

# 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.

# Learning Outcomes

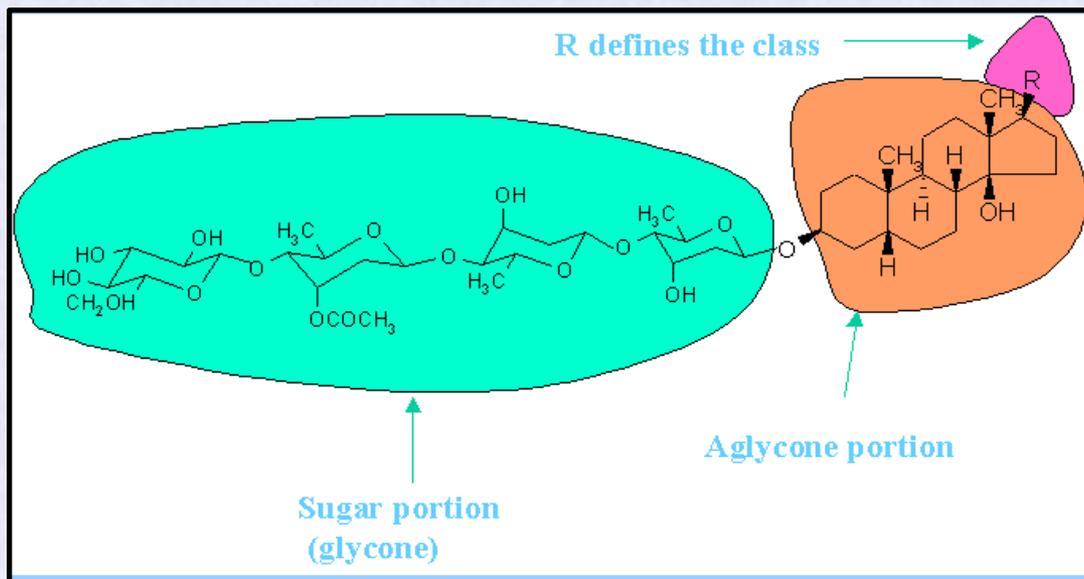
- ❑ The student should be able to cover the following items: Definition, distribution, localization and function of cardiac glycoside drugs.
- ❑ Physicochemical properties of cardiac glycoside drugs.
- ❑ Extraction, detection, identification and characterization of cardiac glycoside drugs.
- ❑ Biosynthetic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

# References

- ❑ Pharmacognosy by W.C. Evans. Trease and Evan's, 12<sup>th</sup> edition. London. Page Number 23-153; 170-205; 250-289.
- ❑ 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 2<sup>nd</sup> edition 30-75; 77-156.
- ❑ Organic Chemistry by IL Finar Page Number 368-473; 170-205; 250-289

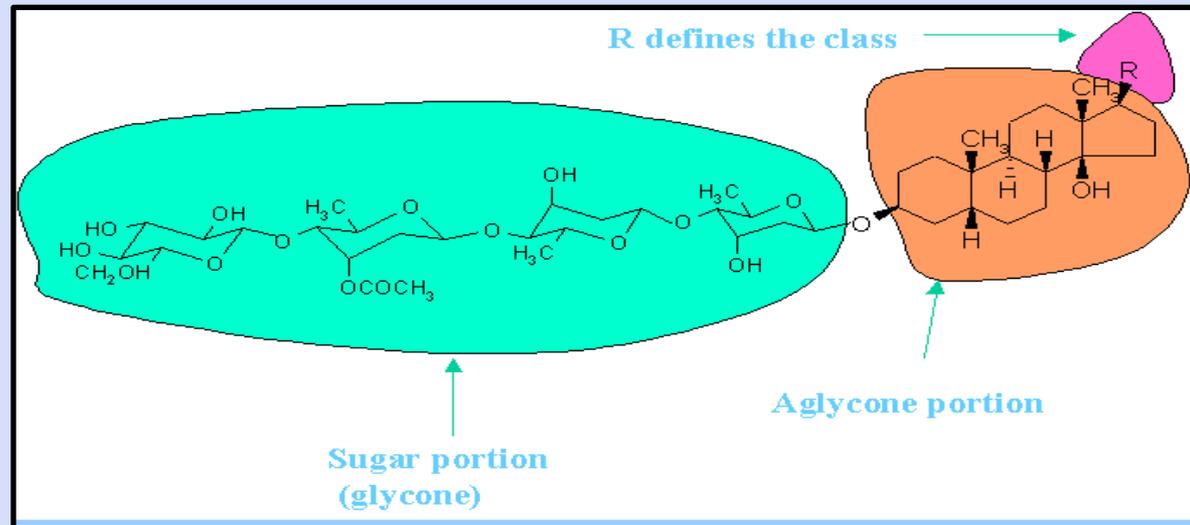
# Glycosides

- 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**

# CLASSIFICATION OF GLYCOSIDES

According to the chemical nature of the aglycone, the glycosides are divided into the following :

