Cardiac Glycosides drugs
Learning Objectives

- Definition, classification, distribution, localization and function of cardiac glycoside drugs.
- Physicochemical properties of cardiac glycoside drugs.
- Extraction, detection, identification and characterization of cardiac glycoside drugs.
- Structure-activity relationship, biogenesis etc
- Biosynthetic origin of cardiac glycoside drugs. Pharmacological activity and uses of cardiac glycoside drugs.
- Official names, synonyms, biological sources, chemical constituents, uses, precautions, adverse reactions, contraindications and toxicity of some selected drug contain cardiac glycoside.
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References

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Glycosides are compounds containing a carbohydrate and a non-carbohydrate residue in the same molecule.
Glycosides

- The carbohydrate residue is attached by an acetyl linkage at carbon atom to a non carbohydrate residue or AGLYCONE.

- The non sugar component/part is known as the AGLYCONE. The sugar component/part is called the GLYCONE.

- If the carbohydrate portion is glucose, the resulting compound is a GLUCOSIDE.
According to the chemical nature of the aglycone, the glycosides are divided into the following:

1. Anthracene glycosides
2. Saponin glycosides
3. Flavonoids glycosides
4. Cyanogenetic glycosides
5. Isothiocyanate glycosides
6. Phenol glycosides
7. Alcoholic glycosides
8. Lactone glycosides
9. Citic glycosides
10. Aldehydric glycosides
11. Cardiac glycosides
The extraction procedure for glycosides are also varies.

- The general method for extraction is Stass Otto method.
- The powder drugs is extracted continuously by Soxhlet method with alcohol.
- Extract is treated with lead acetate to precipitate tannins and filtered to remove non glycosidal impurities.
- Excess lead acetate is precipitated as lead sulphide by passing $\text{H}_2\text{S}$ through the solution.
- The extract is filtered and concentrated to get glycosides.

**Extraction of glycosides**

![Soxhlet Apparatus](image)
Chemical tests for cardiac glycosides

Baljet tests
Substance + Sodium Picrate + Alkaline = Orange colour

Legals tests
Substance + Sodium nitroprusside + Alkaline + pyridine = Red colour

Raymond tests
Substance + Alcoholic nitrobenzene + Alkaline = Violet=Blue colour
Glycosides drugs are used as an antiarrhythmic agent to control heart rate (pulse), particularly in the irregular (often fast) atrial fibrillation (rapid irregular heartbeat).

They are used to increase cardiac contractility or force of contraction (contraction of heart).
Digitalis glycosides are prescribed for patients in atrial fibrillation, especially if they have been diagnosed with heart failure.

Heart failure: It is also called congestive heart failure. It is a condition in which the heart can no longer pump enough blood to the rest of the body.

The most common cause of heart failure is coronary artery disease and narrowing of the small blood vessels that supply blood and oxygen to the heart.
General Structure of Cardiac Glycosides

- Cardiac glycosides are one type of **steroid**
- Steroids form an important group of compounds based on the fundamental saturated tetracyclic hydrocarbon: Example: Sterane
Skeleton of cardiac glycoside

Examples of Steroids
Cardiac glycosides are composed of two structural features (parts): **Sugar (glycoside)** and non-sugar (aglycone-steroid) moieties/parts.
Types of Cardiac Glycosides

Cardenolides type

The Digitalis group and the Strophanthus group.

Bufadenolides type

The squill-toad group (scillarins and the toad poison Bufotoxin).
Cardenolides

- The aglycones of the cardenolides are (23) C-steroids with methyl groups at C-10 and C-13 and a five-membered lactone at C-17.

- Digitoxigenin is given as a typical example of cardenolides genin.
Cardenolides

- They are widely distributed in plants mainly as glycosides.
- They are either toxic or insect deterrents/repel (Digoxin)
The aglycones of the **bufadenolides** are (24) C-steroids with a six-membered lactone ring at C-17.

**Hellebrigenin** is a typical example of bufadenolides genin.
They have been isolated from plants and animals.

In plants, they are glycosides with one to three sugars in a chain linked to the 3-hydroxyl group.

They are important for their cardiotonic activity.

They possess insecticidal and antimicrobial properties.

Bufadenolides produced by the toad skin are strongly poisonous.
The aglycones of the bufadenolides differ from those of the cardenolides in having at position 17 a six-membered doubly unsaturated lactone ring.

- **Cardenolides** having at position 17 a five-membered ring
- **Bufadenolides** having at position 17 a six-membered ring
In plants cardiac glycosides appear to be confined to the Angiosperms.

