Glycosides

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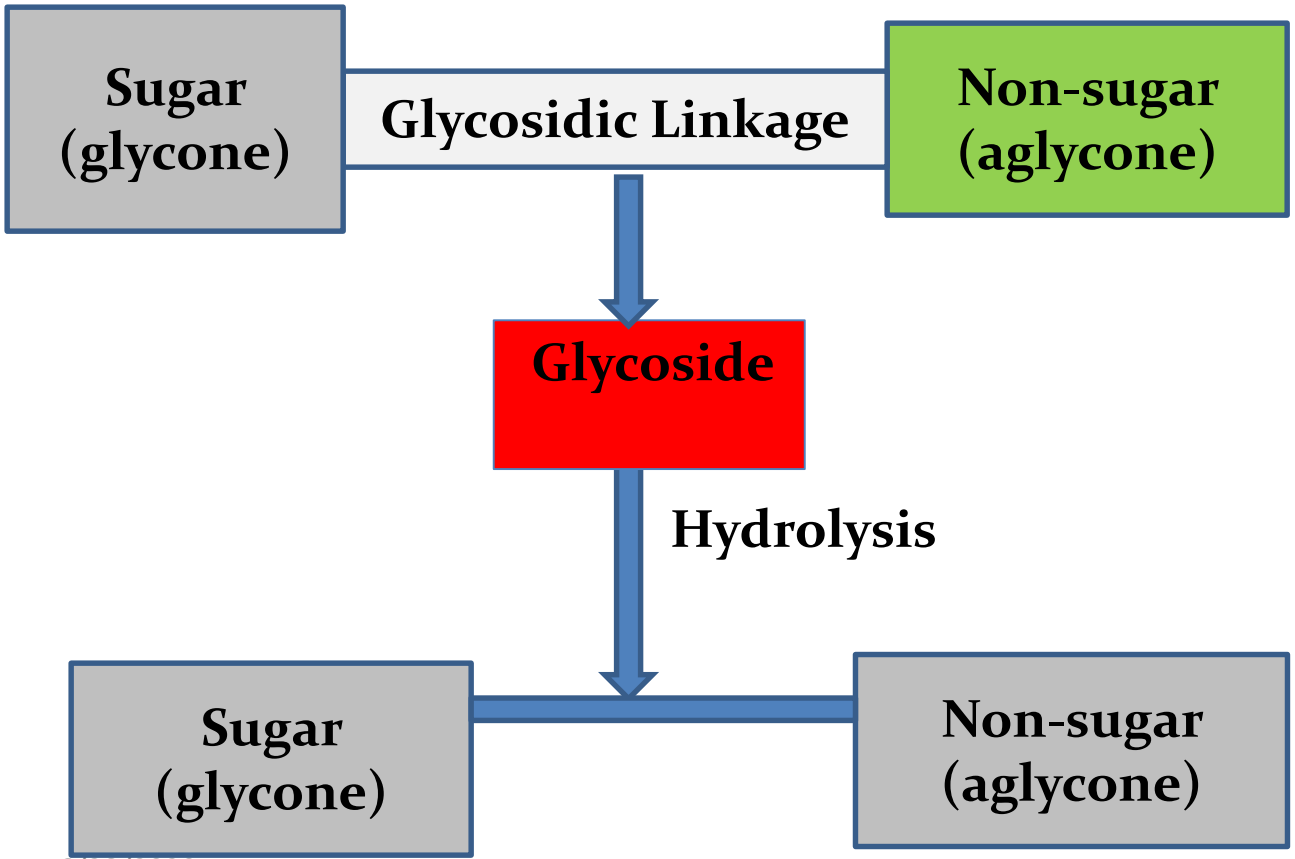
Introduction

- Glycoside refers to any natural product which can potentially occur bound to sugars.
- Glycosides or sugar ethers, are a complex compounds that can broken down to yield one or more sugars (glycone) and non-sugar parts (aglycone or genin).
- Glycosides are most commonly classified according to the chemical nature of the aglycone, and have vast medicinal applications

General formula of glycosides



Why do we study glycosides?

- Glycosides are **widely distributed** in plants and responsible for their medicinal value.
- Many Glycosides
  - are **toxic**
  - are ecologically important
  - Serve as potential source of new drugs.
  - Serve as starting materials for semi-synthetic drugs.

General properties of glycosides

A. Distribution

- Glycosides are mostly found in plants and microorganisms. however, very few important glycosides are obtained from animals.
- They are generally present in vacuoles of cells (intracellular).
- The amount of glycosides may vary in the same plant due to seasonal, climatic conditions, and growth stage of the plant.

B. Chemical properties

- Generally, glycosidic compounds occur as a combination of an aglycone with glycone (s).
- However, the aglycone part could sometimes be found free.

- D-glucose is the most common sugar that occurs in glycosides.
- Most glycosides have a true sugar moiety; however, in some glycosides the sugar moiety is not a true sugar but rather a sugar derivative such as uronic acids.
- In glycosides, the aglycone is attached to the C_1 of sugars.
- More than one sugar molecule may be present in glycosides.
    - The sugar molecules may be attached to
        - At different points of the aglycone, or
        - attached to each other as disaccharides, trisaccharides
- *Most glycosides are hydrolysable by boiling on acids.*

- Almost all glycosides are accompanied by enzymes which can hydrolyze them.
- These enzymes are found in different cells of the plant or in the same cells bound with membrane bound.
  - During injury to the tissue, germination or other physiological activity, the enzymes may come with the glycosides, and the hydrolysis of glycosides takes place.

C. Physical properties

- Most glycosides are amorphous, colorless, nonvolatile compounds.
- They are optically active forming levorotary solutions in water and alcohol

- Glycosides are soluble in water or alcohols and insoluble in organic solvents
  - Exception: resin glycosides
  - Their solubility in organic solvent decrease with increase in the sugar content
- The aglycone part is soluble in organic solvents like benzene or ether
- They are hydrolyzed by water, enzymes and mineral acids.
- Most glycosides have bitter taste.

