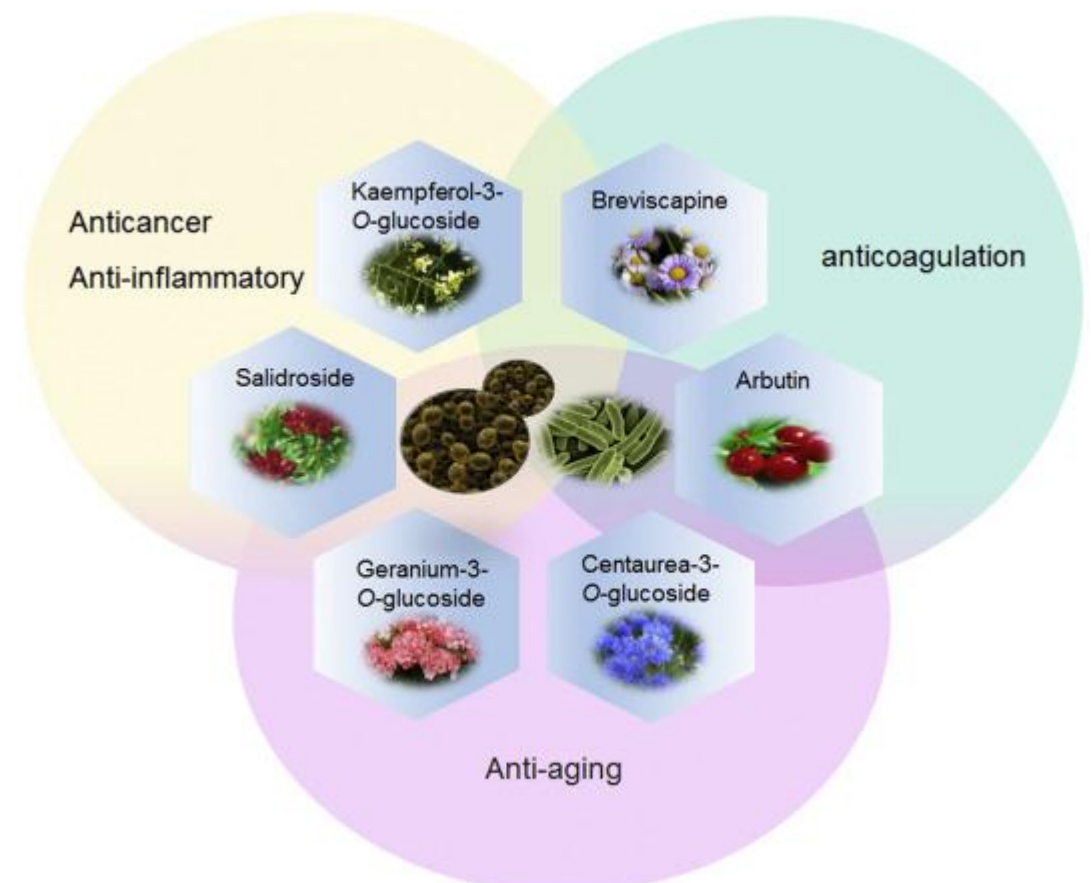


Cardioactive Glycoside



Dr. Amani Amer Tawfeeq

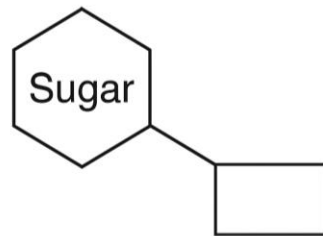


Glycosides

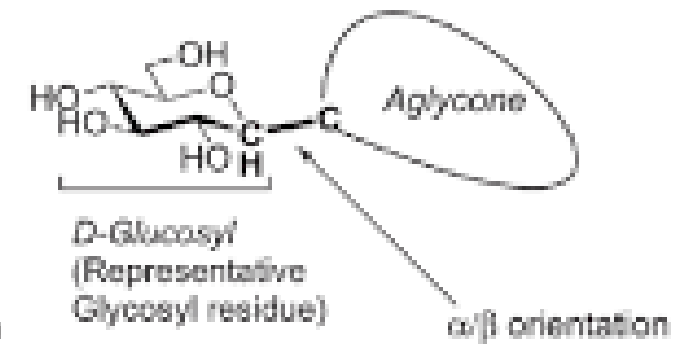
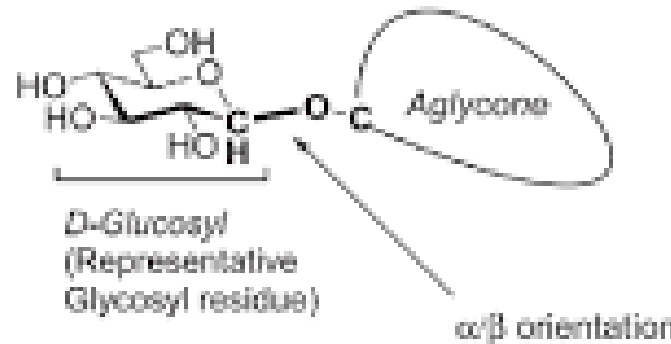
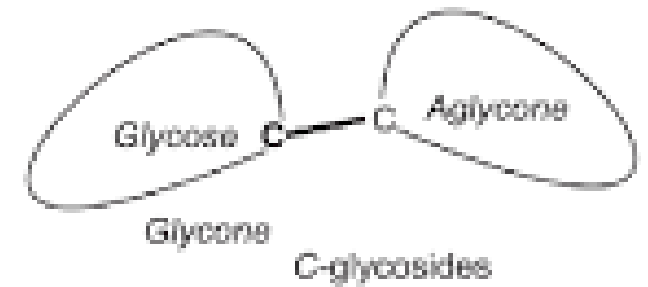
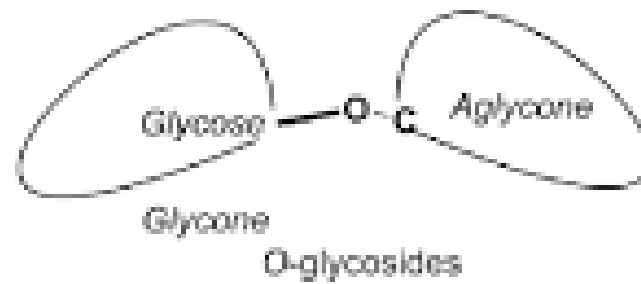
- ❖ It is Natural products consisting of a sugar + aglycone.

Aglycone: Can be a terpene, flavonoid, coumarin, triterpene, or other natural product.

If steroidal → sometimes called **genin**



Carbon-carbon bond



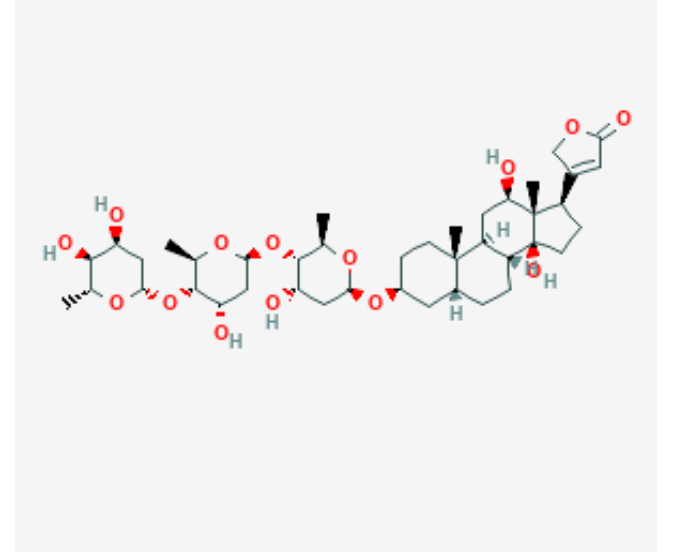
Types:

O-Glycosides

The sugar (glycone) is linked to the aglycone (non-sugar part) via an oxygen atom.

- **Examples:**

- **Senna:** Contains glycosides like sennosides, which have laxative properties.
- **Digitalis:** Contains cardiac glycosides such as digitoxin and digoxin.
- **Salicin:** Found in willow trees (genus *Salix*) and has analgesic properties.

