**Glycosides**

**Definition:**

Glycosides are (usually) non-reducing compounds, on hydrolysis by reagents or enzymes yield one or more reducing sugars among the products of hydrolysis.



**1- Alcoholic or phenolic (aglycone): e.g., O-Glycoside**



**2- Sulphur containing compounds: e.g., S-Glycoside**



**3- Nitrogen containing compounds: e.g., N-Glycoside**



**4- C-Glycoside**



1. Sugars exist **in isomeric** ***α*** and ***β*** forms. Both α and β Glycosides are **theoretically** possible.
2. **All natural glycosides** are of the ***β*** Type.
3. Some **α linkage** exists in **sucrose, glycogen and starch**. Also the glycoside **K-strophanthoside** (strophanthidin-linke to **strophanthotriose** (Cymarose + β-glucose + α- glucose).
4. According to the **type of glycosidic linkage**: α- glycoside (α-sugar) and β-glycosides (β-sugar).
5. According to **the chemical group** of the aglycone involved into the acetal union:
   1. O-glycoside (OH group)
   2. S-glycoside (SH group).
   3. N-glycoside (NH group).
   4. C-glycoside (C group).
6. According **to the nature of the simple sugar** component of the glycoside:
   1. Glucosides (the glycone is glucose).
   2. Galacosides (the glycone is galacose).
   3. Mannosides (the glycone is mannose).
   4. Arabinosides (the glycone is arabinose).
7. According to the number of the monosaccharides in the sugar moiety:
   1. Monoside (one monosaccharide) e.g., salicin.
   2. Biosides (two monosaccharide) e.g., gentobioside.
   3. Triosides (three monosaccharide) e.g., strophanthotriose.
8. According to the physiological or pharmacological activity ‘therapeutic classification)
   1. Laxative glsycosides.
   2. Cardiotonic glycosides.
9. according to **the correlation to the parent natural glycoside**:
   1. primary glycosides e.g., amygdalin, purpurea glycoside A,
   2. Secondary glycosides e.g., prunasin, digitoxin.
10. According to the **plant families**.
11. According **to the chemical nature of the aglycone**:
    1. **Alcoholic and phenolic glycosides** (aglycones are alcohols or phenols)
    2. **Aldehydic G** (aglycones are aldehydes).
    3. **Cyanogenic G** (aglycones are nitriles or derivatives of hydrocyanic acid).
    4. **Anthracene or anthraquinone G** (aglycones are anthracene der.).
    5. Steroidal G (aglycones are steroidal in nature, derived from cyclopentanoperhydrophenanthrene) .
    6. **Coumarin G** (aglycones are derivative of benzo α-pyrone).
    7. **Chromone glycosides** (aglycones are derivatives of benzo-δ-pyrone)
    8. **Flavonoidal G** (aglycones are 2-phenyl chromone structure).
    9. **Sulphur containing or thioglycosides** (aglycones are contain sulphur).
    10. **Alkaloidal glycosides** (aglycone is alkaloidal in nature) e.g., glucoalkaloids of solanum species.

**Sugars in glycosides:**

1. Monosaccharide (glucose in salicin, rhamnose in ouabain)
2. Disaccharides (gentiobiose in amygdalin).
3. Trisaccharides (strophanthotriose).
4. Tetrasaccharides (purpurea glycosides)
5. Rare sugers (deoxy sugers)
6. Sugar linked in one position to the aglycone rarely in 2 positions as sennosides.

**A- 6-deoxy sugars**

**e.g., 1- methylpentoses**



**2- α-L-rhamnose.**



**B- 2,6-deoxy sugars (called rare sugars)**

e.g.,

**1- D.digitoxose 2- D.cymarose 3- diginose**



**C- 2-deoxy sugars**

e.g.,

**2-deoxy-D-ribose**



**Characteristic of 2-deoxy sugers:**

1. Give positive Schiff’s test for aldehydes.
2. Positive Keller-Kelliani test.

**Diversity in structure makes it difficult to find general physical and chemical properties:**

1. A- Most glycosides are **water soluble** and soluble in alcohols.

B- Either **insoluble** or **less soluble** in non polar organic solvents.

C- **More sugar units** in a glycoside lead **to more soluble** in polar solvents.