Role of glycosides in plants

- Involved in **sanitary** (detoxification), **regulatory**(growth) or **protective** activities.
- Storing harmful substances like phenol
- Attraction of pollinators due to beautiful color (flavonoids such as anthocyanins)
- Protection from infection due to their antimicrobial constituents
  - Bitter almond contains **Amygdalin** which upon hydrolysis release **HCN** that have **bactericidal activity**
- Modify solubility of compounds using monosaccharide
- Stabilize some liable compounds.
- Some glycosides are also used as **sugar reserves** (Source of energy), for example, for germinating seeds.

Pharmacological activity

- The aglycone part is responsible for the Pharmacological activity of glycosides.
- The sugar part influences stability, solubility and ultimaetly PK phenomena (absorption and distribution) of the drug in the body..
- Some glycosides are not active in the glycosidic form but on hydrolysis, they yield active aglycone.

✓ Such drugs are known as " reactionary drugs".

Classification of glycosides

1. **Based on the type of glycone**

- Glucoside ----glucose. E.g. Sennoside.
- Fructoside-----fructose.
- Rhamnosides----rhamnose. E.g. frangullin.
- Rhamnoglucosides---- rhamnose and glucose E.g. Rutin
- Glucuronide----glucuronic acid, etc.

2. On the Basis of Glycosidic Linkage

A. O-glycosides: Sugar molecule is combined with alcoholic

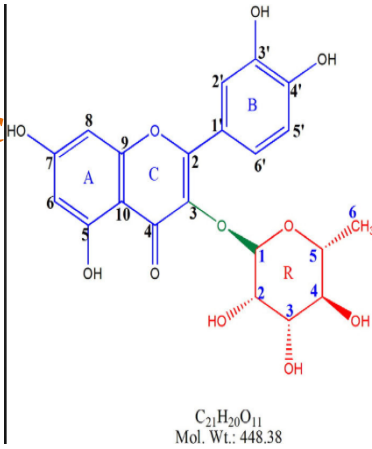
– Phenolic OH group, or carboxylic group of the aglycone.

– O-glycosides are regarded as **sugar ethers.**

– O-glycosides are the most abundant glycosides.

– They can easily be hydrolyzed boiling in mineral acids

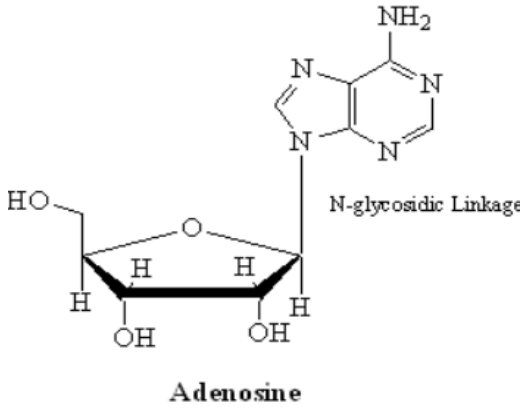
– Example: Amygdaline, Indesine, Arbutin, Salicin, cardiac glycosides



Classification…

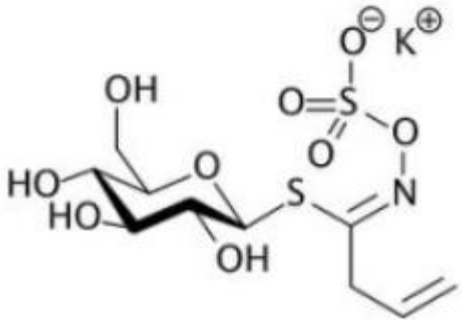
B. N-glycosides: Sugar molecule combined with N of the amino group of aglycone

- They can easily be hydrolyzed by boiling in mineral acids.
- Example: nucleosides, DNA, RNA



Adenosine

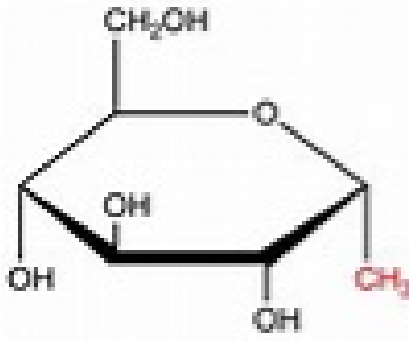
C. S-glycosides: Sugar molecule is combined with the S or –SH sulfahydral (thiol group) of aglycone,



- **Example:** Sinigrin
- *Natural S-glycosides are very few.*
- They can easily be hydrolyzed by boiling in mineral acids

Classification…

D. C-glycosides: Sugar molecule is directly attached with C—atom of aglycone.



- They are highly resistant to acid hydrolysis.
- They can only be hydrolyzed **oxidatively.**
- Example
  - Anthraquinone glycosides : Aloin, Barbaloin, Cascaroside
  - Flavan glycosides, etc.

Classification…

Primary and secondary glycosides

- **Primary glycosides:** are those which have an oligosaccharide unit and are extracted intact, **without losing any sugar unit**.
- **Secondary glycosides**: Extraction and drying processes can result in the removal of one or two sugars from primary glycosides giving rise to a new glycoside with less number of sugar units.

Classification…

3. Based on pharmacological activity

Example

- Cardiac glycosides are those which have pharmacological effects on the heart.

4. Based on the chemical nature of the aglycone

- Anthraquinone
- Saponin
- Flavonoids
- Alcohol
- Simple phenolic glycosides
- Cyanogenetic (cyanophoric) glycosides
- Aldehyde glycosides
- Isothiocyanate glycosides
- Lactone glycosides

Nomenclature

1. Trivial names

- Have an “in” ending and
- The name indicates the source of the glycoside.
- E.g.
  - ✓Digitoxin from digitalis
  - ✓Salicin from salix and
  - ✓Prunasin from pronus

Nomenclature…

2. Systemic names

- Formed by replacing the " ose" suffix of the parent sugar with "oside"
- The anomeric prefix (α or β) and the configuration prefix (D or L) immediately precede the sugar stem name, and
- The chemical name of the **aglycone** precedes the name of the sugar.
  - E.g. the systematic name for salicin is:

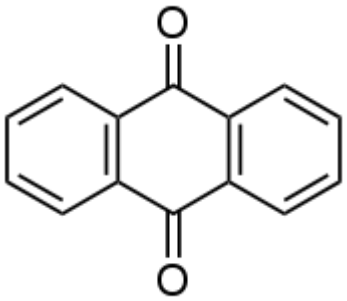
    O-hydroxy methyl phenyl β-D-glucopyranoside

