pharmacognosy

3rd stage/1stterm

Cardioactive Glycosides

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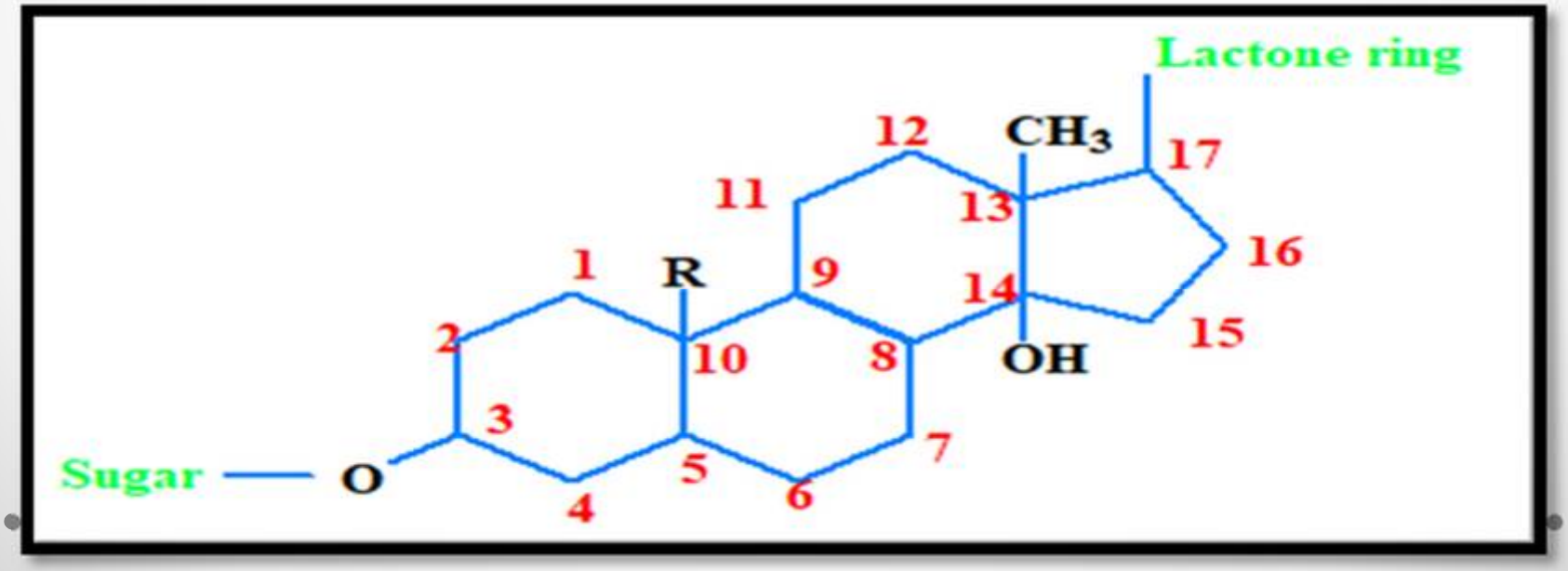
Lec .4

Cardioactive Glycosides

- **Cardioactive Glycosides:** The members of this group are characterized by their highly specific action on cardiac muscle increasing tone, excitability and contractility.

➢ It composed from aglycones and glycone portion.

➢ The aglycones of these glycosides are referred to as **"cardiac genin",** they are steroidal in nature, specifically, they are derivatives of cyclopentaphenanthrene containing an unsaturated lactone ring attached to **C17.**

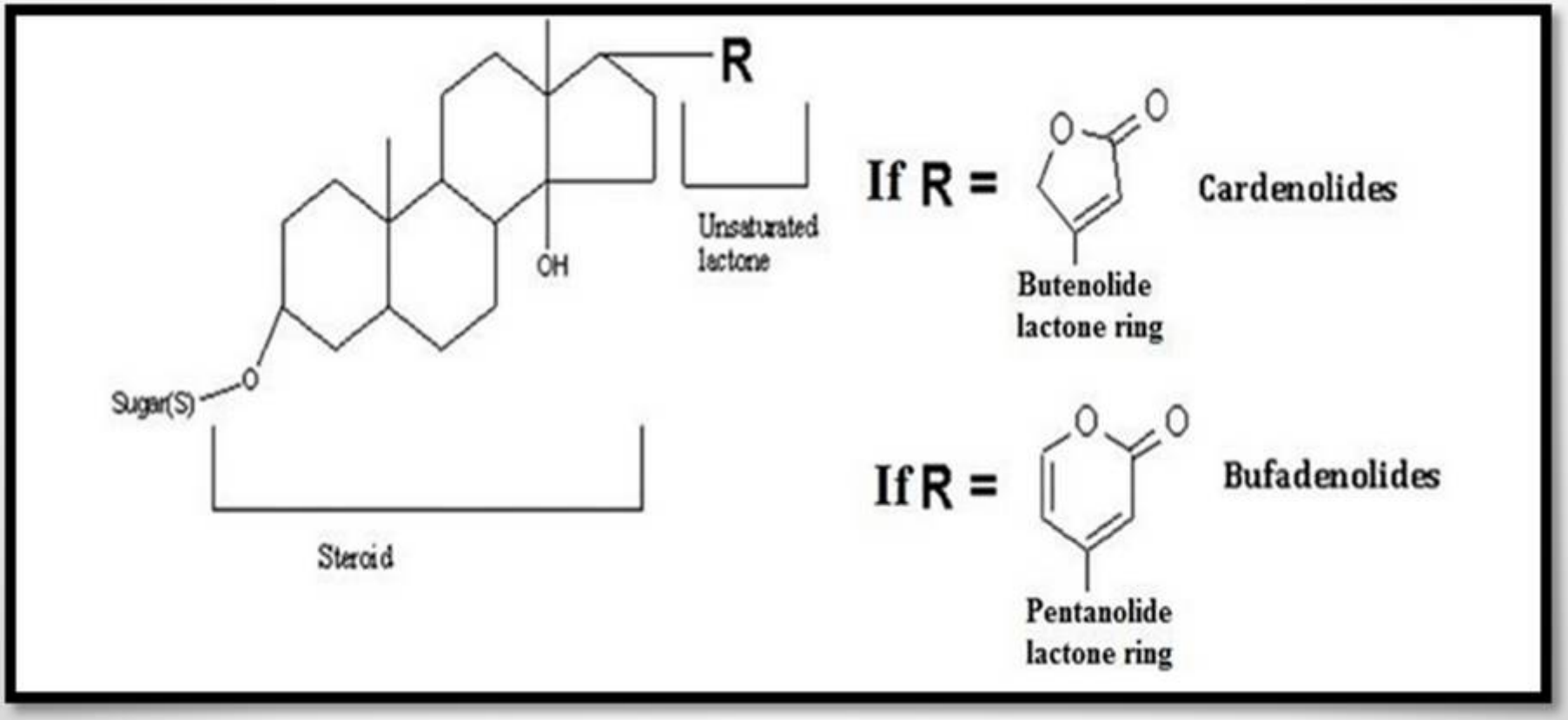


Types of aglycone moiety of cardiac glycosides:

On the basis of the **lactone ring** structure; the **aglycone portions** may be grouped into two groups:

1-The Cardenolides (lactone ring is 4-membered ring)

2-The Bufadienolide (lactone ring is 5-membered ring).

