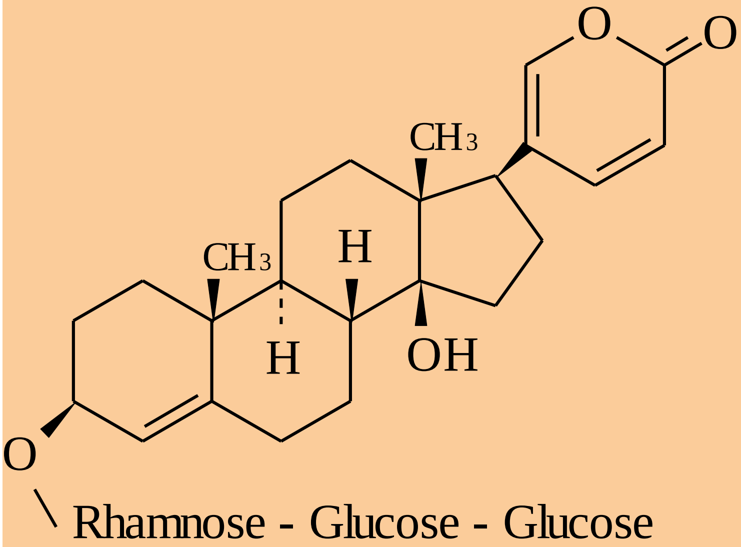
Bufo Bufo

Bufadienolides

Therapeutically they find littel use as cardioactive drugs because of their low therapeutic index and their production of side-effects.

1- Squill

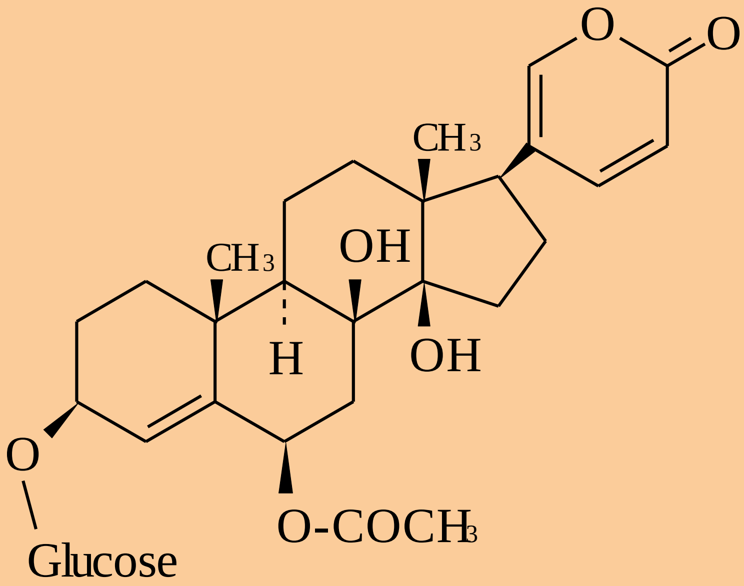
- The bulb of the ***Urginia maritima*** contains up to 4 % bufadienolides.
- The chief glycosides of the white variety are glucoscillaren A, scillaren A and proscillaridin A.
- Proscillaridin A is active orally and is eliminated rapidly and is not cumulative, therefore it is safe to use.
- The chief glycoside of the red variety is the scilliroside, which gives by hydrolysis the aglycon scillirosidine and glucose.
- The red squill is considered a rat poison.



Proscillaridin A

Scillaren A

Glucoscillaren A



Scilliroside

Urginea maritima

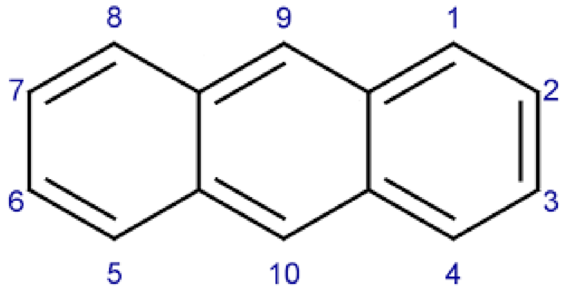
Anthraquinone glycosides

(Part 2)

What are Anthraquinones ??

Definition:

- They derived from anthracene and have a variable degree of oxidation (anthrones, anthranols, anthraquinone).
- They are a natural group of purgative drugs.



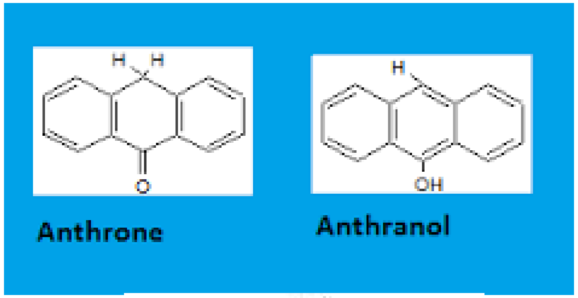
Distribution:

- Liliaceae (aloe), Polygonaceae (rhubarbs), Rhamnaceae (buckthorn, cascara), Leguminosae (senna).
- They are found too in Rubiaceae, Ericaceae, Euphorbiaceae, Scrophulariaceae.

Chemical Strcture and classification

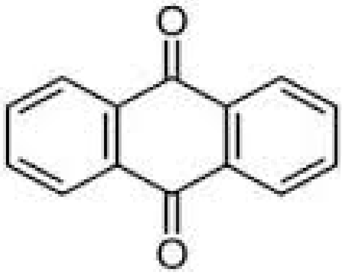
1- The aglycones

A- Anthrones and anthranoles



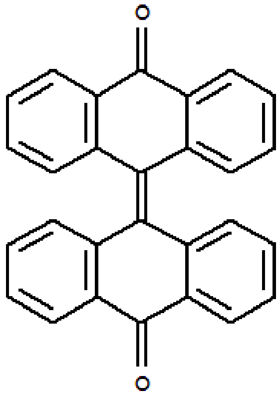
- They are isomeric (tautomeric forms)
- They designated by the term „reduced forms“

B- Anthraquinones



- The oxidized form of Anthranols and anthrones.

C- Dianthrones



- (derived from two anthrone molecules)
- **1- Homodianthron:** composed of 2 identical anthrons.
- **2- Heterodianthron:** composed of 2 differnt anthrons .
- They form as a result of mild oxidation of the anthrone .
- They have two chiral centres (at C-10 and C-10´)

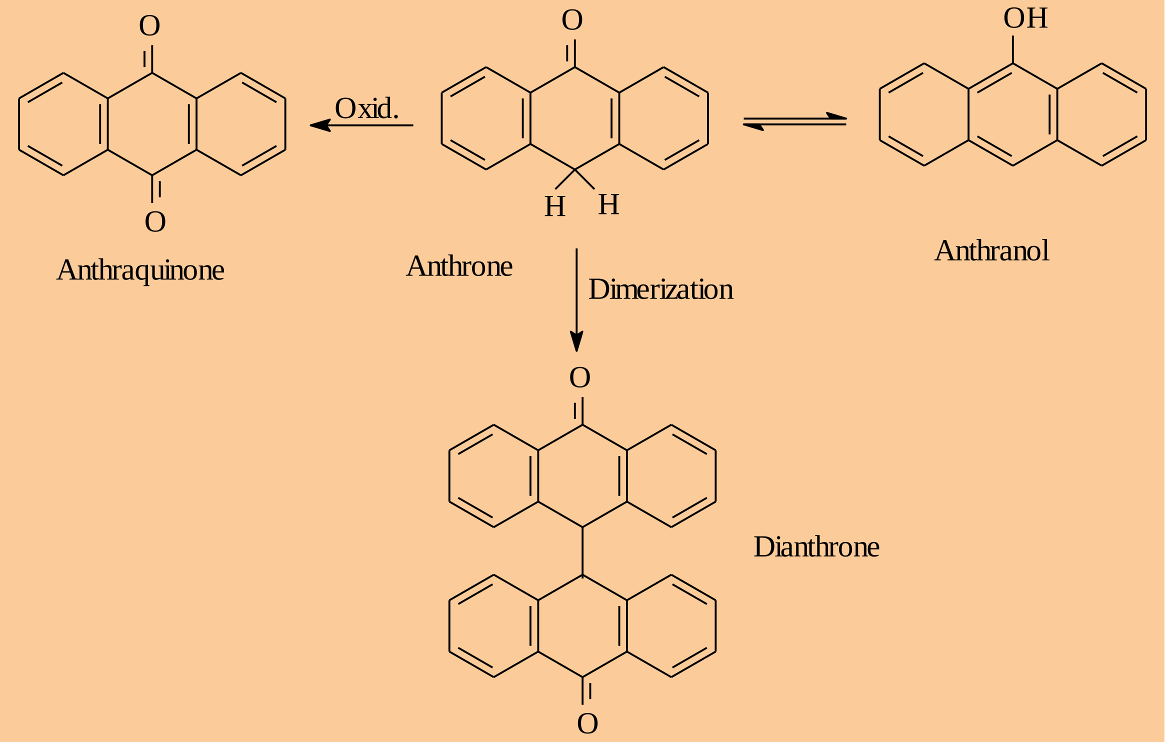
2- The glycosides

In fresh plant occur glycosides of monomeric anthrones.