Medicinally and pharmaceutically important glycosides

I. Anthraquinone (anthracene) glycosides

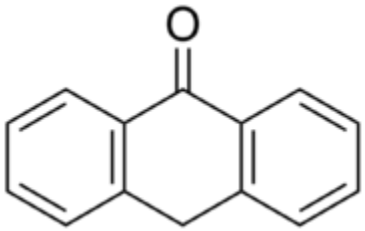
- Anthraquinone glycosides are those glycosides which have anthraquinone derivative aglycones.
- They are also called anthracene glycosides but anthracene does not occur naturally.
- They are mostly C- glycosides but some O-glycosides also occur.
- The anthraquinone aglycones can exist in different oxidation state.

anthracene

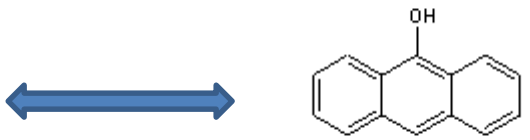


Anthraquinone

4H

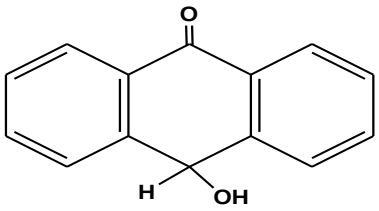


Anthrone



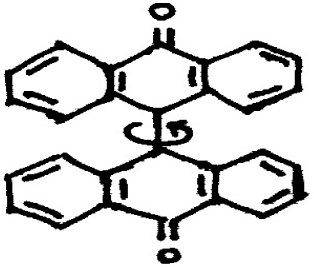
Anthranol

2H



Oxanthrone

-2H



Dianthrone

Pharmacological activity

- Are stimulant cathartics exciting peristalsis acting on large bowel.
  - Increase the strength of peristalic contractions but not the frequency.
  - Their effect may be delayed up to 6 hrs or longer
- Glycosides of anthranols and anthrones elicit a more drastic action than do the corresponding anthraquinone glycosides.
- The glycosides are hydrolyzed by the enzymes of the microflora to the pharmacologically active free aglycones.
- They have anti ageing, hydrating properties & Prevent hair problems
- At larger doses, they cause colic pain.
- They are habit forming.
  - They must not be prescribed for more than 15 days.

Chemical tests for anthraquinone glycosides

1. Borntrager's test

- This test requires free anthraquinone-type aglycones.
- The drug is boiled with dilute sulphuric acid, filtered and to the filtrate benzene, or ether or chloroform is added and shaken well.
- To the filtrate in the test tube an equal amount of NH_4OH is added and shaken.
- Anthraquinone-type aglycones produce pink, red or violet color with **NH_4OH solution or $NaHCO_3$ solution.**
- Glycosides and reduced anthraquinone aglycones (anthrones, anthranols, oxanthrones and dianthrones) do not give positive result in this test.

2. Schonteten's test (Florsence test for anthranols)

- Anthranols produce a strong green florescence in (borax sodium borate) or other alakli solutions.

Products available in Ethiopia

- Senna tablets: it is unofficial drug for laxative effect by irritating the bowel.
- Cascara tablets

Drugs containing AQG

Crud drug	Botanical source	Active constituents	Use
Senna	Dried leaflets of *cassia acutifolia* or *C. angustifolia* (fam. Fabacieae)	Sennosides A and B	• Stimulant cathartics
Rhubarb	Dried rhizomes and roots of *Rheum officinale* or other spices of Rheum except *R. raponticum* (fam. Polygonaceae)	Sennosides, chrysophanol glycosides, aloe-emidin glycosides and emodin glycosides	Laxative
Cascara	Dried bark of *Rhumunus purshina* (fam. Rhamnaceae)	O-glycosides (10-20%), C-glycosides (80-90%) and some free anthraquinones: e.g. cascarosides	Laxative
Aloe	Dried juice of the leaves of various spp of Aloe like *Aloe barbadensis* (fam. Liliaceae)	Two fractions: an anthraquinone fraction called " aloin" and resins. Barbaloin is the major constituent	Purgative

Senna

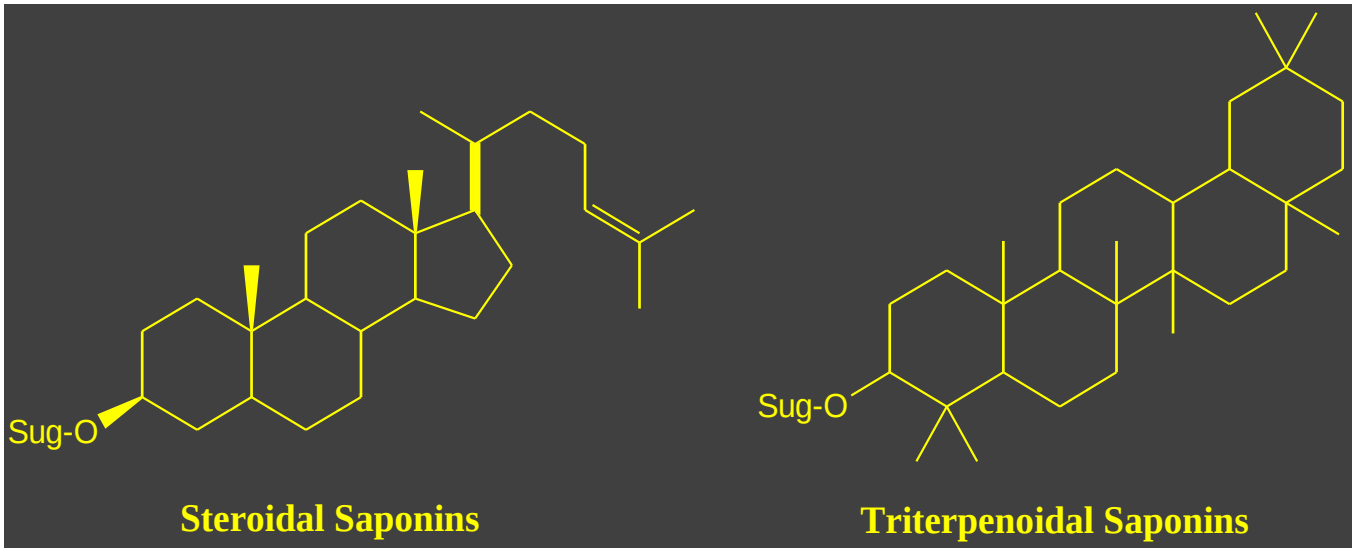
Cascara

Rhubarb

Aloes

II. Saponin glycosides

- Saponins (Soap like) are group of organic compounds that form persistent froth when shaken with water.
- Saponin aglycones are commonly referred to as sapogenins.
- Based on the sapogenin unit, saponin glycosides are classified in to pentacyclic triterpenoids glycosides and steroidal glycosides



