(Glycosides)

- **Introduction:**

A glycoside is any molecule in which a sugar group is bonded through its anomeric carbon to another group via glycosidic bond.

The anomeric carbon is the carbon atom that carries the hemiacetal group (Hemiacetal is any of a class of compounds characterized by the grouping C(OH)(OR)).

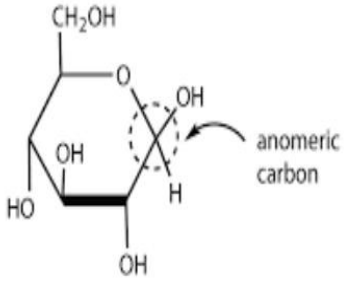

Figure- 1: The anomeric carbon is indicated by the dashed circle

- **Glycosides are composed of two parts:**
  1- **The aglycon (genin):** is the nonsugar component that gives the glycosides its therapeutic activities.
  2- **The glycon**: is the sugar component that increases the solublization of the aglycon part, thus increasing the bioavailability of the drug. Glycone part is water-soluble but insoluble in organic solvents whereas aglycone parts are vice-versa.

The glycone and aglycone portions can be chemically separated by hydrolysis in the presence of acid.

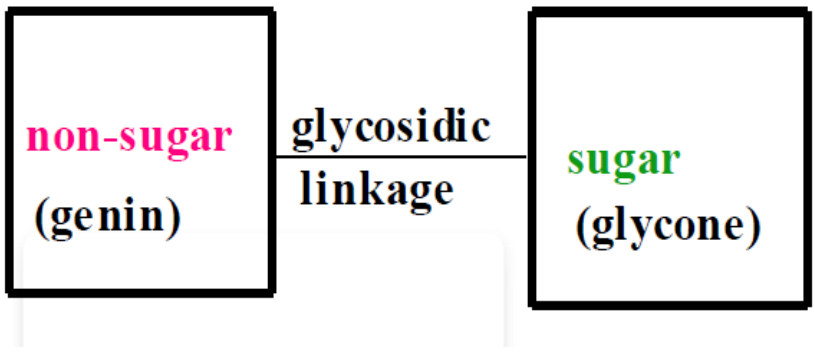

Figure-2: Components of a glycoside molecule

- **A glycosidic bond** is a certain type of chemical bond that joins a sugar molecule to another molecule. When a glycosidic bond is formed between the acetal group of a saccharide (or a molecule derived from a saccharide) and the hydroxyl group of an alcohol then O- glycoside will be produced.

This linkage is breaks by acid or enzyme hydrolysis and both glycone and genin parts are separated.

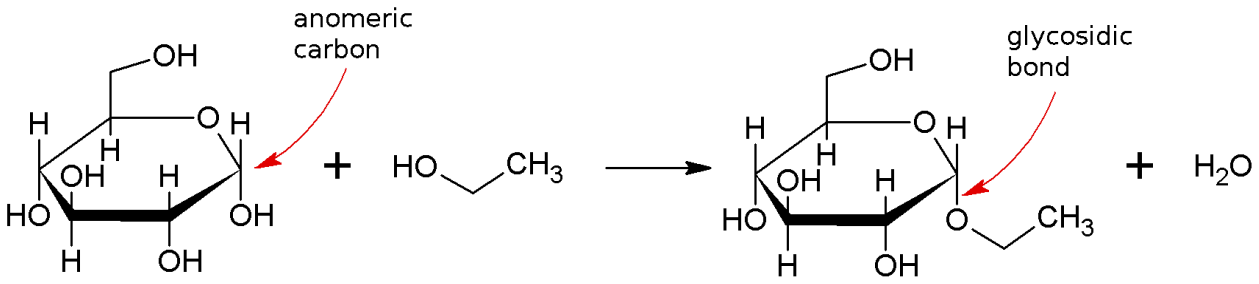

Figure-3: Formation of ethyl glucoside: Glucose and ethanol combine to form ethyl glucoside and water.

- **Functions of glycosides:**

1. As sugar reserves.

2. As waste products of plant metabolism (produced by biochemical reactions that converts non- polar compounds into polar water soluble compounds).

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 micro organisms. Some pointed out that many aglycones are antiseptics & hence bactericidal in character.

