Cardiac Glycosides drugs
Learning Objectives

- Definition, distribution, localization and function of cardiac glycoside drugs.
- Physicochemical properties of cardiac glycoside drugs.
- Extraction, detection, identification and characterization of cardiac glycoside drugs.
- 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.
The student should be able to cover the following items: Definition, distribution, localization and function of cardiac glycoside drugs.

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Biosynthetic origin of cardiac glycoside drugs. Pharmacological activity and uses of cardiac glycoside drugs.

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References

- Pharmacognosy Phytochemistry by Jean Bruneton, Medicinal Plants (1999) Page Number 5-73; 91-256; 312-345
- Pharmacognosy and Pharmacobiotechnology (1996) by Page Number 1-40; 59-121.
- Phytochemical Methods, J. Harborne PDR for Herbal Medicines 2nd edition 30-75; 77-156.
- Organic Chemistry by IL Finar Page Number 368-473; 170-205; 250-289
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 is known as the AGLYCONE. The sugar component 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

Soxhlet Apparatus
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
Medicinal uses

- They 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).
Medicinal uses

- 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.
Cardiac glycosides are a 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: Sugar (glycoside) and non-sugar (aglycone-steroid) moieties.
Types of Cardiac Glycosides

Cardenolides

The Digitalis group and the Strophanthus group.

Bufadenolides

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 (Digoxin)
Bufadenolides

- 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.
Bufadenolides

- 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
Distribution in nature

- In plants cardiac glycosides appear to be confined to the **Angiosperms**.
- **Cardenolides** are the most common and are particularly abundant in the **Apocyanaceae** and **Asclepiadiaceae**.
- 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 temperature (100-270°C)
- Optically active
- Many of them have fluorescence in UV-light.
- Many of them are bad soluble in water, good soluble in water solutions of methyl and ethyl alcohols.
- Glycosides with long carbon chain are better soluble in water and water-alcohol solutions, aglycones-in organic solvents.
- They can hydrolyse.
The pharmacological effectiveness of the cardioactive glycosides is dependent on both the aglycones and the sugar attachments.

Aglycones are resides the inherent 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 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 lactone ring at C-17 must be present and must be in the β-configuration.

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.
Origin: the dried leaves of Digitalis purpurea F. 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
The fresh plant contains chemical compounds:

- Tri glycosides (tetraglycosides)
- Purpurea glycoside A and
- Purpurea glycoside B.
On drying, enzyme degradation takes place with loss of the terminal glucose to give the major glycosides of the foxglove digitoxin and gitoxin.
Chemical Active constituents

1. Cardiac glycosides: Purpurea glycosides A and B
2. Saponins: Gigitonin
3. Flavonoid glycoside: Luteolin
Hydrolysis of Glycosides

Purpurea glycosides A and B (0.3-0.5%)

Hydrolysis/enzyme

Purpurea A → Digitoxin + One mole glucose

Acid/hydrolysis

Digitoxiginin + 3 mole digotoxose

Hydrolysis/enzyme

Purpurea B → Gitoxin + One mole glucose

Acid/hydrolysis

Gitoxiginin + 3 mole digotoxose
Uses:

- Cardiotonic 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, it should be administered with great care.
Digitalis lanata is a species of foxglove (flowering plant). 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
Digitalis lanata

A substitute for *Digitalis purpurea* leaves

Active constituents:

Cardiac glycosides:

- Lannatoside A (Acetyl purpurea A)
- Lannatoside B (Acetyl purpurea 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 in the family Apocynaceae.

**Origin:**
The dried seeds of *Strophanthus kombe, S. gratus* and *S. hispidus F. Apocyanaceae.

**Traditional use:** Diuretic

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

## Uses
- Cardiotonic
- Diuretic
- Improves the tone of cardiac muscle
- Used for the treatment of congestive heart failure and auricular fibrillation
- Sometimes raise the blood pressure and it is not cumulative drug.