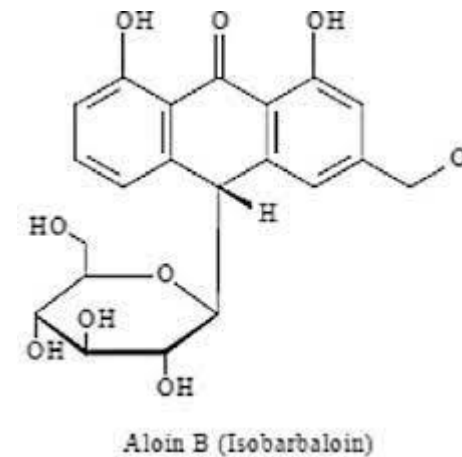
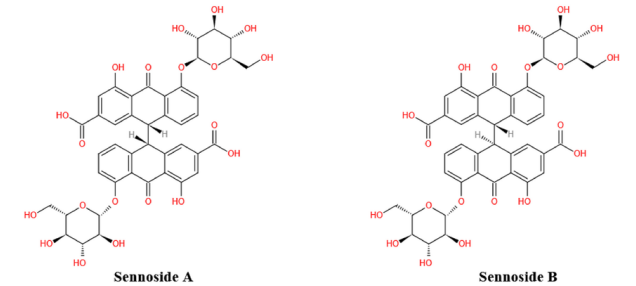


C-Glycosides

The sugar is linked to the aglycone through a carbon-carbon (C-C) bond, making the linkage very stable and resistant to hydrolysis.

- **Examples:**

- **Aloin:** Found in the aloe plant, also known as aloin, and is a well-known example of a C-glycoside.
- **Cascara:** The bark of the cascara tree, which contains C-glycosides.

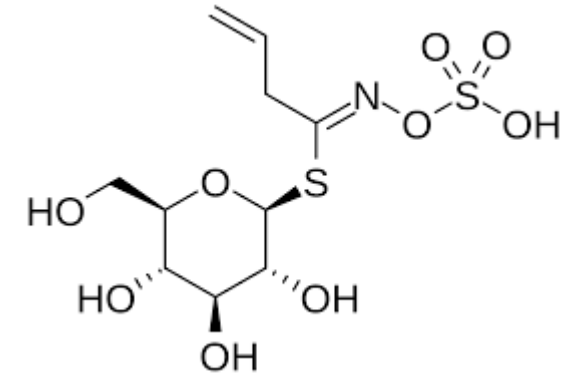


S-Glycosides

- The sugar is attached to a sulfur atom in the aglycone.

- **Examples:**

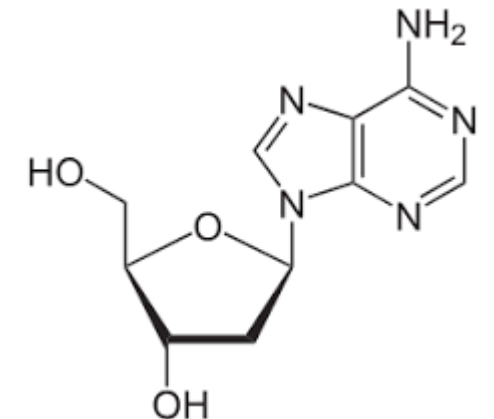
- **Sinigrin:** Isolated from black mustard seeds and is a type of glucosinolate.
- **Glucosinolates:** A class of S-glycosides found in cruciferous vegetables (like mustard, broccoli) that act as a plant defense mechanism



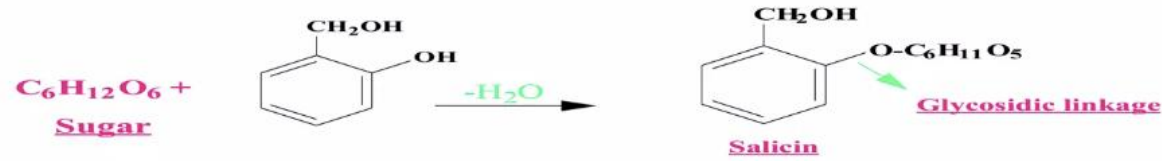
N-glycosidic bond forms when the anomeric carbon of a sugar attaches to a nitrogen atom in an aglycone, creating a C-N-C linkage.

- This differs from O-glycosides, where the sugar links to an oxygen atom.

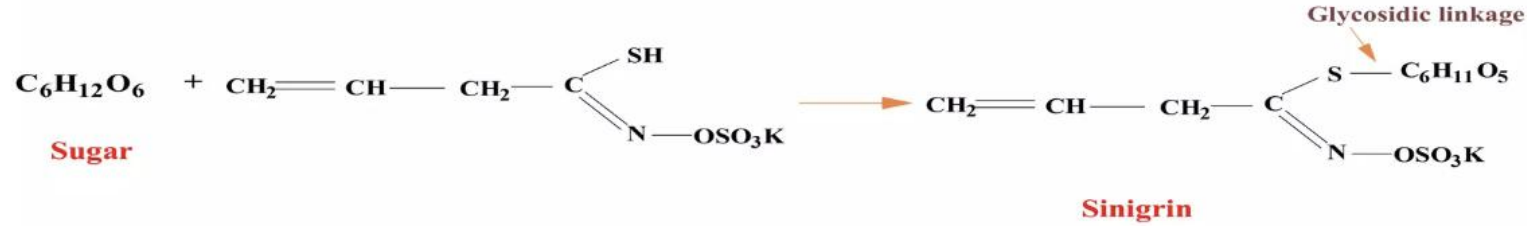
Ex-Nucleosides:



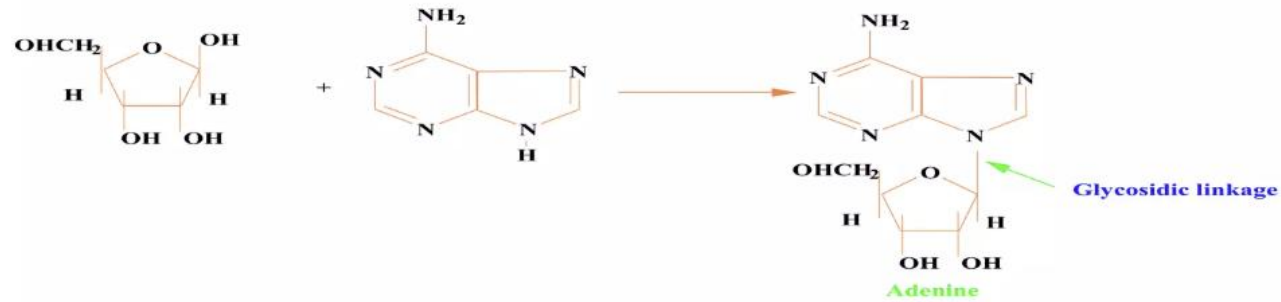
1- Alcoholic or phenolic (aglycone): e.g., O-Glycoside



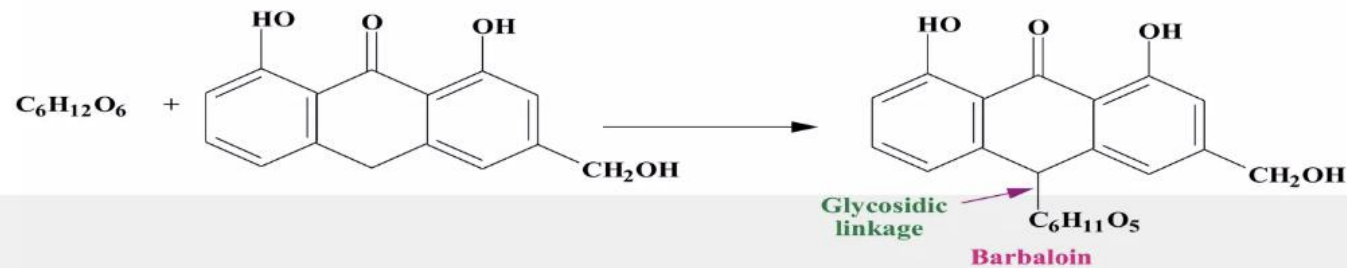
2- Sulphur containing compounds: e.g., S-Glycoside