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

8. Among such a wide variety of compounds one finds many therapeutically active agents. For example:

- ✓ Valuable **cardiac specifics**: glycosides from digitalis, strophanthus.
- ✓ **Laxative drugs**, such as senria, aloe, rhubarb, cascara sagrada.
- ✓ Gaultherin from wintergreen yields methyl salicylate, **an analgesic**.

- **CLASSIFICATION**

The glycosides can be classified on the following bases:

1. According to the stereoconfiguration of glyosidic linkage:

Both alpha and beta glycosides are possible, depending on the stereoconfiguration of the glycosidic linkage.

In a pair of anomers, the anomer in which the hydroxy group on the anomeric carbon is pointing down (below the paper plane) is called the alpha anomer, and the one in which is pointing up (above the paper plane) is called the beta anomer.

Sometrimes **α**- configuration is indicated by solid line while β- configuration is indicated by a dashed line.

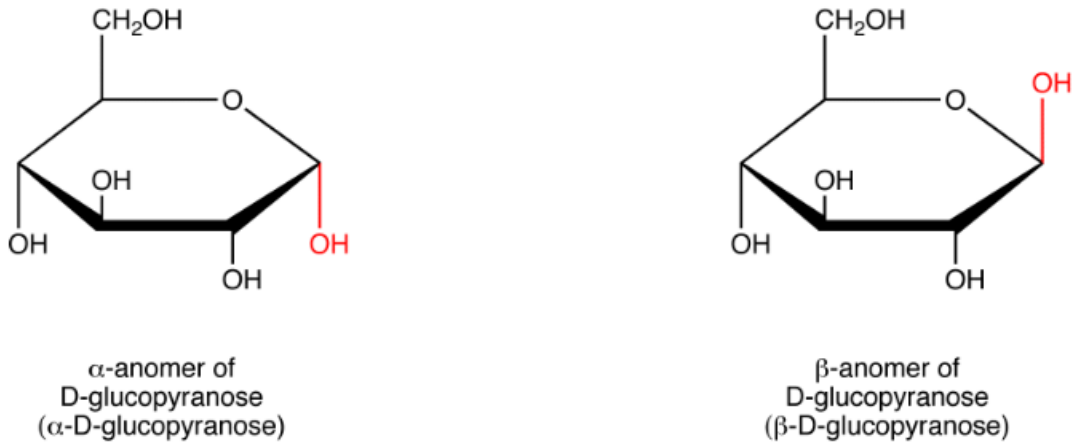

Figure-4: Anomers of D-glucopyranose

2. On the Basis of Glycone:

If the glycone group of a glycoside is glucose, then the molecule is **a glucoside**; if it is fructose, then the molecule is a **fructoside**; if it is glucuronic acid, then the molecule is a **glucuronide**, etc.

3. On the Basis of Glycosidic Linkage:

- **O-glycosides:** in these glycosides the sugar part is linked with alcoholic or phenolic hydroxyl or carboxyl group of aglycon, for example cardiac glycosides.
- **N-glycosides:** Sugar molecule is combined with N of the –NH (amino group) of aglycon, for example, nucleosides - in these glycosides the sugar (D-ribose or 2-deoxy-D-ribose) linked with Nitrogen atom of (-NH2, -NH-) amino group of aglycone (purine or pyrimidine) by a C-N glycosidic bond. These glycosides

are better known as ribonucleoside & deoxyribonucleosides as found in RNA & DNA.