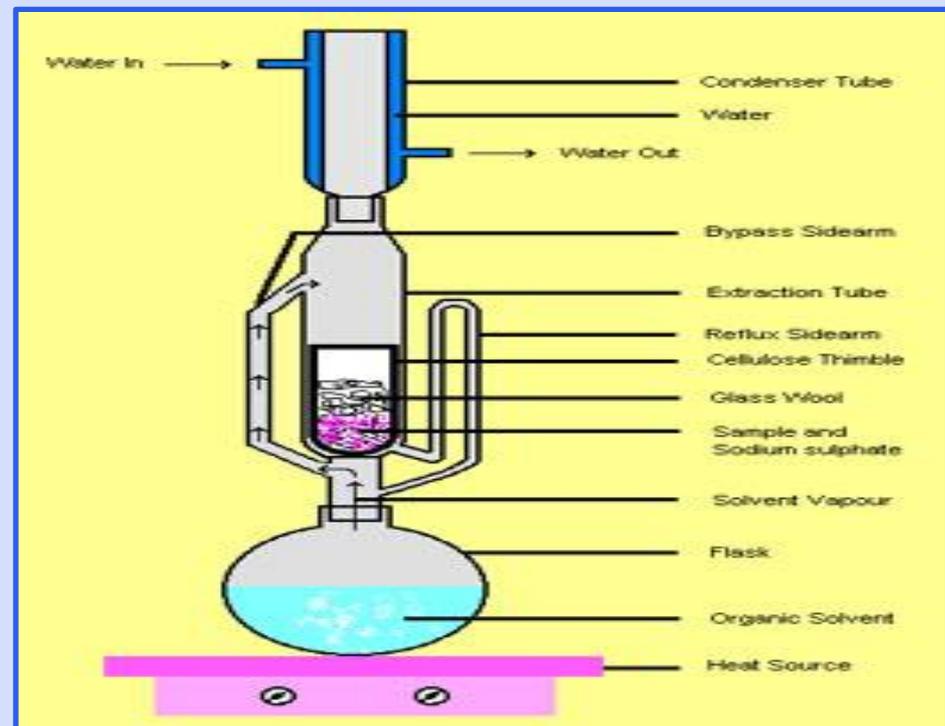
1. Anthracene glycosides
2. Saponin glycosides
3. Flavonoids glycosides
4. Cyanogenetic glycosides
5. Isothiocyanate glycosides
6. Phenol glycosides
7. Alcoholic glycosides
8. Lactone glycosides
9. Cardiac glycosides



# Extraction of 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  $H_2S$  through the solution
- ❑ The extract is filtered and concentrated to get glycosides

## Soxhlet Apparatus



# Chemical tests for identification of cardiac glycosides

## Baljet tests

Substance + Sodium Picrate + Alkaline = Orange colour

## Legals tests

Substance + Sodium nitropruside + 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.