During desiccation, two transformation processes come to play:

1- Oxidation, which leads to anthraquinone glycosides

2- Dimerization, which yields glycosides of dianthrones.

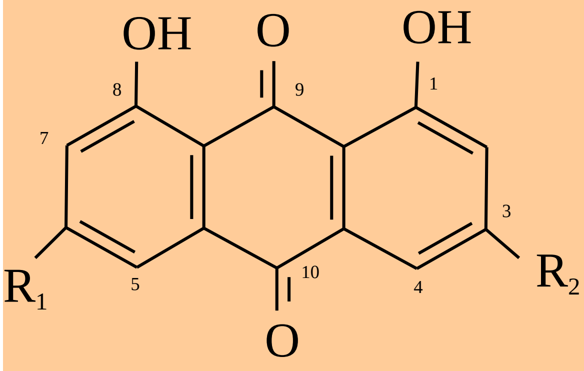


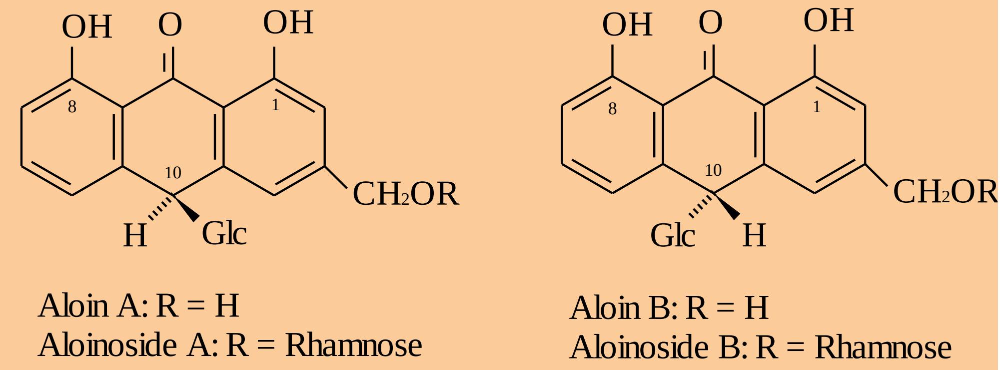
- The importent saccharides are D-glucose, D-galactose, L-rhamnose and in rare cases D-apiose.

- The bond with the aglycone normally involves the phenolic OH-gruop in 8-position (in the case of glucose), or in the 6-position (in the case of rhamnose and apiose).

- The aglycone may be linked to 2 sugars (e.g. glucofrangulin A)

- It is not rare for 1,8-dihydroxyanthrones to occur as C-glycosides, with the bond forming between the C-1 of glucose and the C-10 of the aglycone (aloin A and B)





Aloin A: R = H
Aloinoside A: R = Rhamnose

Aloin B: R = H
Aloinoside B: R = Rhamnose

Physico-chemical Properties

- Anthraquinones are colored, **orange-red** compounds, springly soluble in cold water and soluble in organic solvents and alcohols.
- The glycosides are soluble in water and hydroalcoholic solutions.
- Treating the O-glycosides in acidic medium causes their hydrolysis.
- Cleavage of the C-C bond of C-glycosides can only be obtained in the presence of **ferric chloride**.

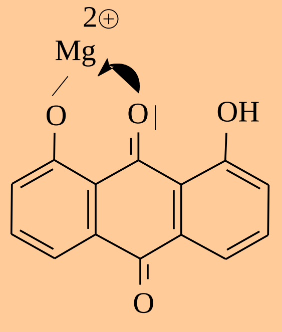
Chemical Characterization

1- Bornträger reaction: (for aglycone)

- upon dissolving the anthraquinone derivatives in alkaline aqueous medium (**KOH**), a **red color**, more or less purplish, develops.
- only positive with the **free anthraquinone** forms.

2- Modified Bornträger reaction (for glycosides)

Acid hydrolysis of the glycoside prior to addition of KOH



Mg- chelat-complex

3- With magnesium acetate

- specific to 1,8-dihydroxyanthraquinones.
- intense red color
- Like the Bornträger reaction, this reaction is positive only with the oxidized and free forms.

Pharmacological action

Pharmacological properties:

- They exert a more or less violent laxative activity.
- They affect intestinal motility (they increase peristalsis, particularly in the left colon and in the sigmoid).
- They affect the absorption of water and electrolytes.

Mechanism of the action:

- By **inhibting the Na-K ATPase** activity of the enterocytes, they cause an inhibition of water, sodium and chloride resorption.

Uses:

- As **laxative**, they are used crude (as herb teas), or as galenicals (powders and extracts).

Main anthraquinone glycoside-containing drugs:

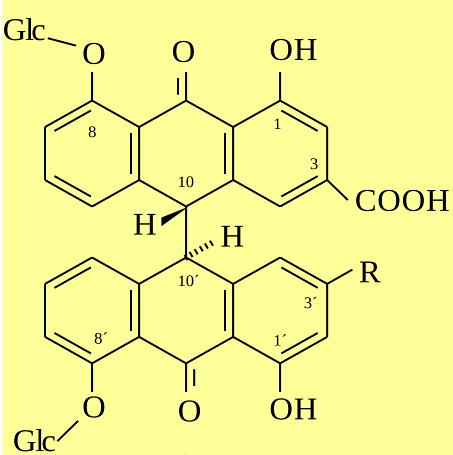
1- Senna

- leaves and fruits of ***Cassia senna*** (***C. acutifolia***) known as **Alexandrian senna** and of ***Cassia angustifolia*** known as **Tinnevelly senna**.

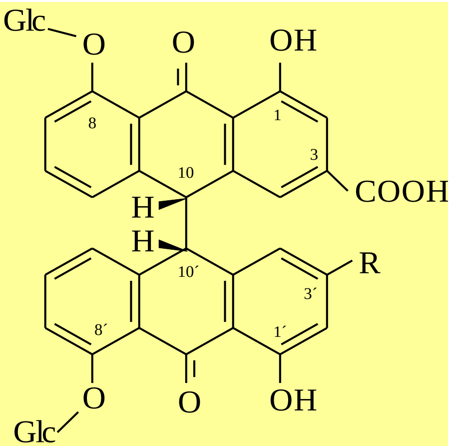
- The dried drug contains:

1- 3-4 % dianthrone glycosides (**sennosides A-D**), Sennosides A and B are the major components

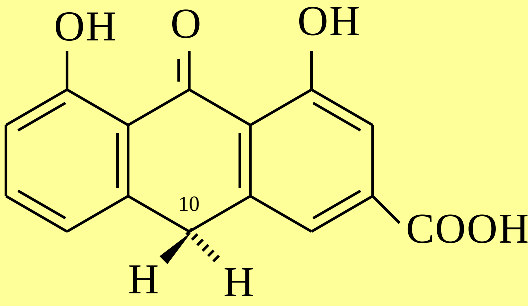
2- Traces of free anthraquinones and anthraquinone glycosides



Sennoside A: R = COOH
Sennoside C: R = CH_2OH



Sennoside B: R = COOH
Sennoside D: R = CH_2OH

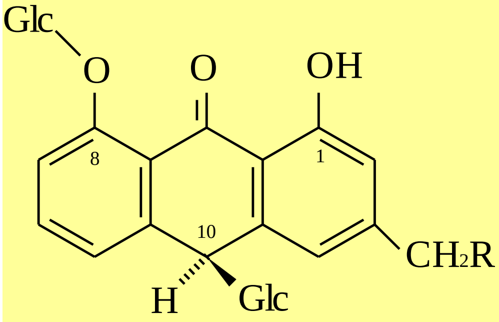


Rhein-anthrone

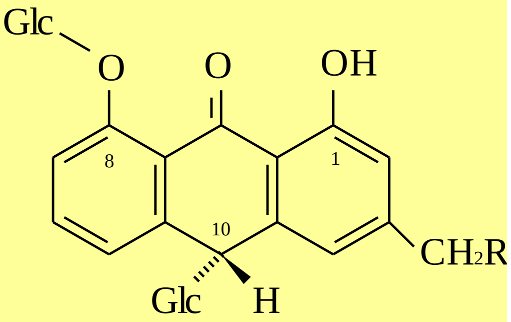
Laxative drugs containing *Senna* extract.

2- Cascara bark (sacred bark):

- \- It is the bark of ***Rhamuns purshianus*** **(Fam. Rhamnaceae).**
- \- The drug contains 6-9 % anthraquinone glycosides.
- \- The chief constituents are O-glycosides of C-glycosides, namely cascarosides A, B, C and D.
- \- Also present as anthraquinone and dianthrone O-glycosides.



