Pharmacognosy and Phytochemistry

Glycosides-Part 1

B. Pharm. Semester-1

Course Code: 0510221; Session: 2022-2023

Dr. BALAKUMAR CHANDRASEKARAN

Professor-Faculty of Pharmacy

Philadelphia University-Jordan

Learning Outcomes

At the end of this lesson, students will be able to explain

- Definition of Glycosides and Classification of Glycosides
- Cardiac Glycosides
    - **Digitalis**
    - **Strophanthus**
    - **Squill**
    - **Oleander**

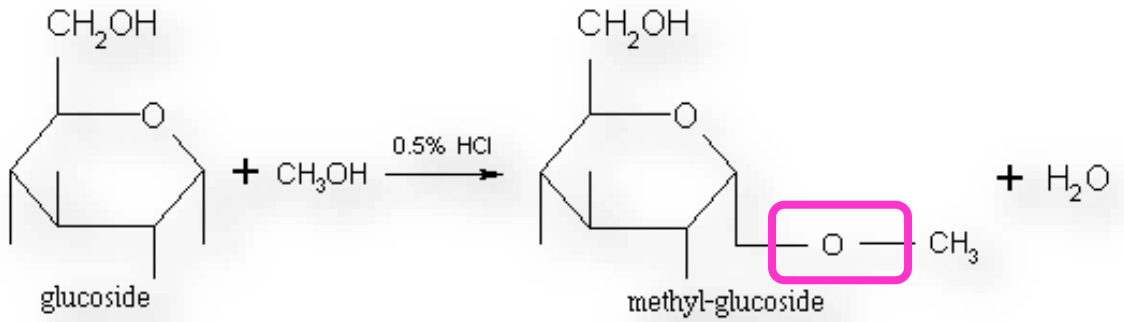
Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the Glycosides as major phytoconstituents.

Glycosides

- They are compounds containing a **carbohydrate (sugar)** and a **noncarbohydrate** residue in the same molecule.
- The **carbohydrate** residue is **attached by an acetal linkage at carbon atom 1** to a **noncarbohydrate** residue.
- The **carbohydrate (sugar) component** is called the **GLYCONE**.
- The **noncarbohydrate component** is known as the **AGLYCONE**.

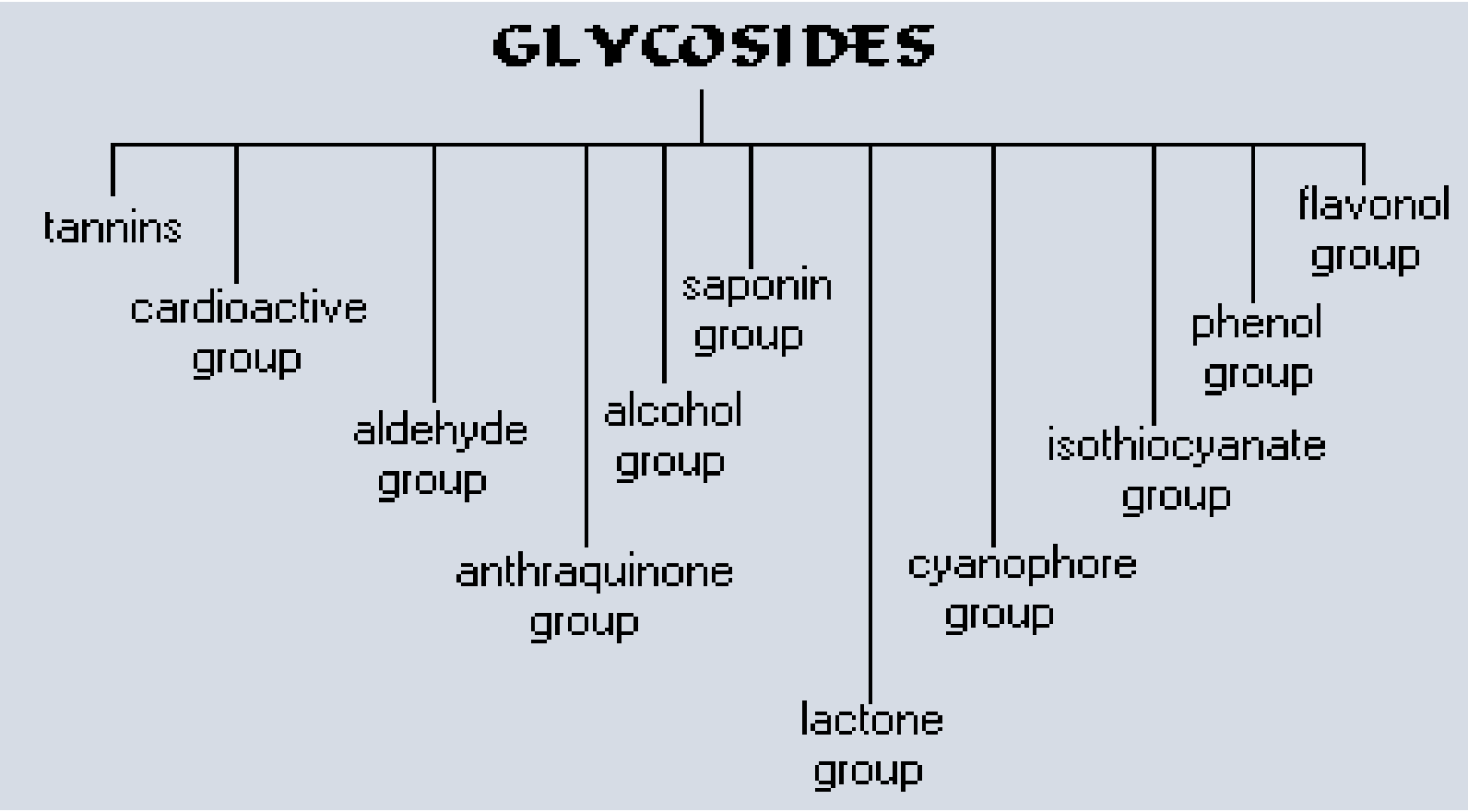
- The sugar moiety can be joined to the aglycone in various ways:-
  1. **Oxygen *(O-glycoside)***
  2. **Sulphur *(S-glycoside)***
  3. **Nitrogen *(N-glycoside)***
  4. **Carbon (*C-glycoside)***



Classification of Glycosides

- The aglycone may be methyl alcohol, glycerol, a sterol, a phenol, etc.