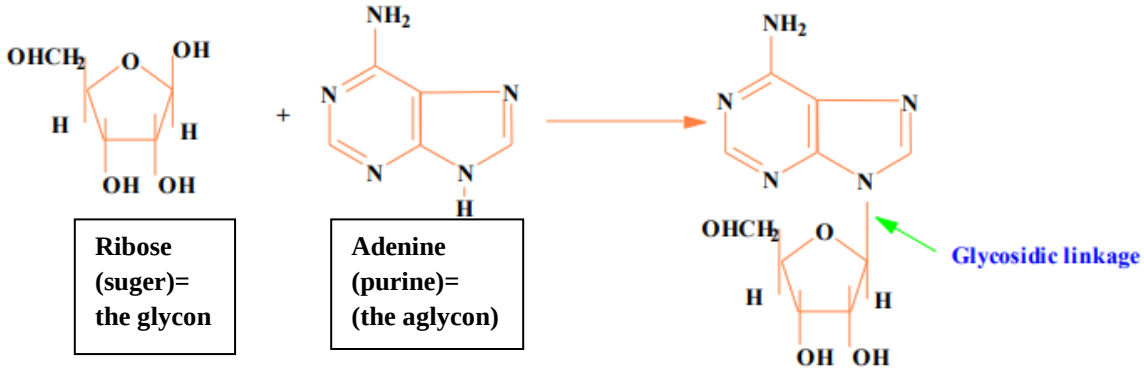

Figure- 5: Ribonucleoside (N- glucoside)

- **S-glycosides:** Sugar molecule is combined with the S or SH (thiol group) of aglycon, for example, Sinigrin.

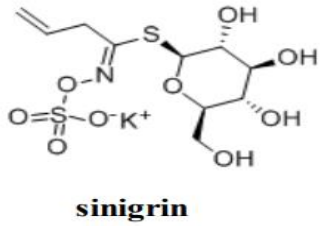

Figure- 6: Sinigrin (S- glucoside)

- **C-glycosides:** Sugar molecule is directly attached with C—atom of aglycon, for example, anthraquinone glycosides like Aloin, Barbaloin, Cascaroside and Flavan glycosides, etc.

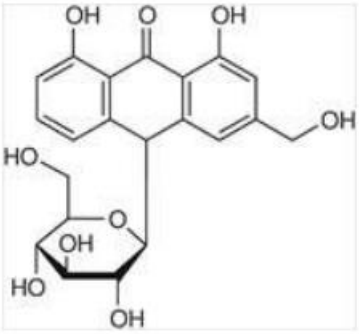

Figure- 7:Aloin (C- glucoside)

4-On the Basis of Aglycone:

Table- 1: Glycosides classification on the basis of the aglycon part

S. No.	Class	Examples
1.	Anthraquinone glycosides	Senna, Aloe, Rhubarb, etc.
2.	Sterol or Cardiac glycosides	Digitalis, Thevetia, Squill, etc.
3.	Saponin glycosides	Dioscorea, Liquorice, Ginseng, etc.
4.	Cyanogenetic and Cyanophoric glycosides	Bitter almond, Wild cherry bark, etc.
5.	Thiocynate and Isothiocynate glycosides	Black mustard
6.	Flavone glycosides	Ginkgo
7.	Aldehyde glycosides	Vanilla
8.	Phenol glycosides	Bearberry
9.	Steroidal glycosides	Solanum
10.	Bitter and Miscellaneous glycosides	Gentian, Picrrohiza, Chirata, etc.

- **Physico-chemical properties of glycosides(general):**

1. Solid, amorphous, nonvolatile, and colorless (except: 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 (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.

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

- **Biosynthesis of glycosides:**

Available evidences indicate that the principle pathway of glycosides formation involves:

1- The transfer of a uridylyl group from uridine tri phosphate to a sugar-1-phosphate catalyzed by the enzyme uridylyl transferases.
2- 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.

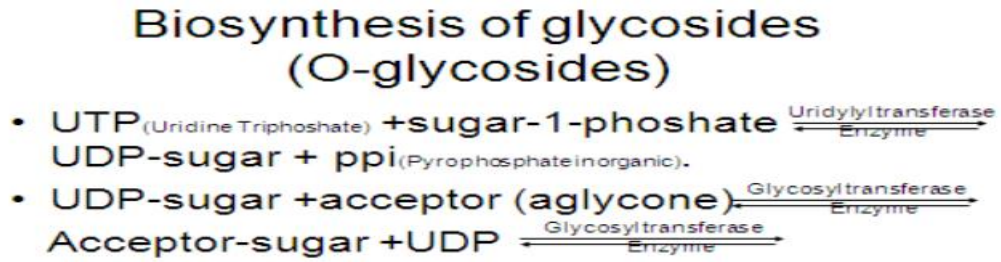

Figure- 8: Biosynthesis of glycosides

(Cardioactive Glycosides)

• Cardioactive Glycosides: Cardiac glycosides are naturally occurring steroids with a powerful stimulating action on the cardiac muscle. It composed from aglycones and glycone portion.