Cascaroside A: R = OH
Cascaroside C: R = H



Cascaroside B: R = OH
Cascaroside D: R = H

Rhamuns purshianus

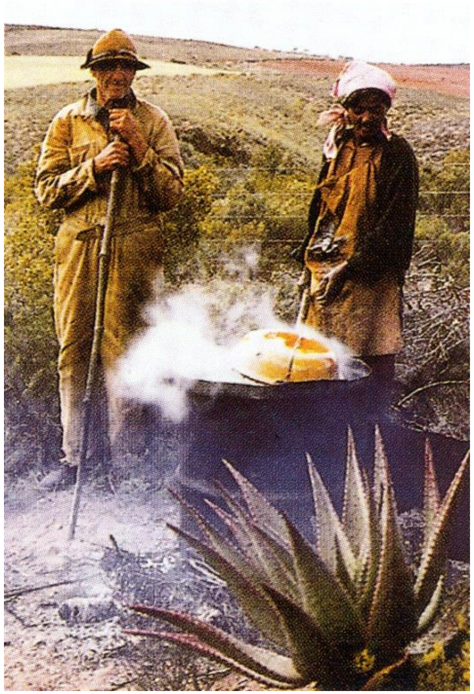
3- Aloes

- Aloe is the concentrated juice from the transversely cut leaves of various ***Aloe*-species** **(Fam. Liliaceae).**
- About 180 species of aloe are known, the drug is mainly obtained from the following:

1- Cape variety from ***Aloe ferox*** (from South Africa and Kenya). (dark-brown or greenish-brown glassy masses).

2- Curacao variety from ***Aloe barbadensis*** **(*A. vera*)** (from West Indian Islands). (yellowish-brown to chocolate-brown).

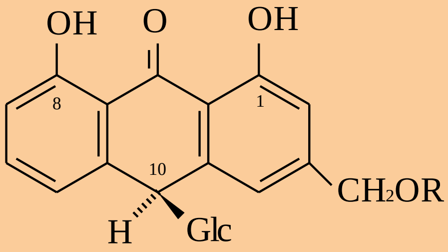
3- Socotrine and **Zanzibar** varieties from ***Aloe perryi*** (no longer official).



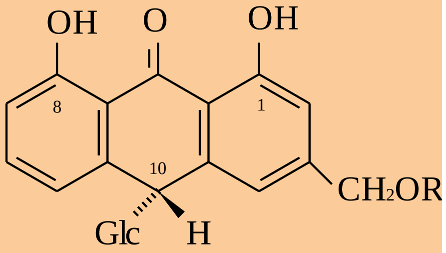
Aloe ferox

Cape aloe

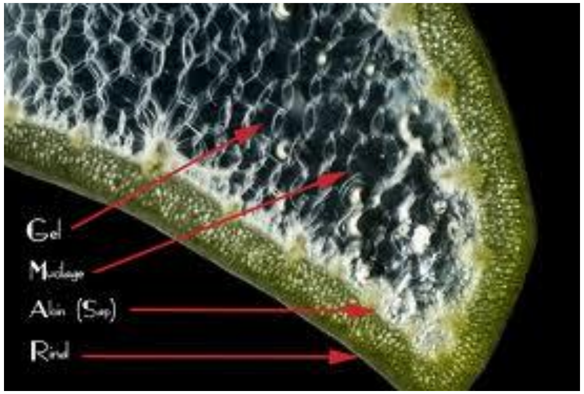
- Aloe contains 15-40 % C-glydosides (aloe-emodin-anthrone 10-C-glucosides).
- The chief constituent is **aloin (barbaloin)**, which is a mixture of **aloin A** and **aloin B**.



Aloin A: R = H
Aloinoside A: R = Rhamnose

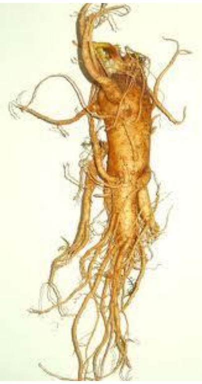


Aloin B: R = H
Aloinoside B: R = Rhamnose



Saponin glycosides

(Part 3)



Saponins

They are widely distrubuted glycosidic compounds which are characterized by:

1- Their surface-active properties.
2- Their property of producing a frothing in aqueous solution.
3- They have also haemolytic properties.
4- Some have piscicidal activity.

Classification:

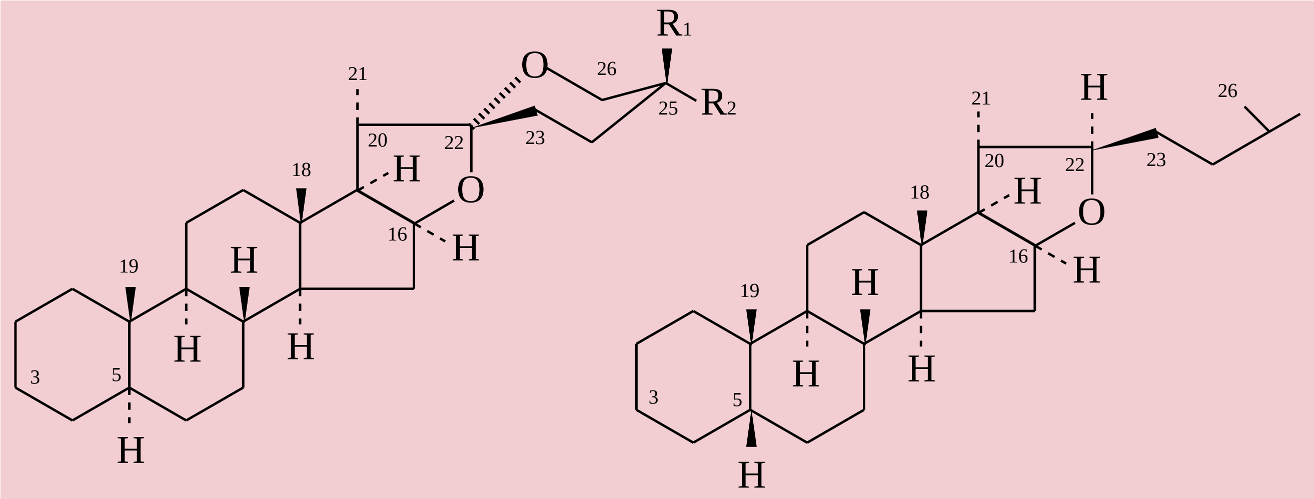
The major classes of saponins can be considered:

1- **Steroid glycosides** (present mainly in the Monocotyledons).
2- **Triterpene glycosides** (present in the Dicotyledons) .
3- **Steroidal alkaloid glycosides.**

Chemical structure

1- Steroidal saponins glycosides:

- Skeletons with **27 C-atoms**, we distinguish two types:
  - 1- **Spirostane glycosides** (16β,22:22,26-Diepoxy-cholestan)
  - 2- F**urostane glycosides** (16β,22-Epoxy-cholestan).



Chemical structure

2- Triterpene glycosides: (C_{30}-derivatives)

The triterpenoid saponines may be classified into 2 groups:

1- Tetracyclic triterpenoid saponins (e.g. dammarane derivatives**).**

2- Pentacyclic trietrpenoid saponins.

- The triterpenoid sapogenins that are by far the most common are in fact **pentacyclic** compounds

Structure of the glycosides:

- All classes have the existence of one or more sugar chains.
- The chains may be linear or branched.
- D-glucose, D-galactose, D-glucuronic acid, L-rhamnose, and D-fucose are commonplace.
- **Monodesmosidic saponins** have a single sugar chain normally attached at carbon C-3.
- **Bidesmosidic saponins** have two sugar chains, usually with one attached through C-3 and one attached through C-28 (in case of triterpenoid saponins) or at C-26 (in case of steroidal saponins).

Bidesmosidic saponins are easily transformed into monodesmosidic saponins by hydrolysis of the esterified sugar at C-28 or C-26.

Distribution

- The steroidal saponins are less widely distributed in nature than the pentacyclic triterpenoid type.

- The **steroidal saponins** are found in many families, e.g. **Dioscoreaceae**, **Amaryllidaceae**, **Liliaceae** and **Leguminosae**.

- The **steroidal alkaloids** are found in **Solanaceae, Buxaceae, Liliaceae and Apocynaceae.**

- The **pentacyclic triterpenoid saponins** are rare in monocotyledons but are abundant in many dicotyledonous families.

Characterization and identification

1- Haemolysis

One of the properties of saponins, namely their ability to rupture erythrocytes, has been for decades as a detection and quantitation method.

2- Froth test

Saponins and drugs containing saponins give persistent froth (foam) when shaken with water.

3- Color reaction and thin layer chromatography

No color reaction is particularly specific to these compounds.

- **Liebermann** for steroidal saponins.
- Reaction with **antimony trichloride**, **vanillin or Anisaldehyde in the presence of sulfuric acid**) can be used for triterpenoid saponins.