- Based on the chemical nature of the aglycone group, glycosides can be classified as follows:



Cardiac Glycosides

- Heart diseases can be primarily grouped into three major disorders:
  - **Cardiac failure, Ischemia** and **Cardiac arrhythmia.**
- **Cardiac failure** can be described as the **inability of the heart to pump blood effectively** at a rate that meets the needs of the metabolizing tissues.
- This occurs when the muscles that perform contraction and force the blood out of heart are performing weakly.
- Thus cardiac failures primarily arise from the **reduced contractility of heart muscles, especially the ventricles**.
- Reduced contraction of heart leads to **reduced heart output** but new blood keeps coming in resulting in the **increase in heart blood volume.** The **heart feels congested**. Hence the **term congestive heart failure.**
- Congested heart **leads to lowered blood pressure and poor renal blood flow.** This results in the **development of edema in the lower extremities** and the **lung (pulmonary edema)** as well as **renal failure**.

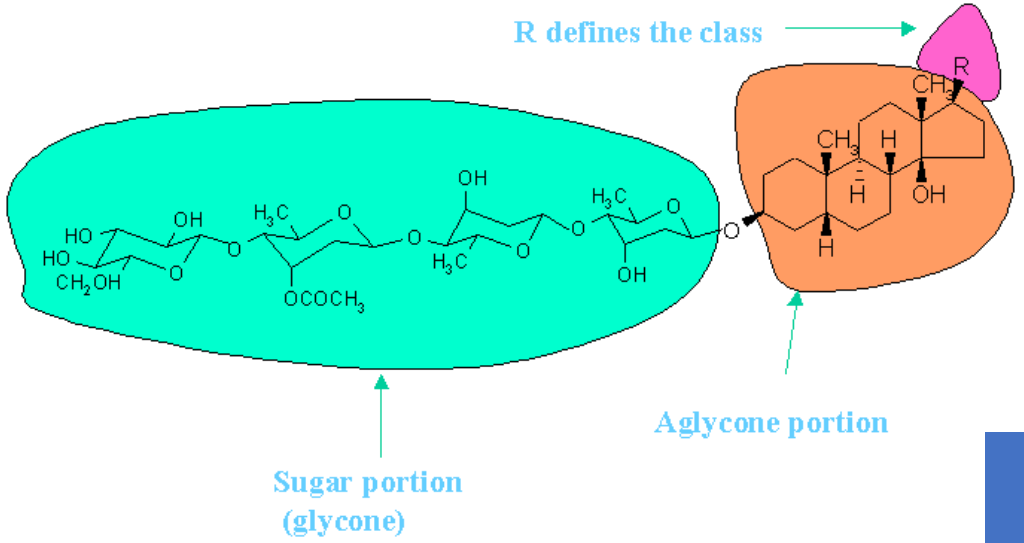
- **Increasing the force of contraction of the heart (positive inotropic activity) is very important for most heart failure patients.** There are several mechanisms by which this could be achieved. **Cardiac steroids are perhaps the most useful.**
- The **cardiac glycosides** are an important class of naturally occurring drugs whose actions include both **beneficial** and **toxic effects** on the **heart.**
- Plants containing cardiac steroids have been used as poisons and heart drugs at least since 1500 B.C. Throughout history these plants or their extracts have been variously used as arrow poisons, emetics, diuretics, and heart tonics.
- **In large doses they are toxic** and bring about **cardiac arrest in systole**, but **in lower doses** they are important drugs in the **treatment of congestive heart failure.**
- They have a **diuretic activity**. Since, the **improved circulation tends to improve renal secretion,** which **relieves the edema often associated with heart failure.**

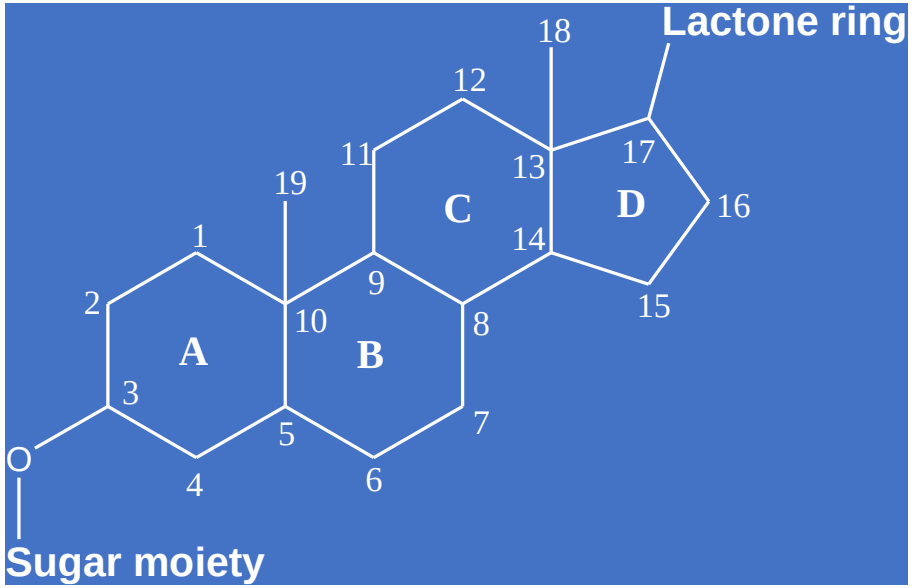
Distribution of Cardiac Glycosides in nature

- **Cardiac glycosides** occur in small amounts in the **seeds, leaves, stems, roots or barks** of plants of wide geographical distribution, particularly of the Family:
  - ✓***Apocyanaceae*** (e.g. seeds of *Strophanthus*, roots of *Apocynum* and fruits of *Acokanthera);*
  - ✓***Scrophulariaceae*** (e.g. leaves of *Digitalis sp.*),
  - ✓***Liliaceae*** (e.g. scales of the bulbs of *Urginea* and *Convallaria*), and
  - ✓***Ranunculaceae*** *(Adonis).*
- Cardiac glycosides are also found in **animals**, only in exceptional cases: **Bufadienolides occur in toads (*Bufo*).**

Structure of Cardiac Glycosides

Cardiac glycosides are composed of two structural features : the sugar (most often an oligosaccharide) and the non-sugar (aglycone - steroid) moieties.