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



4- C-Glycoside



Types of Glycosides

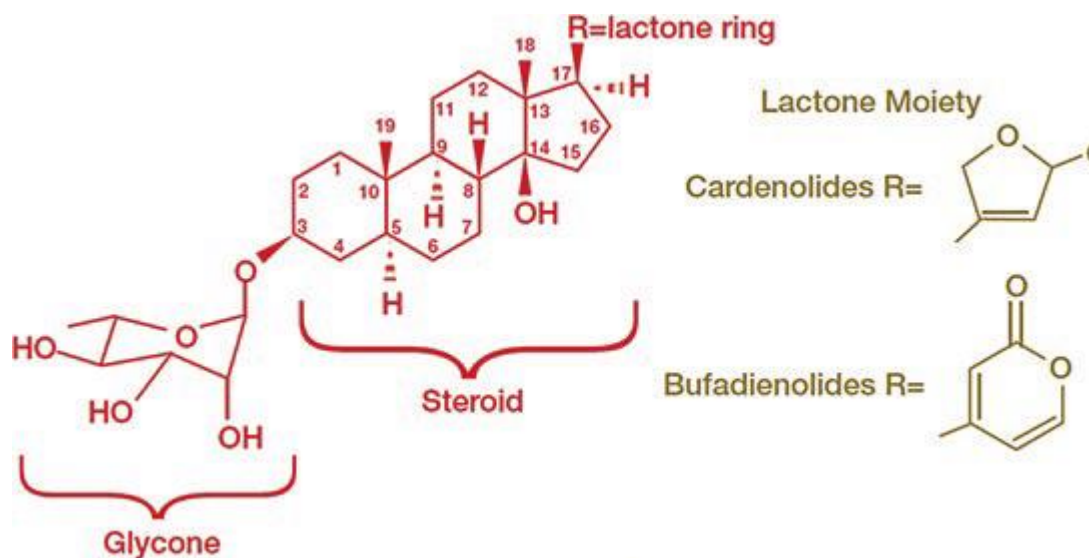
- ✓ Cardiac glycosides
- ✓ Anthraquinone glycosides
- ✓ Cyanogenic glycosides
- ✓ Flavonoid glycosides
- ✓ Saponin glycosides
- ✓ Iridoid glycosides
- ✓ Phenolic glycosides
- ✓ Coumarin glycosides
- ✓ Lignan glycosides
- Stilbene glycosides

Dr. Amani Amer Tawfeeq

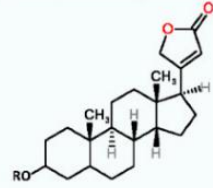
Cardiac glycosides



- **Cardiac glycosides (CGs)** are a structurally diverse class of naturally derived compounds. Found as secondary metabolites in various flowering plants, they are also produced by certain animals as a means of predator deterrence. The term *cardiac glycosides* stems from their characteristic chemical framework and their historically established use as **cardiotonic drugs**



CARDENOLIDES



Thevetia neriifolia
thevetin



Strophantus gratus
ouabain



Digitalis purpurea
digitoxin
gitoxin
gitalin



Chrysomelidae sp.
sarmentogenin
periplogenin
bipindogenin



Nerium oleander
oleandrin



Asclepias curassavica
periplocin
strophantidin

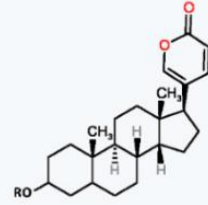


Adonis vernalis
cyamarin
adonitoxin
substance N



Convallaria majalis
convallatoxin

BUFADIENOLIDES



Urginea maritima
proscillaridin A



Kalanchoe lanceolata
bryotoxin B
bryophyllin A



Photinus ignitus
lucibufagins



Bufo bufo
Bufalin
resinobufogenin
marinobufogenin



Atelopus sp.
arenobufagin
cinobufagin
telocinobufagin



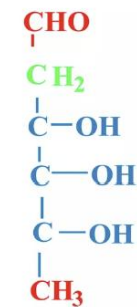
Rhinella marina
marinobufagin
bufalin
telocinobufagin

What is the Chemical classification and structures ?

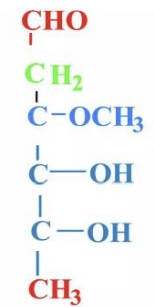
- **Cardioactive glycosides are a class of steroidal natural products** composed of a **steroidal aglycone** (the **cardenolide** or **bufadienolide**) linked glycosidically to one or more sugar residues. They exert potent effects on cardiac muscle contractility and conduction by inhibiting the membrane enzyme **Na⁺/K⁺-ATPase**. Historically, preparations from *Digitalis* species (foxglove) formed the basis of digitalis therapy for congestive heart failure and certain arrhythmias. Due to their narrow therapeutic index and potential for fatal toxicity.

Sugar Moieties

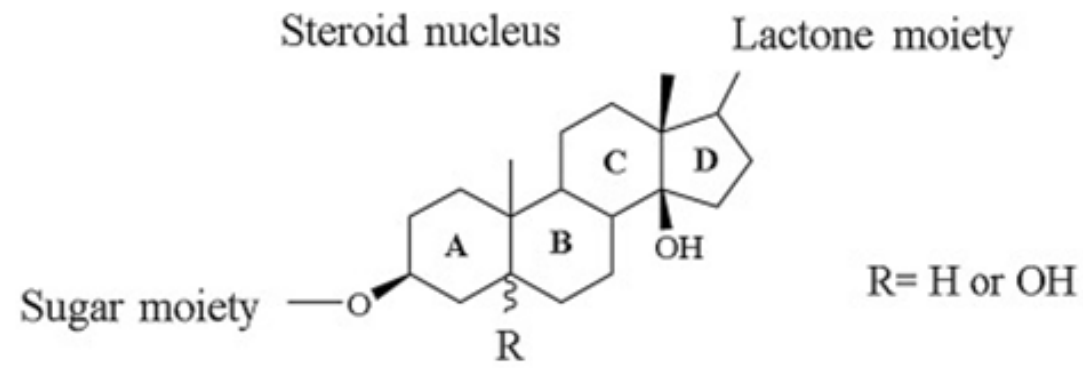
- Glycosylation at C-3 with sugars such as **digitoxose, glucose, rnamnose, cymarose**.