Pharmacological activities and Indications

- **Antibiotic activity against both bacteria and fungi, e.g. α-hederin from ivy (*Hedera helix*).**
- **Haemolytic properties, which are attributed to the interaction with the sterols of the erythrocyte membrane that induces an increase in permeability and a loss of hemoglobin.**
- **Anti-inflammatory and anti-rheumatic activity (*Glycyrrhiza galbra* and *Aesculus hippocastanum*).**
- **Anti-exudative activity such as in *Aesculus hippocastanum* and *Glycyrrhiza glabra***

Pharmacological activities and Indications

- Anti-tussive and expectorant activity (*Glycyrrhiza galbra*, *Polygala senega*, *Hedera helix* and *Primula veris*)
- Some saponins have been found to possess CNS-stimulating activity and anti-fatigue action (saponins from ginseng)
- Stimulating action on the circulation (extract of *Aesculus hippocastanum*)
- A number of plants with spermicidal activity have a long history of use as anti-fertility agents in indigenous medical systems.

Natural steroidal saponins for the production of pharmaceuticals

- They are of great pharmaceutical importance because of their relationship to compounds such as the sex hormones, cortisone, diuretic steroids and vitamin D and the cardiac glycosides.
- Some used as starting materials for the synthesis of these compounds.
- **Diosgenin** is suitable for the manufacture of oral contraceptives and the sex hormones. It can also be used for corticosteroid synthesis.
- **Hecogenin** provides a practical starting material for the synthesis of the corticosteroids.

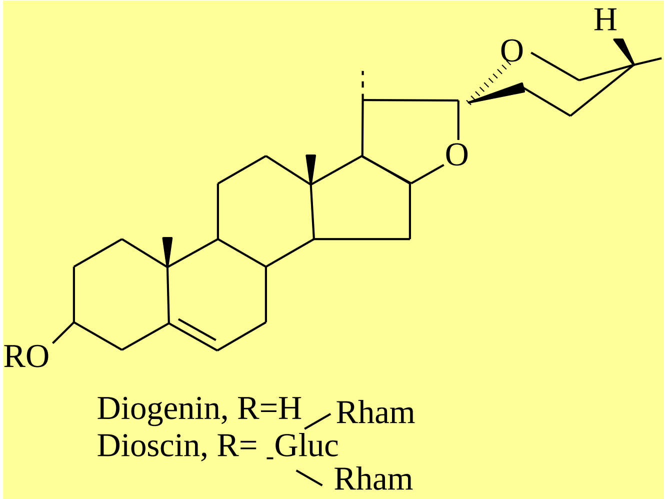
Sources of Diosgenin:

Yams

The drug consists of the tuberous roots of ***Dioscorea* species (Dioscoreaceae)**, such **as *D. esculenta, D. alata* and *D. opposita*.**

Untile 1970 diosgenin isolated from the Mexican Dioscorea was the sole source for steroidal contraceptive manufacture.

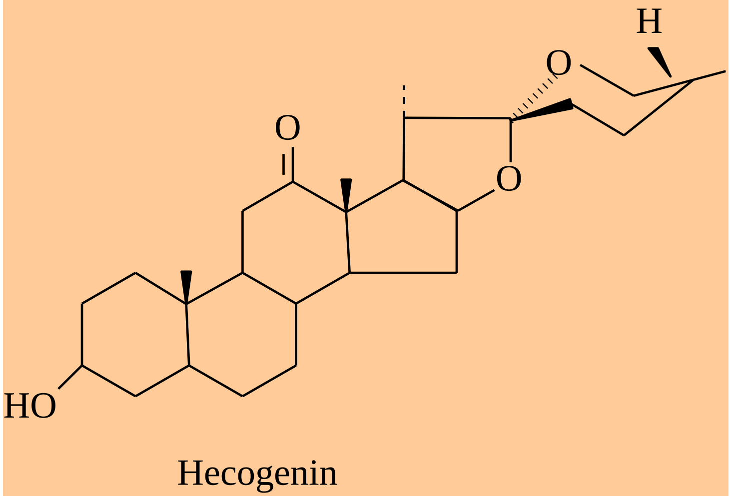
Diosgenin occurs as dioscin, which comprises two molecules of rhamnose and one molecule of glucose.



Diogenin, R=H
Dioscin, R= Gluc (Rham, Rham)

Sources of hecogenin:
Agave, Sisal

Hecogenin is obtained commercially as the acetate form about 0.01% yield from sisal leaves **(*Agave sisalana*, Fam. Amaryllidaceae)**.



Hecogenin

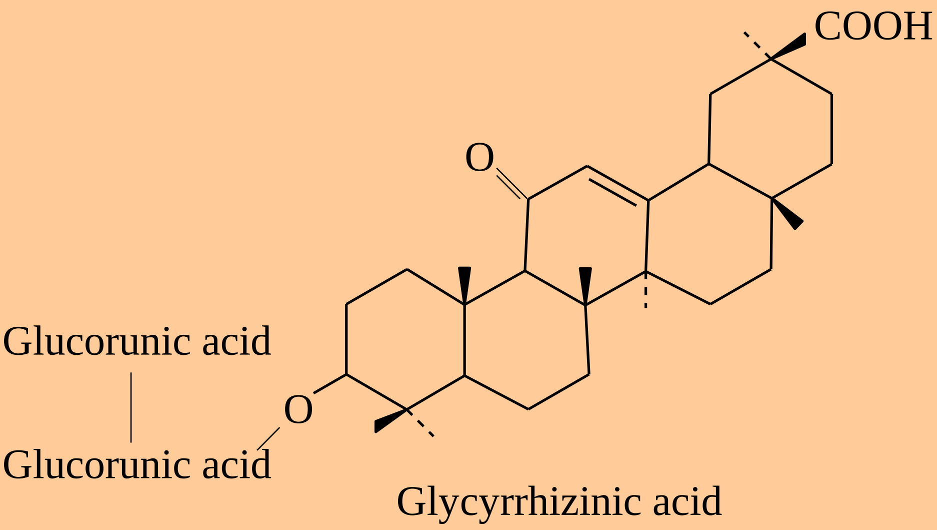
Chief triterpenoid saponins-containing drugs

1- Saponin-containing drugs as expectorant and anti-tussive

1- Liquorice

- roots and stolons of the ***Glycyrrhiza glabra*** **(Fam. Leguminosae).**

- It contains **glycyrrhizin** (a mixture of K- and Ca-salts of **glycyrrhizinic acid**). **Glycyrrhizinic acid** is the diglucopyranosiduronic acid of **glycyrrhetic acid**.

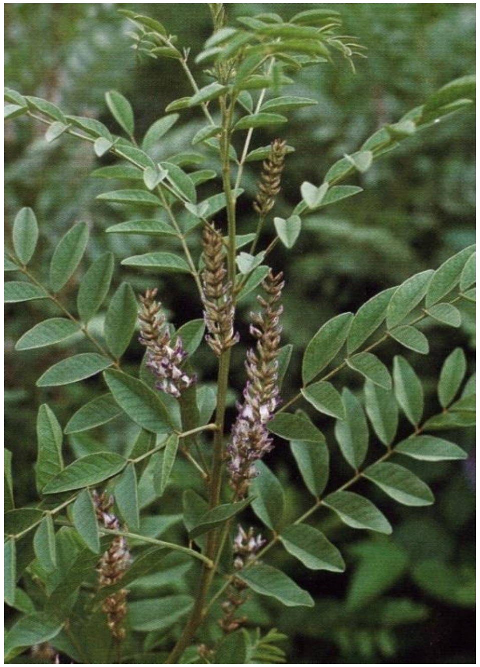


Glycyrrhizinic acid

Uses:

- flavoring agent, mild expectorant and as demulcent, and for the treatment of rheumatoid arthritis, Addisons´s disease and various inflammatory conditions.

- **Glycyrrhizinic acid** exhibits inhibiting of the Δ4-5-β- reductase activity, which is responsible for the degradation of corticoids.




LifeStyle
Cough Zero
Cough Syrup
100%
120 ml
Cough Zero
Cough syrup

Saponin-containing drugs with anti-exudative activity

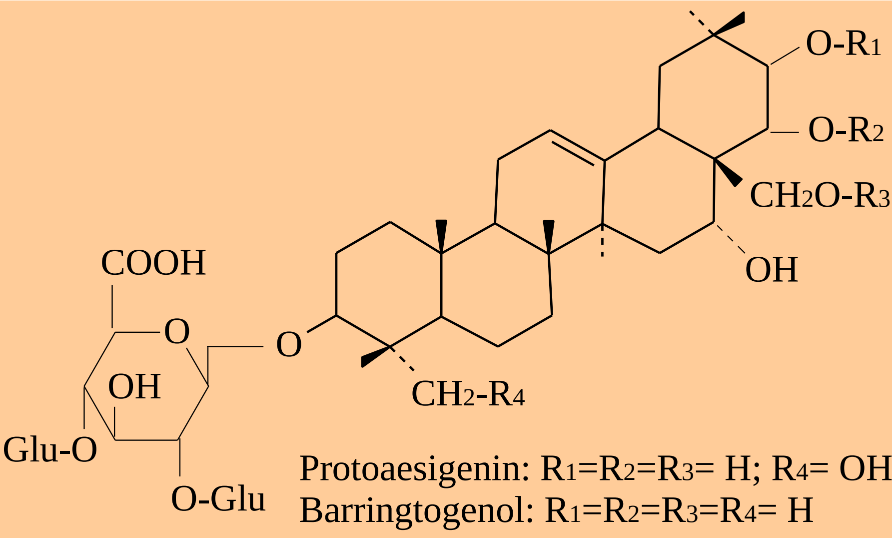
Seeds of Horse chestnut

- seeds of ***Aesculus hippocastanum*** **(Fam. Hippocastanaceae)**.