2- Glycosides do not reduce Fehling’s solution, but when are susceptible to hydrolysis give reducing sugars (C-glycosides are exceptions).

**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 non specific (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 hydrolysed by the same enzyme.

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

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

1. Water mixed with different proportions of methanol or ethanol (most suitable extracting solvent).
2. Non-polar organic solvents are generally used for de-fating process.
3. Glycosides are not precipitate from aqueous solutions by lead acetate.

**1- Destruction of hydrolysing enzymes.**

* 1. Drying for 15-30 min. at 100 C˚.
  2. Place plant in boiling water or alcohol 10-20 min.
  3. Boiling with acetone.
  4. Cold acid pH treatment.
  5. Extract at very low temperature.

1. De-fating or purification of the plant material (**in case of seeds**).
2. Extraction of the glycosidal constituents by **alcohol, water or dilute alcohols**. Some times ether saturated with water for dry material.
3. Concentrate the alcoholic extract (to get rid of the organic solvent). Add water (or hot water)→ filter any precipitate.
4. Purify aqueous extract:
   * 1. Extract non glycosidal impurities by org solvent.
     2. Water soluble impurities precipitate by lead acetate.
5. Precipitate excess lead salts.
6. Isolation of the glycosides from the purified aqueous solution, by crystallization.

They do not themselves reduce Fehling’s. but reducing sugars upon hydrolysis.

To test for the presence of glycosides

Estimate reducing sugars before and after hydrolysis. (by acids or enzymes)

1. **Steroidal or cardiac glycosides:**

Give positive **Liebermann’s test** (**steroidal structure**).

1. **Anthraquinone glycosides and/or aglycone:**

Give positive **Borntrager’s test,** characteristic reddish coloration with alkalies.

1. **Flavonoidal glycosides and/or aglycones:**

Characteristic color with, **NH4OH, AlCl3, FeCl3**.

1. **Cyanogenetic glycosides** give upon hydrolysis hydrocyanic acid can be easily tested by change **Na bikrate** paper (yellow) to red color.
2. **Sulphur containing glycosides** give black precipitate of **silver sulphate** upon treatment with **AgNO3** solution.

**1- Keller Killiani’s test for 2-deoxy sugers:**

Specificity of action of the hydrolyzing enzymes is often applied for the identification of the sugar moieties of glycosides or even the glycoside as alcohol.

1**- Scillarin A** [acid hydrolysis] →→→ Scillaridine A + Scillabiose

Scillabiose [Scillabiase] →→→ Rhamnose + glucose.

2- **Prunasin** [Prunase] →→→ glucose + HCN + 

3- **Amygdalin** [amygdalase] → Prunasin + glucose

**4- Myrosin enzyme** is specific for **thio D- glucosides** e.g., **Sinigrin** and **sinalbin**.

**Determination of the glycosidic linkages**:

1. By the use of α and β glycosidases.
2. **By acid hydrolysis** of glycosides, immediate optical activity measurement of the resulting solution.

**Color reactions based on the sugar moiety [2-deoxy sugars]:**

1. **Keller Killiani:**

glacialacetic acid containing + FeCl3 + H2SO4 → brown ring free from red (acetic acid a quire blue).

**2- Xanthydrol:**

xanthydrol in glacial acetic containing 1% HCl + glycoside [heat]→ red color.

N.B. Stability indicating after extraction. U.S.P.

**Medicinal importance of glycosides:**

1. **Cardiac drugs:** cardiotonic glycosides e.g., digitalis glycosides, strophanthus, squill.
2. **Laxatives e.g.,** anthraquinone glycosides of senna, aloes, rhubarb, cascara, frangula.
3. **Counter irritants** e.g., thioglycosides and their hydrolytic products ‘allylisothiocyanate’
4. **Analgesics e.**g., methylsalicylate ‘a hydrolytic product of gaultherin.
5. **Anti rheumatic** e.g., salicin.
6. Some glycosides are claimed to reduce **the capillary fragility** e.g., flavonoidal glycosides, rutin, hisperidin.
7. **Anti-inflamatory**: e.g., the glycoside glycyrrhizin has a demulcent, expectorant and antispasmodic action.
8. More recently as an **anticancer agent** e.g., amygdalin known in the U.S. as Laetrile.