Properties of saponin glycosides :

- Soluble in water, alcohol and mixture of them.
- Form persistent foam (froth) with water and used as detergent and emulsifying agents.
- Are hemolytic to red blood cells.
- Have poor oral absorption but they enhance absorption of other drugs.
- All saponin glycosides have β-O- glycosidic linkages at C-3.
- Some may have O- or C- glycosidic linkage at other site.
- They form a 1:1 addition complex (precipitate) with cholesterol, esp. in the presence of Ca^{2+} which is responsible for their *hemolytic* activity.

Triterpenoidal Saponins (Pentacyclic triterpenoid saponins)

- They are C-30 compounds.
- Much more distributed in nature.
- Have pentacyclic skeleton with 8 methyl groups.

1. Licorice

- Dried unpeeled roots and rhizomes of *Glycyrrhiza glabra* (fam. Fabaceae)
- Contains glycyrrhizin which yields glycyrrhetic acid (glycyrrhetinic acid) on complete hydrolysis.
- Uses:
  - As sweetening agent and appetite enhancer
  - Treatment of rheumatoid arthritis and other inflammatory conditions

2. Quilliaja bark

- Dried inner bark of Quilliaja (fam. Rosaceae)
- Contains quillia saponins e.g. QS-21A
- Uses:
  - ✓ As emulsifier
  - ✓ As detergent in shampoos

Steroidal Saponins

- They are C-27 with 5 methyl groups.
- Less distributed in nature comparing to triterpenoidal saponins.

❑ Pharmaceutical application of saponin glycosides

- Due to their structural similarity steroidal glycosides are used as starting material for the semi-synthesis of **steroid based drugs** like
  - Sex hormones (for replacement therapy and preparations of oral contraceptives).
  - Cortisones (steroidal anti-inflammatory drugs), and
  - Diuretic steroids (e.g. spironolactones)
  - Vitamin D

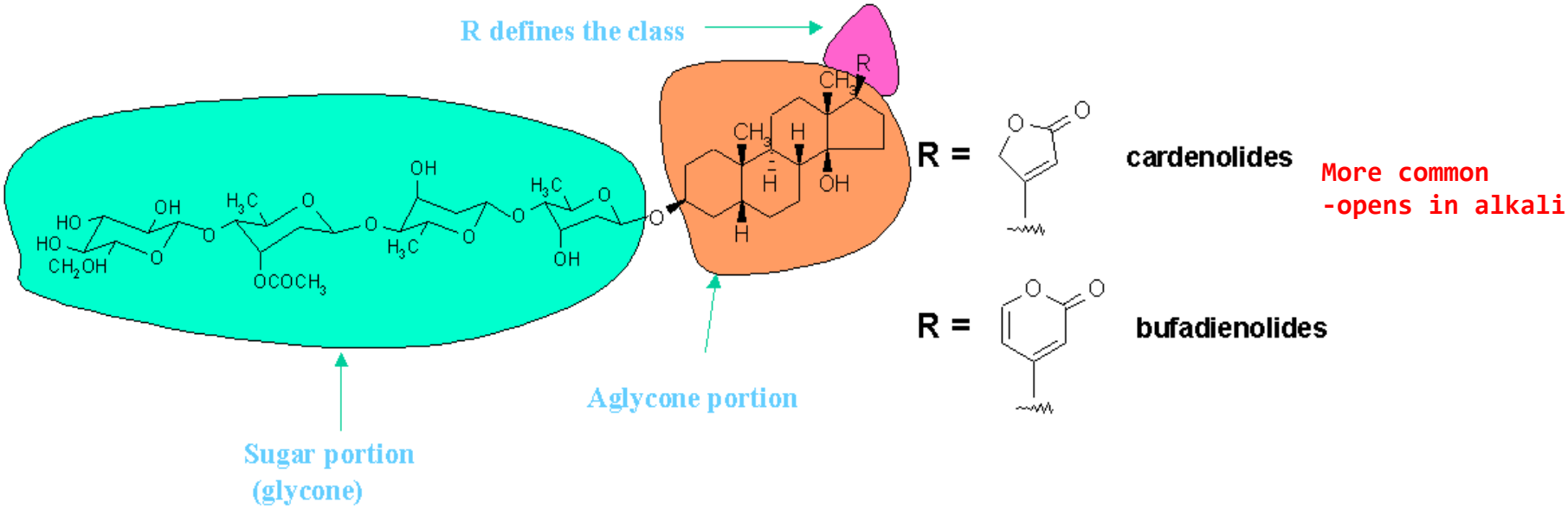
Botanical sources of steroidal glycosides

Crude drug	Botanical sources	Steroidal saponin isolated
Diaoscoria (yam)	Dried rizomes of several spp. Of Diaoscoria such as *D. macrostachya* (fam. Diaoscoreaceaea)	Dioscin (diosgenin)
Sisal	*Agave sisalana* (fam. Agavaceae)	hecogenin
Fenugreek seeds	Seeds of *Trigonella feonum-graecum* (fam. Fabaceae)	Dioscin (diosgenin)
Soya bean sterols	The seeds of *glycine max* (fam.Fabaceae)	β-sitosterol and stigmasterol

III. Cardiac Glycosides

- The aglycones of these glycosides have a steroidal nucleus with a lactone functional group.
- According to the size of the lactone ring, cardiac glycosides are classified into two groups:
    - Cardenolides, which have 5-membered lactone (ɤ-lactone)
    - Bufadienolides, which have 6-membered lactone (α-lactone)

- Steroids in nature exerts powerful action on the cardiac muscle.
  - ✓ Plant glycosides with specific action on heart
  - ✓ Historical use:
    - To assassinate people, arrow poisons
- Modern use:
  - To treat congestive heart failure
  - Aglycone structure important for activity



- Cardenolides are obtained almost entirely from plants whereas most Bufadienolides are obtained from frogs (Bufa spp.) and very few come from plants.
- If drying is not carried out with precaution, β-glycosidase removes the terminal glucose in many primary glycosides resulting 2^{ndry} glycosides .