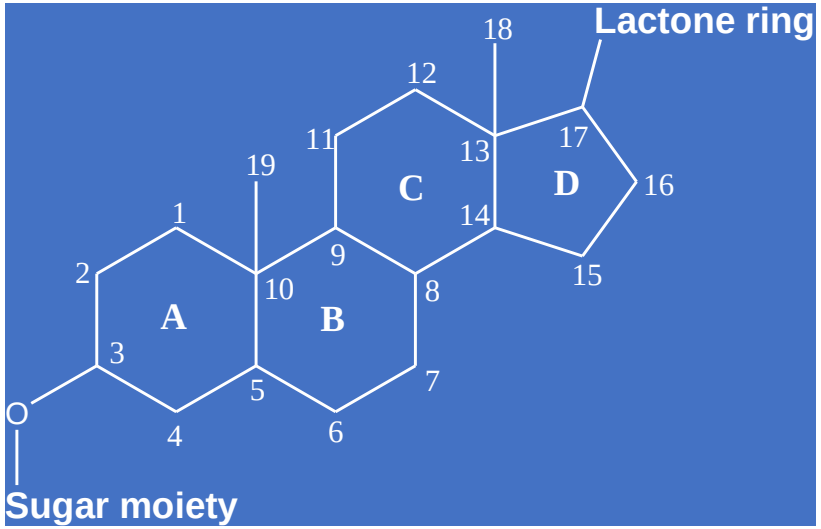


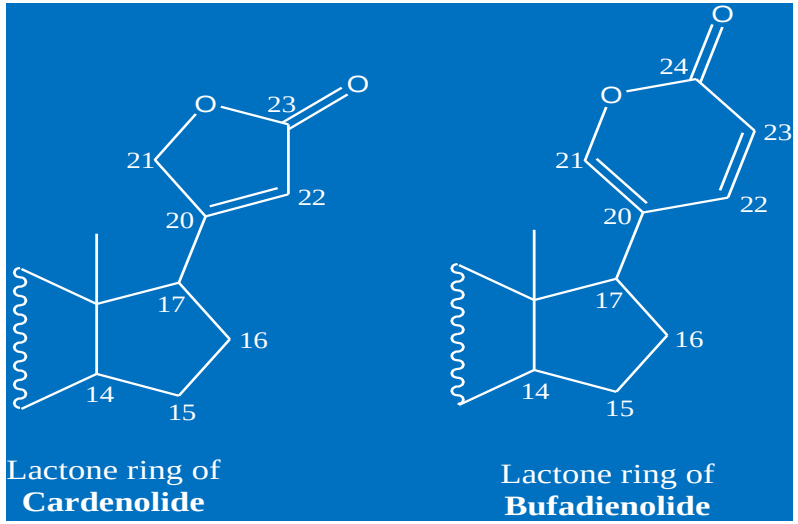
A. Structure of the Aglycones

- All of the **aglycones have** in common the tetracyclic, **steroidal nucleus.**
- The **A, B, C and D rings** normally have a ***cis-trans-cis*** configuration or less often, a ***trans-trans-cis*** configuration.
- Also common to all the **aglycones** is the presence of **two hydroxyl groups**: one is a **3β secondary alcohol**, the other is a **14β tertiary alcohol**.
- All of the aglycones have a β constituent at C-17: an α,β-unsaturated lactone.
- The **lactone ring** at the 17-position defines the class of cardiac glycoside.

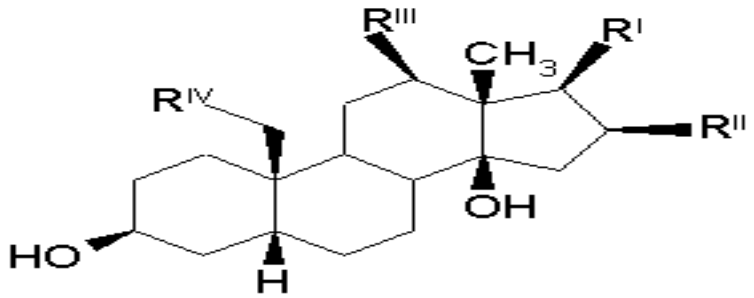
a) Cardenolides (C23) having an **α,β-unsaturated γ-lactone (butyrolactone ring = butenolide)**

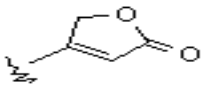
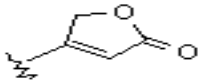
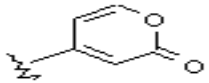
a) Bufadienolides (C24) having an **di-unsaturated δ-lactone (= pentadienolide)**





- The name **digitoxin** refers to a agent consisting of **digitoxigenin (aglycone)** and **sugar moieties (three).** **Digoxin** refers to a agent consisting of **digoxigenin (aglycone)** and **sugar moieties (three).** The **aglycone portion of cardiac glycosides is more important** than the glycone portion.



	R^I	R^{II}	R^{III}	R^{IV}
Digitoxigenin		H	H	H
Digoxigenin		H	OH	H
Gitoxigenin		OH	H	H
Ouabagenin		H	H	H
Strophanthidin		H	H	=O
Bufalin		H	H	H

