Pharmacognosy II *Lecture ((2))*
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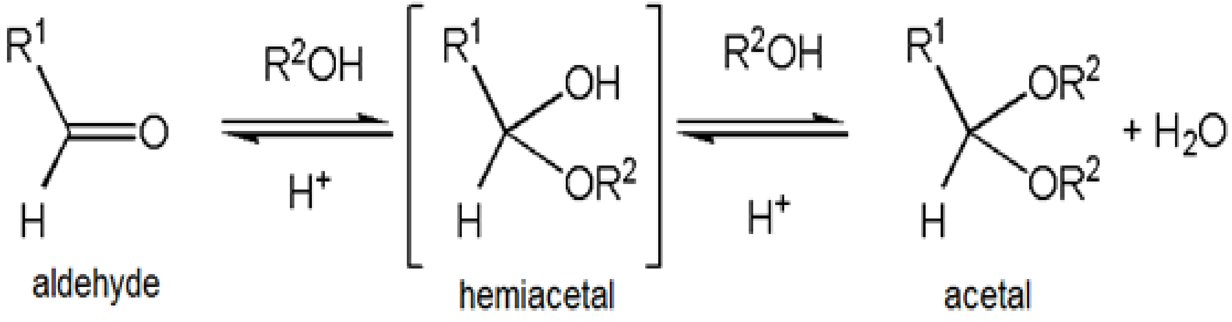
Glycosides

Glycosides are compounds that yield upon hydrolysis, one or more sugar molecule with an organic hydroxide. The fact that a number of plant constituents yielded sugars other than glucose led to the suggestion of the less specific general term " glycosides". If the sugar formed is glucose, the substance may be called a "glucoside". Also there are more specific terms can be used for example fructoside, rhamnoside, & others. The non-sugar portion of the glycoside generally is referred as the **aglycone or genin.**

Genin part ((A Glycone part)) Glycosidic → non genin part ((Glycone))
((Non – sugar part)) linkage ((sugar part))

Chemically glycosides are acetals in which the hydroxyl of the sugar is condensed with a hydroxyl group of the non-sugar component. This type of glycosides is more specifically known as O-glycosides i.e. to denote that the linkage is through oxygen. Two forms of this type as well as all other glycosides are possible i.e. alpha & beta, because of the asymmetry centering about carbon atom No. 1 of the sugar residue that contains the acetal structure.

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first.



It is interesting to note, however, that only β forms occur in plants. This is because the enzyme emulsion, which cannot hydrolyze synthetic α-glycosides, hydrolyzes naturally occurring α-glycosides.

Glycosides usually are hydrolyzed by acids & are relatively stable toward alkalis. Some glycosides are much more resistant to hydrolysis than others.

The sugar components of glycosides may be a mono, di, tri, or tetra saccharides.

- Glucose - glucoside group like in Sennoside.
- Rhamnose - Rhamnoside like in frangullin.
- Digitoxose -Digitoxoside like in digoxin.
- Glucose and Rhammnose -Glucorhamnoside - glucofrangulin.
- Rhamnose and glucose -Rhamnoglucoside - Rutin.

The aglycone or non-sugar portions of glycosides are represented by a wide variety of organic compounds as ex: cardiac, saponin glycosides …etc.

Because of the complexity of the structures of the naturally occurring glycosides, no generalizations are possible with regard to their stabilities. It also follows that considerable differences in their solubility properties.

Many glycosides are soluble in water or hydro alcoholic solutions because the solubility properties of the sugar residues exert a considerable effect i.e. sugar moiety increases water solubility.

Glycone part: - water soluble, insoluble in the organic solvents.

Aglycone part: - water insoluble, soluble in the organic solvents.

Some glycosides soluble in alcohol.

Glycosides occur widely distributed in nature. They are found in varying amounts in seeds, fruits, roots, barks, & leaves. In some cases, two or more glycosides are found in the same plant.

Glycosides often are accompanied by enzymes that are capable of synthesizing or hydrolyzing them. This phenomenon introduces problems in the isolation of glycosides because the disintegration of plant tissues, with no precautions to inhibit enzymatic activity leads in some cases, to partial or complete hydrolysis of the glycosides.

physico-chemical properties of glycosides (general)

1.Colorless, solid, amorphous, nonvolatile (flavonoid- yellow, anthraquinone-red or orange.

