1-The genins of all cardiac glycosides are steroidal in nature, that act as cardiotonic agents.

2-They are characterized by their highly specific action cardiac muscle, increasing tone, excitability and contractility of this muscle, thus allowing the weakened heart to function more efficiently.



**All cardio active glycosides are characterized by the following structural features:**

1. The presence of ***β*-OH** at position **C-3**, which is always involved in a glycosidic linkage to a mono, di, tri, OR tetra saccharide.
2. The presence of another ***β*-OH** group at **C-14**.
3. The presence of unsaturated **5 or 6-** membered **lactone ring** at position **C-17**, also in the ***β*** configuration.
4. The **A/B** ring junction is usually **(cis),** while the **B/C** ring junction is always **(trans)** and the **C/D** ring junction is in all cases **(cis).**
5. Additional **OH groups** may be present at **C-5, C-11** and **C-16.**

1- Cardiac glycosides that **α-β unsaturated** **5-membered lactose** **ring** in position **C-17** are known as **cardenolides. These are represented by the digitalis and straphanthus group.**

2- **Digitalis glycosides** contain angular methyl group at **C-10,** while **strophanthus glycoside** are characterized by presence of either an **aldehydic** (CHO) or **primary alcoholic** (C`H2OH) group at **C-10.**



**Cardenolides**

**Digitalis glycosides R=CH3**

**Strophanthus glycosides R=CHO OR CH2OH**

3- Cardiac agents that have **doubly unsaturated 6-membered** lactone ring in position **C-17** are referred to as **Bufadienolides**.

4- This group includes the **squill** **glycosides** and the **toad venom, Bufotoxin.**



**Bufadienolides**

**Squill glycosides**   **R1=OH, R2=H**

**Bufotoxin**   **R1 & R2 = ester group**

**5- 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.

6- With the exception of D-glucose and L-rhamnose, all the other sugars that are found in cardiac glycosides are uncommon **deoxy-sugars** e.g., Digitoxose, Cymarose, Thevetose.



**Digitoxose Cyamarose Thevetose**

**Isolation difficulties:**

1. Major difficulty in the isolation of 1ry glycosides from the crude drug.. **why**? because 1ry glycosides are converted into secondary glycosides by hydrolysable enzymes.
2. Other difficulty is the existence of several closely related glycosides in the same drug, which are extremely difficult to separate and purify.

**Origin:** ***D. purpurea, D. lanata, D. lutea and D. thapsi***

**The structures of the common aglycones of the digitalis group are indicated below:**



|  |
| --- |
|  **Compounds R1 R2** |

**Digitoxigenin H H**

**Gitoxigenin H OH**

**Digoxigenin OH H**

**DX = Digitoxose, DX (AC)=Acetyldigitoxose,G = Glucose.**

**1- Glycosides derived from Digitoxigenin:**

**a- Lanatoside A = Digitoxigenin---DX---DX----DX(AC)---G.**

**b- Acetyl-digitoxin = Digitoxigenin---DX---DX----DX---(AC).**

**c- Digitoxin = Digitoxigenin------DX---DX----DX.**

**d- Purpurea gly A = Digitoxigenin---DX---DX----DX---G**

**2- Glycosides derived from Gitoxigenin:**

**a- Lanatoside B = Gitoxigenin---DX---DX----DX(AC)---G.**

**b- Acetyl-gitoxin = Gitoxigenin---DX---DX----DX---(AC).**

**c- Gitoxin = Gitoxigenin------DX---DX----DX.**

**d- Purpurea gly B = Gitoxigenin---DX---DX----DX---G**

**3- Glycosides derived from Digoxigenin:**

**a- Lanatoside C = Digoxigenin---DX---DX----DX(AC)---G.**

**b- Acetyl-digoxin = Digoxigenin---DX---DX----DX---(AC).**

**c- Digoxin = Digoxigenin------DX---DX----DX.**

**d- Deslanoside = Digoxigenin---DX---DX----DX---G**

1. The 1ry glycosides **Lanatoside A, Lanatoside B, Lanatoside C** are acted by **specific enzyme** which split the **terminal glucose**, give the 2ry glycosides **acetyldigitoxin, acetylgitoxin and acetyldigoxin** respectively.
2. The **deacetyl-lanatosides A, B and C** can be obtained by the **alkaline hydrolysis** of the corresponding lanatosides.
3. **Digitoxin, gitoxin and digoxin** are obtained by the action of **alkali** on their acetyl-derivatives.