# **Types of Cardiac Glycosides**

## **The Cardenolides**

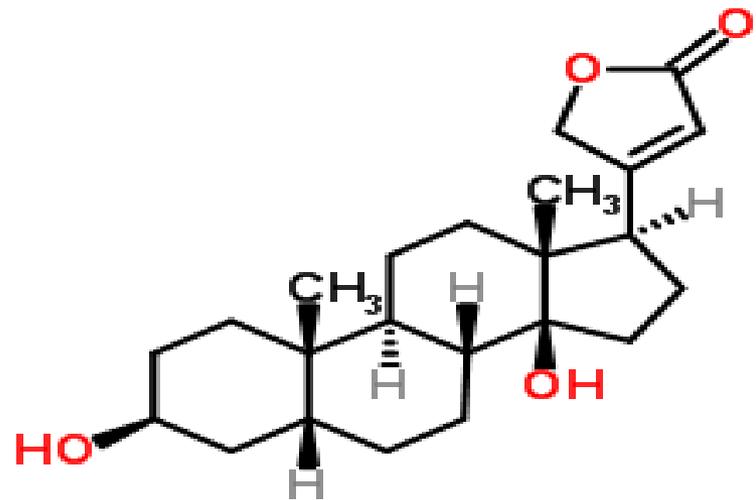
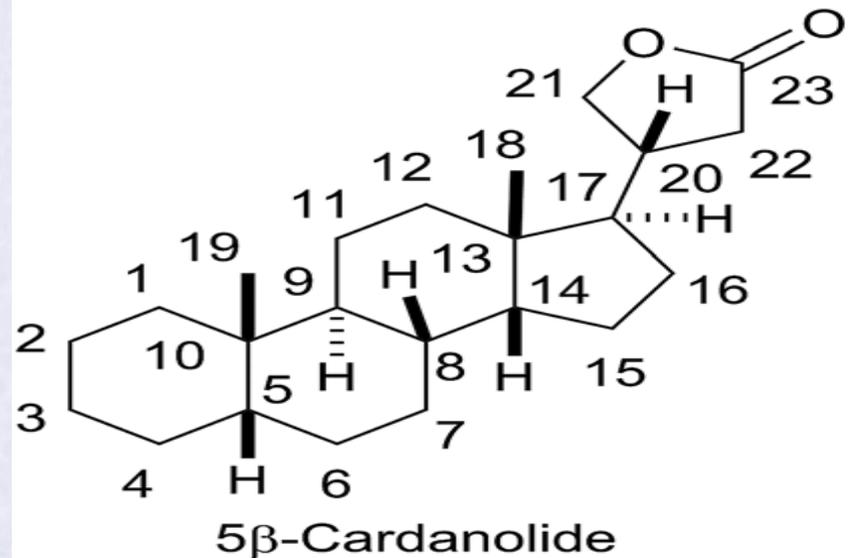
- The Digitalis group and the Strophanthus group.

## **The Bufadenolides**

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

# The 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.

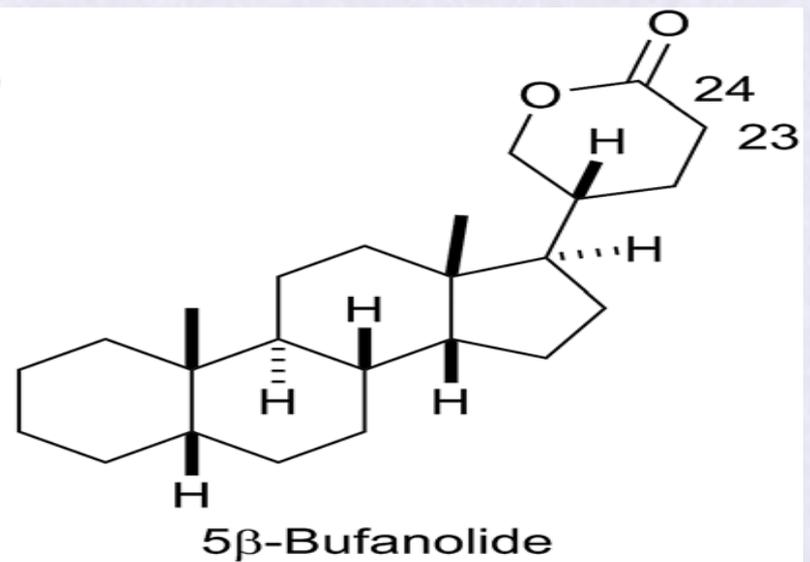
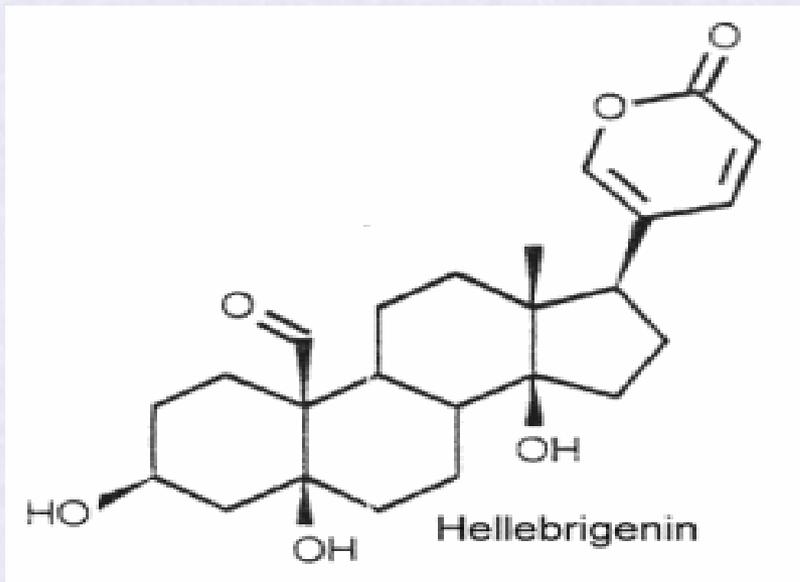