- The glycon part can be mono-, di-, or tri-saccharide, or a series of monosaccharides arranged in chains.

- The aglycones of these glycosides are referred to as **"cardiac genin",** they are steroidal in nature, specifically, and they are derivatives of cyclopentaphenanthrene containing a β oriented functional group at C- 14 and an unsaturated lactone ring attached to **C-17.**

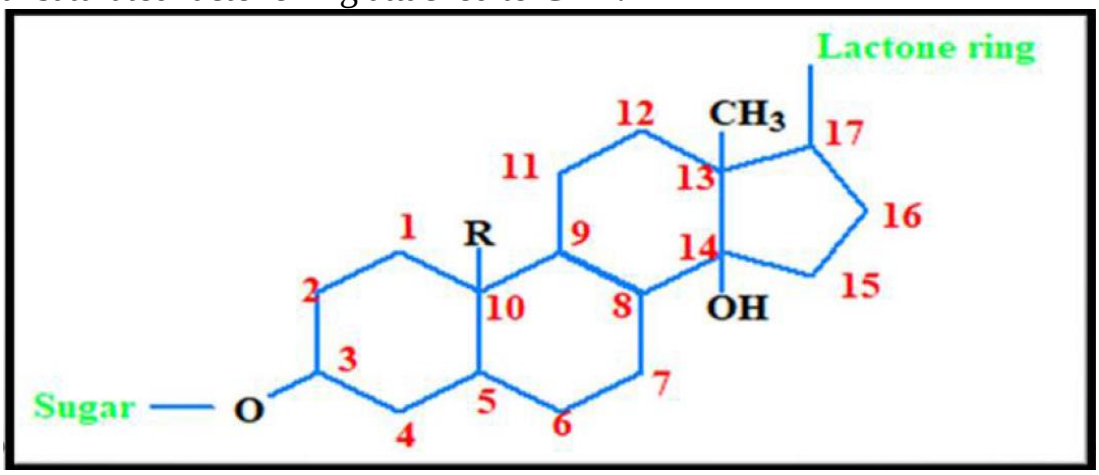

Figure- 8: A glycoside molecule

The cardiac glycosides is of two types according to the structure of the lacton ringof the aglycon moiety

1- If the lacton ring is four membered then the glycoside is termed a Cardenolide.

2- If the lacton ring is five membered then the glycoside is termed a Bufadienolide

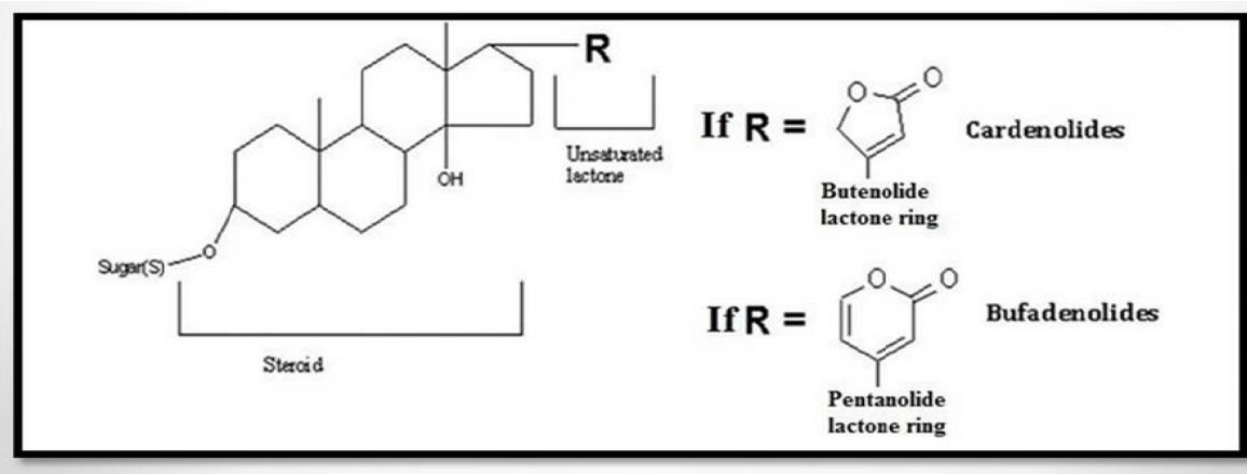

Figure- 9: Classification of cardiac glycosides according to the lacton ring structure

1- The cardenolide:

In the cardenolide (aglycones with 23 carbons), the lactone ring attached at C17 is a butenolide (4 carbons), which is also referred as α, β-unsaturated lactone ring. E.g. the glycosides of **digitalis** and **strophanthus** species.