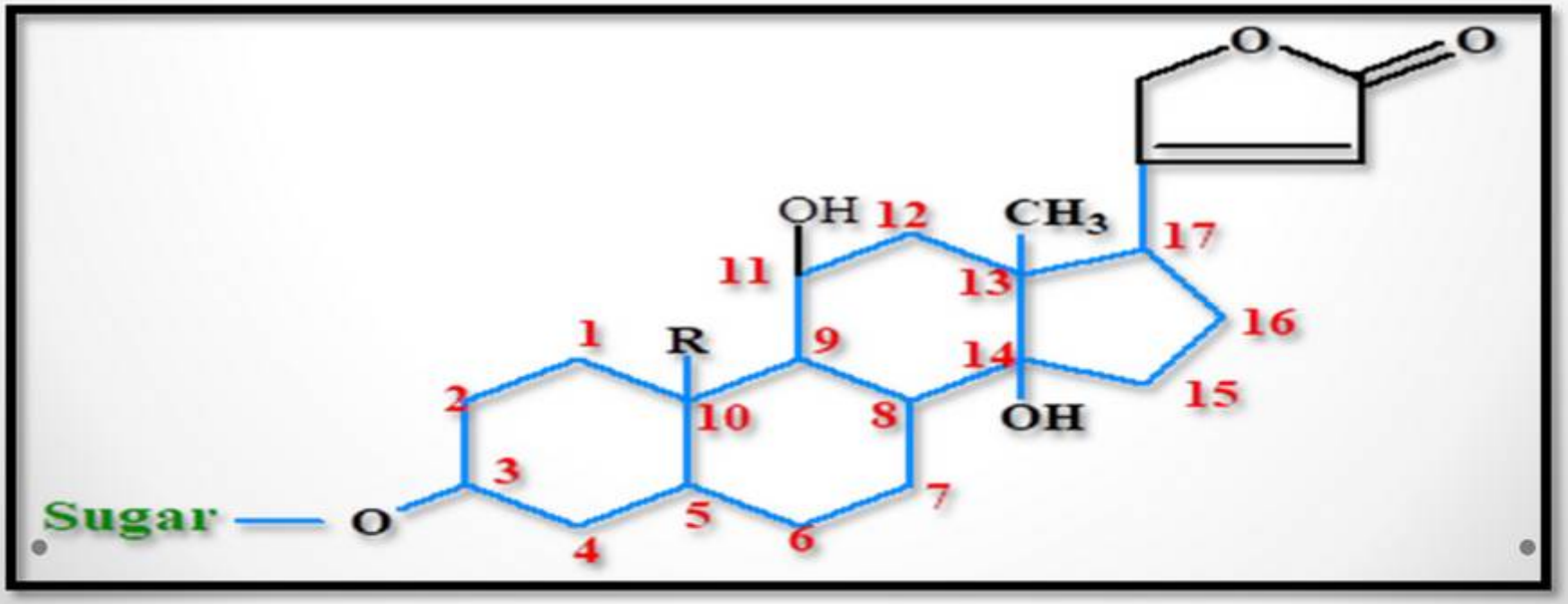


1- The cardenolide

In the cardenolide (aglycones with 23 carbons), the lactone ring attached at C_{17} is a butenolide (4 carbons), which is also referred as α, β-unsaturated lactone ring.

E.g. the glycosides of **digitalis** and **strophanthus** species.

- If the **R=CH_3 at C-10** ⟶ **Digitalis glycosides**
- If the **R= aldehyde (CHO) or alcohol (CH2OH)** ⟶ **Strophanthus glycosides**



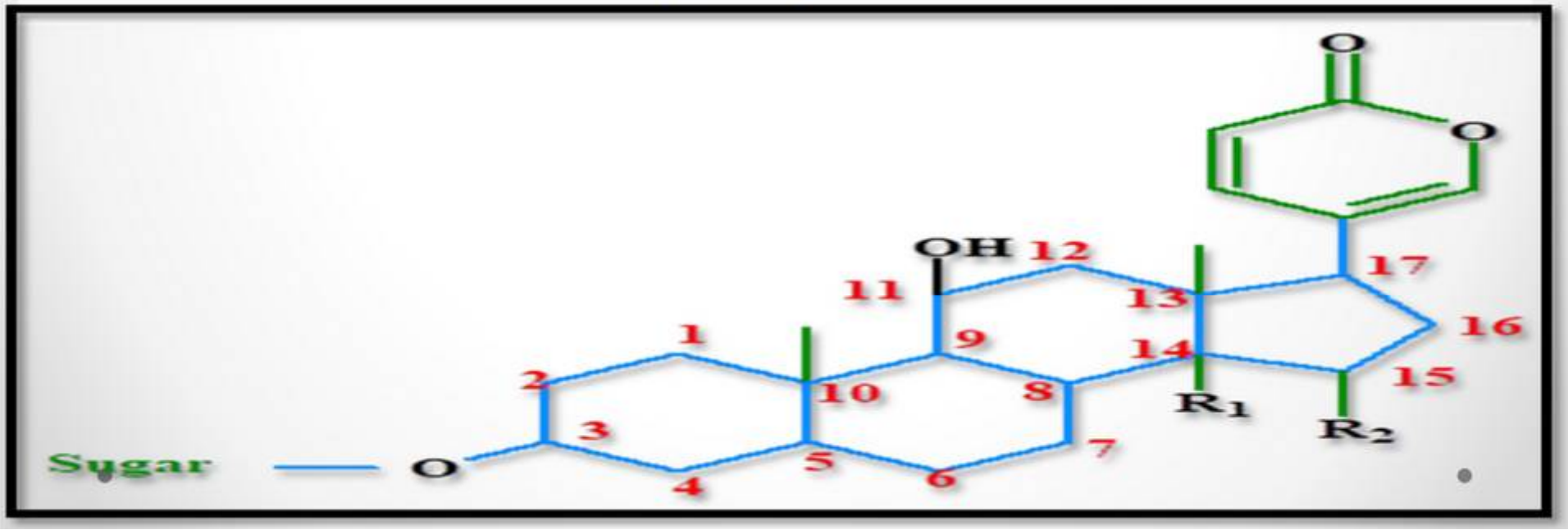
2- The bufadienolide (which are referred to as scilladienolide)

In the scilladienolide (aglycone with 24 carbons), the lactone ring attached at C_{17} 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.**

If the R_1=OH, R_2=H ⟶ Squill glycosides

If the R1 & R2 = ester group ⟶ Bufotoxin



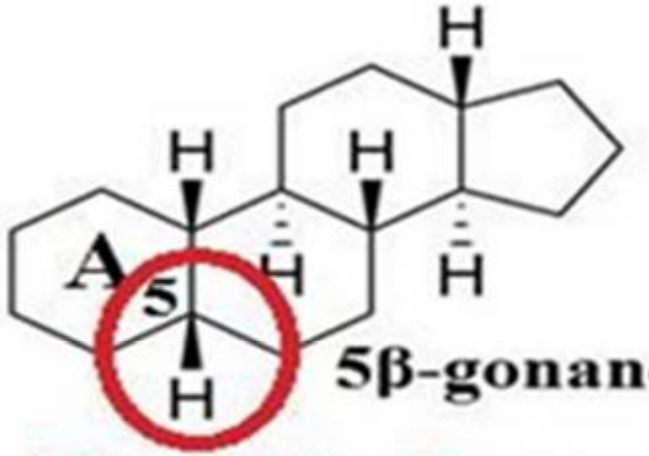
- **The glycone portion** at position **C-3** of cardiac glycosides may contain **four monosaccharide molecules** linked in series.
- Thus, from a single genin one may have a monoside, a bioside, a trioside or a tetroside.

Relation between steroids and cardioactive glycosides

- An atom or group attached to a ring is termed **α (alpha)** if it lies **below** the plane of the paper or **β (beta)** if it lies **above** the plane of the paper.
- In formulas, bonds to atoms or groups attached in **α configuration are shown as broken lines**, and bonds to atoms or groups attached in a **β configuration are shown as solid lines.**
- Both steroids and cardioactive glycosides have the same basic **structure, namely, cyclopentaphenanthrene**.
- The use of a steroid name implies that atoms or groups attached at the ring junction positions 8, 9, 10, 13, 14 and 17 are oriented as follows:

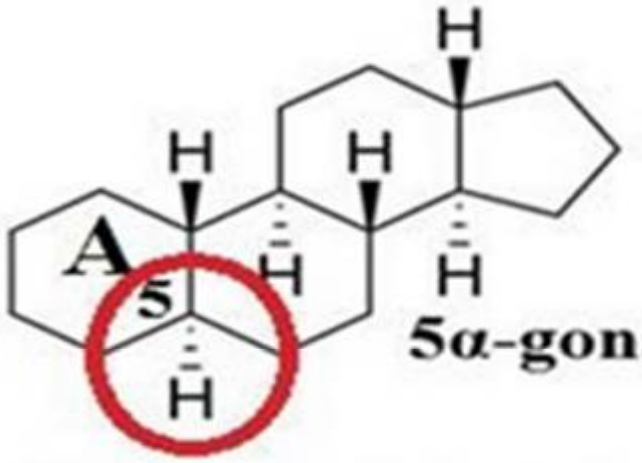
- **α: 9, 14**
- **β: 8, 10, 13, 17**
- **5 may α or β**