Pharmacological activity & therapeutic uses of cardiac glycosides(CG)

- CG have specific and strong action on the heart's muscle.
- CG increase the strength of the heart contraction and thus used for cardiac insufficiency and congestive heart failure (dropsy).
  - increase CO & decrease heart rate and heart volume.
  - Improved circulation increases renal secretion which relieves edema.
  - Cardenolides are commonly used for treatment but Bufadienolides are highly toxic.
- The MoA of CG is proposed to be through indirect increase of intercellular Ca+ through the inhibition of Na^+, K^+-ATPase and subsequent stimulation of Na^+, Ca^+ exchange has been proposed.

- Both the glycosides and the free aglycone show more or less equal activity.
- However, the sugar units greatly influence absorption, on set of action and half life of the glycosides in the body since they affect water solubility.

Number of sugars	Water solubility	Route of administration	On set of action	Elimination
Less	Less	Oral	Slow	Slow
More	More	Parentral (IV)	Very fast	Fast

Drugs containing cardiac glycosides

Crude drug	**Botanical source**	**Important cardiac glycosides isolated**
Digitalis (foxglove)	Dried leaves of *Digitalis purpurea (fam.* Scrophulariaceae)	Digitoxin, gitoxin, and gitaloxin and other nearly 30 glycosides.
Grecian foxglove	Dried leaves of *Digitalis lanta (fam.* Scrophulariaceae)	Lanatosides A-E, digoxin and other nearly 65 glycosides.
Strophanthus	Dried ripe seed of *strophanthus kombe* and *S. hispidus* (fam. Apocyanaceae)	K-strophanthoside
Squill (squill bulb)	The cut and dried, fleshy inner scales of the bulb of the white variety of *Urginea maritima*	Scillaren A (a bufadienolide)

- **Remarks**
  - CG are very potent and toxic drugs which have very narrow marigin of safety
  - Crude drugs containing CGs & their galenicals are not used because of their irreproducible activity.
  - Pure glycosides are extracted from plants for medicinal use
  - Dose has to be adjusted experimentally.
  - They accumulate in the body and cause chronic toxicity.
  - Thus, continuous monitoring of serum level is mandatory.
  - Orally administered CGs have variable bioavailability.
  - Thus, changing brands is not recommended.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Sources

- Digoxin is available in Ethiopia in the form of elixir, injection and tablet.
- Scrophulariaceae
    - *Digitalis purpurea* leaves (foxglove)
    - *Digitalis lanata* leaves – white flowers
- Apocyanaceae
    - *Strophanthus* vine seeds – Africa
- Liliceae
    - *Urginea* bulbs (squill) – Europe, India
    - *Convallaria* leaves (lily of the valley) – also produces a volatile oil perfume

Toxicity of cardiac glycosides

1. Toxic concentration – glycosides may increase cardiac automaticity -- ectopic tachyarrhythmia
2. Inhibition of Na+, K+ ATPase ---- increase Na^+, decrease K^+ in the cell
   - Stimulates a secondary Na^+, Ca^+ exchange, removing intracellular Na.

3. Increase intracellular Ca ----- positive inotropic action (muscle contraction).

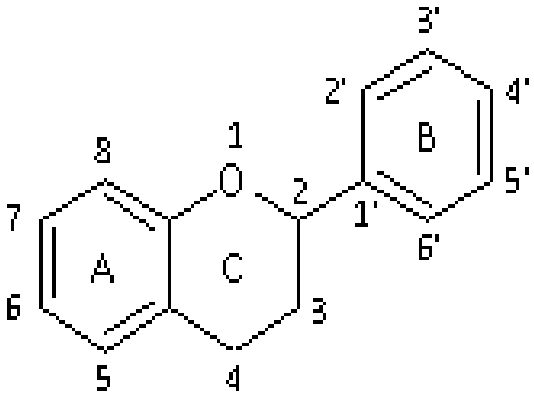
- Depletion of intracellular potassium increases susceptibility to CG

IV. Flavonoid glycosides(FG)

- Flavonoids are water soluble polyphenolics having 15 carbon atoms.
- They are visualized as two benzene rings joined together with a short three carbon chain(C_6-C_3C_6).
- One of the carbons of the short chain is always connected to a carbon of one of the benzene rings, either directly or through an oxygen bridge, thereby forming a third middle ring, which can be five or six-membered.

Flavonoid glycosides(FG)

- FGs have aglycone with C_6-C_3-C_6 nucleus.
- They are responsible for the color of flowers, fruits and sometimes leaves.
- Flavonoidal compounds occur mainly as O-glycosides, sometimes as C-glycosides, and free aglycones.



Flavonoid glycosides(FG)…

❑ They can be subdivided into different subgroups depending on

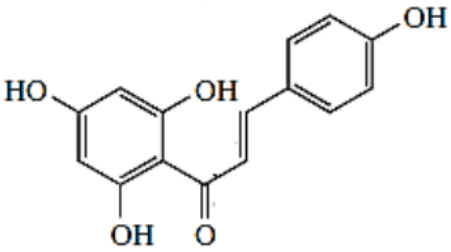
✓ the carbon of the C ring on which B ring is attached,

✓ the degree of unsaturation and

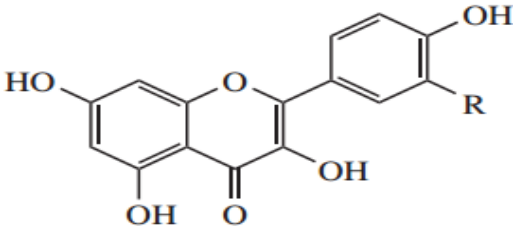
✓ oxidation of the C ring.