Cardenolides are the most common and are particularly abundant in the Apocyanaceae and Asclepiadaceae.

But are also found in some Liliaceae, Ranunculaceae, Moraceae, Cruciferae, Euphorbiaceae, Tiliaceae, Leguminosae and Scrophulariaceae.
Cardiac glycosides are

- Colourless or white crystals, or amorphous substances
- Without odour, taste is bitter
- They have melting points (100-270°C)
- Optically active
- Many of them have fluorescence in UV-light.
- Many of them are bad soluble in water. However, good soluble in water solutions of methyl and ethyl alcohols.
- Glycosides with long carbon chain are better soluble in water and water-alcohol solutions. But, aglycones-good soluble in organic solvents.
- They can hydrolyse easily by dilute acid.
The pharmacological effectiveness/activity of the glycosides is dependent on both the aglycones and the sugar attachments.

Aglycones are resides the inherent activity (constant activity).

The sugars part render the compounds more soluble and increase the power of fixation of the glycosides to the heart muscle.
1. Most commonly, the sugar moiety is attached to the aglycone through the C-3 position.

2. This sugar moiety consists of a monosaccharide or very frequently of an oligosaccharide composed of two to four units.

3. When glucose is present, it is always terminal.
The cardiac activity is directly linked to the aglycone. The sugar moiety does not participate directly in activity, but enhances the activity by modulating the polarity of the compound.

The activity is maximized if configuration of cycles is cis-trans-cis and greatly diminished when A and B rings are trans fused. The C and D rings must be cis fused.

The activity is maintained when the A ring is partially unsaturated.
Digitalis purpurea

- **Origin:** The leaves of *Digitalis purpurea* (Family: Scrophulariaceae) collected and rapidly dried at temperature not exceeding 65°C.

- The use of *Digitalis purpurea* extract for the treatment of heart conditions was first described in the medical literature, in 1785, which is considered the beginning of modern therapeutics.

- **Traditional Use:** Congestive heart failure
Constituents of Digitalis purpurea

The plant contains chemical compounds:
- Tri glycosides (tetraglycosides)
- Purpurea glycoside A and Purpurea glycoside B.
- Saponins: Gigitonin
- Flavonoid glycoside: Luteolin

Purpureaglykosid A
On drying, enzyme degradation takes place with loss of the terminal glucose to give the major glycosides digitoxin and gitoxin.
Hydrolysis of Glycosides

Purpurea glycosides A and B (0.3–0.5%)

**Purpurea A**

Hydrolysis/enzyme → Digitoxin

Digitoxiginin + 3 mole digotoxose

**Acid/hydrolysis**

**Purpurea B**

Hydrolysis/enzyme → Gitoxin + One mole glucose

**Acid/hydrolysis**

Gitoxiginin + 3 mole digotoxose
Uses of Digitalis purpurea:

- They are used mainly as cardio tonic and diuretic
- Increases the force of systolic contractibility
- Improves the tone of cardiac muscle
- Used for the treatment of congestive heart failure and auricular fibrillation

N.B.: Digitoxin is cumulative and highly toxic. Therefore, it should be administered with great care.
Digitalis lanata is a species of foxglove (flowering plant). Family: Scrophulariaceae.

- It gets its name due to the texture of the leaves.
- Digitalis lanata, like some other foxglove species, is highly toxic in all parts of the plant.

Traditional Use: Heart failure and increase the heart pump.

![Chemical structures of Digoxin and Lanatosid A](https://example.com/chemical_structures.png)
Digitalis lanata leaves contains:

Active constituents:

Cardiac glycosides:

- Lannatoside A (Acetyl purpuraea A)
- Lannatoside B (Acetyl purpuraea B)
- Digitoxin
- Gitoxin

Uses:

Digitalis lanata is used for manufacture of pure glycosides particularly digoxin and lannatoside A.
Strophanthus is a genus of flowering plants. Family: Apocynaceae.

Origin: Three varieties available:
The dried seeds of *Strophanthus kombe*, *S. gratus* and *S. hispidus*.

Traditional use: Diuretic

Active constituents:
- K-strophanthoside-A
- K-strophanthin-B
- Cymarin glycosides
- Ouabain (G-strophanthin)
Uses of Strophanthus Seed

Uses

- It is used as cardio tonic
- Diuretic
- Improves the tone of cardiac muscle
- Used for the treatment of congestive heart failure and auricular fibrillation
- Sometimes raise the blood pressure. However, it is not cumulative drug.