Cardioactive glycosides like steroids except **C14 is β.**



5β-gonane

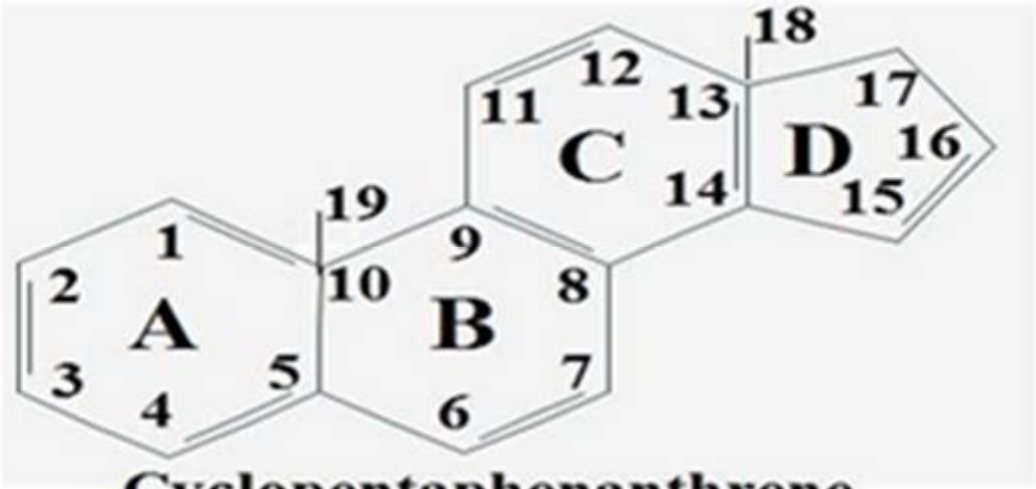
The (H) is above the plane of the paper



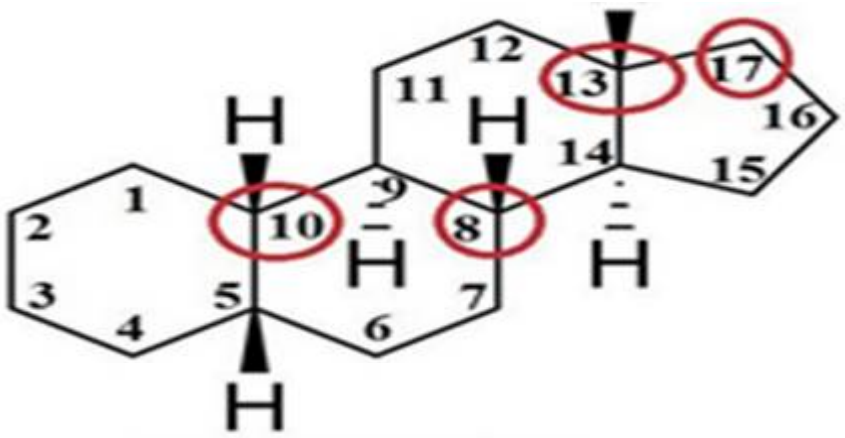
5α-gonane

The (H) is below the plane of the paper

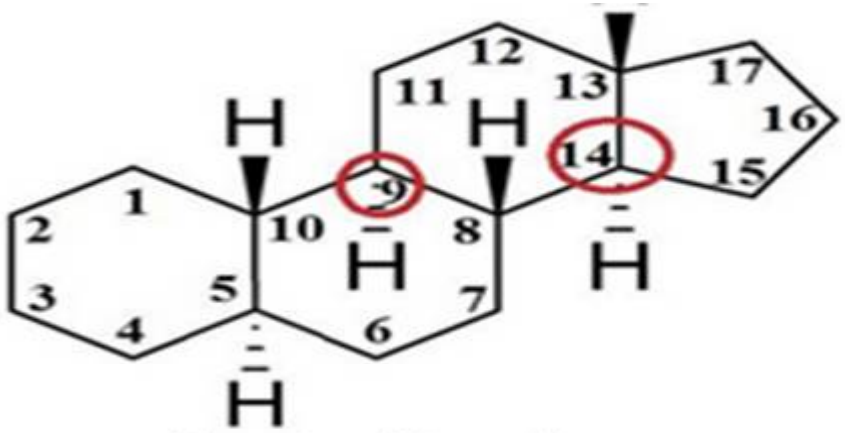
Cardiac glycosides are steroidal in nature



Cyclopentaphenanthrene



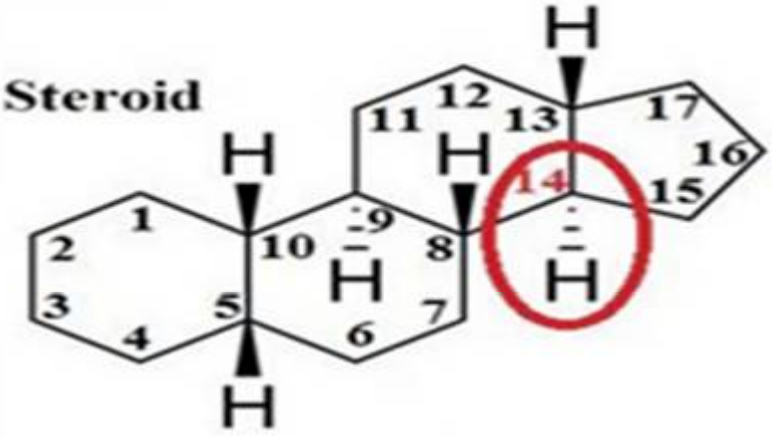
5-β steroid nucleus



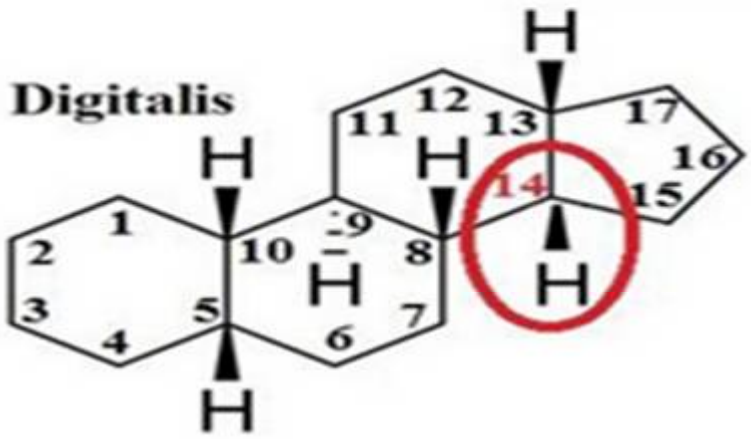
5-α steroid nucleus

Alpha: The atoms at 9 and 14 are below the plane, so termed as alpha atoms
Beta: The atom at 8, 10, 13, 17 are above the plane , so termed as beta atoms

Steroid



Digitalis



In steroids: the atoms attached to C14 are alpha
In digitalis: the atoms attached to C14 are beta

For cardiac glycosides to be active as cardiotonic medicines; the following requirements should be applied and those are:

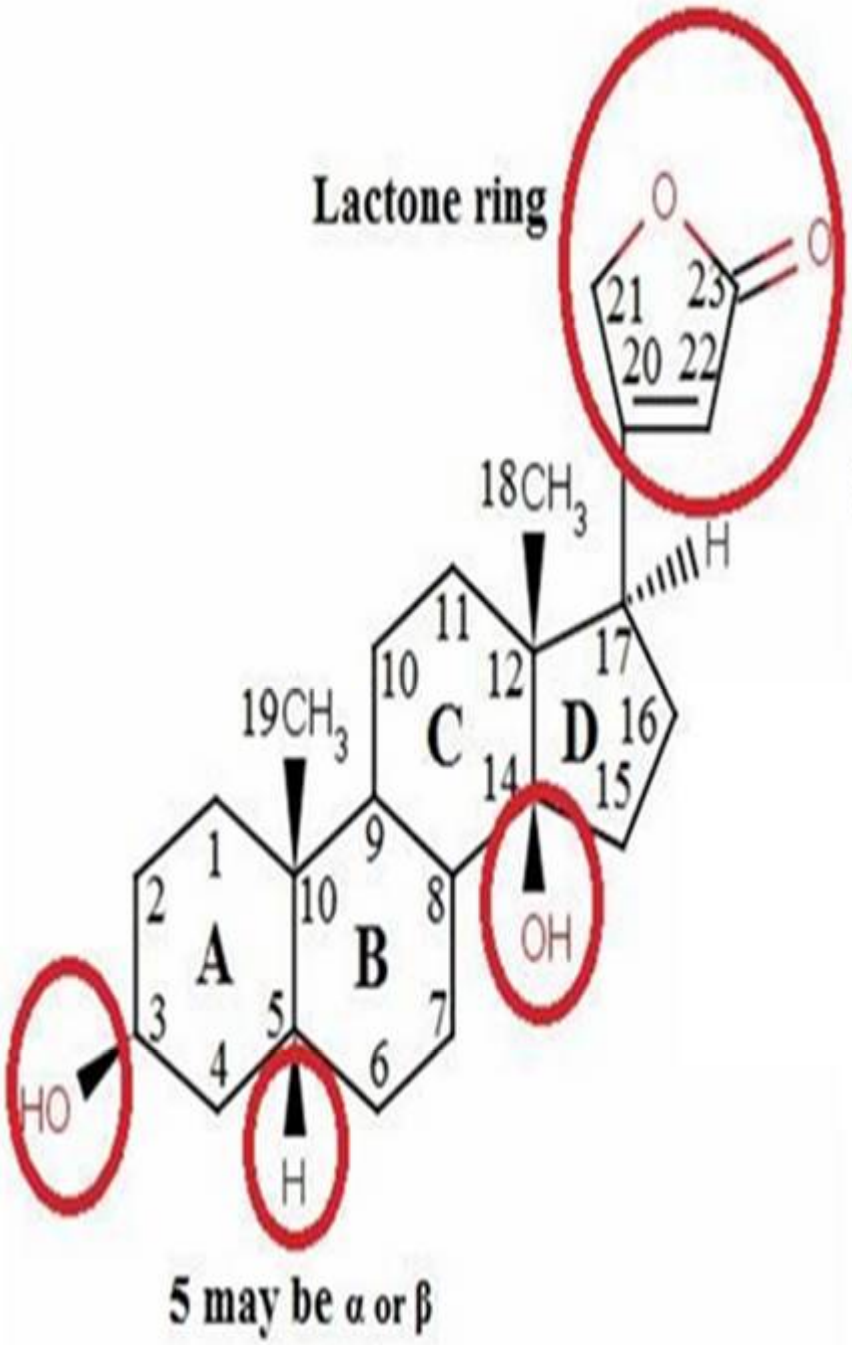
1-There should be a beta-hydroxyl atom at C3; where sugar molecule is attached.

2-There should be a beta-hydroxyl group at C14.

3-There should be alpha or beta unsaturated lactone ring at C17.

4-5 may be alpha or beta.

So a typical structure for cardioactive glycosides could be drawn as follows:



For cardiac glycosides to be active as Cardiotonic medicines; the following requirements should be applied and those are:

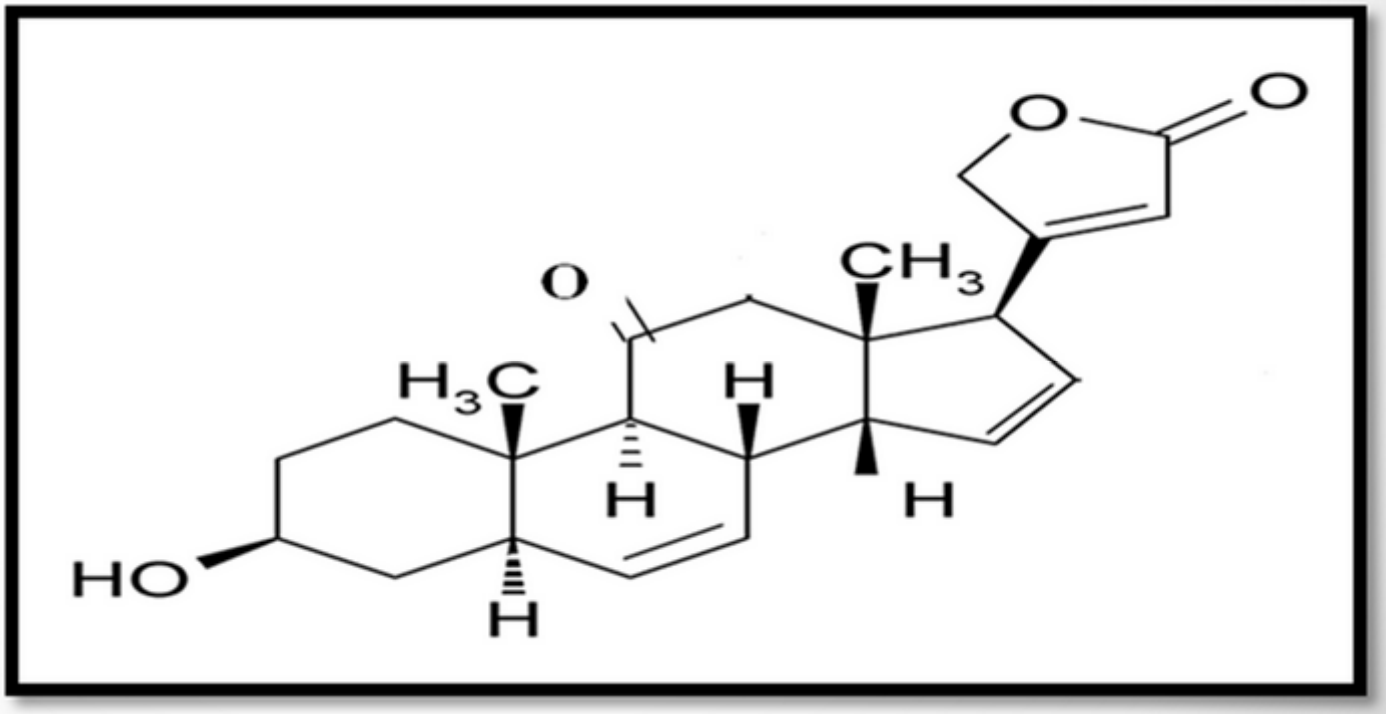
- ✓ There should be a beta-hydroxyl atom at C3; where sugar molecule is attached.
- ✓ There should be a beta-hydroxyl group at C14.
- ✓ There should be alpha or beta unsaturated lactone ring at C17.
- ✓ 5 may be alpha or beta

Nomenclature of cardioactive glycosides

The sequence of nomenclature is as follows:

1. Arrange the functional groups and denote their configuration.
2. Denote 5 whether α or β.
3. Denote the type of glycoside.
4. Denote the position of the double bonds.

Example:



3 β hydroxyl-11-oxo-5α-card-6,15,20-trienolide

- If the compound has one double bond then it is called **cardenolide**,
- if has two double bonds then it's called **dienolide**, but
- if it has no double bond then it is called **cardanolide** and **bufanolide**.

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.

Drugs containing cardioactive glycosides

1. Digitalis or foxglove

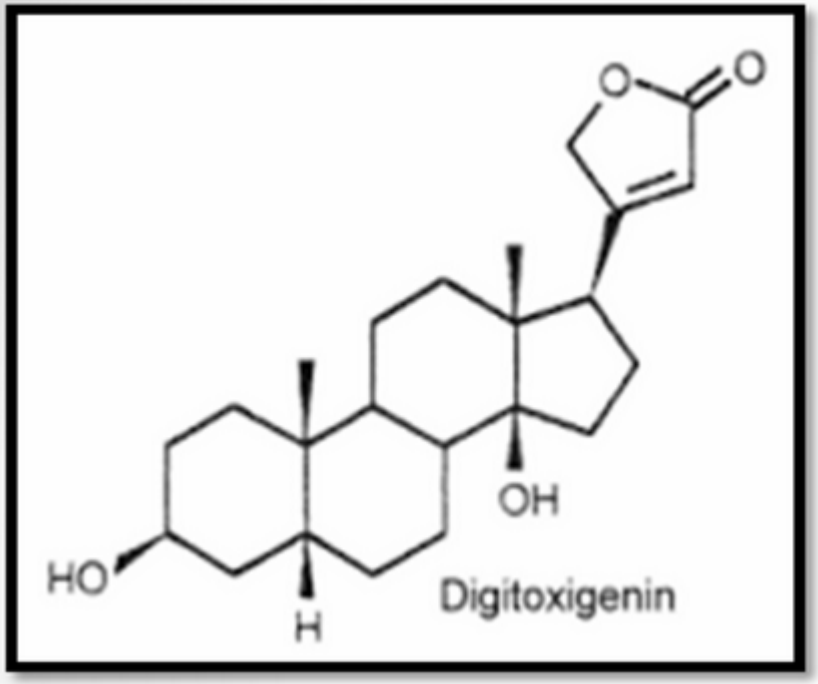
It's the dried leaf of Digitalis purpurea, F: Scrophulariaceae.