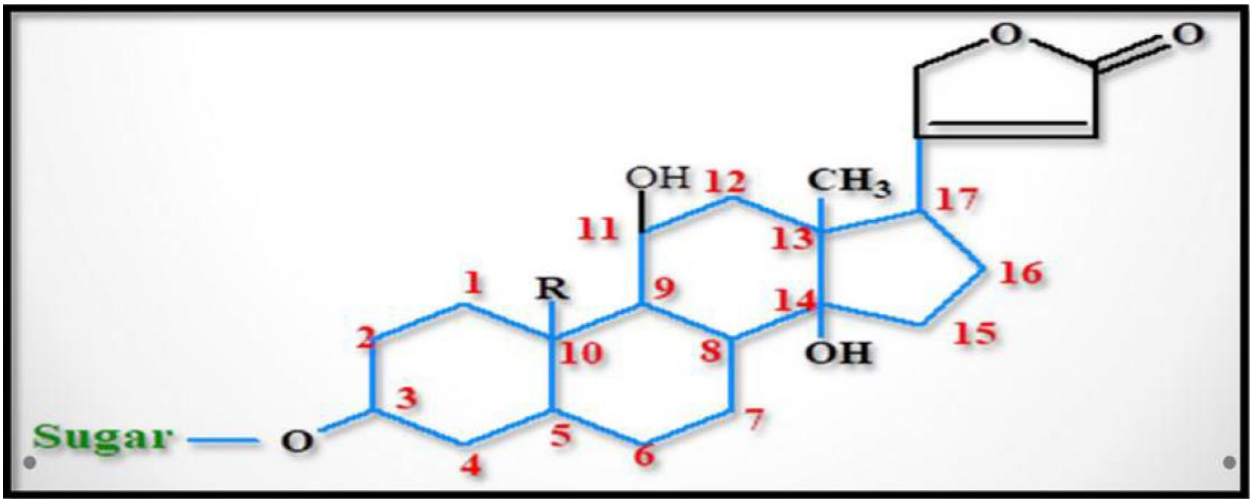

Figure- 10: The cardenolides (If the R=CH3 at C-10, the compound is digitalis glycosides, while if R= aldehyde (CHO) or alcohol (CH2OH) at C-10, the compound is Strophanthus glycosides).

2- The bufadienolide (scilladienolide):

In the scilladienolide (aglycone with 24 carbons), the lactone ring attached at C17 is a pentadienolide (5 carbons with two double bonds) which is also called a pentanolide. E.g. the **squill glycosides** and the **toad venom, Bufotoxin.**