- Isoflavones: Flavonoids in which B ring is linked in position 3 of the ring C
- Neoflavanoids: those in which B ring is linked in position 4
- flavonoids with B ring is linked in position 2 includes flavones, flavonols, flavanones, flavanonols, flavanols or catechins and anthocyanins.
- Chalcones : are flavonoids with open C ring that serve as precursor to other flavonoid derivatives.

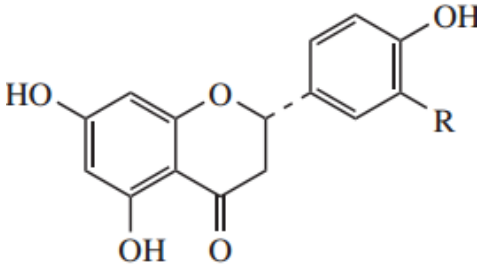
Flavonoid glycosides(FG)…



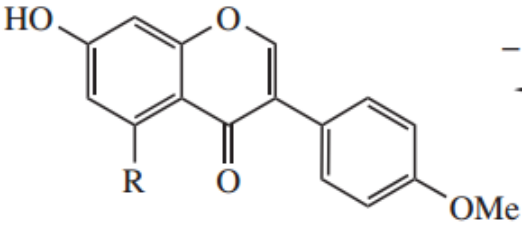
Chalcone



R = H, kaempferol
R = OH, quercetin
(*flavonols*)



R = H, naringenin
R = OH, eriodictyol
(*flavanones*)

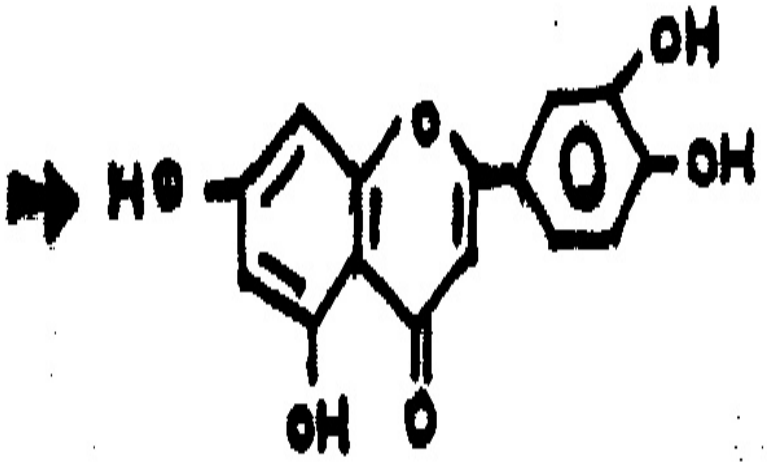


R = H, formononetin
R = OH, biochanin A
(*isoflavonoids*)

- Many flavonoids have yellow color but
- **Anthocyanins** (glycosides of anthocyanidins) have red, blue or purple color.
- Most flavonoids absorb in the UV region
  - Thus, they protect leaves from the damaging effects of ultraviolet light.
  - Flavonoids exhibit various pharmacological activities including antioxidant, anti-inflammatory, antimicrobial effect, hepatoprotective property, antidiabetic activity, anticancer effect, etc.

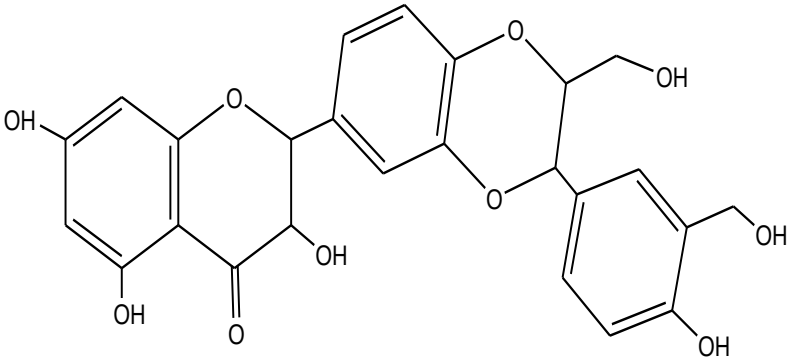
Some medicinally important flavonoids…

- **Rutin** (Vitamin P)
  - Used for the treatment of capillary bleeding and increased capillary fragility.
- From *Fagopyrum esculentum* (buck wheat)
- rhamnoglucoside of quercetin

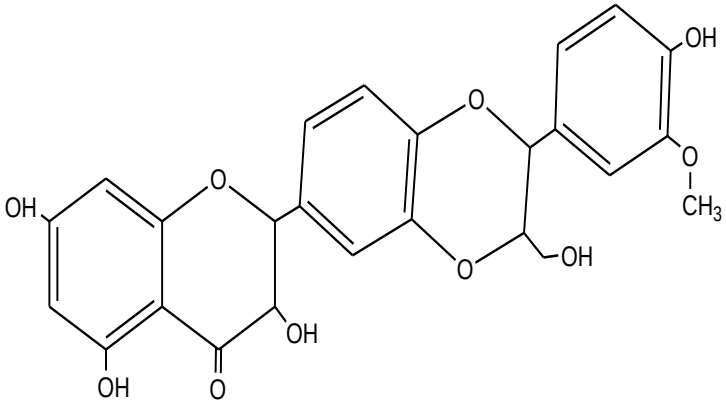


Some medicinally important flavonoids…

- **Silybin**
  - Silybin is the major active compound isolated from silymarin, a hepato protective Flavonoidal fraction obtained from Silybum mariamum (Astraceae) (Milk Thistle, St. Mary Thistle) .
  - Silybin and also silymarin are used for wide range of liver problems.