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.

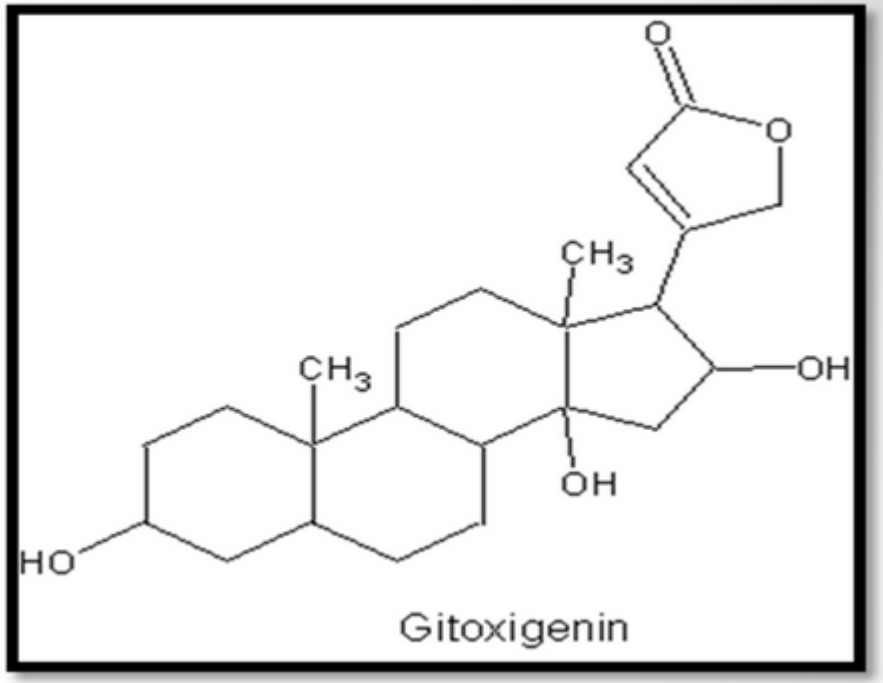
Constituents

The drug contain a large number of glycosides of which the most important from the medicinal view point are:

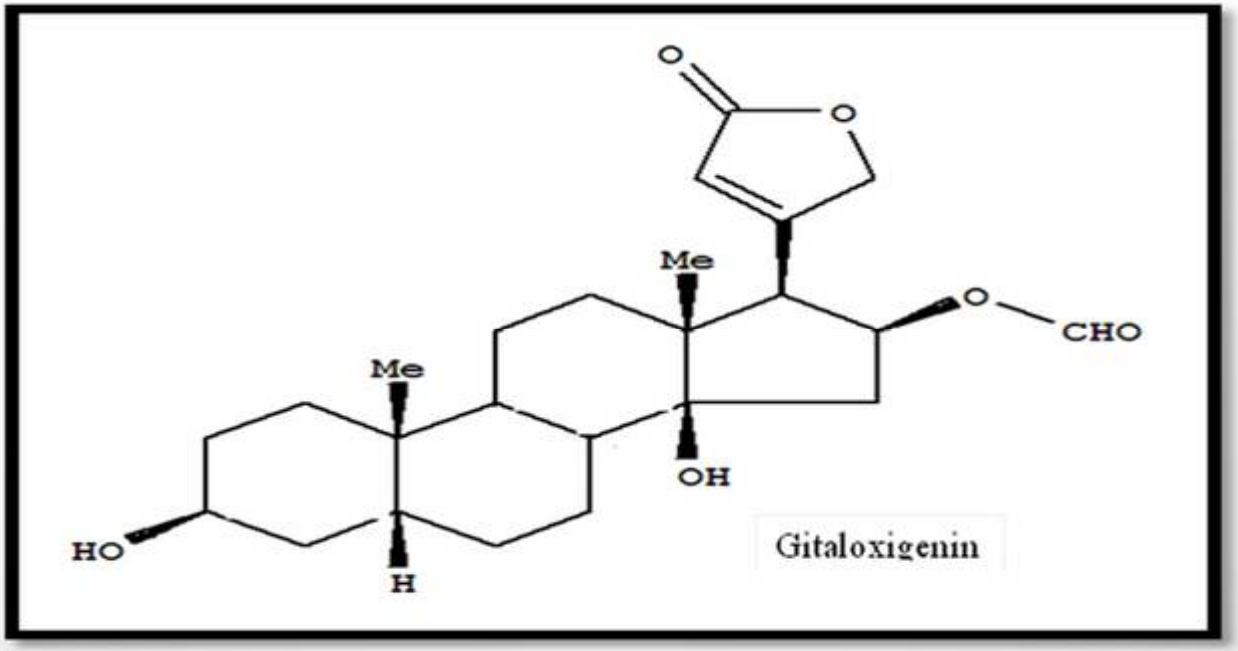
- **Digitoxin, gitoxin and gitaloxin**.
- The average concentration is about 0.16%.
- Nearly 30 other glycosides have been identified in the drug e.g. purpurea glycosides A, purpurea glycoside B, gluco-gitaloxin, gluco-digitoxigenin.