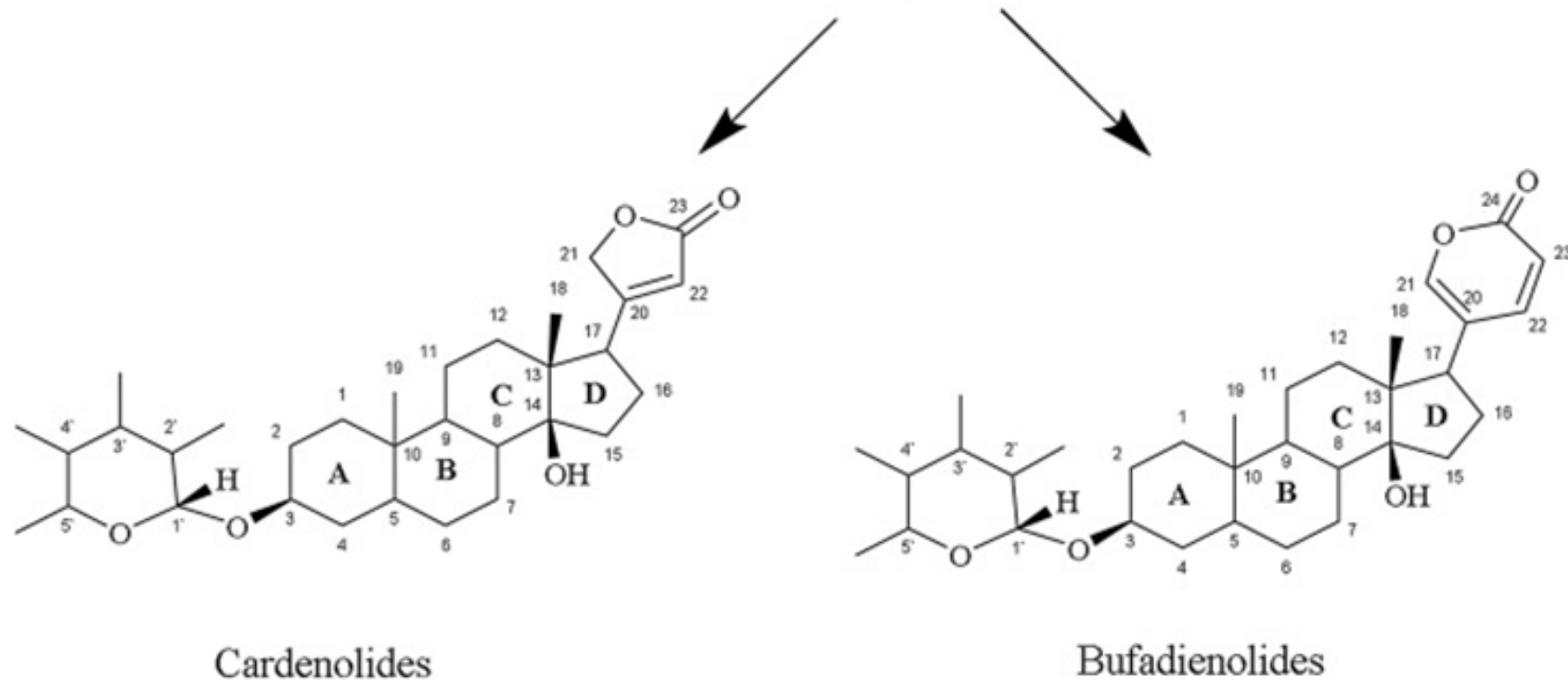
Digitoxose



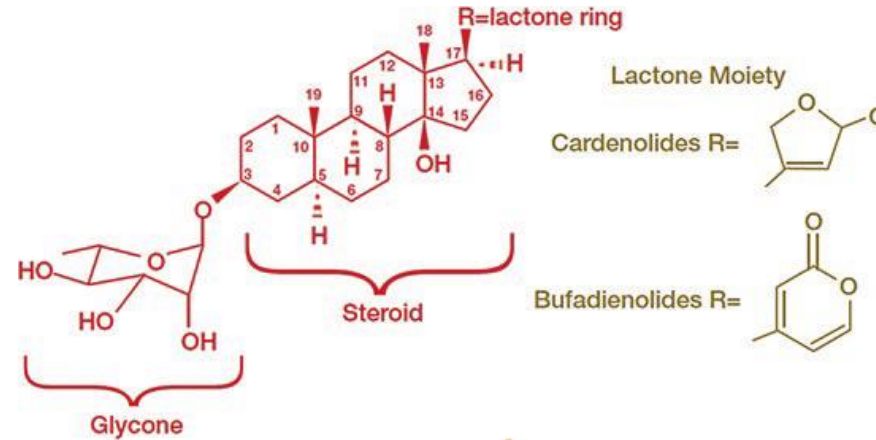
Cymarose



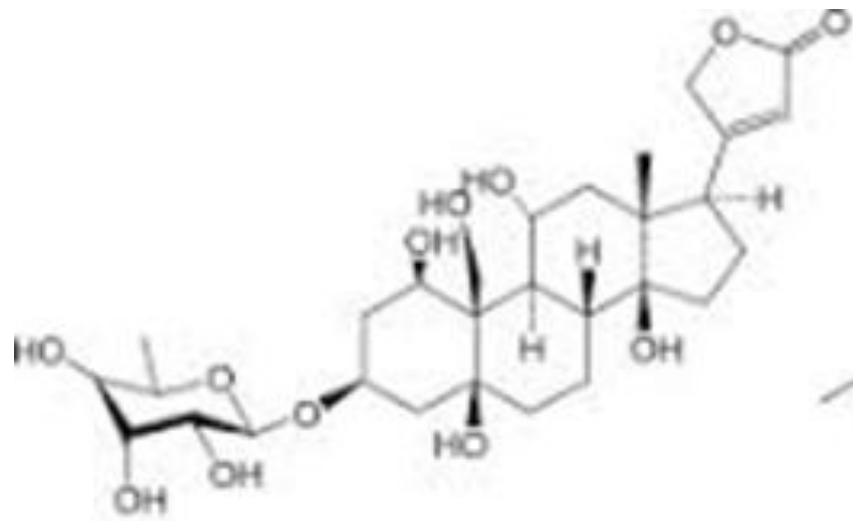
Cardiac glycosides



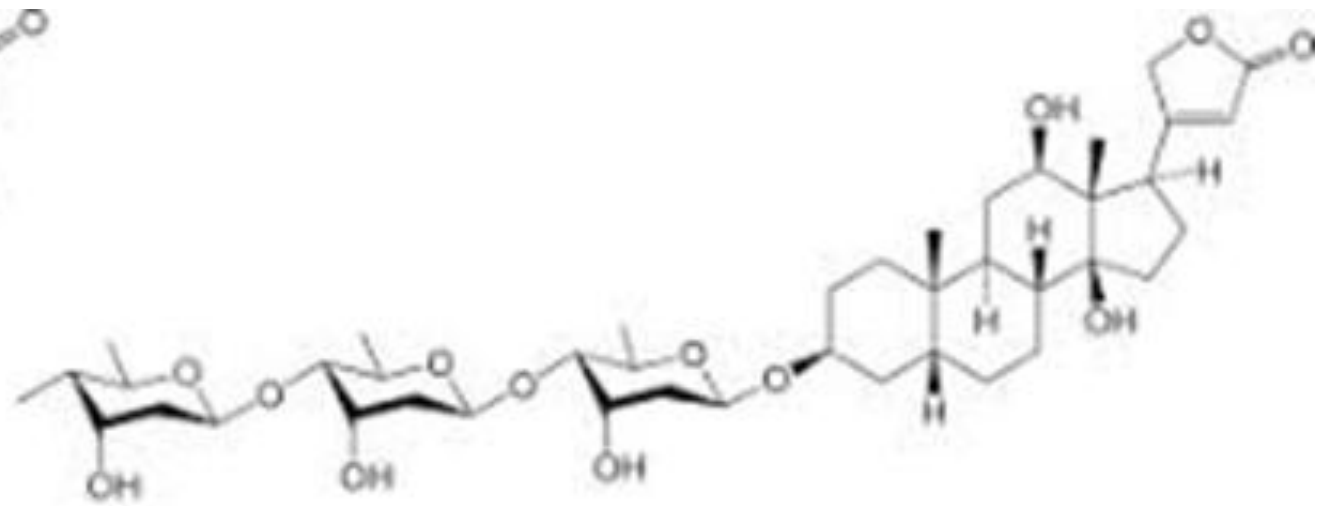
1-Cardenolides



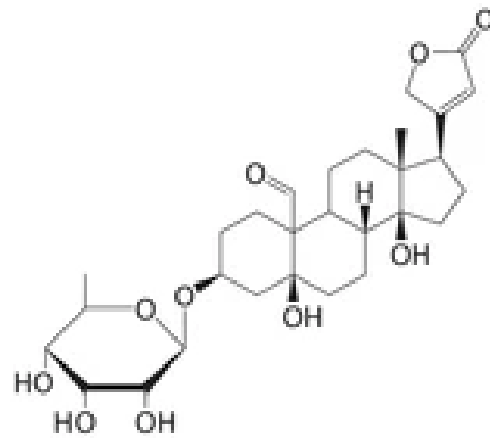
- characterized by a five-membered unsaturated lactone (butenolide) attached at C-17 of the steroid nucleus. Typical examples: **digoxin, digitoxin, ouabain, convallatoxin.**
- Cardiac glycosides featuring an α - β unsaturated five-membered lactone ring at the C-17 position are classified as cardenolides. This category includes compounds from the digitalis and strophanthus families.