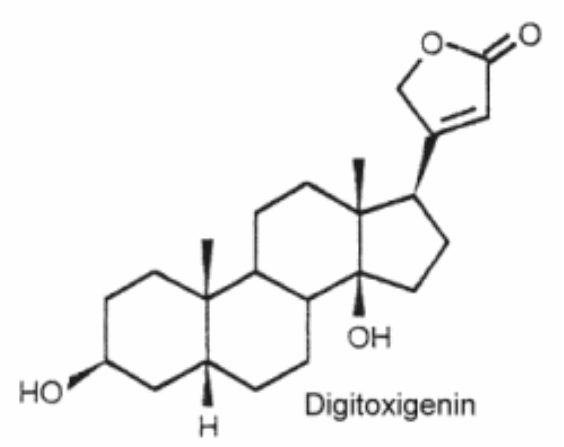
B. Structure of the sugar moiety

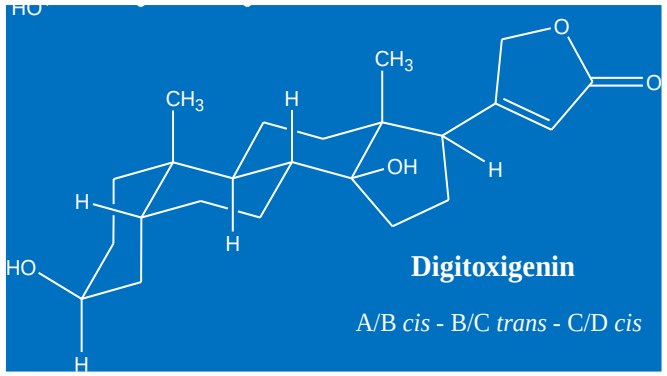
- The **sugar moiety is generally linked to** the aglycone through the **hydroxyl group at C-3.**
- The majority of the saccharides found in cardiac glycosides are highly specific:
  1. 2,6-dideoxyhexoses, e.g. D-digitoxose
  2. 2,6-dideoxy-3-methylhexoses, e.g. D-diginose
  3. 6-deoxyhexoses, e.g. L-rhamnose
  4. 6-deoxy-3-methylhexoses, e.g. D-digitalose
  5. Hexose, e.g. glucose (*when these is a glucose unit, it is always terminal*).

The sugars can modify **the activity** (potency, toxicity), **the solubility, the diffusion** through membranes, the rate of **absorption and transportation** of the glycosides.

Cardenolides: Chemistry

- Their structure is closely related to bufadienolides but **these C23 steroids possess a butenolide ring located at C-17**. The structure of digitoxigenin is given below as a typical example of cardenolides.





Monarch butterfly on milkweed

- They are **widely distributed in plants mainly as glycosides** and are **either toxic or insect deterrents.**
- **These steroids were largely studied as potent cardiotonics.**
- **Monarch butterfly** is well known to be **highly toxic to birds** because of **cardenolides** which come from the **milkweed leaves** eaten by its caterpillar.

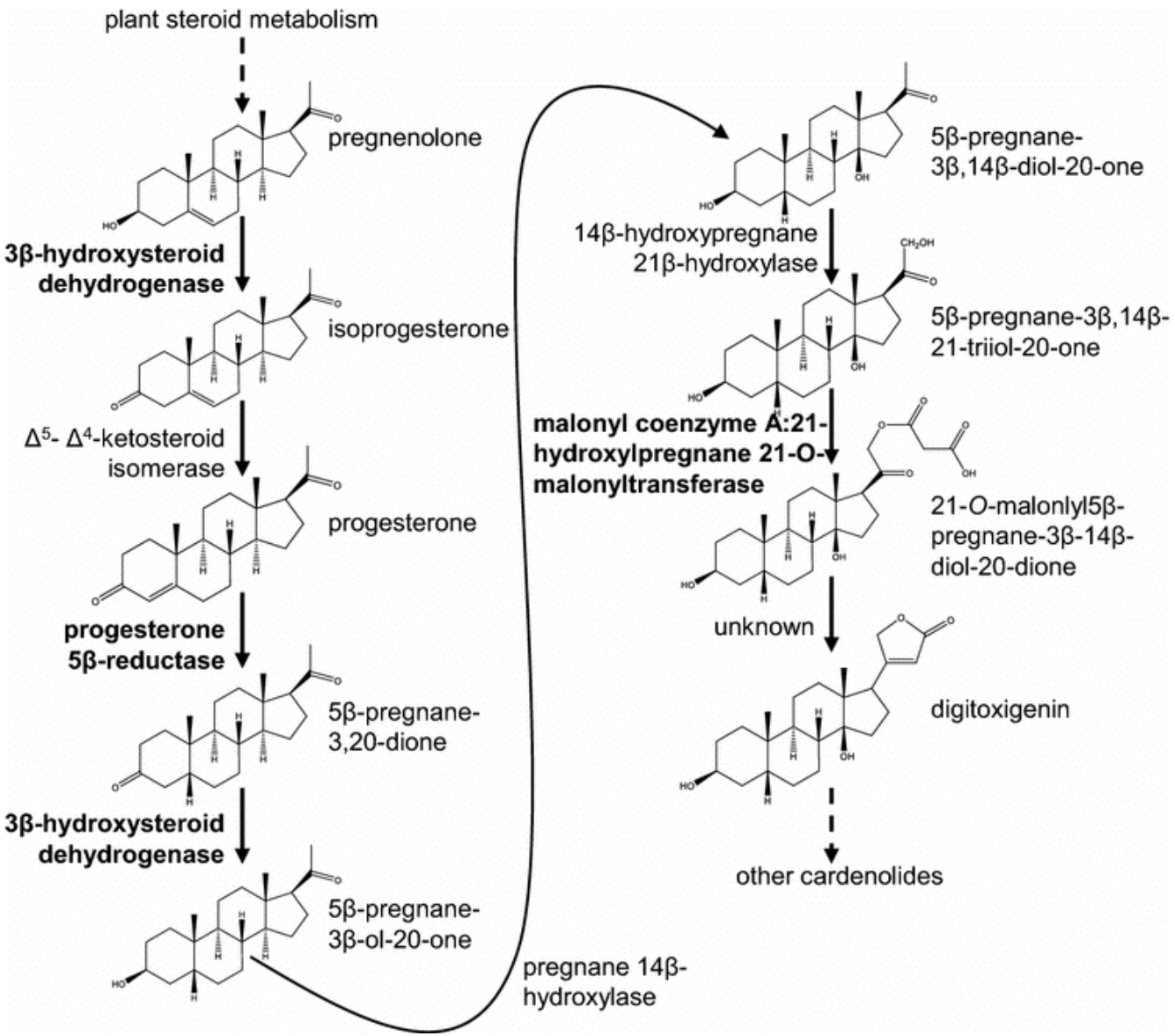
- Cardenolides (most prevalent) are **C23 steroids.**
- Cardenolides have a hormonal nature as substances. Their effects are on the **heart** and **kidney**.
- Strong, bitter and disagreeable taste.
- **Cardiotonic = affect contractions of the heart muscle.**
- Break down in fermentation by enzymatic action.