Digitoxigenin



Gitoxigenin

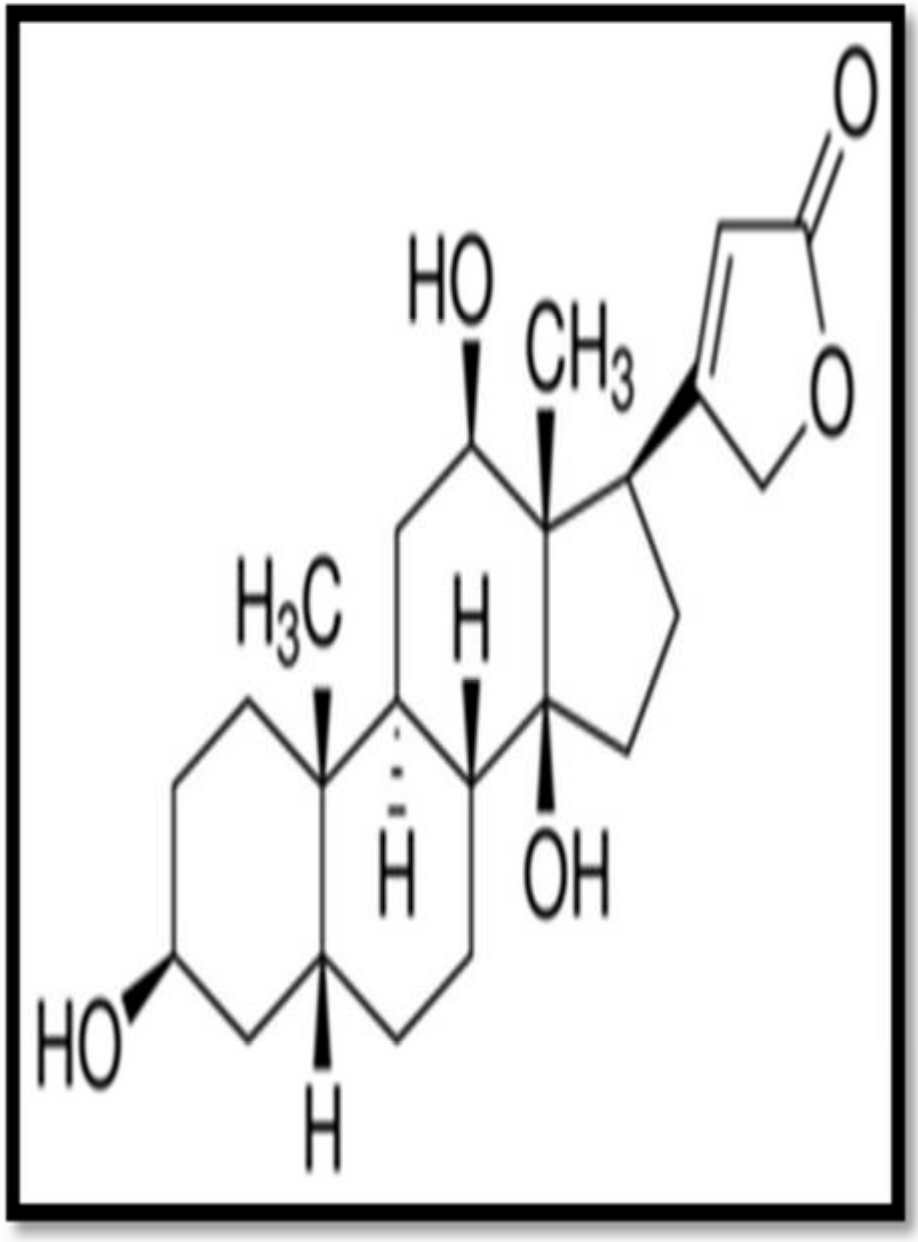


Gitaloxigenin

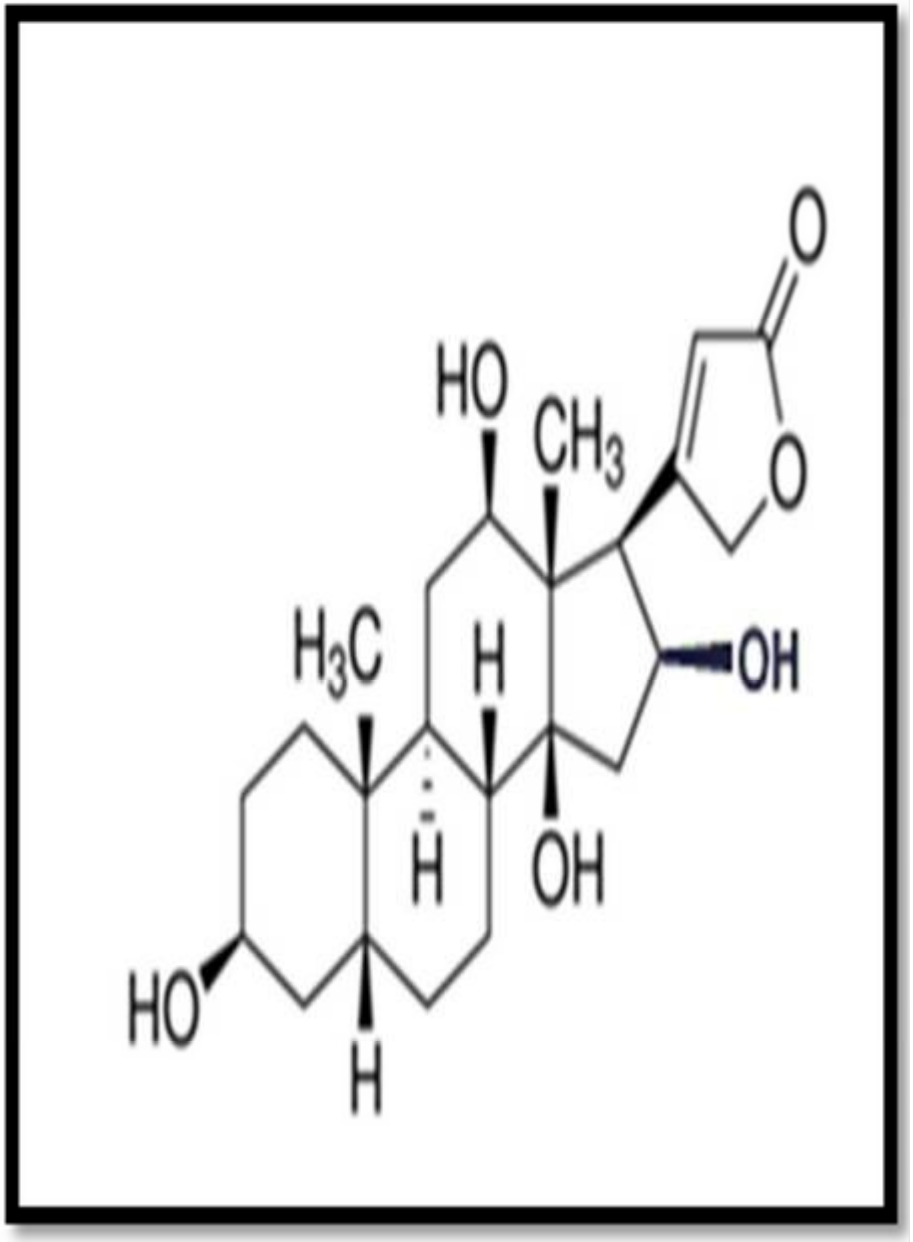
Constituents of Digitalis lanata

- 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

Digitalis lanata but not in digitalis purpurea.



Digoxigenin



Diginatigenin

Uses of digitalis glycosides

1- **Digitoxin**: Is a cardiotonic (increasing the tone of cardiac muscle).

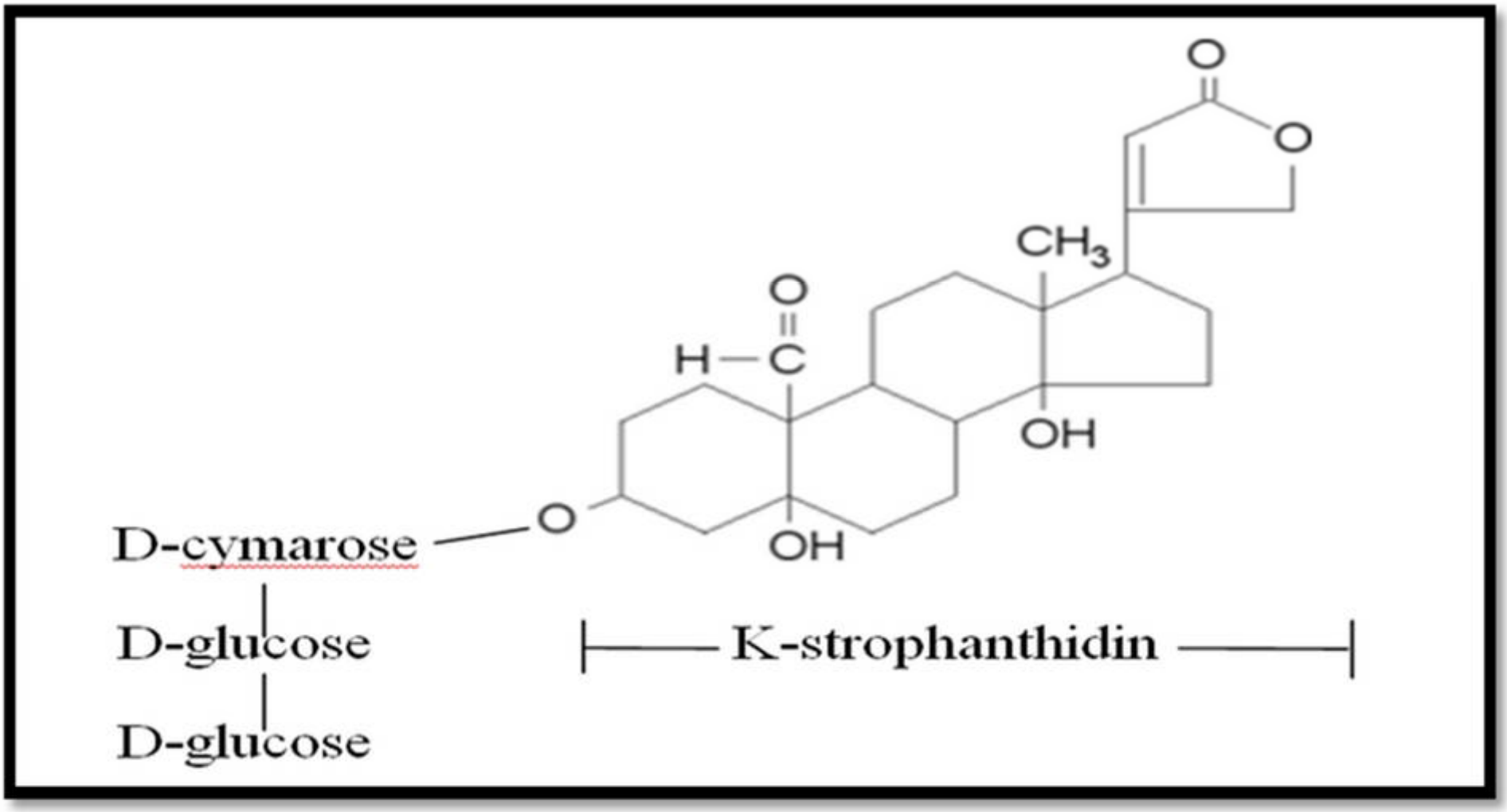
2- **Digoxin:** is a cardiotonic. Used for the treatment of congestive heart failure.

2. Strophanthus

Is the dried ripe seeds of Strophanthus kombe or Strophanthus hispidus F: Apocyanaceae.