## Chemical tests:
- With 66% H$_2$SO$_4$ → emerald green
- With FeCl$_3$ + H$_2$SO$_4$ → red colour → green colour.
Squill Bulb

Origin: the sliced and dried scale leaves from the bulb of *Urginea maritime* F. Liliaceae.

Traditional use: Chronic bronchitis.

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

Uses:
- Cardiotonic
- Expectorant and used in chronic bronchitis.
Anthraquinone Glycosides

Anthraquinone glycosides from a number of plants (e.g., [Aloe (Liliaceae), Rhamnus (Rhamnaceae)] are widely used as laxatives.

Traditional use: Laxatives

Uses
- Laxatives, anti-inflammatory, antibacterial, antifungal & natural dyes.
- Act as stimulant
- Increase tone of smooth muscles in wall of colon & stimulate secretion of water & electrolytes in large intestine.
- Glycosides of anthranols & anthrones have a more drastic action than anthraquinone glycosides.
Chemical test for free anthraquinones

Powdered drug + microsublimation = needle crystals (anthraquinone) + alkali = red color.

Borntrager's test for anthraquinone glycosides

- Powdered drug + dilute acid + boil for 2 min (hydrolysis of glycosides), filter & cool.
- Filtrate + organic solvent (benzene or chloroform) + shake.
- Organic layer (aglycones) + ammonium hydroxide (10%) + shake vigorously = immediate rose pink or cherry red color in aqueous layer.
Senna Leaf (Folium Sennae)

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

Traditional use: Acute constipation
Active constituents:

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

Uses

- Laxative or purgative used in acute constipation
- Haemorrhoids
- Anal fissures
Chemical tests:

Modified Borntrager's test for dianthrone glycosides

- Powdered drug + alcoholic KOH + boil & filter.
- Filtrate + Dilute HCl (acidification) + ether + shake.
- Ethereal layer + FeCl₃ + NH₃ + shake = aqueous layer rose-red to intense red.
Flavonoid containing drugs, Buchu Leaf

Origin

The dried leaves of Buchu Leaf belong to F. Rutaceae.

- *Barosma betulina* known as short Buchu
- *B. cranulata* known as oval Buchu
- *B. serratifolia* known as long Buchu

Traditional use: Urinary tract infection

Active constituents:

- Crystalline flavone glycosides diosmin and hesperidine.
- Mucilage: Pectose type present in epidermal cells.
- Volatile oil with mint like odour containing mainly diosphenol.
**Uses:**

- Diuretic and urinary tract disinfectant due to volatile oil.
- Treatment of capillary fragility due to diosmin and hespiridin.
- Used for the treatment of varicose veins.
- Pile and different types of bleeding.

**Chemical tests:**

- 1 gm powder sample and add alcoholic KOH solution to give canary yellow colour.
Origin:
The dried unpeeled or peeled roots and stolons of *Glycyrrhiza glabra* 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:** spasmolytic, antitussive, demulcent and expectorant, so used in 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**
Coumarin containing drugs
Ammi visnaga Fruit (Fructus Ammi Visnagae)

Origin: the dried ripe fruit of *Ammi visnaga* F. Umbelliferae

Traditional use: asthma

Active constituents:
- Furanochromone bitter principle: Khellin and visnagin.
- Pyranocoumarin bitter principle: visnadin (a potent vasodialator).

Uses:
- Relaxation of smooth muscle of the ureter
- Antispasmodic
- Bronchial asthma
**Ammi majus (Fructus A. majus)**

**Origin:** The dried ripe fruits of *Ammi majus* F. umbelliferae

**Traditional use:** Leukodermia

**Active constituents:**
- Furanocoumarin bitter principles: Xanthotoxin, ammoidin and imperattonin.

**Uses**
- Treatment of leukodermia and alopecia and in combination herbal therapy for psoriasis.

**Chemical tests:** Powder with NaOH solution gives no rose red colour.
Thank you for Your Kind Attention