Ouabain 159

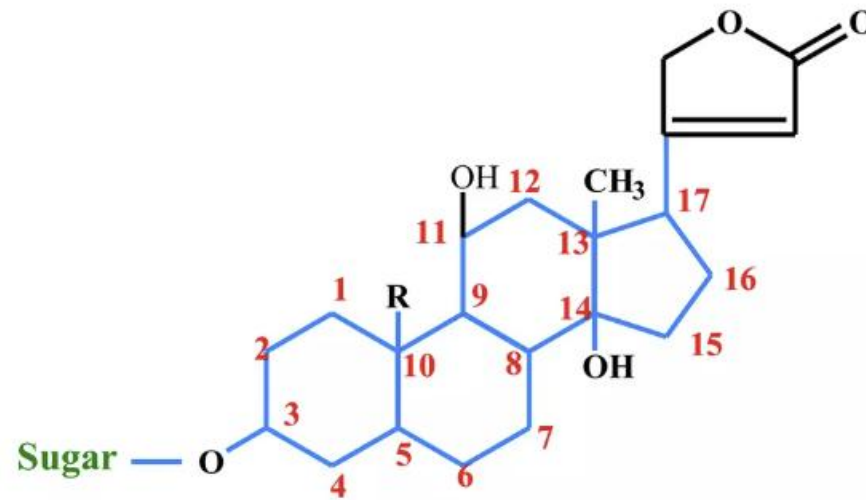


Digoxin 160



Convallatoxin

Digitalis glycosides are distinguished by an angular methyl group located at carbon 10, whereas **strophanthus glycosides** possess either an aldehyde ($-\text{CHO}$) or a primary alcohol ($-\text{CH}_2\text{OH}$) group at the same carbon position.



Cardenolides

Digitalis glycosides

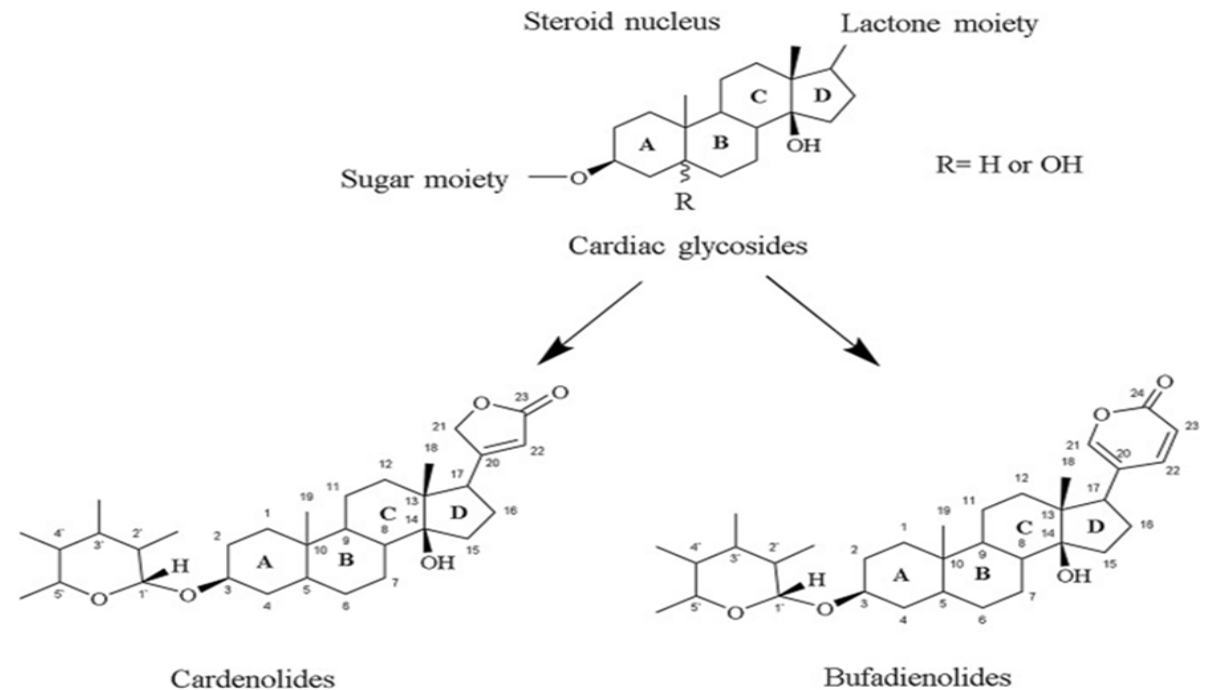
$\text{R}=\text{CH}_3$

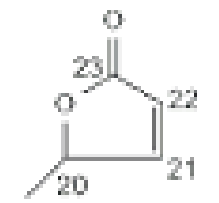
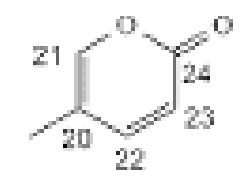
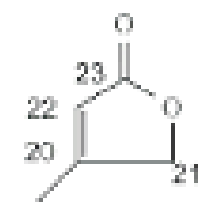
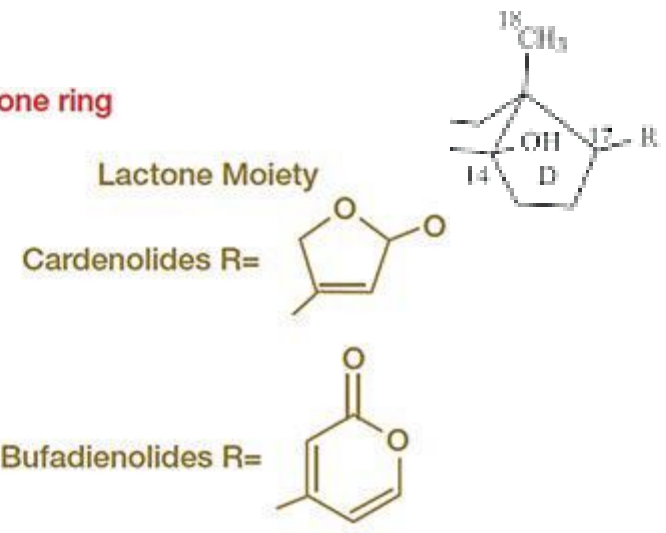
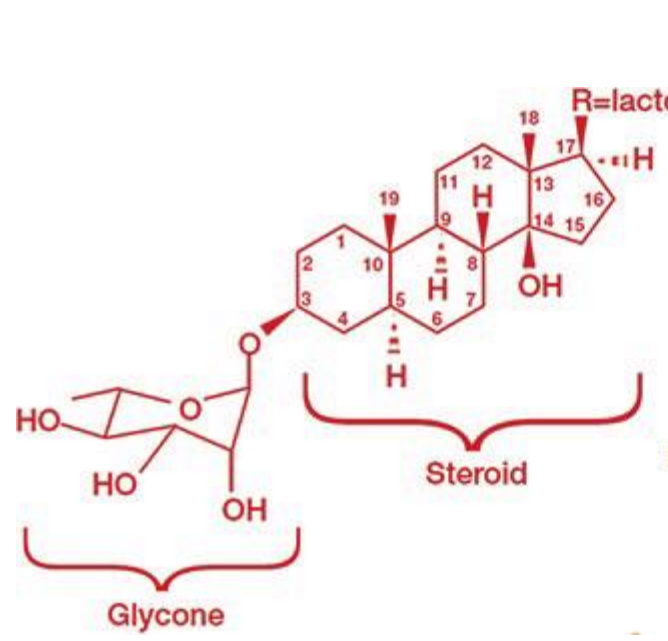
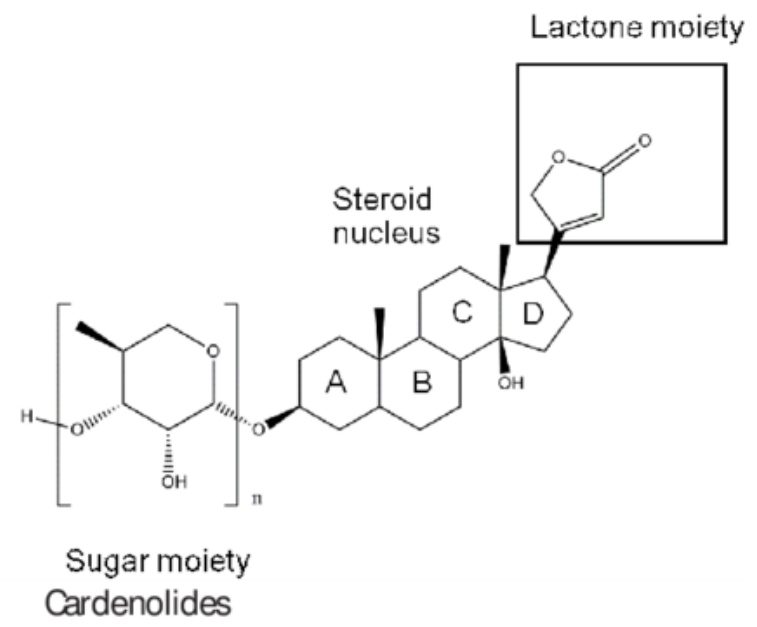
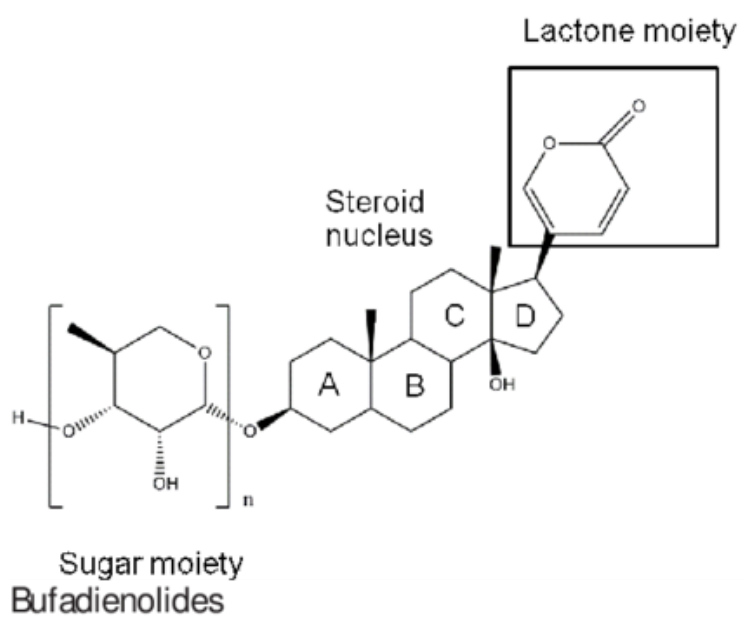
Strophanthus glycosides