Constituents:

- k-strophanthoside, also known as strophoside. Is the main glycoside in both Strophanthus kombe and Strophanthus hispidus.
- it is composed of the genin strophanthidin coupled to a trisaccharide consisting of **cymarose, β-glucose and α-glucose.**
- Strophanthin is used I.V. as a cardiotonic.



Strophanthidin + D-cymarose = cymarin

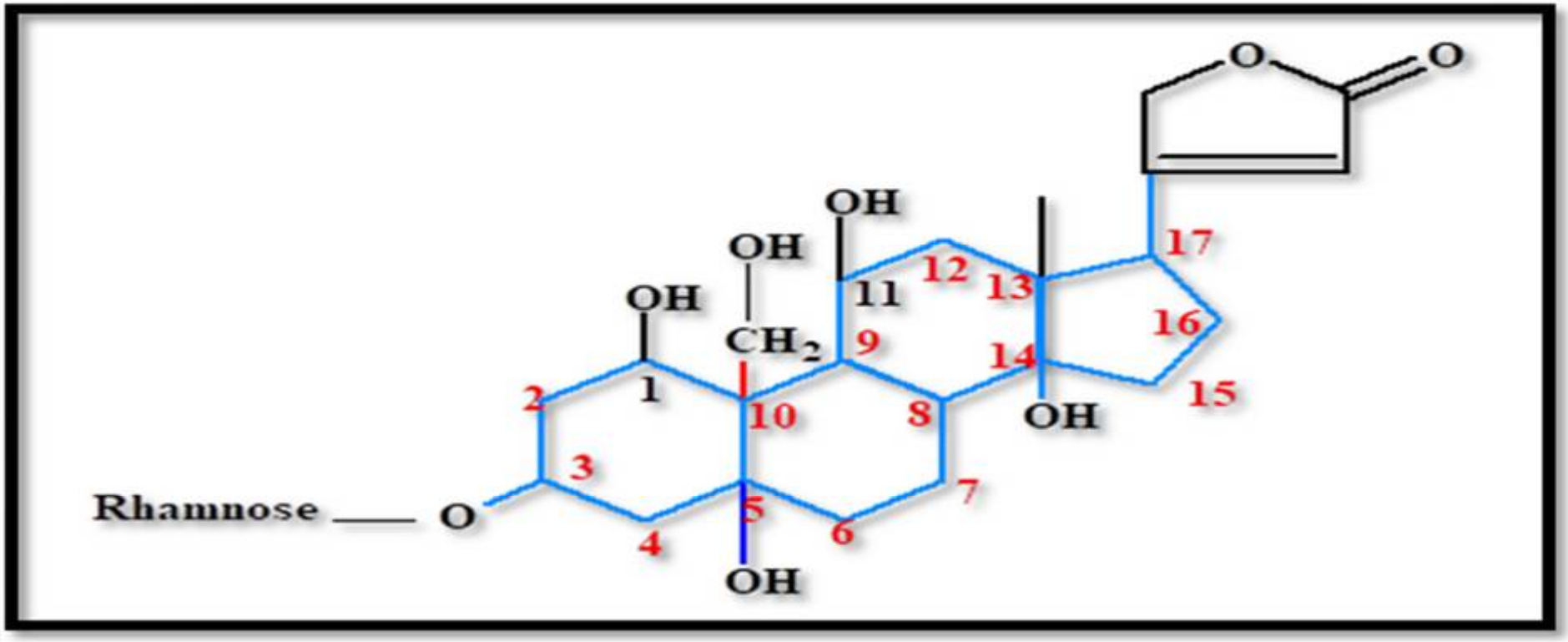
Strophanthidin + D-cymarose + D-glucose = k-strophanthin

Strophanthidin + D-cymarose + 2 D-glucose = strophanthoside

3. Ouabin (G-strophanthin)

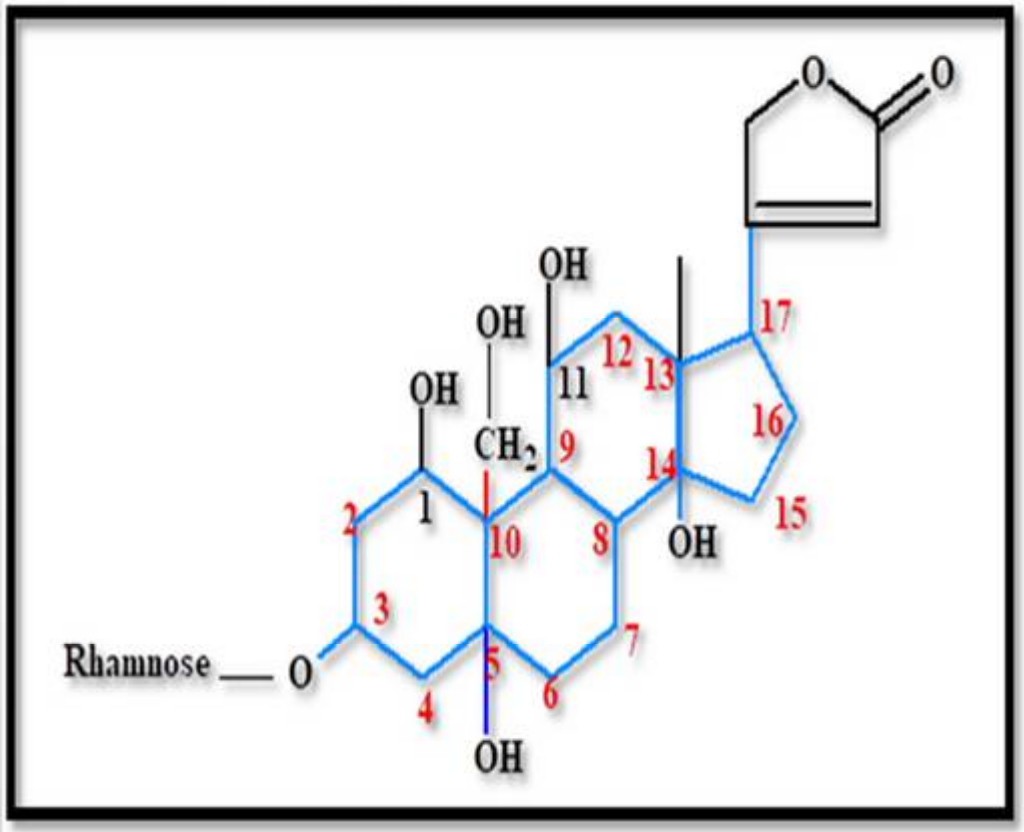
It is obtained from Strophanthus grantus, F: Apocynaceae

Uses: it is a **cardiotonic. i.v.** for prompt therapeutic effect. It is absorbed so slowly and irregularly from the alimentary canal that the oral administration is not recommended and is even considered unsafe.



(Ouabagenin, the sugar is rhamnose)

- **Ouabagenin** differs from **K-strophanthidin** in having 2 additional (OH) groups at C-1 and C-11 and having an alcoholic group at C-10 instead of the aldehydic group.