2. Give positive reaction with Molisch's and Fehling's solution test (after hydrolysis).

3. They are water soluble compounds, insoluble in organic solvents

4. Most of them have bitter taste although there are among that are not.

(except: populin, glycyrrhizin, stevioside)

5. Odorless except saponin (glycyrrhizin).

6. Glycosides hydrolyzed by using mineral acids and temperature or by using enzymes such as:

a- Emolsin → Bitter almond seeds.

b- Myrosin or Myrosinase → black mustard seeds.

c- Rhamnase → glycosides containing rhamnose as sugar part.

Functions of glycosides: -

They may serve as:

1. As sugar reserves

2. As waste products of plant metabolism.

3. As a mean of detoxification.

4. To regulate osmosis.

5. To stabilize labile substances or regulate the supply of substances of importance in metabolism.

6. As a role of defense against the invasion of the tissues by microorganisms. Some pointed out that many aglycones are antiseptics & hence bactericidal in character.

From the biological view point, glycosides play an important role in the life of the plant involving its regulatory, protective, & sanitary functions.

Classification and Nomenclature

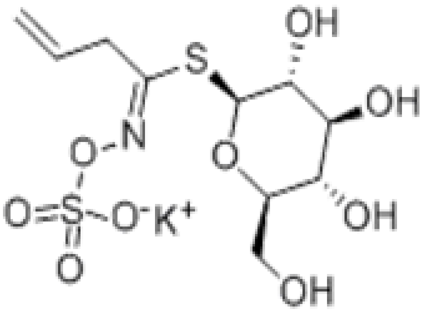
1.According to the type of glycosidic linkage: α- glycoside (α-sugar) and β-glycosides (β-sugar).

2. Classification of glycosides on the basis of the linkage between glycone and aglycone part.

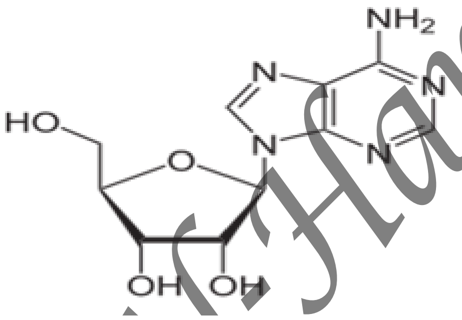
O-glycosides: - in these glycosides the sugar part is linked with alcoholic or phenolic hydroxyl or carboxyl group.

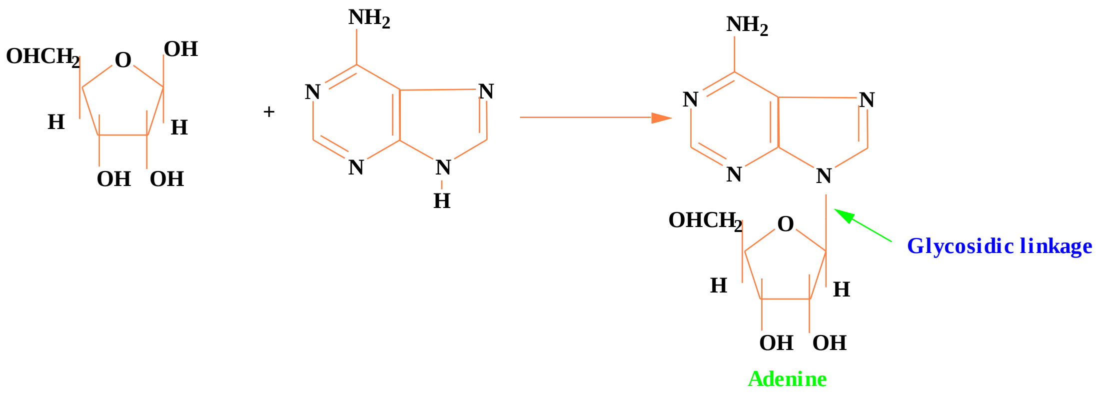
S-glycosides: - in these glycosides the sugar attached to a Sulfur atom of aglycone such as in sinigrin.