$\text{R}=\text{CHO}$ OR CH_2OH

2-Bufadienolides

- possess a six-membered doubly unsaturated lactone (α -pyrone) at C-17. Typical examples: **bufalin** (also found in toad venoms and some plants contains these potent steroidal compounds). **Examples:** Bufalin, Scillaren A, Proscillaridin A.





Steroidal Nucleus, Substitutions & SAR

Basic framework: A tetracyclic **cyclopentanoperhydrophenanthrene** steroid skeleton (rings A, B, C, D).

- **Ring junctions:** C/D ring junction = **cis**. A/B junction = **cis**.
 - C-3: Hydroxyl group, usually glycosylated with mono- or oligosaccharides.
 - C-14: Common hydroxylation site, enhances polarity and affects receptor binding. (affect binding orientation and pharmacokinetics. Hydroxyl groups → faster onset & elimination)
 - C-17: Site of lactone attachment (defining difference between cardenolide vs bufadienolide). (the unsaturated lactone is essential for Na⁺/K⁺-ATPase binding; saturation or removal abolishes activity)
 - Sugars (digitoxose, rhamnose, glucose) at C-3 determine polarity, bioavailability, and half-life
(glycosylation increases water solubility and often reduces membrane permeability; deglycosylated aglycones tend to be more lipophilic and longer-acting).
 - The extended conjugation in the six-membered lactone often makes bufadienolides **more potent but also more toxic** than cardenolides.

Representative structural features

- **Digoxin:** three digitoxose sugars + hydroxyl group at C-12 (makes it more hydrophilic).
- **Digitoxin:** three digitoxose sugars, more lipophilic, longer half-life.
- **Ouabain:** one rhamnose sugar, highly hydrophilic, rapid action but poor oral absorption.

Structural Comparison: Cardenolide vs Bufadienolide

Feature	Cardenolide	Bufadienolide
Lactone	5-membered butenolide	6-membered doubly unsaturated pyrone
Examples	Digoxin, Digitoxin, Ouabain	Bufalin, Proscillaridin A
Distribution	Plants (Digitalis, Nerium, Strophanthus, etc.)	Plants (<i>Scilla</i> , <i>Urginea</i>) and toad venoms
Potency/Toxicity	Potent, narrow therapeutic index	Often more potent and toxic
Clinical use	Digoxin still in use	Limited clinical use, more toxic

Biosynthesis of cardioactive glycosides

it begins with the acetate-mevalonate pathway, similar to cholesterol production, leading to a steroid aglycone which is then joined with a sugar moiety to form the final glycoside

-Biosynthesis of cardioactive glycosides proceeds from the mevalonate (MVA) pathway leading to isoprenoid units and sterol precursors. Key conceptual steps (plant pathway) are:

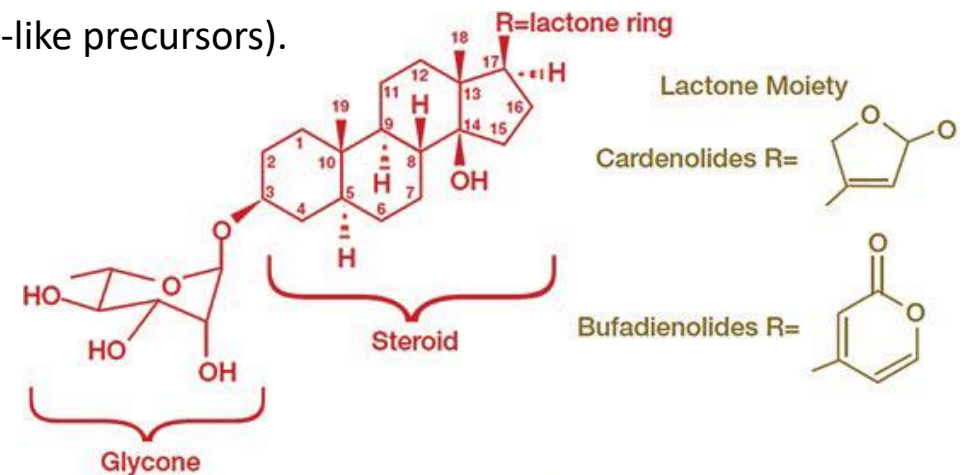
✚ **MVA pathway:** Acetyl-CoA → HMG-CoA → mevalonate → isopentenyl diphosphate (IPP) → squalene

✚ Derived from **isoprenoid pathway** (mevalonate → sterols → cholesterol-like precursors).

- **Sterol cyclization:**
- **Steroid nucleus tailoring:**
- **Lactone ring formation:**
- **Glycosylation:** at C-3

Note

- Lactone ring formed by oxidative cleavage and cyclization of the C-17 side chain.
- Distinct enzymatic steps dictate whether the 5-membered or 6-membered lactone is formed.