- Symptoms of poisoning include dizziness, vomiting, irregular heart beat, and delerium or halucinations.
- Treatment: atropine and activated charcoal, lidocaine

Mechanism of action:

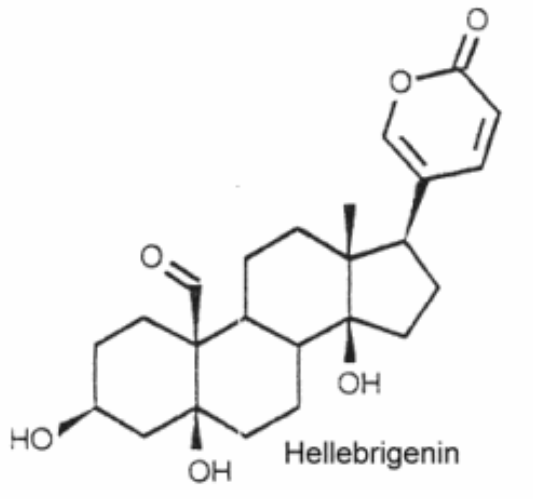
- **Inhibition of the Na+, K+-ATPase** resulting in **increased intracellular sodium and subsequent intracellular calcium** leading to **enhanced muscle contraction in cardiac tissue.**

Biosynthesis of Cardenolides



Bufadienolides: Chemistry

- They are typically polyhydroxy **C24 steroids** with a **pentadienolide ring at C-17.**
- The structure of **hellebrigenin** is given below as a typical example of bufadienolides.



Hellebrigenin

- They have been isolated from plants and animals. More than 250 compounds have been identified.
- In plants, they are mostly glycosides with **one to three sugars** in a chain linked to the **3-hydroxyl group**. They are **important for their cardiotonic activity.**
- Furthermore, they possess insecticidal and antimicrobial properties, those produced by the toad skin are strongly poisonous.

Structure - Activity Relationships

- The sugar moiety possesses no biological activity, but its presence enhances the activity and modulates it by modifying the polarity of the compound.
- The **cardiac activity is linked to the aglycone.**
- **A/B cis fusion is important** (not mandatory). Conversion to A/B trans system leads to a marked drop in activity.
- **C/D cis fusion is important.** Structures with **C/D trans fusion are inactive.**
- The **lactone at C-17**, must be in the ***β*-configuration.**
- The **unsaturated 17-lactone plays an important role in receptor binding.** Saturation of the lactone ring dramatically reduced the biological activity.
- The lactone ring is not absolutely required. For example, using α,β-unsaturated nitrile (C=C-CN group), the lactone could be replaced with little or no loss in biological activity.

Digitalis glycosides

Several species of ***Digitalis*** yield pharmacologically active principles. The most important of these species are ***Digitalis purpurea*** and ***Digitalis lanata*.**

1. ***Digitalis purpurea*** (**Purple foxglove leaves**)

   0.15% – 0.4% total cardenolides, ~ 30 glycosides

   Purpurea glycosides A and B (~60%),

   digitoxin (~12%), gitoxin (~10%) and

   gitaloxin (~10%).

2. ***Digitalis lanata*** (**White foxglove leaves**)

   0.5% – 1.5% total cardenolides, ~ 60 glycosides

   Lanatosides A and C (~50%),

   lanatosides B, D, E as well as **digoxin** and **digitoxin**.

Digitalis purpurea (Purple Foxglove)

- **Biological Source:**
  Dried leaves of ***Digitalis purpurea*.**
- **Family**: **Scrophulariaceae**
- **Parts Used: Leaves**
- **Habitat:** Native to Western Europe. Although the plant is cultivated, **wild plants are thought to be superior.**
- Also contains Anthraquinone glycosides, Saponins, Sopogenins, Flavonoids

Medical Uses:

- Tonic effect on the diseased heart.
- Glycosides enable the heart to beat more strongly, slowly and regularly, without using or needing more O_2.
- Stimulates urine production - lessening the load on the heart.

Some cardio-active glycosides from ***D. lanata***:-

Glycoside	*Aglycone*	*Sugar moieties*
Lanatoside A	Digitoxigenin	Glucose–acetyldigitoxose–$(digitoxose)_2$–
Acetyldigitoxin	Digitoxigenin	Acetyldigitoxose–$(digitoxose)_2$–
Digitoxin	Digitoxigenin	$(Digitoxose)_3$–
Glucoevatromonoside	Digitoxigenin	Glucose–digitoxose–
Digitoxigenin-*O*-glucosyl-6-deoxyglucoside	Digitoxigenin	Glucose–glucomethylose–
Glucodigifucoside	Digitoxigenin	Glucose–fucose–
Lanatoside B	Gitoxigenin	Glucose–acetyldigitoxose–$(digitoxose)_2$–
Glucogitoroside	Gitoxigenin	Glucose–digitoxose–
Digitalinum verum	Gitoxigenin	Glucose–digitalose–
Lanatoside C	Digoxigenin	Glucose–acetyldigitoxose–$(digitoxose)_2$–
Acetyldigoxin	Digoxigenin	Acetyldigitoxose–$(digitoxose)_2$–
Deacetyl-lanatoside C	Digoxigenin	Glucose–$(digitoxose)_3$–
Digoxin	Digoxigenin	$(Digitoxose)_3$–
Digoxigenin-glucosyl-bis-digitoxoside	Digoxigenin	Glucose–$(digitoxose)_2$–
Lanatoside D	Diginatigenin	Glucose–acetyldigitoxose–$(digitoxose)_2$–
Lanatoside E	Gitaloxigenin	Glucose–acetyldigitoxose–$(digitoxose)_2$–
Glucolanadoxin	Gitaloxigenin	Glucose–digitoxose–
Glucoverodoxin	Gitaloxigenin	Glucose–digitalose–

Digitoxin Vs Digoxin

- **Digitoxin** is a cardiotonic glycoside obtained from ***D. purpurea, D. lanata.***
- It is the **most lipid-soluble of the cardiac glycosides** used in therapeutics.
- The major pharmacokinetic parameters for digitoxin include **complete oral absorption**, which distinguishes it from other cardiac glycosides.
- Digitoxin may be **indicated in patients with impaired renal function.**

- **Digoxin** is the most widely used of the cardiotonic glycosides, and it is obtained from the leaves of ***D. lanata.***
- It is a **highly potent drug** and should be handled with exceptional care.
- Digoxin tablets are **60 to 80% absorbed.**
- Digoxin is **indicated when the risk of digitalis intoxication is great,** since it is **relatively short-acting and rapidly eliminated when compared with digitoxin.**

Mechanism of action of Cardiac glycosides

- Digitalis increases force of cardiac contraction (positive inotropic effect) by a direct action independent of innervation.
- It selectively binds to extracellular face of the membrane associated Na^+K^+ ATPase of myocardial fibres and inhibits this enzyme.