# The Cardenolides

- They are widely distributed in plants mainly as glycosides.
- They are either toxic or insect deterrents.(Digoxin)

# The 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.

# 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 Asclepidiaceae, but are also found in some Liliaceae, Ranunculaceae, Moraceae, Cruciferae, Euphorbiaceae, Tiliaceae, Leguminosae and Scrophulariaceae.

# Physicochemical properties

- 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.
- Glycosides with long carbon chain are better soluble in water and water-alcohol solutions, aglycones- in organic solvents.
- They can hydrolyse.

# Biological action

- The pharmacological effectiveness of the cardioactive glycosides is dependent on both the aglycones and the sugar attachments; the inherent activity resides in the aglycone, but the sugars render the compounds more soluble and increase the power of fixation of the glycosides to the heart muscle.

## Structure of the glycosides and SAR

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 structure activity relationship (SAR)

1. The cardiac activity is linked to the aglycone. The sugar moiety does not participate directly in activity, but it enhances the activity by modulating the polarity of the compound.
2. The lactone ring at C-17 must be present and must be in the  $\beta$ -configuration.
3. 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.
4. The activity is maintained when the A ring is partially unsaturated.

The inversion of configuration at C-3 diminishes the activity but 3-deoxy compounds are not completely inactive.

# *Digitalis purpurea*

## Common Foxglove



# Digitalis purpurea

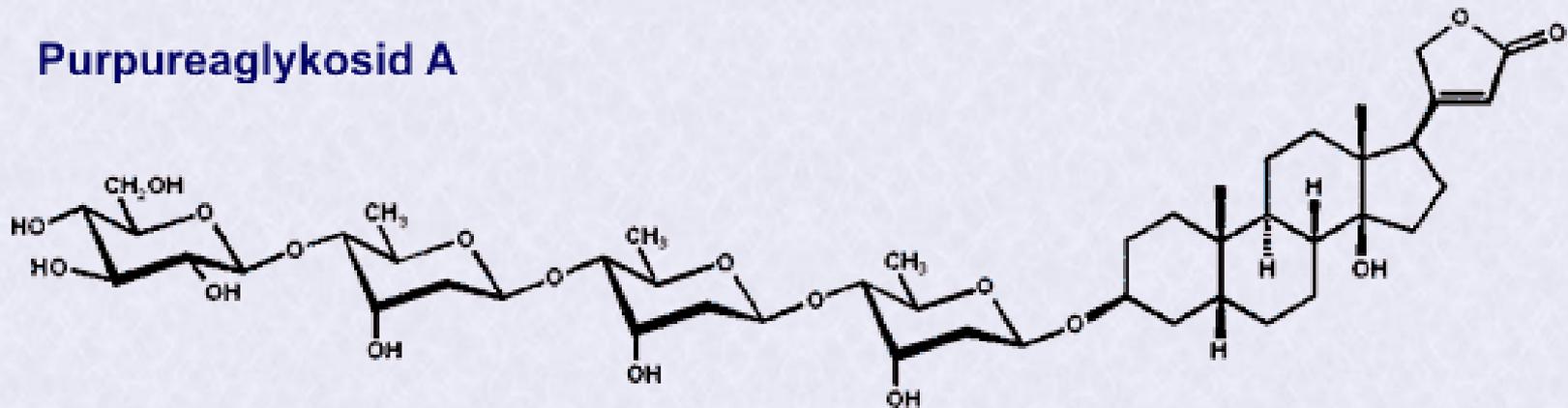
**Origin:** the dried leaves of *Digitalis purpurea* F. Scrophulariaceae, collected and rapidly dried at temperature not exceeding 65°C.

- 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.

# Digitalis purpurea

- The fresh plant contains:
- purpurea glycoside A and
- purpurea glycoside B.

**Purpureaglykosid A**



# Digitalis purpurea

- On drying, enzyme degradation takes place with loss of the terminal glucose to give the major glycosides of the foxglove digitoxin and gitoxin.