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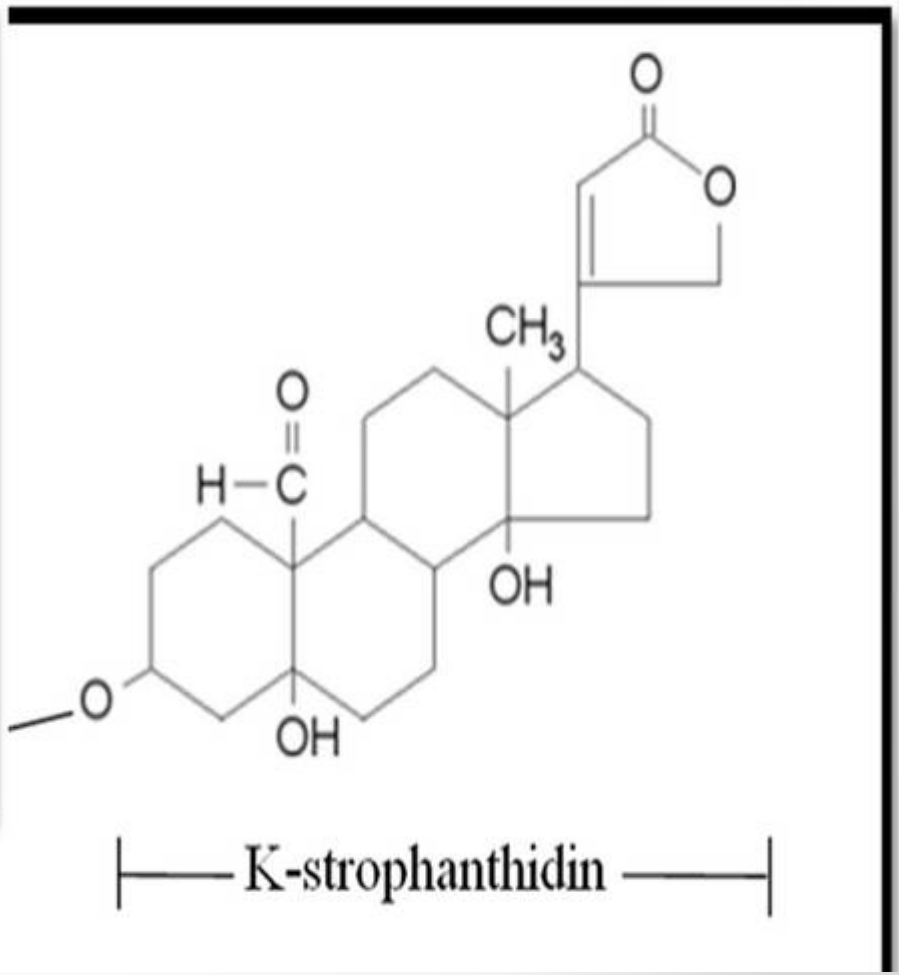
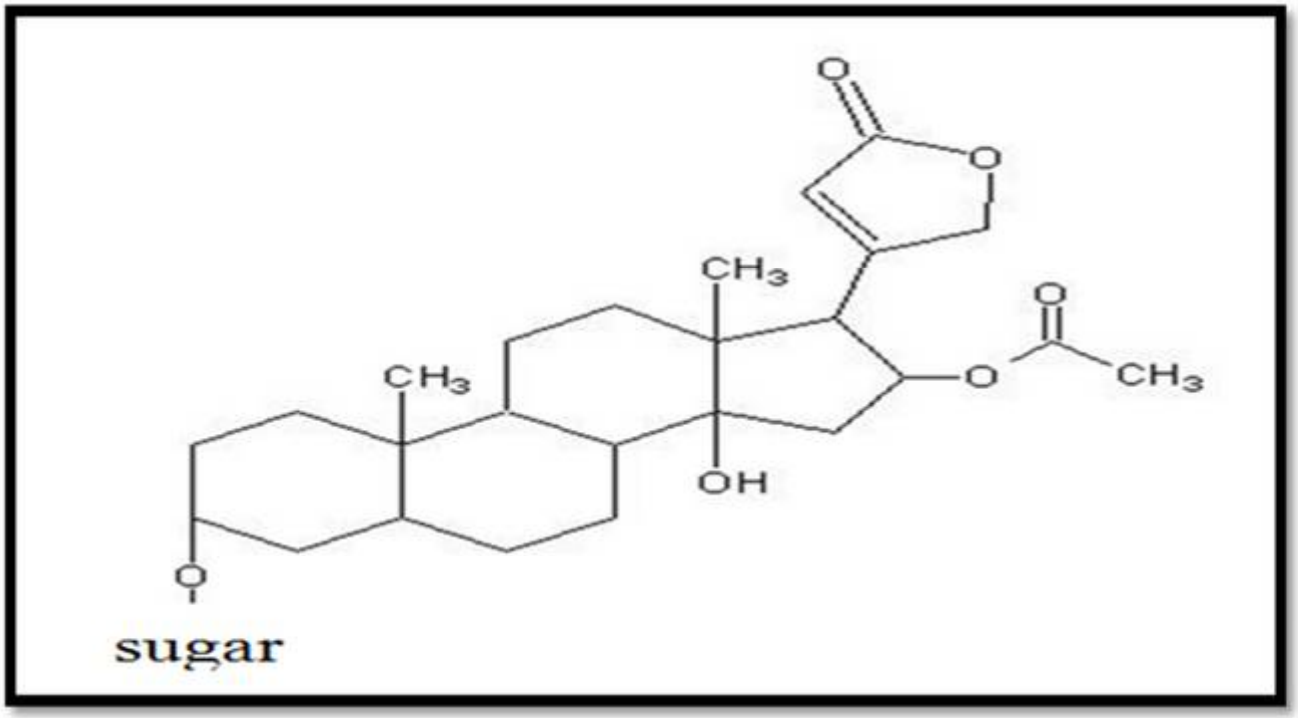


K-strophanthidin

4- Oleander

- Is another plant that contains cardiac glycosides.
- The leaves of Nerium oleander, F: Apocyanaceae have been used to treat cardiac insufficiency.
- The main constituent is oleanderin (is a promising agent for anticancer treatment) .



Oleanderin

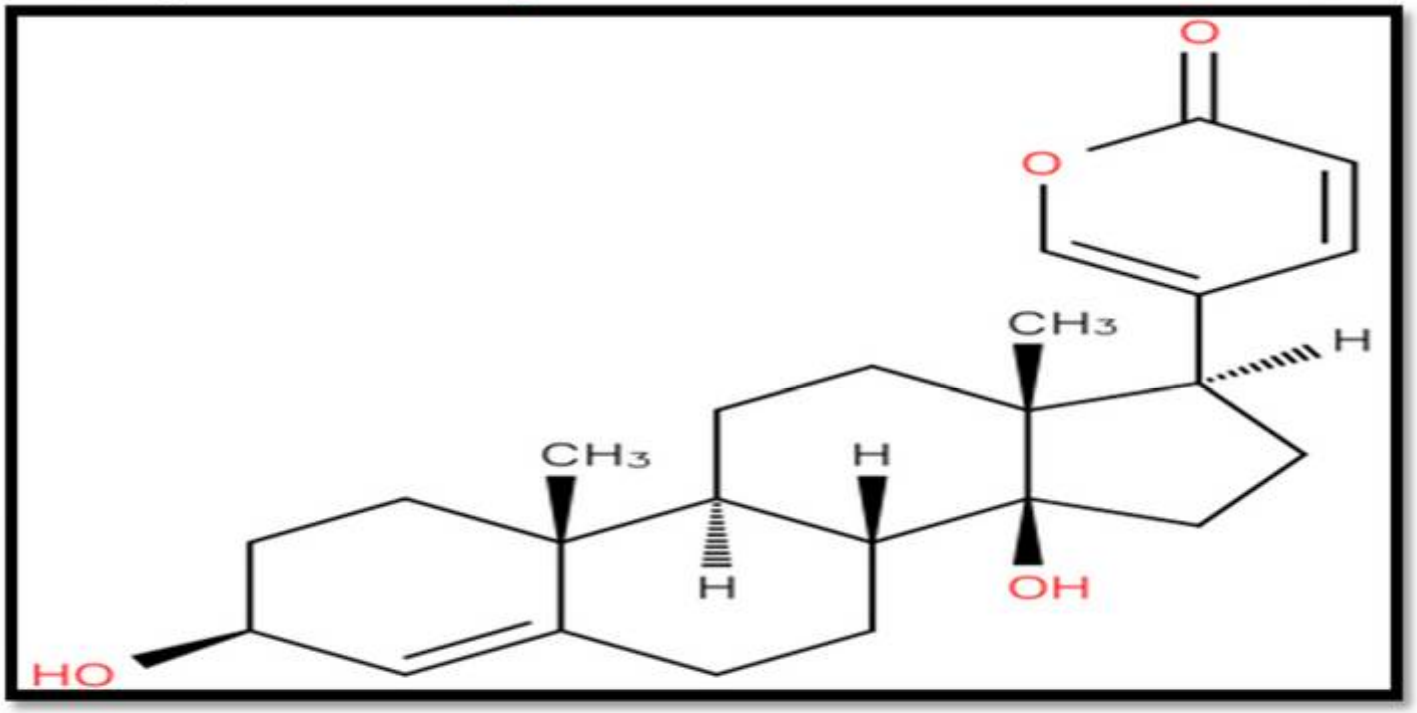
5. Squill

- The squill bulb of the white variety of **Urginea maritima** known as white or Mediterranean squill, or of Urginea indica known in commerce as indian squill, F: liliaceae.

Constituents: the principal glycoside- scillaren A- on hydrolysis it yields the aglycone **scillarenin** plus rhamnose and glucose.

Uses: as an expectorant but it also possesses **emetic, cardiotonic and diuretic properties.**

Red squill consists of the bulb of the red variety of Urginea maritima, which is mostly used as **rat poison.**



Scillarenin

Thank You