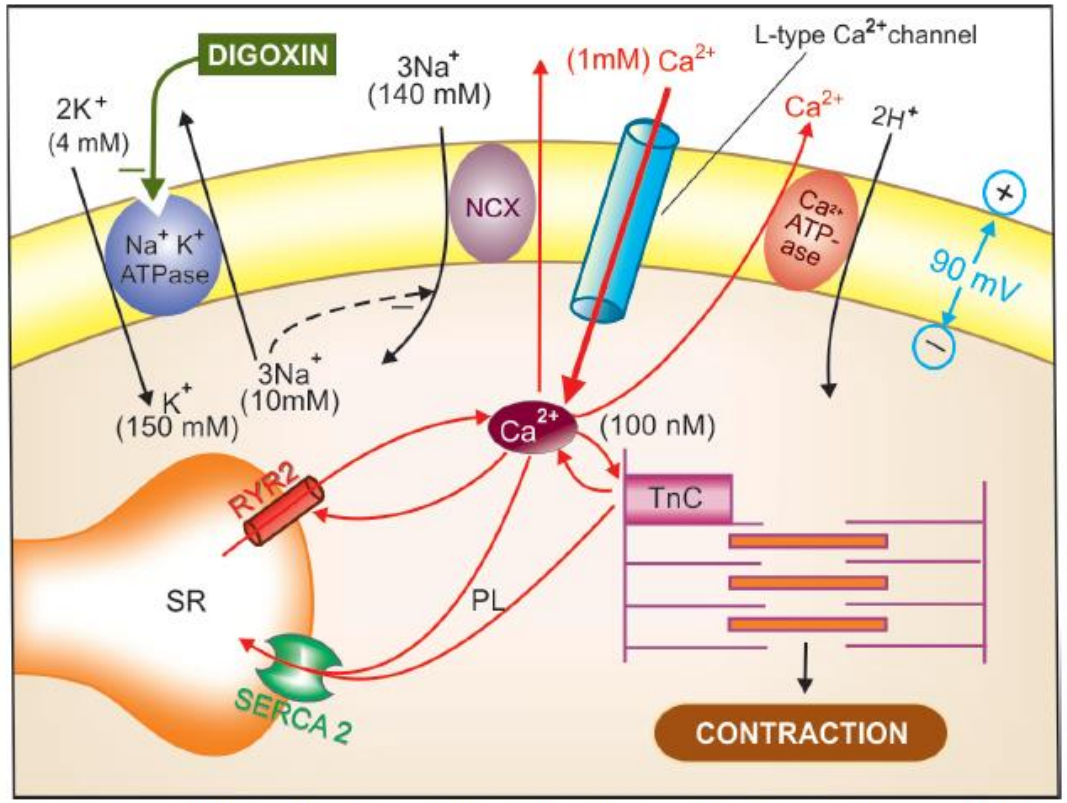


Fig. 37.3: Mechanism of positive inotropic action of cardiac glycosides. SR—Sarcoplasmic reticulum; TnC—Troponin C; NCX—Na^+-Ca^{2+} exchanger; RyR2—Ryanodine receptor calcium channel 2; PL—Phospholamban; SERCA2—Sarcoplasmic-endoplasmic reticulum calcium ATPase 2.

Mechanism of action of Cardiac glycosides

- Inhibition of this Na^+K^+ cation pump results in progressive accumulation of Na+ intracellularly.
- This indirectly results in intracellular Ca^{2+} accumulation.
- During depolarization Ca^{2+} ions enter the cell driven by the steep Ca^{2+} gradient (>1 mM extracellular to < 100 nM cytosolic during diastole) through voltage sensitive L type Ca^{2+} channels.
- This triggers release of larger amount of Ca^{2+} stored in sarcoplasmic reticulum (SR) → cytosolic Ca^{2+} increases transiently → triggers contraction by activating troponin C on myofibrils.
- Binding of glycoside to Na^+K^+ ATPase is slow. Moreover, after Na^+K^+ ATPase inhibition, Ca^{2+} loading occurs gradually.
- As such, inotropic effect of digitalis takes hours to develop, even after i.v. administration.