- 10 % Triterpen saponins, referred to as **Aescin**, (a mixture of several glycosides derived from 2 triterpenoid aglycones from the olean-12-ene series **protoaescigenine** and **barringtogenol C).**

- The drug showed **anti-inflammatory**, **anti-edema** and **anti-exudative** activity.

- It is used to treat the symptoms of varicose symptom complex (VSC) such as pains, heaviness, tension in the legs and pruritus.



Protoaesigenin: $R_1=R_2=R_3=$ H; $R_4=$ OH
Barringtogenol: $R_1=R_2=R_3=R_4=$ H

Aescin- and *Aesculus extract*-containing drugs

Saponin-containing drugs as Adaptogens

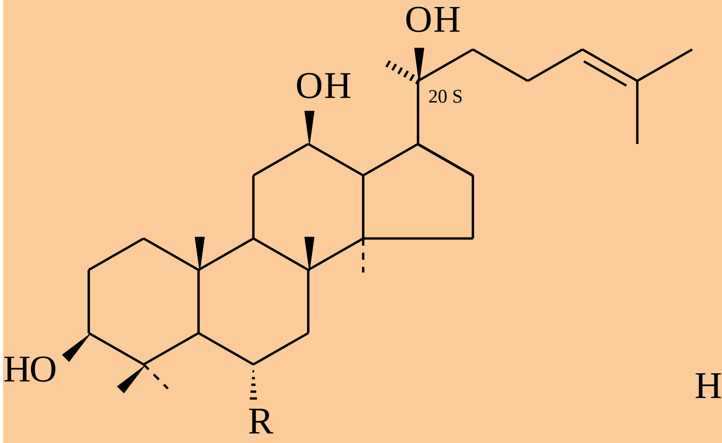
Ginseng

- The drug consists of the dried roots of ***Panax ginseng*** (Korean ginseng) or ***Panax quinquefolium*** (American ginseng) Fam. Araliaceae**.**

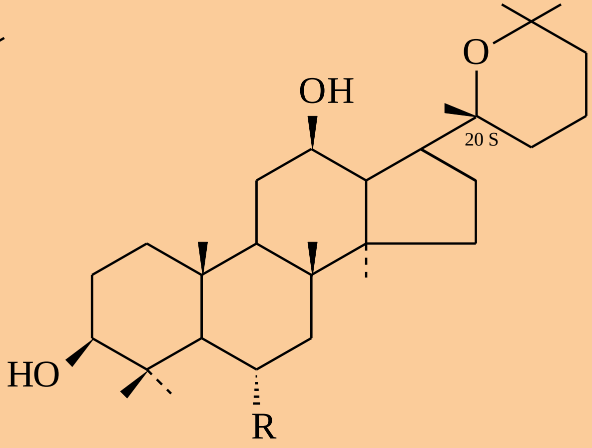
- Ginseng contains 2-4 % saponins. (about 20 glycosides of **tetracyclic aglycones of the** dammarane-series (**ginsenosides).**
- **important types are:**

1- Trihydroxylated type (**protopanaxadiol**)

2- Tetrahydroxylated type (**protopanaxatriol**).



R=H: Protopanaxadiol
R=OH: Protopanaxatriol



R=H: Panaxadiol
R=OH: Panaxatriol

Uses:

- CNS stimulant (used as adaptogen).

(increase resistance to fatigue and stress and improve memory)

- used for the symptomatic treatment of functional asthenia, for the treatment of anemia, diabetes and sexual impotence and conditions arising from the onset old age.
- improves general health and lack of concentration.

Panax ginseng

Roots

Ginseng-containing drugs

www.chinaslimming.com

Flavonoid glycosides

(Part 4)

What are Flavonoids??

Flavane-derivatives

- Chemically, they are **2-phenylchroman derivatives**.
- Flavonoids are virtually universal plant pigments.
- They are responsible for the color of flowers, fruits and sometimes leaves.
- They ensure tissue protection against the damaging effects of UV radiation.

Classification

They fall into many classes depending on the degree of oxidation of the central pyran ring:

1- **Flavanones** (**4-Oxo-flavane**) such as naringenin.

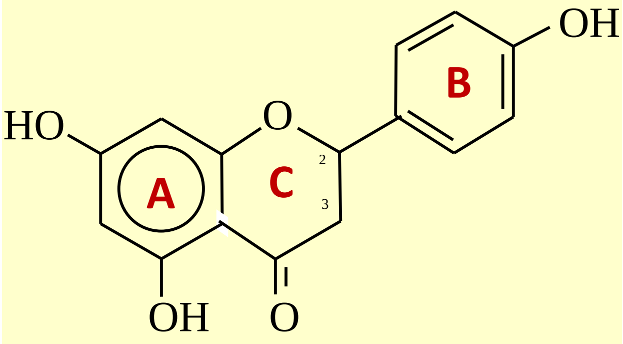
2- **Flavones** (**4-Oxo-flav-2-ene**) such as apigenin.

3- **Flavonols** (**3-Hydroxy-4-Oxo-flav-2-ene)** such as quercetin.

4- **Flavanols** (**3-Hydroxyflavane, Catechine**) such as (+)-catechine.

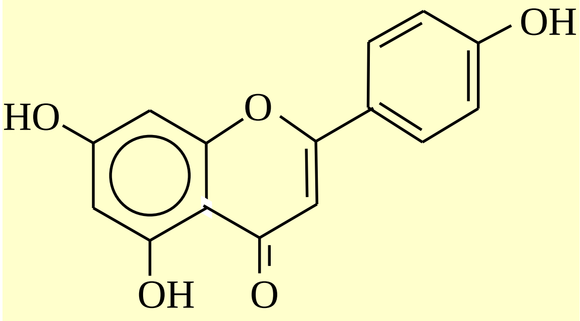
5- **Flavandiols** (**3,4-dihydroxyflavane)** Leukoanthocyanidine).

6- **Flavylium-salts** (**Anthocyanidine**) such as cyanidine.



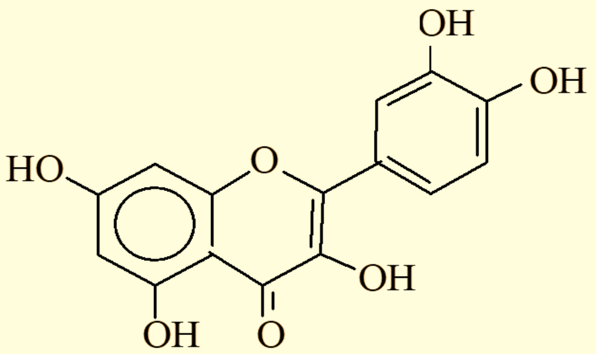
Flavanone [naringenin]

(4-Oxo-flavane)



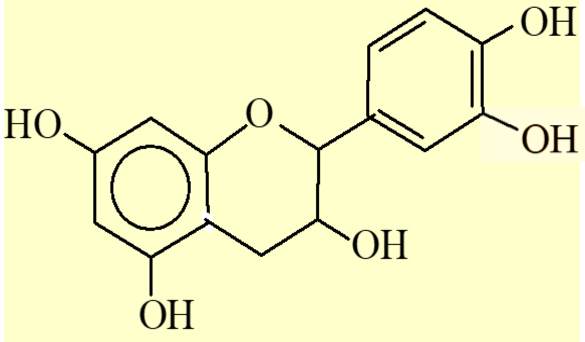
Flavone [apigenin]

4-Oxo-flav-2-ene



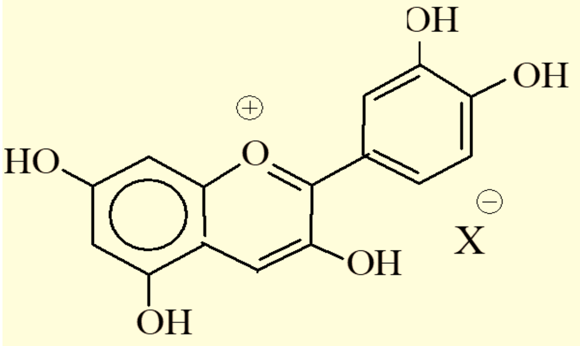
Flavonol[quercetin]

3-Hydroxy-4-Oxo-flav-2-ene



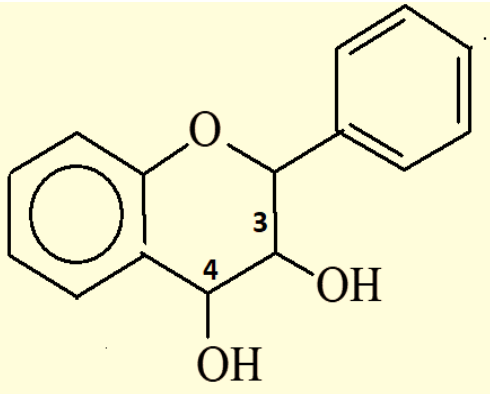
Flavanol
(Catechine)

3-Hydroxyflavane



Flavylium salt
(Anthocyanidine)

[Cyanidine]



Flavandiol

(3,4-dihydroxyflavane)

[Leukoanthocyanidine]

Distribution

- Flavonoids are common in the plant kingdom, Bryophytes (mosses and hepaticas), and in Pteridophytes.
- No flavonoids have been found in algae.
- More than 3000 of these compounds are now known, with nearly 500 aglycones.
- They are abundant in the Polygonaceae, Rutaceae, Rosaceae, Leguminosae, Umbelliferae, Lamiaceae and Compositae.