# Some cardiac glycosides of *D. purpurea*

<b>Glycosides</b>	<b>Aglycone</b>	<b>Sugar</b>
Purpurea glycoside A	Digitoxigenin	- (Digitoxose) <sub>3</sub> – glucose
Purpurea glycoside B.	Gitoxigenin	- (Digitoxose) <sub>3</sub> – glucose
Digitoxin	Digitoxigenin	- (Digitoxose) <sub>3</sub>
Gitoxin.	Gitoxigenin	- (Digitoxose) <sub>3</sub>

**Uses:** cardiotonic and diuretic, increases the force of systolic contractibility and improves the tone of cardiac muscle, so used in 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 "Grecian Foxglove"





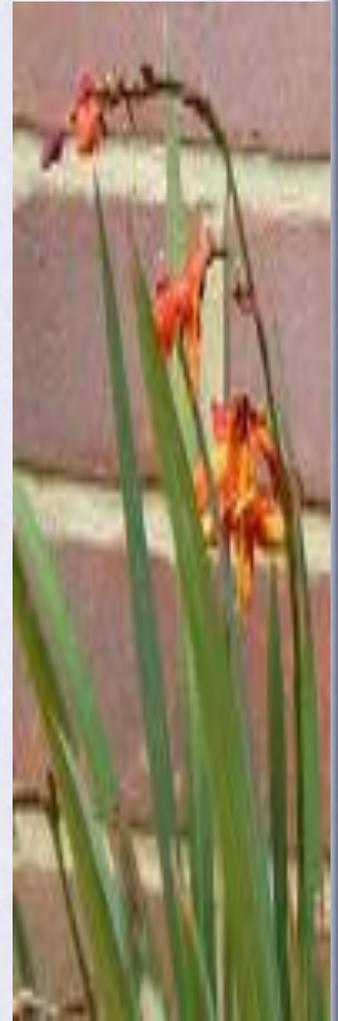
# Digitalis lanata "Grecian Foxglove"

A substitute for *Digitalis purpurea* leaves.

## Active constituents:

Cardiac glycosides: lannatoside A  
lannatoside B ,digitoxin and  
gitoxin.

N.B. they are twice to four times as  
active as official drug.



# 2- Strophanthus Seed

## Origin:

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

## Active constituents:

K-strophanthoside, K-strophanthin-B and cymarin glycosides and Ouabain (G-strophanthin)

## Uses

It resemble digitalis in its effect, cardiotonic, diuretic,

## Chemical tests:

- 1- With 66%  $H_2SO_4$  → emerald green
- 2- With  $FeCl_3 + H_2SO_4$  → red colour → green colour.



# 3- Squill Bulb

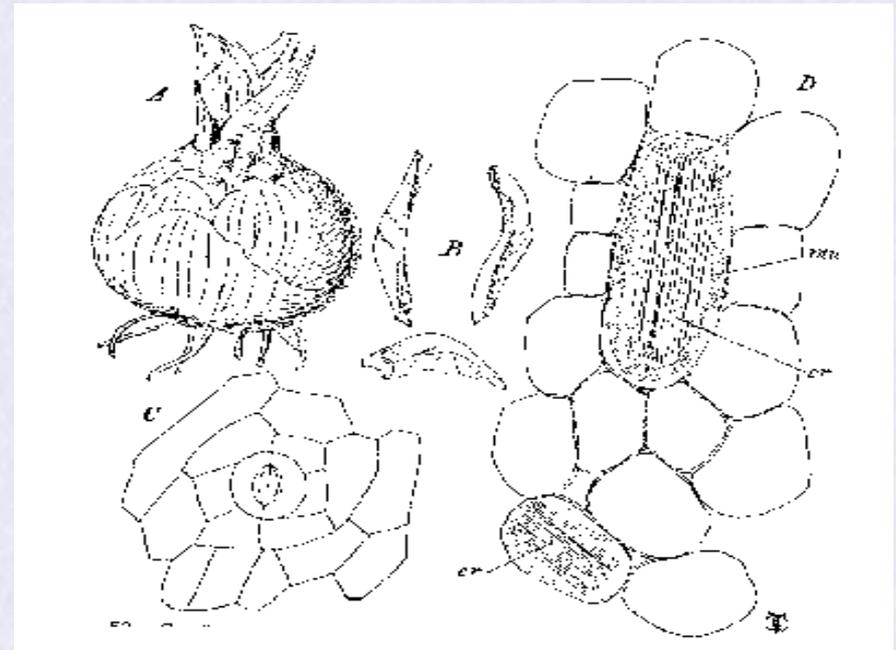
**Origin:** the sliced and dried scale leaves from the bulb of *Urginea maritime* F. Liliaceae.