Strophanthus glycosides

Botanical Name: ***Strophanthus kombe***

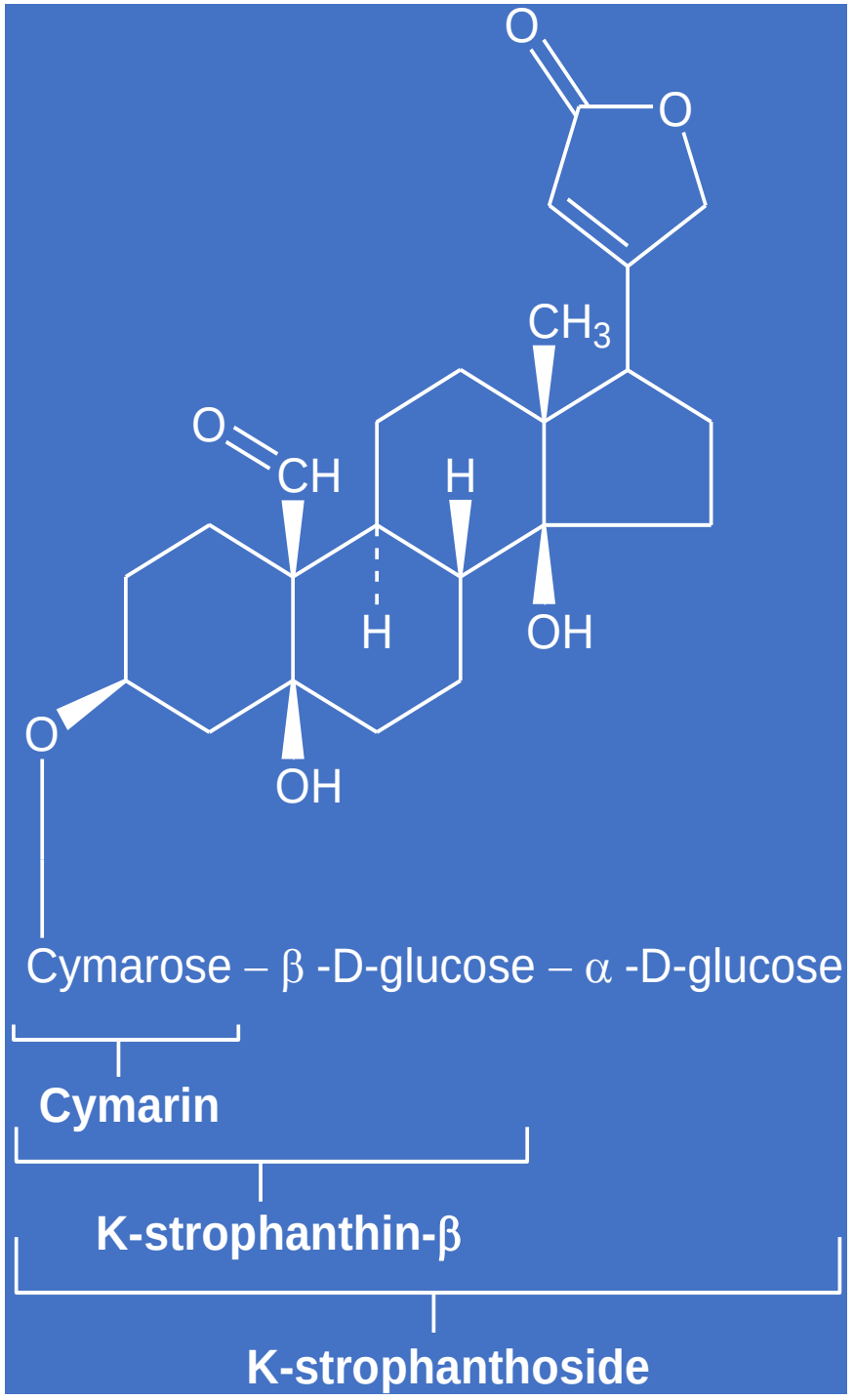
Family: **Apocynaceae**

Part Used: Dried seeds (ripe)

The principle glycosides are:

1. **K-strophanthoside**
2. **K-strophanthin-β**
3. **Cymarin**

Habitat: East Africa. It is not a cultivated species and is usually seen growing as a wild plant. It is not typically seen growing in other regions.



Uses

- **Uses** - similar to *Digitalis*
- Chronic cardiac weakness
- Diuretic action (thought to be more powerful than *Digitalis*)
- Can be administered IV
- **Actions**
- Similar to *Digitalis*
- POISONOUS

Squill glycosides

0.1% – 2.4% total **bufadienolides**, ~15 glycosides

- **White variety:**
- **Botanical Name:** ***Urginea maritime***
- **Family**: **Liliaceae**
- average 0.2%-0.4% proscillaridin A, scillaren A, glucoscillaren A, scilliphaeoside, scilliglaucoside (**aglycone: scillarenin**)

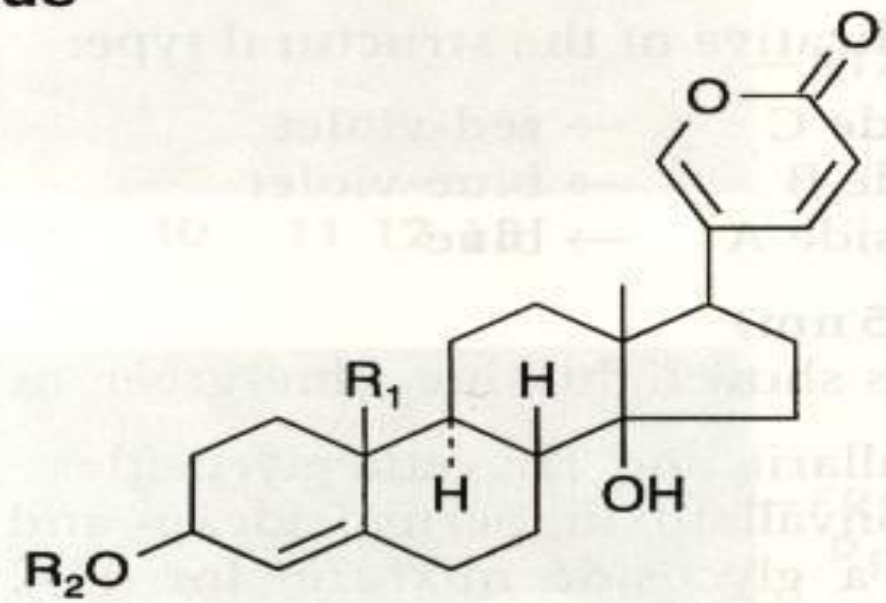
- **Red variety:** < 0.1% scilliroside and glucoscilliroside (**aglycone**: **scillirosidin**);
  proscillaridin A and scillaren A as in the white variety

- **Habitat:** This squill is native to coastal regions of the Mediterranean in sandy soil, but it is widely cultivated.