Flavonoid glycosides

- The sugar moiety may be a mono-, di-, or trisaccharide, linear or branched.
- Monosaccharides include D-glucose, D-glalctose or D-allose, L-rhamnose, or D-glucuronic or D-galacturonic acid.
- The glycosidic bond may be established through any of the phenolic OH-group on the aglycone (**O-glycosides**).
- **C-glycosides** are not rare, more than 300 are known, the bond is established between the asymmetric carbon on the sugar and the C-6 or C-8 of the aglycone.

Identification and Characterization

- with 5% **$AlCl_3$** in methanol (yellow-green fluorescent spots in UV light)

- with 1 % solution of **diphenylboric acid-2-aminoethyl ester (Naturstoff Reagent A)** (red-brown color is formed).

- with **$FeCl_3$, anisaldehyde-reagent:** for phenols.

- **Pacheco´s test for dihydroflavonols (with sodium acetate/acetic anhydrid/HCl)** (Red color).

- **Pew´s test for dihydroflavonols (with Zinc/HCl):** deep purple-red with dihydroflavonols and brownish color Flavanones and other flavonoids.

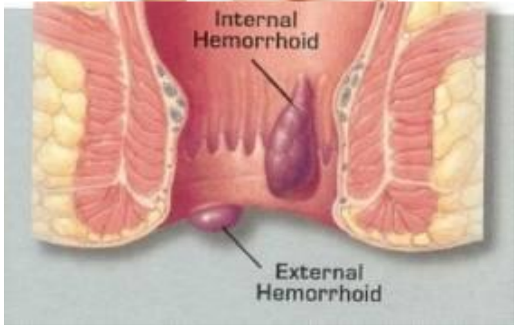
- **Shinoda test for flavanones and dihydroflavonols (with Mg/HCl)** Deep-red or magenta color is produced.

Pharmacological and biological properties

- They **decrease capillary permeability and fragility**
- They are **enzyme inhibitors** such as **lipooxygenase, cyclooxygenase, histidine decarboxylase, hyaluronidase, cAMP phosphodiesterase**.
- Many flavonoids are **antioxidants**, because they react with free radicals.
- Therefore, they show **anti-inflammatory**, **antiallergic**, **hepatoprotective** and **antispasmodic**.
- They can **decrease blood cholestrol**, be **diuretic**, **antibacterial** and **antiviral**.

Therapeutic uses

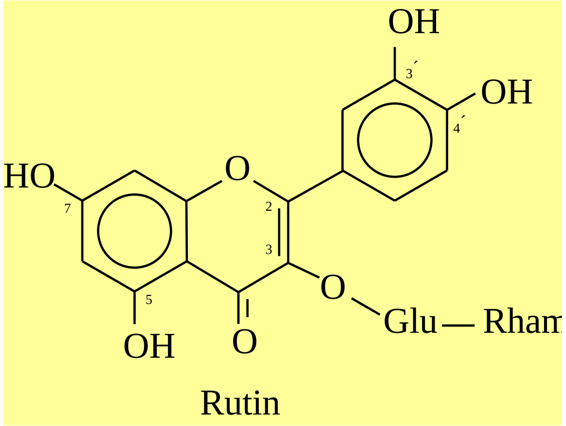
- Treatment of the symptoms of venous and lymphatic vessel insufficiency (tiredness or fullness in the legs, cramps, pains and other dysfunctions, edemas)
- Treatment of circulatory disturbances.
- Treatment of capillary fragility disorders of the skin (ecchymosis, petechiae) and of mucosas (gingival hemorrhage, epistaxis).
- Treatment of dysfunctions linked to the acute attack of piles.
- Metrorrhagia linked to intra-uterine contraceptive devices.



Chief flavonoids on the Market

1- Rutin

- It is a flavonol glycoside. Chemically, it is quercetin-3-O-(6-O-rhamnoside) glucoside. [Quercetin-3-O-rutinoside]



Rutin

It occurs as yellow crystals, soluble in boiling water and alcohol.

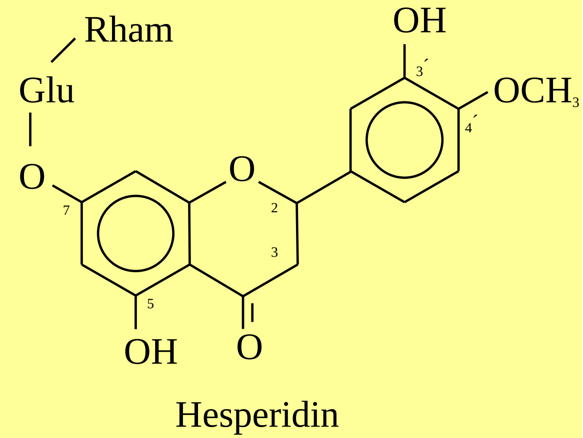
- Rutin alone or in combination with other substances is used as described previously, particulaly to treat **hemorrhages** linked to diabetes and hypertension, and to treat the functional symptoms of the **acute attack of piles**.

2- Citroflavonoids (especially Hesperidin)

- They are extracted from Pericarps and pulbs of Citrus fruits (F. Rutaceae) as Ca and Mg derivatives.
- Hesperidin is hesperitin-7-O-(6-O-rhamnoside) glucoside, it occurs up to 8 % in the pericarp.

Uses:

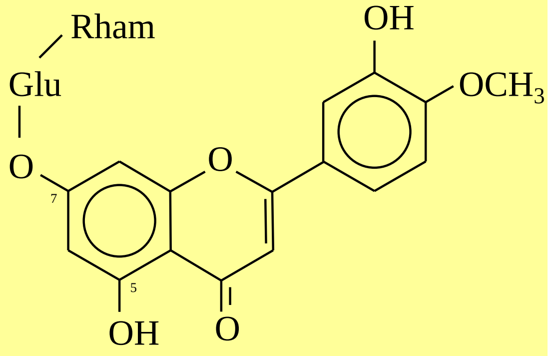
- in the treatment of the leg symptoms of chronic, functional and organic venous insufficiency,
- and as adjuvant or prophylactic with vitamin C for the treatment of common cold and infections.



Hesperidin

3- Diosmin

- It is a flavone glycoside found in Buchu leaves (***Barosma*** sp.) Fam. Rutaceae
- It occurs in pale yellow needles or powder.
- Acid hydrolysis of diosmin yields diosmetin (aglycone) besides one molecule of rhamnose and glucose.



Diosmin

- **Uses:**
- diuretic and diaphoretic effect
- also in the treatment of venous disorders.

Barosma betulina

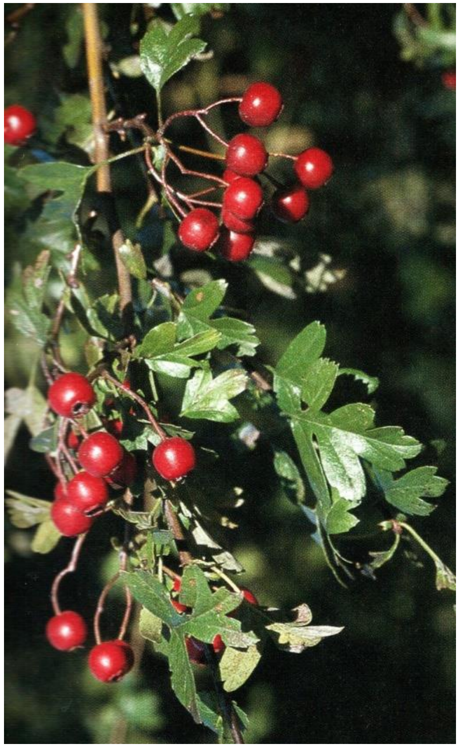
Flavonoid containing drugs

1- White thorn herb

- The drug consists of the herb and sometimes of the fruits of ***Crataegus monogyna, C. laevigata*** **and of *C. pentagyna* (Fam. Rosaceae)**
- The drug contains:
- 2 % flavonoids (0.7 % as hyperoside), other chief constituents are vitexin, rutoside, apigenin- and luteolin-derivatives.
- Up to 1 % oilgomeric procyanidines (4,8- or 4,6 dimeric, trimeric to hexameric flavan-3-ols).