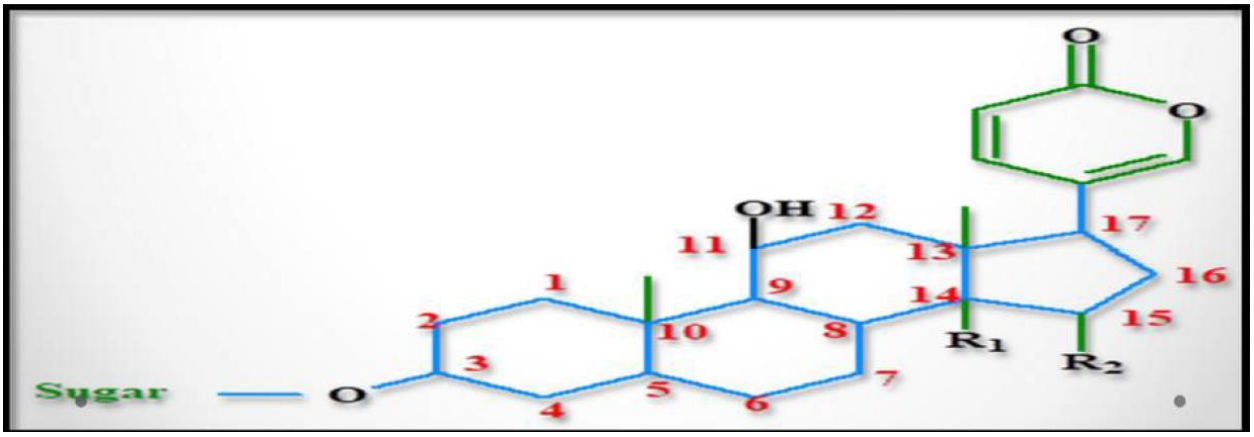

Figure- 11: The bufadienolide (If the R_1 at C- 14=OH and R_2 at C-15= H, the compound is squill glycosides, while if both R_1 and R_2= ester group (R–COO–R) the compound is bufotoxin glycosides).

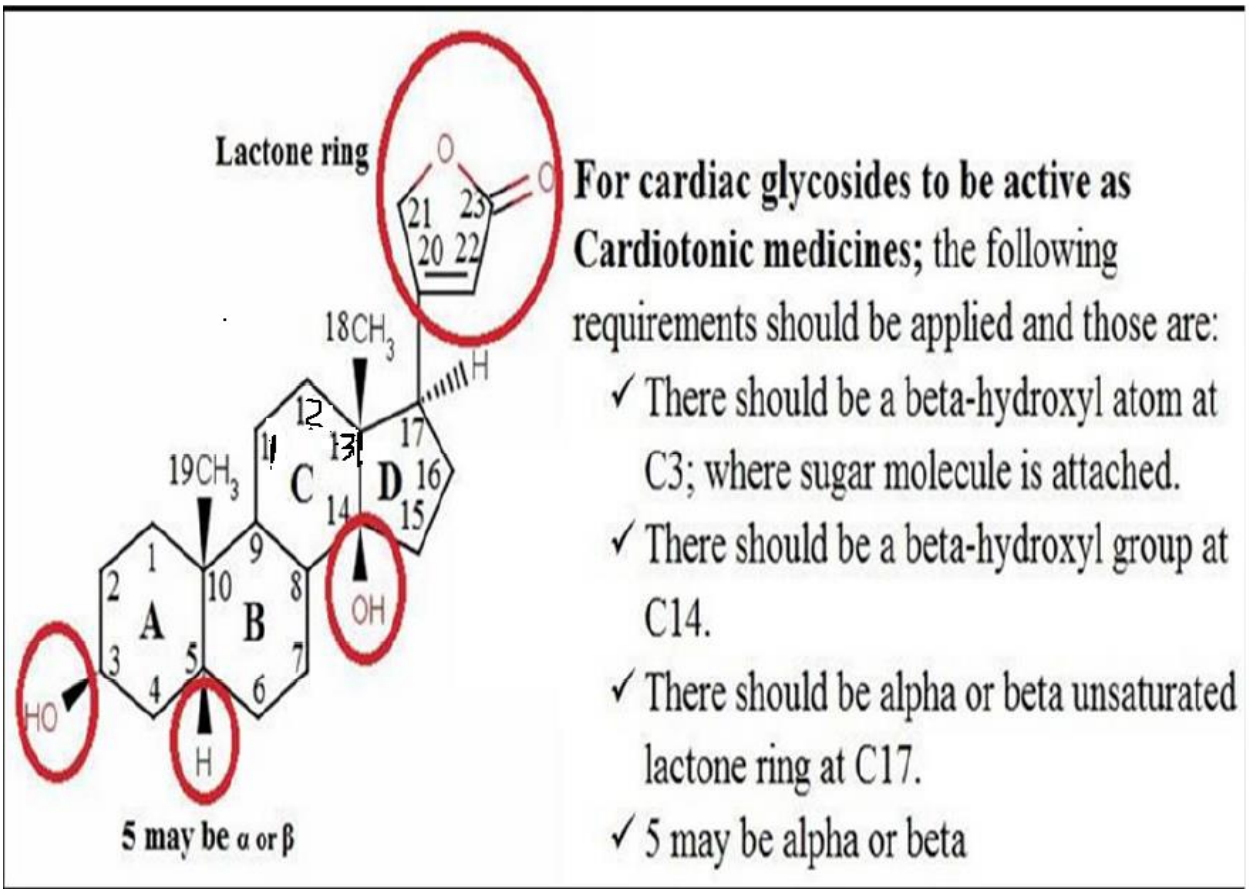

Figure- 12: (Right side): requirements For cardiac glycosides to be active as cardiotonic. (Left side): Typical structure of a cardioactive glycoside.