sinigrin



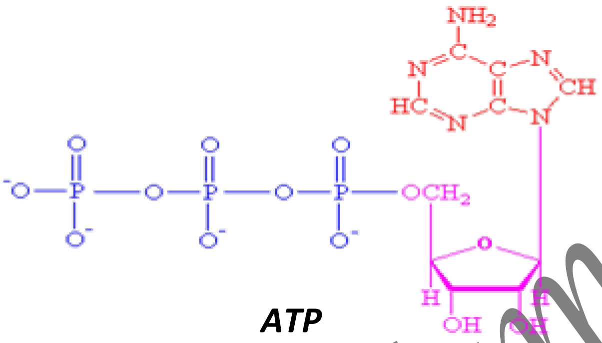
N-glycosides: - in these glycosides the sugar linked with Nitrogen atom of (-NH2, -NH-) amino group of aglycone like in nucleosides DNA, RNA of particular importance biologically, in which the sugar residue is D-ribose or 2-deoxy-D-ribose & the aglycone is attached to the sugar by a C-N bond involving a derivative of a nitrogen base, usually pyrimidine or purine. These glycosides are better known as ribo nucleoside & deoxy ribo nucleosides as found in RNA & DNA.





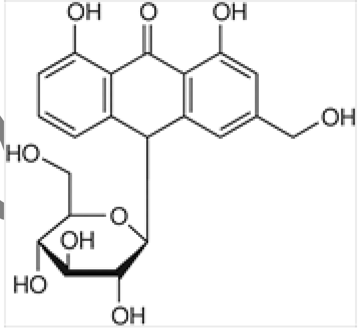
Adenosine

Adenosine is one example of a purine ribo nucleoside & when esterified at the 5′ position with tri phosphate group, is known as adenosine tri phosphate (ATP) a so called "energy rich" compound present in muscle tissues.



ATP

C-glycosides: - in these glycosides the sugar linked (condensed) directly to Carbon atom of aglycone like in aloin.



3.According to the nature of the simple sugar component of the glycoside: -

a. Glucosides (the glycone is glucose).

b. Galacosides (the glycone is galacose).

c. Mannosides (the glycone is mannose).

d. Arabinosides (the glycone is arabinose).

4. According to the number of the monosaccharides in the sugar moiety: -

a. Monoside (one monosaccharide) e.g., salicin.

b. Biosides (two monosaccharide) e.g., gentobioside.

c. Triosides (three monosaccharide) e.g., strophanthotriose.

5. According to the physiological or pharmacological activity therapeutic classification): -

a. Laxative glsycosides.

b. Cardiotonic glycosides.

Extraction of glycosides from plants: -

Glycosides are usually soluble in water, alcohol or acetone & insoluble or very sparingly soluble in ether. The former solvents are used in extraction. Since the glycosides are accompanied in the plant by the specific enzyme capable of affecting their hydrolysis, this enzyme must first be inactivated. The plant tissue may be treated with steam or extracted with hot water or hot alcohol to achieve this result.

The method by which glycoside are isolated is called stas-otto method.

During this method at first take drug containing glycoside, finely powdered that, and it is extracted with alcohol or water by using soxhlet apparatus. After extraction, collect the extract and treat with lead acetate to precipitate tannins after that filter it and to the filtrate pass H_2S gas, no lead acetate the precipitate as lead sulphide as this is toxic.

Now after the extract again filter the filtrate is subjected to fractional crystallization, distillation or chromatography gives pure component and the extract molecular structure is determined by the spectrophotometer, Ultra Red assays, Infra-red, NMR and mass spectroscopy etc.

In other word: -

As glycosides are readily hydrolyzed by acids, acidic conditions must be avoided during extraction, & it is customary to add calcium carbonate, to the extracting medium in order to ensure neutral conditions. When the extract contains co-extracted protein or other non-glycosidic constituents it may generally be clarified by the addition of lead acetate with subsequent removal of lead from the filtrate by hydrogen sulfide.

The clarified neutral extract is evaporated in vacuum to a syrupy liquid from which the glycosides may separate in crystalline form. Re crystallization from an organic solvents ex: alcohol, acetone, ethyl acetate, …. etc is always desirable.

Maintenance of neutral conditions

- pH should be assured before and during extraction because:
- Acidity may result in hydrolysis. This is overcome by addition of CaCO3.
- Mild alkalinity may sometimes produce racemization.

Defatting of fat-rich organs (e.g. seeds) before extraction:-

High amounts of lipoids hinder glycoside extraction. Defatting is usually carried with petroleum ether.