1- The glycoside **K-strophanthoside** **(a trioside)**, **K-strophanthin B** **(bioside)** and **cymarin** **(a monoside)** were isolated from different ***strophanthus*** species.

2- The 1ry glycoside **K-strophanthoside** gives by hydrolysis one molecule of **glucose** and the 2ry glycoside **K-strophanthoside B** or **K- strophanthin B**.

3- The later gives by hydrolysis one molecule of **glucose** and the **tertiary glycoside** **cymarin,** which on turn hydrolyze into the genin **K-strophanthidin** and the deoxysugar **cymarose.**



The seeds of *Strophanthus gratus* contains another glycoside named **Ouabain** or **(G-strophanthin),** which yield on hydrolysis **rhamnose** and the **aglycone ouabagenin**.

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



**Ouabain (G-strophanthin)**

This group of cardioactive agents includes **the squill** glycosides (the scillarins) and the **Toad poison** (Bufotoxin).

**The genins of squill glycosides differ from those of the cardenolides in two important aspects**:

1. They have **six membered doubly unsaturated lactone** ring in position **C-17.**
2. They have at least **one double bond** in the steroid nucleus.



**The Bufadienolides of Squill**

**Name of glycosides Structure**

**Glucoscillarin Scillaridin A ---RH—G---G**

**Scillarin A Scillaridin A ---RH—G**

**Proscillaridin A Scillaridin A ---RH**

**\*** The different cardiac glycosides show different solubilities in aqueous and organic solvents. They are usually soluble in water or aqueous alcohol and insoluble in the fat solvents with exception of chloroform and ethylacetate.

\* The higher number of sugar units in the molecule, the greater solubility in water but lower soluble in chloroform.

\* Alcohols are good solvents for both the glycosides and the aglycones. Therefore, they are considered as the solvents of choice for the extraction of all CG from drugs.

\* pet.ether and ether are used for defatting process of drug, they do not dissolve CG.

1- Acid hydrolysis cleavage of the glycosides into aglycones and sugar residues.

2- Specific enzyme usually coexist with CG in plants, which may split the **primary** G into **G with less sugar units**. Thus, CG deteriorate during drying and storage unless special precautions are taken.

3- So it is required by many **pharmacopoeias** that CG containing drugs must contain not more than specified **moisture content** and that these drugs should be stored in sealed containers over **dehydrating** agents.

4- It is recommended to **heat stabilize** these CG, by destroying the enzymes at higher temperatures. At higher temperature, the **tertiary OH gp at C-14** may split off as water, leading to formation of an **inactive anhydro-form** of CG.



5- The gitoxin has in addition to tertiary OH at C-14 another **secondary OH** at **C-16**. Both OH gps split as water by the action of H2SO4 with the formation of **two additional double** **bonds**. These with the double bond of the lactone ring from a **conjugated double bond system** that makes the compound **fluorescent in UV light**.



**The detection of gitoxin in other digitalis G is based on the above mentioned reaction.**

1. CGs are **steroidal** in nature, give +Ve with **Liebermann’s** and **Salkoviski’s test**.
2. CG that contain **deoxy-sugars** are distinguished by **Keller Kiliani’s test,** e.g., digitoxose and cymarose.
3. **Cardenolides** are distinguished from the **scillarins** by **a** **group of color reagents**, that are all alkaline solutions of **aromatic** **nitro compounds**, namely,

**Kedde’s reagent**, **3,5 dinitrobenzoic,**

**Raymond’s reagent**, **metadinitrobenzene,**

**Baljet’s reagent**, **picric acid,**

**Legal’s test**, **alkaline solution of sodium nitroprusside**.

1. All these **nitrocompounds** react with the **active methylene** of the **five membered lactone** ring (in alkaline medium) to give characteristic colors.
2. Cardiotonics, CHF, rheumatic heart disease, atherosclerosis, HTN.
3. Diuretics (capillary of the kidneys are dialated).
4. The **glycone** part displays a great influence on the solubility and the rate of absorption and distribution of the glycosides to the site of action.
5. Small change in the molecules such as a change of the location of the **OH gp**, modify the cardiac activity or even eliminate it completely.
6. The saturation and/or cleavage of the **lactone ring,** destroys the cardiac activity.

**Therefore, the closely related CG, differ greatly in the rate of absorption, duration of action and their cumulative effect**.

1. digitalis leaf (digitalis tablets)
2. digitoxin tablets 200μg/tablet
3. digoxin injection contain 0.0025% digoxin
4. digoxin tablets contain 250μg/tablet
5. gitalin, lanatoside C, deslanoside, strophanthus, strophanthin, ouabain and squill.

Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor

sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.