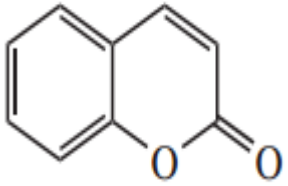
Silybin



Silymarin

V. Coumarin (lactone) glycosides

- These are glycosides which have coumarin based aglycone.



coumarin

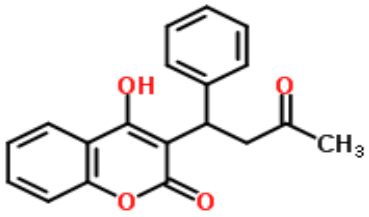
- In the plant, coumarin is believed to exist in a glycoside form but upon injury to the plant, it losses the sugar part.
- They are widely distributed in nature.

V. Coumarin (lactone) glycosides…

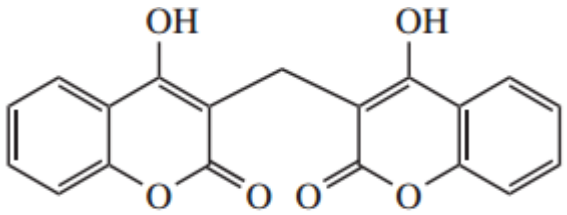
- Coumarin glycosides have anticoagulant activity
  - By competitively inhibiting the synthesis of vitamin K dependent factors that are involved in thrombin synthesis due to its structural resemblance to vitamin K.
    - It blocks vitamin K epoxide reductase enzyme complex
- Most naturally occurring coumarins lack anticoagulant activity but they are converted to active derivatives by microbial action (e.g. Dicoumarol).

V. Coumarin (lactone) glycosides…

- Dicoumarol (bishydroxycoumarin) is very potent anticoagulant which can not be used for treatment purpose.
- However, it was used as a lead compound for the synthesis of coumarin based oral anticoagulants such as warfarin.



Warfarin



dicoumarol

VI. Alcohol glycosides

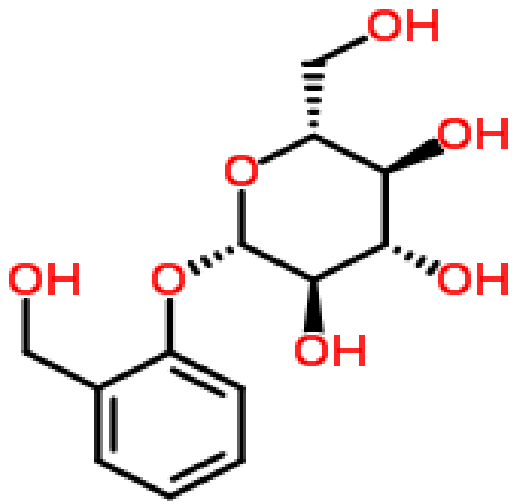
- These are glycosides which give an alcoholic aglycone
- **Salicin** is an alcoholic glycoside isolated from willow bark (*Salix fragilis* or *S.purpurea*: fam. Solanaceae).
- Traditionally willow bark has been and still is used
  - For fever and flu-like symptoms
  - As an analgesic (for headaches and toothaches)
  - Treatment of joint pain & rheumatoid disorders.

Due to salicylic acid of Salicin

Alcohol glycosides…

Salix fragilis

Salicin

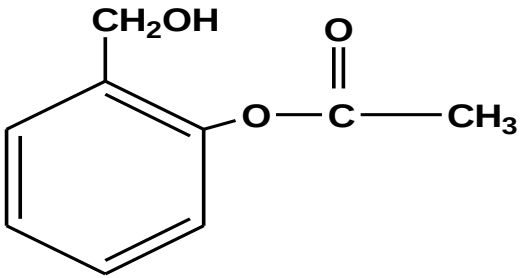


Alcohol glycosides…

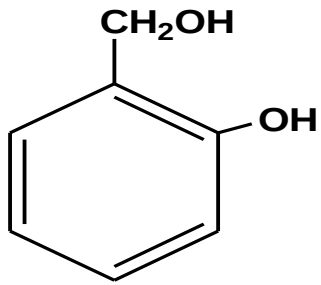
- By the enzyme **emulsin**,
- As a result of drying and soaking process or
- By the action of intestinal flora.

hydrolyze Salicin to salicyl alcohol (saligenin) which is oxidized to **salicylic acid** in the human

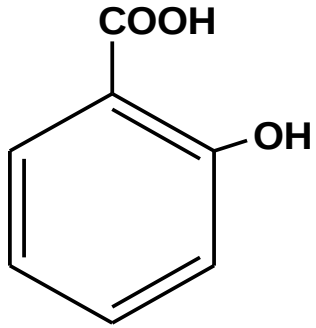
- Salicin, is the natural lead compound for the synthesis of **acetyl salicylic acid.**
- Note that salicin and salicyl alcohol are examples of prodrugs or reactionary drugs.



Acetyl salicylic acid



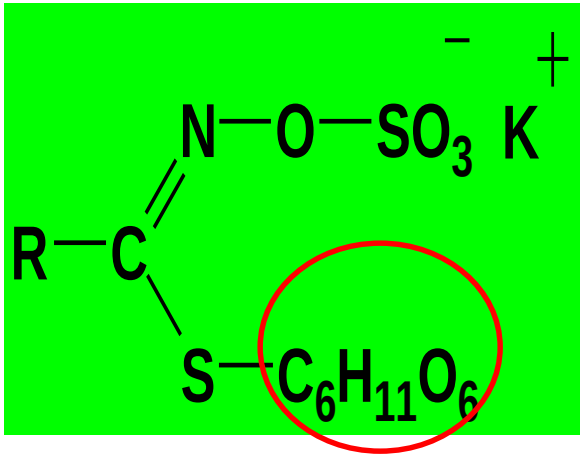
Salicyl alcohol



Salicylic acid

VII. Isothiocyanate glycosides (glucosinolates or thioglucosides)

- The basic structure of glucosinolates comprise
  - a **glucose** residue,
  - a **sulfate group** found as potassium salt
  - a variable **aglycone**.



- They are common in the family **Brassicaceae**- a medium-sized family of flowering plants (Angiosperms),
- They are ionic compounds and can be separated on ion exchange resin.

Cont..