- **Biosynthesis of cardioactive glycosides:**

Most of the knowledge of the biosynthesis of steroids has been derived from studies of cholesterol production.

It biosynthesized via acetate-mevalonate biosynthesis pathway through which cholesterol will be formed then pregnenolone which will be add either C2 unit or C3 unit to form cardenolide or bufanolide respectively.

- **Plants containing cardioactive glycosides**

1. Digitalis or foxglove

It's the dried leaf of Digitalis purpurea, F: Scrophulariaceae. Digitalis is from the latin digitus, meaning **finger** and refers to the finger shaped corolla, purpurea is latin and refer to the **purple color** of the flower.

Figure- 13: Digitalis purpurea

- **Constituents of Digitalis purpurea:**

The plant contain a large number of glycosides of which the most important from the medicinal view point are: **Digitoxin, gitoxin and gitaloxin**.

The average concentration is about 0.16%. Nearly 30 other glycosides have been identified in the planet e.g. purpurea glycosides A, purpurea glycoside B, gluco-gitaloxin, gluco-digitoxigenin.

- **Constituents of Digitalis lanata**

Nearly 70 different glycosides have been detected in the leaves of Digitalis lanata.
All are derivatives of five different aglycones, three of which (digitoxigenin, gitoxigenin and gitaloxigenin) also occur in Digitalis purpurea. The other **two types** of glycosides are derived from **digoxigenin, and diginatigenin** occur in D**igitalis lanata but not in Digitalis purpurea.**

Figure- 14: Digitalis lanta

- **Mechanism of action**

Cardioactive glycoside **binds to and inhibits the sodium/potassium-ATPase (sodium pump) within the plasma membrane of cardiac myocytes**. This inhibition increases the intracellular sodium content which in turn increases the intracellular calcium content which leads to increased cardiac contractility.
It also increses the vagal stimulation to the heart leading to reduced conduction through the AV- node.

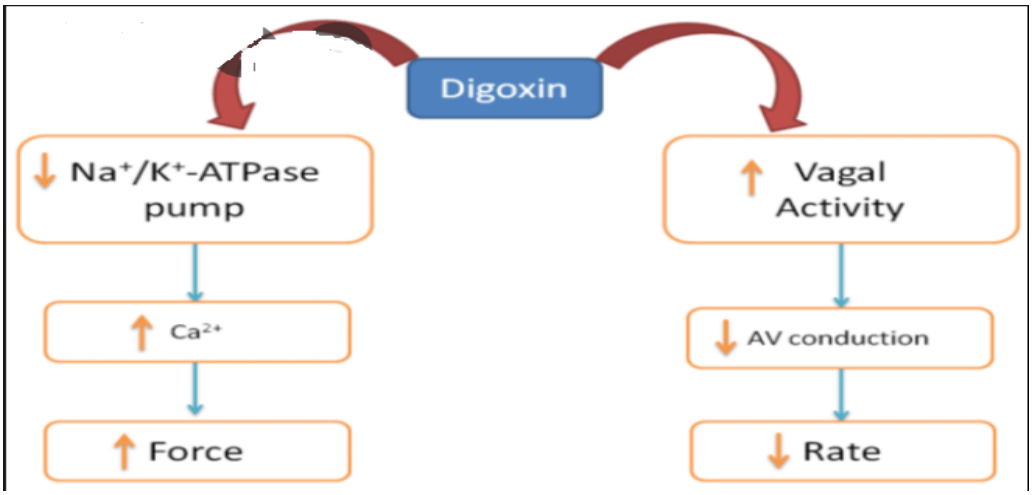

Figure- 15: Mechanism of cardioactive glycosides action

- **Uses of digitalis glycosides**

Digoxin is used to treat **congestive heart failure**, usually in combination with a diuretic (water pill) and an angiotensin-converting enzyme (ACE) inhibitor. It is also used to treat a heart rhythm problem called atrial fibrillation.