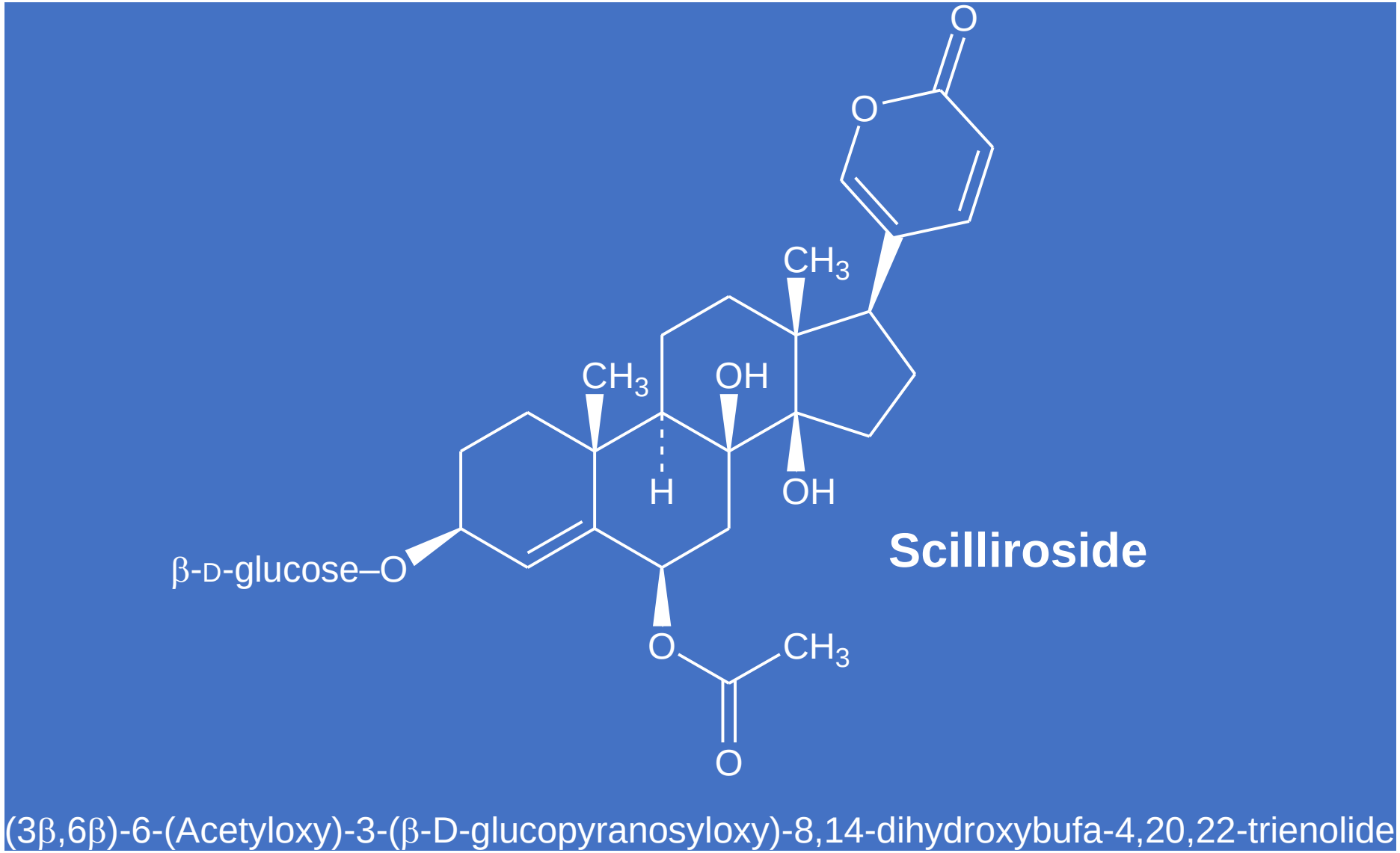
Pharmacological properties of squill

- **White squill:** It is an expectorant, but it also possesses emetic, **cardiotonic** (proscillaridin A), and **diuretic** properties.
- **Red squill:** It is used as a **rat poison (scilliroside)**, because rodents lack the vomiting reflex, which makes red squill particularly lethal to these animals.

Scillae bulbus



	R_1	R_2
Scillarenin	CH_3	H (Aglycon)
Proscillaridin A	CH_3	Rham
Scilliphaeoside	H	Rham
Scillaren A	CH_3	Gluc-Rham
Glucoscillaren A	CH_3	Gluc-Gluc-Rham



Scilliroside

(3β,6β)-6-(Acetyloxy)-3-(β-D-glucopyranosyloxy)-8,14-dihydroxybufa-4,20,22-trienolide

Nerium Oleander

Nerium oleander is an evergreen shrub or small tree in the dogbane family **Apocynaceae**

It is the only species currently classified in the genus ***Nerium***.

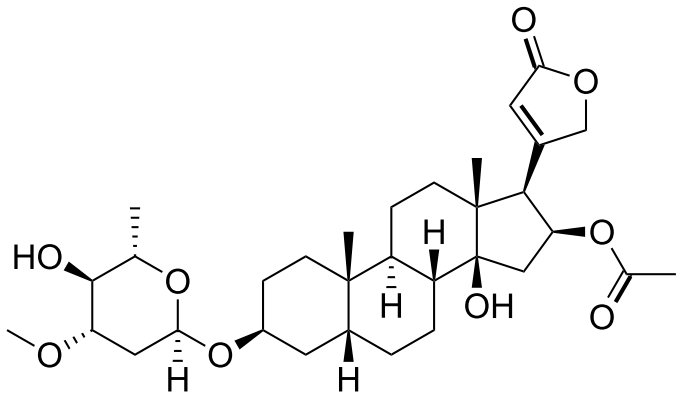
It is most commonly known as oleander, from its superficial resemblance to the unrelated olive Olea.

It is extensively used as an ornamental plant in landscapes, in parks, and along roadsides.

Oleander has historically been considered a poisonous plant because some of its compounds may exhibit toxicity, especially to animals, when consumed in large amounts.

Nerium Oleander

oleandrin



Pharmacologically active compounds are **oleandrin** and **oleandrigenin**, known as cardiac glycosides, which are known to have a narrow therapeutic index and can be toxic when ingested.

REFERENCES

Textbooks:

1. **Trease And Evans Pharmacognosy, 16th Edition, 2019, Author: William C Evans, Publisher: Elsevier, ISBN: 978-8131261187.**
2. **Textbook of Pharmacognosy and Phytochemistry 2nd Edition, 2019, Authors: B. Shah, A. N. Kalia, Publisher: Elsevier, ISBN: 978-978-9386217738.**
3. **Medicinal Natural Products: A Biosynthetic Approach, 2nd Edition, 2002, Author: Paul M Dewick, Publisher: John Wiley and Sons Ltd, ISBN: 0471496405.**

Supplementary book:

Fundamentals of Pharmacognosy and Phytotherapy. A Guide for Health Care Professionals by Carol A. Newal, Linda A. Anderson and J. David Phillipson. (2010). the Pharmaceutical Press, London, UK; ISBN: 0 85369-474-5.