- **Uses:**

It is used in the treatment of cardiac insufficiency (grade I-II to NYHA), in treatment of brady arrhythmia and to improve the circulation of the coronary artery.



C. monogyna

2- Maidenhair tree

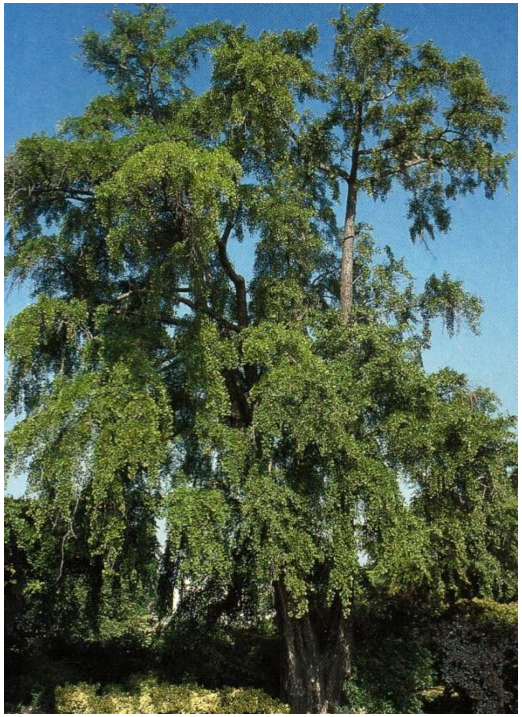
- Leaves of ***Ginkgo biloba*** **(Fam. Ginkgoaceae)**
- found in China and Japan, but also cultivated in Europe.
- The drug contains:

1- 0.4-2 % biflavonoids (amentoflavone, bilobetin, and ginkgtin)

2- 0.5-2 % flavonol glycosides. (quercetin and kaempferol-derivatives)

3- 4-12 % flavan-3-ols and proanthocyanidins

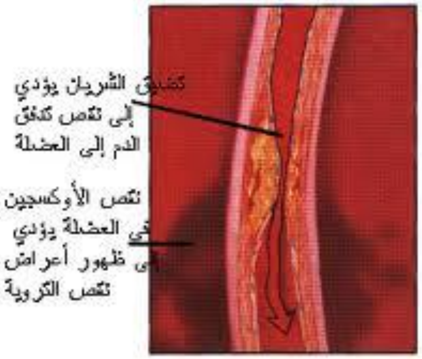
4- 0.02-0.2 % ginkgolides (complexes of diterpenlactones)

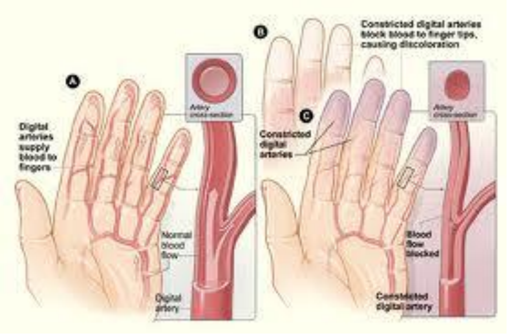


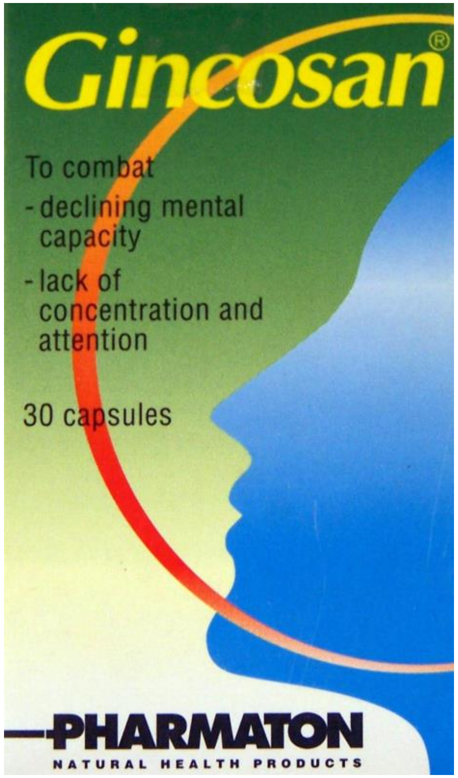
Uses:

- In the treatment of the symptoms of **senile cerebral insufficiency (vertigo, tinnitus and hearing loss, lack of concentration).**

- In the treatment of the **intermittent claudication** and of **Raynaud´s disease.**






Gincosan®
To combat
- declining mental capacity
- lack of concentration and attention
30 capsules
PHARMATON
NATURAL HEALTH PRODUCTS

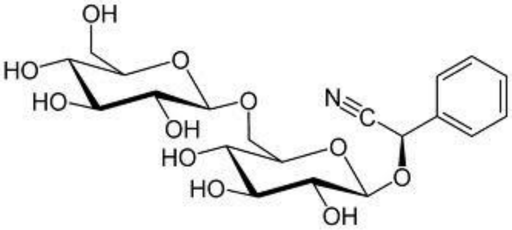

Natural
Ginkgo biloba extract 60 mg
Ginseng extract 100 mg
Royal jelly 600 mg
البلسم الشامي
GINKOFIT
Memory Enhancer & General Tonic
10 capsules


Tablets
Bio-Biloba™
Tablets
100 mg Ginkgo biloba extract
Pharma Nord


TEBONIN
EGb 761
Memory
Mental Performance
Blood Circulation
Tinnitus
Vertigo
30 TABLETS

Cyanogenetic glycosides

(Part 5)



What are cyanogenetic glycosides ??

- **Cyanogenesis** is the ability of certain living organisms, plants in particular, to produce hydrocyanic acid.

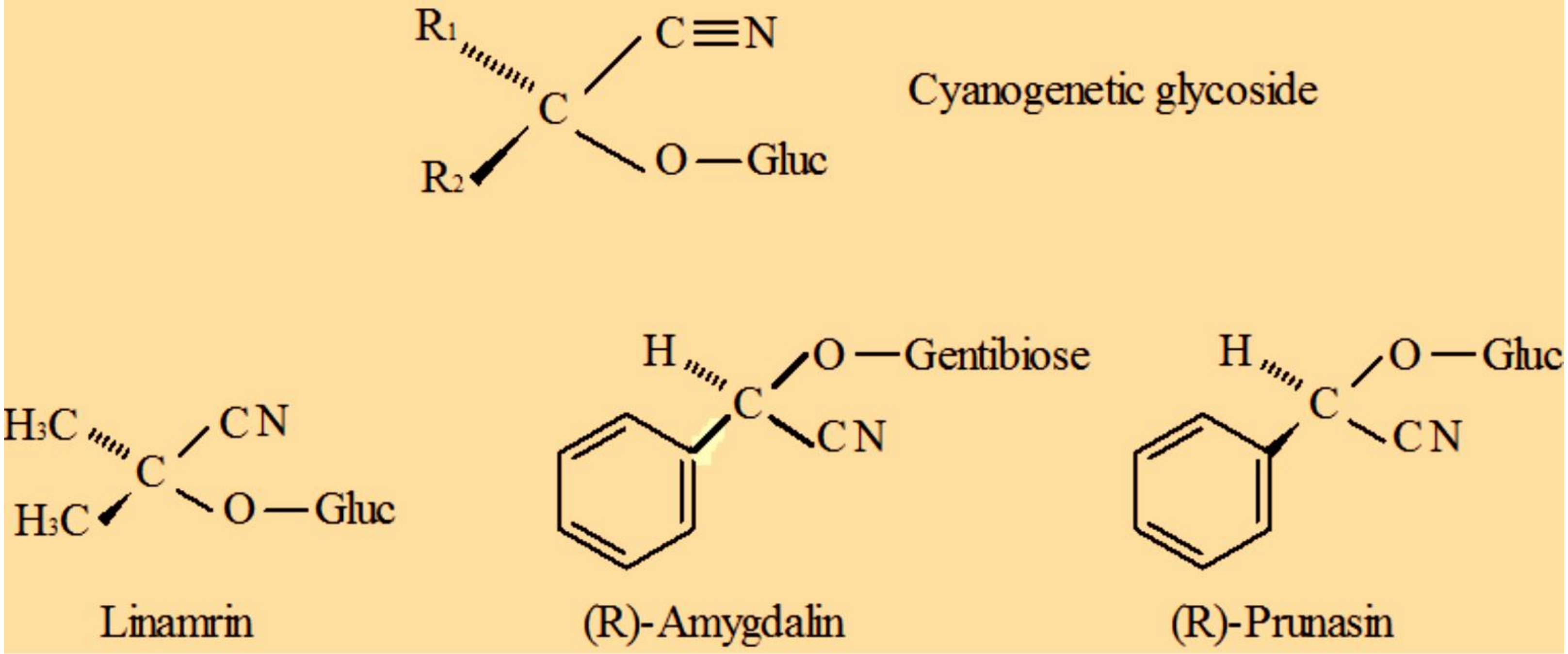
Definition:

- **Cyanogenic substances are always glycosides of α-hydroxynitriles (cyanohydrines) commonly known as cyanogenic (or cyanogenetic) glycosides.**

Distribution:

- The cyanogenetic glycosides are particularly found in Rosaceae, Fabaceae, Poaceae, Araceae, Euphorbiaceae and Passifloraceae.