- **Thioglucosidase**
  - Is commonly known as **myrosinase** (myrosin)
  - Is always found in glucosinolates-containing plants
  - Hydrolyze glucosinolates when plant tissues are damaged
- In all cases the freed aglycone is unstable and rearranges.
- If the pH is neutral, the product will be a strong-smelling volatile **isothiocyanate.**

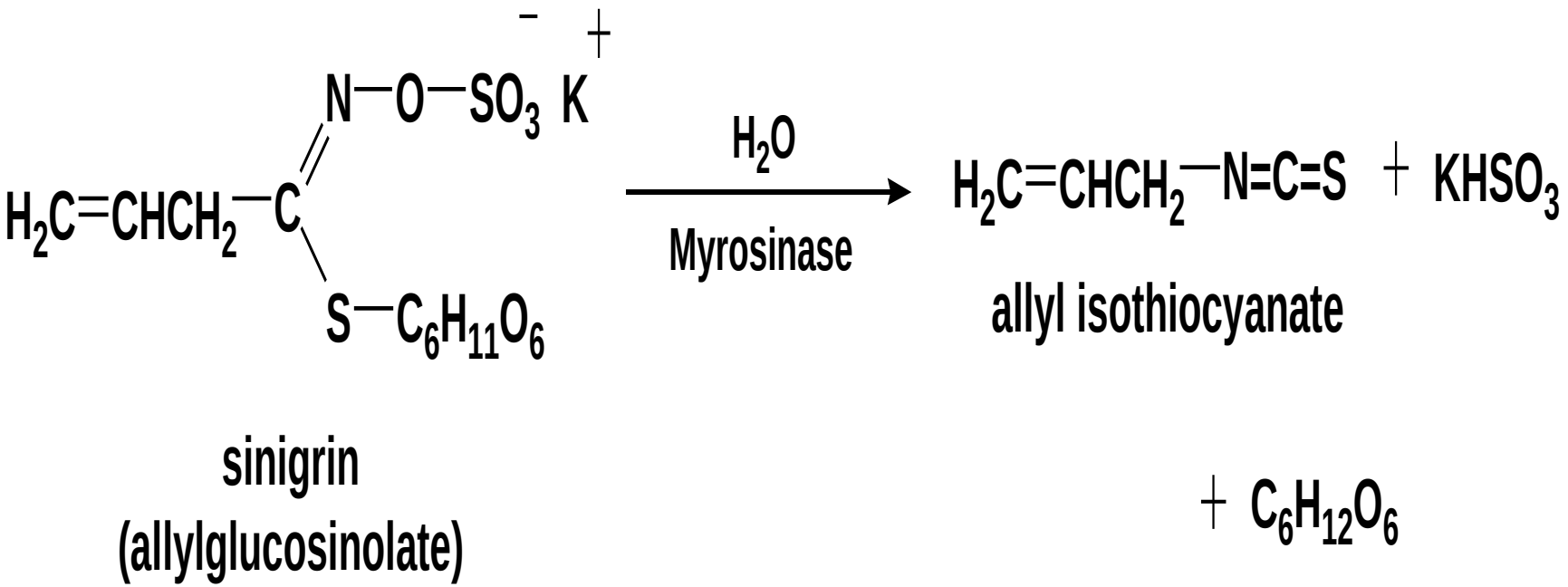
- A notable example of glucosinolates is **sinigrin**

❑ Sinigrin

- ➢ Occurs in the seeds of black mustard (***Brsssica nigra***: fam. Brassicaceae) or Indian mustard (*B. juncea*: fam. Brassicaceae)
- ➢ Sinigrin is allylglucosinolate and up on hydrolysis by myrosinase, produce allyl isothiocyanate.

- In order to effect hydrolysis, **mustard seeds** have to be soaked in water for few days.

Cont…



sinigrin
(allylglucosinolate)

allyl isothiocyanate

Cont…

- **Allyl isothiocyanate** is
  - strong-smelling volatile compound
  - responsible for the astringent odor and flavor of mustard.
- **Uses of allyl isothiocyanate**
  - as **condiment** (such as salt added to improve taste)
  - It is an **irritant substance** and therefore used as **counter irritant**
    - Used in the form of plasters.
      - If the plasters are applied too long, they can produce skin lesions.

VIII. Cyanogenic glycosides(CG)

- Compelete Hydrolysis of cyanogenic glycosides yield hydrocyanic acid (HCN)
- Over 2500 plant species are potentially cyanogenic from which .
  - Some are edible, even stable foods.
- CGs are very common in Rosaceae, Fabaceae, poaceae etc. family
- Apricot, Bitter almond, Peach, Pear , Apple, Plum, Wild cherry contain CGs
- Bitter almond contain amygdalin, cyanogenic glycosides
  - The hydrolysis of amygdalin is results in benzaldehayde
  - Benzaldehayde which is used as flavor.

Cyanogenic glycosides(CG)…

- Injury to plant cells leads to mixing of glycosides with hydrolyzing enzymes
- Cyanogenic glycosides are important plant toxins.
  - The glycosides themselves are not toxic
  - However, the hydrolysis product, HCN.
- Poisoning by cyanogenic glycosides due to HCN can arise from:
  - Ingestion of plants contaning them (common in children)
  - Ingestion of inadequately processed food staffs.
  - Intentional taking of cyanogenic glycosides for cancer t/t

Cyanogenic glycosides(CG)…

Effect of HCN

- **HCN blocks the utilization of O_2 by cells**
  - NB- O_2 is required for oxidative phosphorylation (energy production)

✓ Cells then resort to an anaerobic metabolism

  - This results in increase in **lactic acid**.

✓ The lactic acid could result in

  - Cell death and even the death of the organism.

✓ Oral dose of 50 mg HCN can be fatal.

- **HCN can displace I^- and this results in low production of thyroxin**

- Antibacterial activity of **Bitter almond**

Bitter almond → Amygdalin → (Hydrolysis: Emulsin enzyme) → HCN → kill → Bacteria

Symptoms of HCN toxicity

Acute

- Dizziness, drowsiness
- Headache
- Nausea/vomiting
- Palpitation/ hypotension
- Respiratory failure
- Convulsion/ paralysis
- Deep coma

Chronic

- Hypothyroidism/goiter/thyroid cancer
- Lesion of optic nerve/ blindness
- Lesion of auditory nerve
- Ataxia
- Mental retardation

Thank you