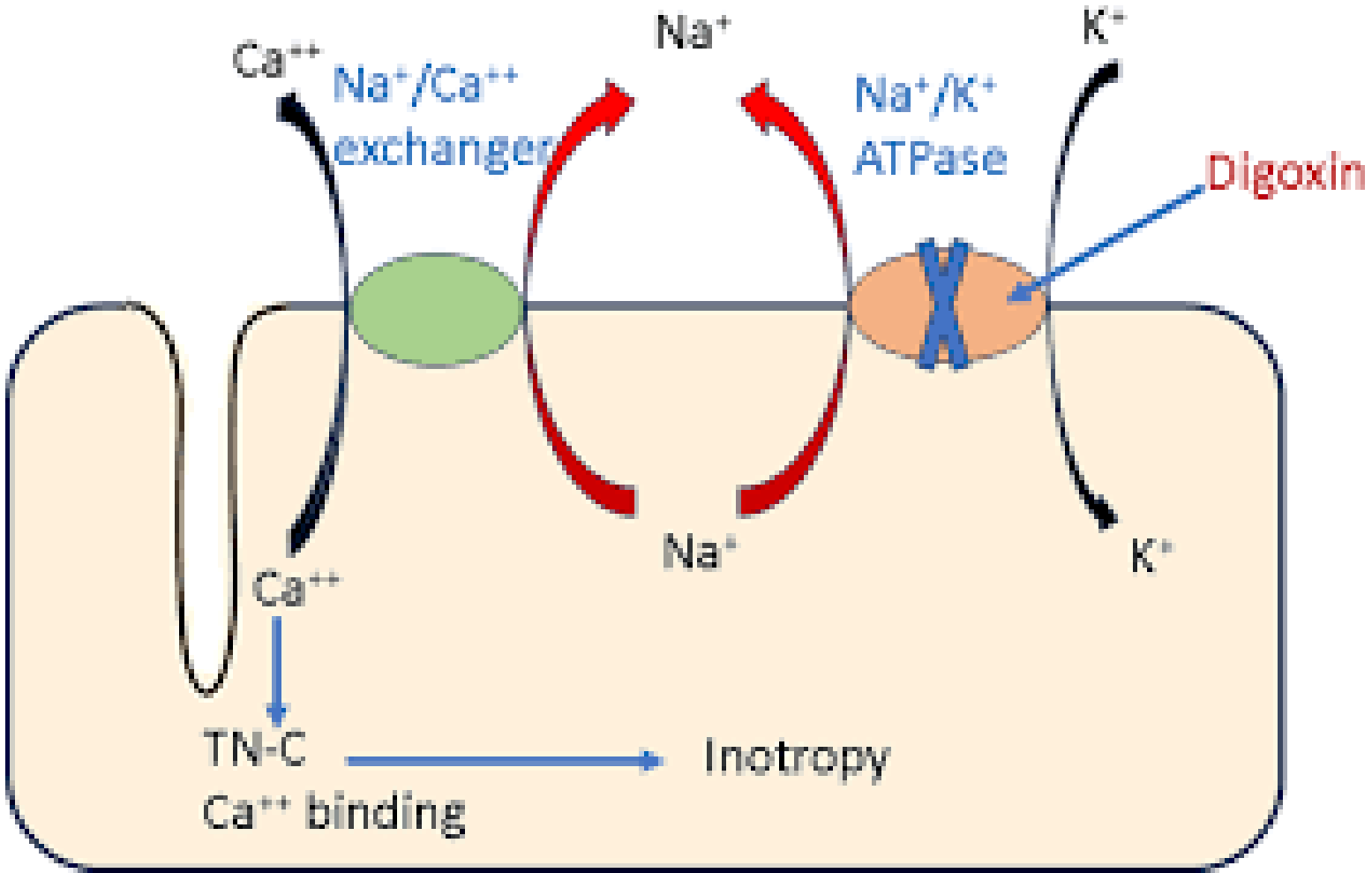


Mechanism of action & pharmacology

Na⁺/K⁺-ATPase inhibition

Cardioactive glycosides bind to the extracellular face of the α -subunit of the Na⁺/K⁺-ATPase, stabilizing the enzyme in a phosphorylated conformation and preventing ion translocation. The pharmacologic consequences include:

- ✓ **Increased intracellular Na⁺**, reducing the driving force for the Na⁺/Ca²⁺ exchanger (NCX), thereby **increasing intracellular Ca²⁺** in cardiomyocytes and enhancing contractility (**positive inotropy**).
 - **Vagal tone augmentation** and direct effects on cardiac conduction that can slow atrioventricular (AV) nodal conduction, useful in certain supraventricular tachyarrhythmias.
- ✓ **↑ Systolic contraction force → better ventricular emptying.**
- ✓ **Shortens systole → more rest for heart.**
- ✓ **Reflex vagal effect → ↓ heart rate.**
- ✓ **Improved circulation → better renal secretion → ↓ edema.**



Toxicity and antidotes

Therapeutic index and toxicodynamics

- Narrow therapeutic window , signs of toxicity include gastrointestinal symptoms, visual disturbances (xanthopsia), bradyarrhythmias, ventricular arrhythmias, hyperkalemia in acute overdose.
- **Drug interactions:** hypokalemia (e.g., from diuretics) increases sensitivity; drugs that reduce clearance (e.g., quinidine) raise glycoside levels.

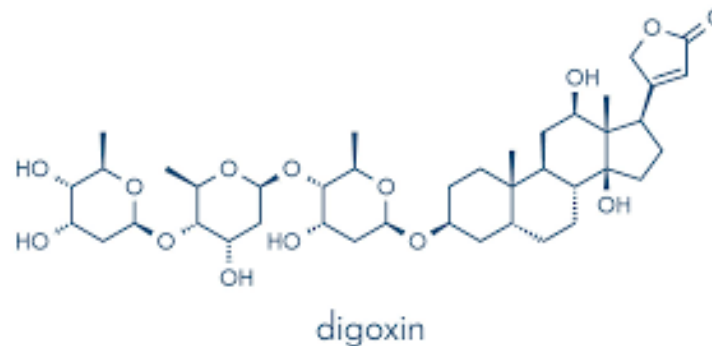
- **Acute toxicity management:** supportive care, correction of electrolyte abnormalities.
- **Specific antidote: digoxin-specific antibody fragments (digoxin immune Fab)** for life-threatening overdoses (bind circulating glycoside and allow renal elimination).
- **Activated charcoal** may be used early after ingestion; cholestyramine can interrupt enterohepatic recycling for some glycosides

cardio active Plants

Digitalis spp. (Plantaginaceae)

1- ***Digitalis purpurea, D. lanata.***

- **glycosides:** digitoxin, digoxin (primarily from *D. lanata*), gitoxin, lanatoside C (a precursor to digoxin).
- **Notes:** Digoxin (glycosylated with three digitoxose units) is water-soluble and renally excreted; digitoxin is more lipophilic and hepatically metabolized.



• Dr. Amani Amir Taftefi

Summary

Digoxin is a cardiac glycoside used in the treatment of mild to moderate heart failure and for ventricular response rate control in chronic atrial fibrillation.

Brand Names

Digox, Lanoxin

Generic Name

Digoxin

**DrugBank Accession
Number**

DB00390



Background

Digoxin is one of the oldest cardiovascular medications used today.⁵ It is a common agent used to manage atrial fibrillation and the symptoms of heart failure.⁷ Digoxin is classified as a cardiac glycoside and was initially approved by the FDA in 1954.²⁵

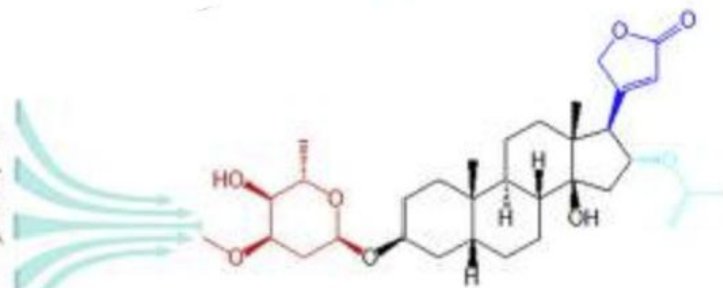
This drug originates from the foxglove plant, also known as the *Digitalis* plant²¹, studied by William Withering, an English physician and botanist in the 1780s.^{8,9} Prior to this, a Welsh family, historically referred to as the *Physicians of Myddvai*, formulated drugs from this plant. They were one of the first to prescribe cardiac glycosides, according to ancient literature dating as early as the 1250s.⁹

<https://go.drugbank.com/drugs/DB00390>

2-*Nerium oleander* (Apocynaceae)

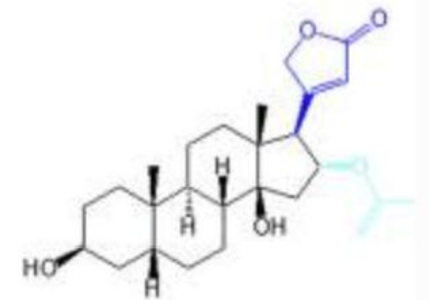
- **Key glycosides:** oleandrin, oleandrigenin, neriifolin.
- **Notes:** Highly toxic; all parts poisonous. Oleandrin has been studied for antiviral and anticancer claims (controversial) but is a potent Na⁺/K⁺-ATPase inhibitor with narrow margin of safety.