Chemical Structure



Cyanogenetic glycoside

Linamrin

(R)-Amygdalin

(R)-Prunasin

Physicochemical Properties

- The glycosides are readily hydrolyzed, at near neutral pHs, by more or less specific **β-glucosidases** which release **monosaccharide** and a **cyanohydrin** (a cyano and a hydroxy group attached to the same carbon atom with the formula $R_2C(OH)CN$).
- Cyanohydrin is unstable and dissociates to **HCN** and **carbonyl compound**, either an **aldehyde** or **ketone,** this second reaction is catalyzed by a **hydroxynitrile lyase**.
- **In mildly acidic medium** and at elevated temperatures, the glycosides are hydrolyzed as with glucosidases, and at near neutral pHs, the decomposition of the cyanohydrin is spontaneous and very rapid.

Chemical identification and detection

- Cyanogenetic glycosides are easy to detect with a strip of filter paper impregnated with reagents able to give a colored reaction with the hydrocyanic acid released upon crushing the plant **material.**
- **Important used reagents:**
- **1- picric acid/Na_2CO_3: sodium picrate (yellow, Guignard reagent)** is converted to **sodium isopurpurate (brick-red)**,
- 2- freshly prepared solution of **guaiacum resin** in absolute alcohol and treated with very dilute copper sulfate solution. The test paper turns **blue with prussic acid (HCN).**

Metabolism and Toxicity

- Although hydrocyanic acid is a violent poison, it is important to remember that oral intake of cyanogenic drugs does not necessarily cause severe intoxication.

Why??

1- The range of dangerous concentrations (0.5-3.5 mg/kg) can only be achieved by massive consumption of glycoside-rich plant parts.

2- The human organism is known to have the ability to fairly rapidly detoxify cyanides to thiocyanates using a thiosulfate sulfurtransferase, the resulting thiocyanates are eliminated in urine (30-60 mg/h).

Metabolism and Toxicity

- Massive intoxication manifests itself by multiple symptoms that result from the cytotoxic anoxia.
- **Why anoxia?????!!!!!!!!!!!!!!**
- **Because of the combination of cyanide ions with cytochrome C oxidase, the reoxidation of cytochrome C is interrupted and molecular oxygen can no longer be used by the cell.**
- A change in respiratory rhythm is frequently observed, as well as headaches, dizziness, and inebriation.
- Next are consciousness disturbances, followed by a deep coma and respiratory depression.

Treatment

- If the dose is small enough to not cause rapid death, an appropriate treatment must be applied expeditiously:
- **1- stomach pumping**
- 2- **oxygen therapy**
- 3- **chelation of cyanide ions by hydroxycobalamin infusion**
- 4- **stimulation of detoxification mechanisms (with sodium thiosulfate).**

Drugs containing cyanogenetic glycosides

1- Bitter almond (*Amygdalus communis*, family Rosaceae)

- The seeds contain 0.2-8 % amygdaline.
- It used to prepare **almond water** for the treatment of bronchi-pulmonary conditions and as an aroma.

Other Plants containing cyanogenic glycosides

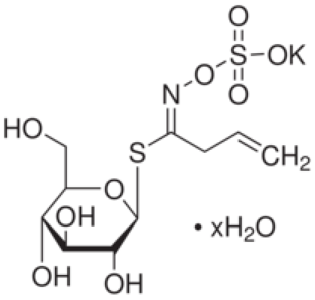
Prunus laurocerasus
(Cherry laurel)

Trifolium repense
(White Clover)

Linum usitattisimum
(Flaxseeds)

Glucosinolates

(Part 5)



What are **Glucosinolates** ??

Definition:

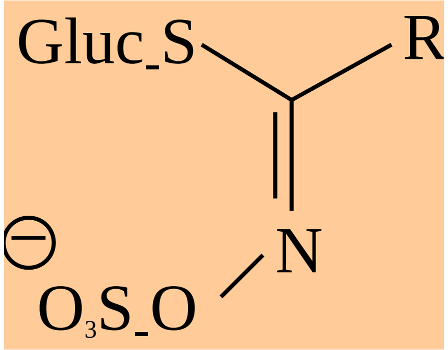
- **Glucosinolates (called thioglucosides)** are anionic glycosides responsible for the potent and characteristic aromas of numerous Brassicaceae (mustard, radish), and of various species pertaining to other botanically close families (Capparidaceae and Resedaceae).

Distribution:

- Brassicaceae, Capparidaceae and Resedaceae.

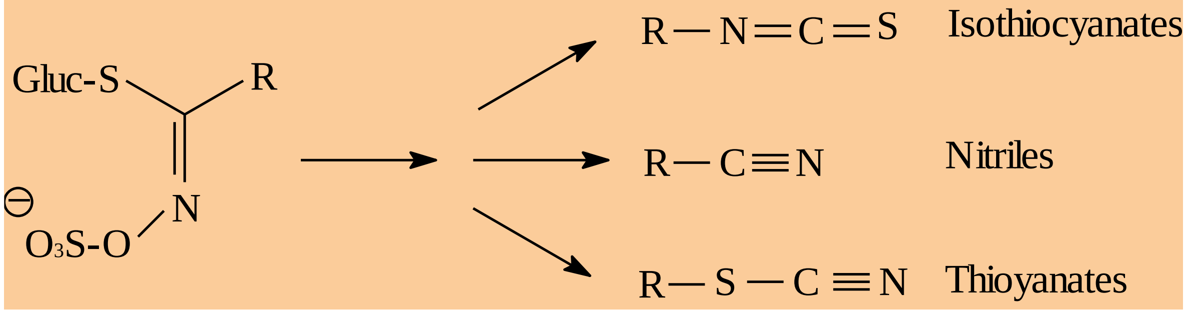
Chemical Structure

- The basic structure of glucosinolates comprises a **glucose residue**, a **sulfate group**, and a **variable aglycone**, with the molecule occurring as a **K-salt**.
- The structural diversity of glucosinolates reflects that of their precursor amino acid:
- 1 - Tyrosine → p-hydroxybenzylglucosinolate → Sinalbin
- 2 - Homomethionine → allylglucosinolat → sinigrin
- 3 - Tryptophan → 3-indolylmethylglucosinolate → glucobrassicin (cabbage)



Glucosinolate hydrolysis

- When the tissues of glucosinolate-containing plants are bruised, the compounds are hydrolyzed by a thioglucosidase (myrosinase) always present in this type of plant.
- In all cases, the freed aglycone is unstable and rearranges as the following:
- 1- If the pH is neutral, Loessen rearrangement tacks place and yields a very reactive, volatile and strong-smelling isothiocyanate.
- 2- In slightly acidic medium, sulfur and nitrile are formed.
- 3- Thiocyanate can be formed in some plants.



Glucosinlate toxicity

- Ingestion of amounts of Brassicaceae species by animals cause hypothyroidisim, which results in goiters, abortions and fetal death in utero.

Mechanism:

- Thiocyanates capture iodide, and prevent its uptake by the thyroid.

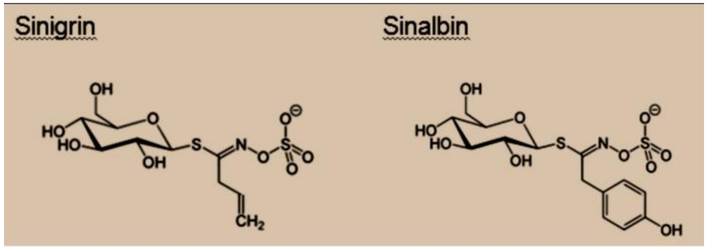
Advantages:

- Glucosinolates can also have advantages, their presence in the diet might have a protective effect against colon cancer.

Drugs containing glucosinolates

1- Mustard seed

- Black or brown mustard (Sinapsis) is the dried ripe seed of ***Brassica nigra*** or of ***Brassica juncea*** **(Fam. Brassicaceae).** Black mustard seeds contain **sinigrin** and **myrosin**
- White mustard seeds of ***Sinapis alba*** contain the glucoside **glucosinalbin** and **myrosin**



Uses:

- The mustards have been traditionally used, in the form of plasters, as **rubefacients** and **counterirritants.**
- Both varieties are used as **condiments**.

Abb. 1 Braune Senfsamen

b. 1 Weiße Senfsaat


Abb. 2 Sareptasenf (*Brassica juncea* (L.) CZERN.)


. 2 Weißer Senf (*Sinapis alba* L. ssp. *alba*)

Brassica juncea ***Sinapis alba***

Drugs containing glucosinolates

- Black radish of *Raphanus sativus*, family Brassicaceae
- Hedge mustard of *Erysimum officinale*, family Brassicaceae.

Raphanus sativus