Stability& hydrolytic cleavage of glycosides

1- Acid hydrolysis: -

a. Acetal linkage between the aglycon and glycone **more unstable** than that between two individual sugars within the molecule.

b. all glycosides are hydrolysable by acids nonspecific (except C-glycosides).

c- Glycosides containing 2-deoxy sugars are **more unstable** towards acid hydrolysis even at room temperature.

d- C-glycosides **are very stable** (need oxidative hydrolysis).

2- Alkali hydrolysis: -

1- mild alkali 2- strong alkali

3- Enzyme hydrolysis: -

1- Enzymatic hydrolysis is specific for each glycoside there is a specific enzyme that exerts a hydrolytic action on it.

2- The same enzyme is capable to hydrolyze different glycosides, **but α and β sterio-isomers** of the same glycoside are usually not hydrolyzed by the same enzyme.

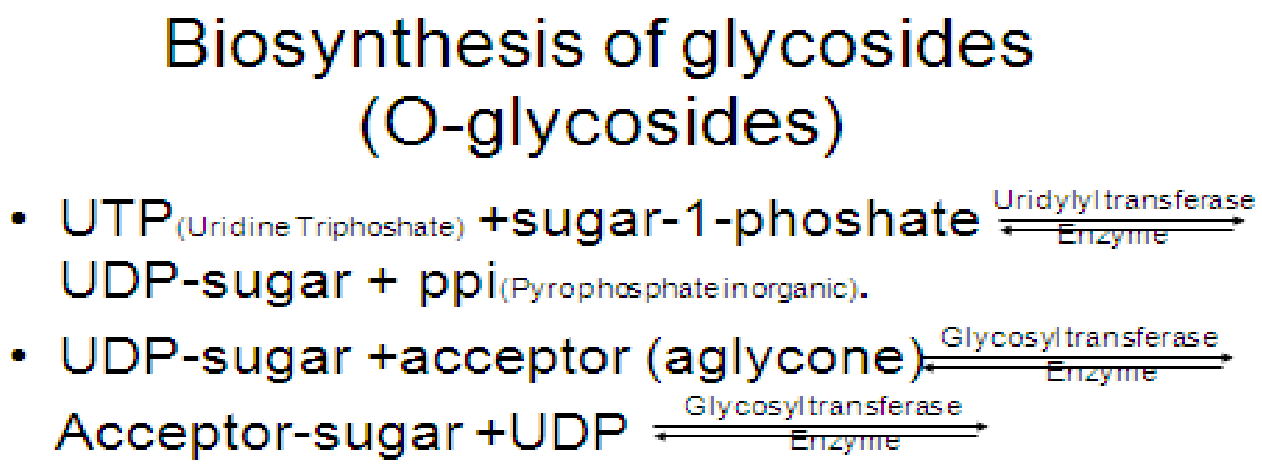
3- **Emulsin is** found to hydrolyzed most **β-glycoside** linkages, those glycosides are attacked by **emulsin** are regarded as β-glycosides.

4- **Maltase** and **invertase** are α-glycosidases, capable of hydrolyzing **α-glycosides only.**

Biosynthesis of glycosides: -

available evidences indicate that the principle pathway of glycosides formation involves the transfer of a uridylyl group from uridine tri phosphate to a sugar-1-phaosphate.

Enzymes catalyzing this reaction are referred to as uridylyl transferases. The subsequent reaction, mediated by glycosyl transferases, involves the transfer of the sugar from uridine di phosphate to a suitable acceptor (aglycone), thus forming the glycoside.



Biosynthesis of glycosides
(O-glycosides)

- UTP (Uridine Triphoshate) +sugar-1-phoshate $\xrightleftharpoons[\text{Enzyme}]{\text{Uridylyl transferase}}$ UDP-sugar + ppi (Pyrophosphate inorganic).
- UDP-sugar +acceptor (aglycone) $\xrightleftharpoons[\text{Enzyme}]{\text{Glycosyl transferase}}$ Acceptor-sugar +UDP $\xrightleftharpoons[\text{Enzyme}]{\text{Glycosyl transferase}}$

Classification of glycosides according to the aglycone part

Using the chemical nature of the aglycone group as a basis of systemization, the classification of glycoside-containing drugs follows this scheme: -

1. Cardio active glycosides

2. Anthraquinone glycosides

3. Saponin glycosides

4. Cyanophore glycosides

5. Isothiocyanate glycosides

6. Flavonoid glycosides

7. Alcohol glycosides

8. Aldehyde glycosides

9. Lactone glycosides

10. Phenol glycosides

11. Miscellaneous glycosides