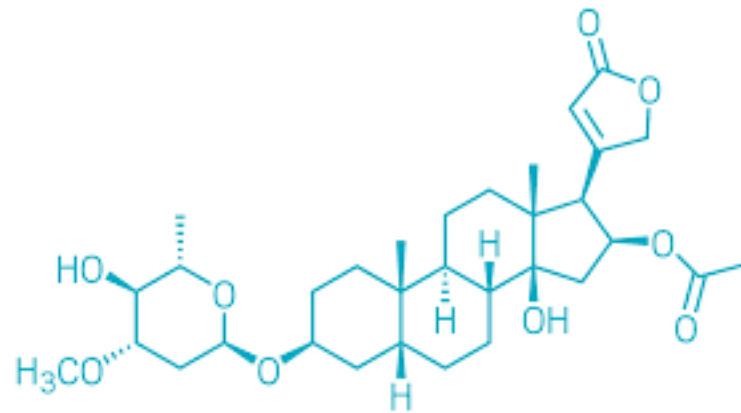


Oleandrin

Hydrolyze



Oleandrigenin



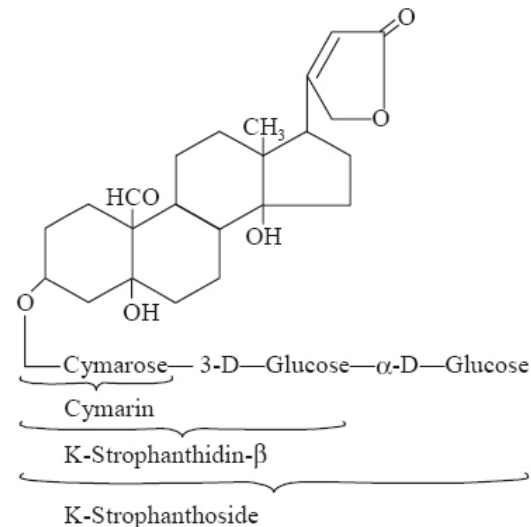
Oleandrin

Poisoning symptoms

- Oleandrin is widely known for its **typical dose-dependent cardiotoxicity**, which inhibits Na/K-ATPase causing electrochemical imbalance, which may **damage the cardiovascular system even at low doses**.
- in 2012 showed that **interstitial pneumonia, cardiac muscle fiber degeneration, and necrosis** occurred in sheep after ingesting oleander extract ([Aslani et al., 2004](#)).
- in 2002 indicated that oleandrin may **cause liver and kidney toxicity** ([Mahendradhata and Moerman, 2004](#)). The liberation of free radicals during oleander metabolism may induce liver injury and **disruption of hepatocyte membranes** ([Kwak et al., 2012](#); [Taheri et al., 2012](#)).
- in 2019 indicated that creatine kinase and creatine kinase-MB levels were elevated, indicating **severe myocardial damage**, confirmed by histopathological examinations ([Abdou et al., 2019](#)).

3-Strophanthus spp. (Apocynaceae)

- **Key glycosides: ouabain**, strophanthin variants (strophanthidin glycosides).
- **Notes:** Historically used in arrow poisons;
- ouabain is a classic Na^+/K^+ -ATPase inhibitor used experimentally.



KEY BENEFITS :

Hispid Strophanthus Q, scientifically known as Strophanthus hispidus, is a plant species belonging to the Apocynaceae family. Strophanthus Hispidus Q is derived from this plant.

Some uses and benefits of Strophanthus Hispidus Q :

Cardiotonic & Cardiovascular Support: Contains cardiac glycosides, such as strophanthin and ouabain. These compounds have a positive inotropic effect, meaning they strengthen the force of the heart's contractions

Palpitations and Arrhythmias: Used to address symptoms such as palpitations (rapid or irregular heartbeats) and arrhythmias (abnormal heart rhythms). Suggested to have a regulatory effect on the heart's rhythm.

Respiratory Support: It may be used to address symptoms associated with conditions like asthma and shortness of breath.

Nervous System Calming: May be used to help relieve anxiety, restlessness and nervousness.

General Weakness and Fatigue: Suggested to help address general weakness and fatigue. It is believed to have properties that may help improve energy levels and promote overall well-being.

DIRECTION FOR USE:

Children above 1 year up to 12 years: Take 5 to 10 drops in half a cup of water daily 3 times or as directed by the Physician

Adults: Take 10 to 15 drops in half a cup of water daily 3 times or as directed by the Physician.

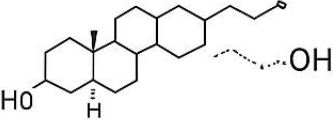
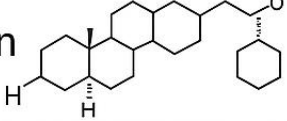
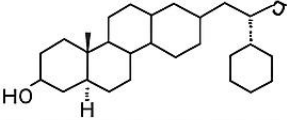
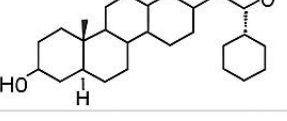
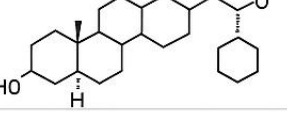
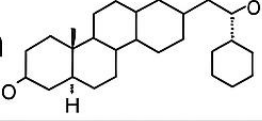
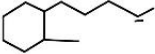
*Note: We recommend you take this under the guidance of a Physician.

Avoid any strong smell in the mouth before taking this medicine.

Maintain a gap of an hour between meal and this medicine.



<https://www.allenhomoeopathy.com/strophanthus-hispidus-q?srsId=AfmBOoo8gApBKb3nvZSD60S8Is-eYNdJWd07DrKhfwEKwgBiwWx9U7mX>

Plant	Representative Glycoside	Key Pharmacological Notes
Digitalis	Digoxin 	Positive inotropic, treats heart failure
Strophanthus	Strophanthin 	Rapid onset, cardiac stimulant
Nerium	Oleandrin 	Toxic, inotropic effects
Thevetia	Thevetin 	Toxic, can cause arrhythmia
Urginea	Scillarenin 	Diuretic, cardiac stimulant
Convallaria	Convallatoxin 	Treats heart failure, arrhythmias
Bufo	Bufalin 	Strong cardiotoxic, toxic

Case study

A 72-year-old woman on digoxin for AF presents with nausea, blurred yellow vision, bradycardia (40 bpm). Serum potassium is 5.6 mmol/L. ECG shows bidirectional ventricular tachycardia. Discussion points: differential between chronic toxicity and acute overdose, role of hyperkalemia (marker of severe toxicity), renal dosing, monitoring drug levels, avoiding interaction.

This patient is most likely suffering from **digoxin toxicity**, likely exacerbated by **renal impairment**, resulting in **hyperkalemia** and potentially life-threatening arrhythmias (bidirectional ventricular tachycardia). The management includes discontinuing digoxin, correcting electrolyte imbalances, and considering **digoxin-specific antibody therapy** for severe toxicity. Regular **digoxin level monitoring** and careful **renal dosing** in the future are necessary to avoid recurrence of toxicity.



SCOPE
Student Activity

How can I prevent Oleander poisoning in my home or community?

What should I do if someone ingests Oleander?

How can I help parents recognize the dangers of Oleander for children?



Dr. Amani Amer Tawfeeq

How can I prevent Oleander poisoning in my home or community?

Avoid planting Oleander in areas where children or pets play. Make sure to educate people about its toxicity. If you already have Oleander plants, ensure they are in secure, fenced areas and disposed of safely when pruned. Always wash your hands after handling the plant.

What should I do if someone ingests Oleander?

If someone is suspected of ingesting any part of the Oleander plant, it is important to immediately contact emergency services or a poison control center. Do not attempt to induce vomiting unless advised by a healthcare professional.

Dr. Amani Amer Tawfeeq



How can I help parents recognize the dangers of Oleander for children?

Educate parents on the importance of keeping potentially dangerous plants like Oleander out of reach of children. Teach them about common signs of poisoning and stress the importance of having emergency contacts, such as the poison control center, readily available.



Dr. Amani Amer Tawfeeq