Chemical tests:

- With $\text{H}_2\text{SO}_4 \rightarrow$ green colour
- With $\text{FeCl}_3 + \text{H}_2\text{SO}_4 \rightarrow$ Red colour
  $\rightarrow$ green colour.
Squill Bulb

Origin: The sliced and dried leaves from the bulb of *Urginea maritima* used as medicine. **Family: Liliaceae.**

Traditional use: Chronic bronchitis.

Active constituents: Cardiac glycosides of bufadienolide type: *Scillarene A* and *Scillarene B*

Uses:
- It is used as cardio tonic
- Chest pain
- Expectorant and used in chronic bronchitis.
Origin

The dried leaflets of *Cassia acutifolia* known as Alexandrian Senna, and *Cassia angustifolia* known as Indian Senna. Family: Leguminosae

Traditional use: Acute constipation
 setActive constituents:

- Anthraquinone glycosides: Sennosides A and B (dianthrone type)
- Aglycones of free anthraquinones: rhein, aloe, emodin.
- Protein

Uses of Senna

- Laxative or purgative used in acute constipation
- Haemorrhoids
- Anal fissures
- Cardiac
Toxic glycosides include:
- Cyanogenetic (nitrile) glycosides
- Goitrogenic substances
- Coumarin glycosides
- Steroid (cardiac and saponic) glycosides

The amount of a particular glycoside elaborated in a plant depends not only on intrinsic factors such as genetics, part of plant, age of plant, and sometimes even sex of plant, but also to a large degree on extrinsic factors such as climate, moisture supply and soil fertility.
Cyanogenetic (nitrile) glycosides

Cassava (Manioc)

Taxonomy:
- Dicotyledon
- Family: Euphorbiaceae
- Genus and species: Manihot esculenta

Medicinal Uses

- Aids digestion
- Constipation
- Prevents cancer
- Promotes skin health
- Lowers cholesterol
- Celiac disease
- Energy
- Boosts immunity
Chemical Constituents

1. Major constituent: Cyanogenic glycosides
2. Linamarin
3. Lotaustralin

They are all β-glucosides. All of these β-glucosides are bound to cyanide group

Adverse effect

1. These chemicals are converted to cyanide in the body when eaten. This may cause cyanide poisoning and lead to certain paralysis conditions.
2. Pregnancy and breast-feeding: It’s LIKELY UNSAFE to eat cassava regularly as part of the diet if you are pregnant. It might also cause birth defects. It is also LIKELY UNSAFE to insert cassava into the vagina. It might cause the uterus to contract. This might cause a miscarriage.
Goitrogenic substances

Goitrogens are compounds that interfere with the normal function of the thyroid gland.

Family: Brassica

Source: Cabbages, kale, soybean, rape seed

Chemical Constituents: Main Chemical: Isothiocyanates

- Allyl isothiocyanate
- 3-Butenyl isothiocyanate
- Protoanemonine
- Ranunculin
- Goitrins
- Thiocyanates
- Flavonoids

Also contain thiocyanates & thiooxazolidone, goitrogenic
**Adverse effect:**

**Blocking iodine:** Goitrogens may prevent iodine from entering the thyroid gland, which is needed to produce thyroid hormones.

**Reducing TSH:** Goitrogens may interfere with thyroid stimulating hormone (TSH), which helps the thyroid gland produce hormones.

**Mental decline:** In one study, poor thyroid function increased the risk of mental decline and dementia by 81% for people under 75 years of age.

**Heart disease:** Poor thyroid function has been linked to a 2-53% higher risk of developing heart disease and an 18-28% higher risk of dying from it.

**Weight gain:** During a 3.5-year long study, people with poor thyroid function gained up to 5 lbs (2.3 kg) more weight.

**Obesity:** Researchers found that individuals with poor thyroid function were 20-113% more likely to be obese.
Origin:
The dried unpeeled or peeled roots and stolons of *Glycyrrhiza glabra* belongs to *F. Leguminosae*.

Traditional use: Arthritis and rheumatism

Active constituents:
- Triterpenoid saponin glycoside: Glycyrrhizine which is K and Ca salts of glycyrrzinic acid.
- Flavonoid glycoside: Liquiritin and isoliqueritin which give the root its yellow colour.
- Sugars.
Saponin containing drugs

Medical Uses

Orally

- Respiratory disorders: Treatment of asthma, acute and chronic bronchitis and chronic cough.
- Gastric, duodenal and esophageal ulceration or inflammation.
- Arthritis and rheumatism, it’s a mild anti-inflammatory due to corticosteroid effect of its glycyrrhizin content.

Topically:

- Inflammatory skin disorders.
- Mouth ulcers.

Chemical tests

- Froth test.
- Powder + H₂SO₄ → orange red colour
Thank you!