**Active constituents:** cardiac glycosides of bufadienolide type: scillarene A and scillarene B

## Uses:

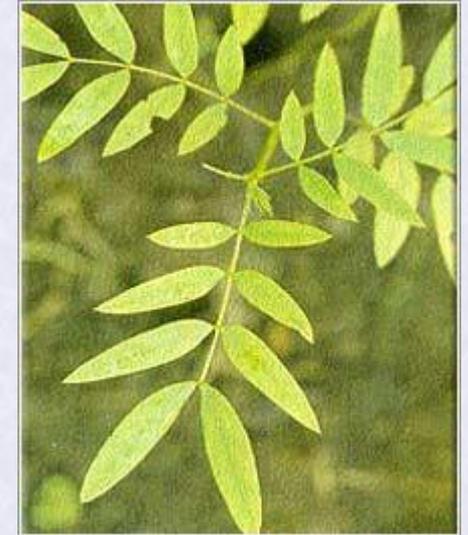
- 1- cardiotonic like digitalis.
- 2- expectorant and used in chronic bronchitis.

N.B. Red squill is a variety of squill contains also anthocyanin dissolved in the cell sap, it is toxic and used only as rat poison.



# **III- Anthraquinone Glycosides**

# Senna Leaf (Folium Sennae)



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

## **Active constituents:**

Anthracene derivatives: Sennosides A, B, C and D

Naphthecene derivatives

**Uses:** laxative or purgative used in acute constipation and in case of:

Haemorrhoids, anal fissures, x-ray examinations, before and after abdominal surgeries.

## **Chemical tests:**

1. Rhuthenium red: for mucilage
2. Borntrager's test: for anthraquinone glycosides gives red colour.

# Rhubarb, Rheum, Chinese Rhubarb

(Rhizoma Rhei)

**Origin:** The dried rhizome and roots of  
*Rheum palmatum*, *R. officinale* F.  
Polygonaceae

## **Active constituents:**

1. Free anthraquinone: rhein, chrysophanol, emodin, aloe-emodin
2. Anthraquinone glycoside.
3. Astringent compounds: catechin, epicatechin, free gallic acid, glucogallin.

## **Uses:**

1. In small dose: bitter stomachic and intestinal astringent.
2. In large dose: purgative followed by astringent effect.

## **Chemical tests:**

1. Borntrager's test: rose-red colour.
2. Microsublimation: yellow needle crystals which gives red colour with KOH.

## IV- Flavonoid containing drugs

### Buchu Leaf (Folium Buchu)

#### Origin:

The dried leaves of *Barosma betulina* known as short Buchu, *B. cranulata* know as oval Buchu and *B. serratifolia* known as long Buchu F. Rutaceae

#### Active constituents:

1. Crystalline flavone glycosides diosmin (present in epidermal cells) and hesperidine.
2. Mucilage: present in epidermal cells.
3. Volatile oil with mint like odour containing mainly diosphenol.

## **Uses:**

1. Diuretic and urinary tract disinfectant due to volatile oil.
2. Treatment of capillary fragility due to diosmin and hespiridin, so can be used in varicose veins, pile and different types of bleeding.

## **Chemical tests:**

1. KOH: canary yellow colour.
2. Sudan III: red colour due to volatile oil.
3. Rhuthenium red: red colour due to mucilage.

## V- Saponin containing drugs (Liquorice Root) (Radix Glycyrrhizae)

**Origin:** the dried unpeeled or peeled roots and stolons of *Glycyrrhiza glabra* F. Leguminosae.

### **Active constituents:**

1. triterpenoid saponin glycoside: **glycyrrhizine** which is K and Ca salts of glycyrrizinic acid.
2. Flavonoid glycoside: liquiritin and isoliqueritin which give the root its yellow colour.
3. Sugars.

# Uses:

## Orally:

1. Respiratory disorders: spasmolytic, antitussive, demulcent and expectorant, so used in treatment of asthma, acute and chronic bronchitis and chronic cough.
2. Gastric, duodenal and esophageal ulceration or inflammation.
3. Arthritis and rheumatism, it's a mild anti-inflammatory due to corticosteroid effect of its glycyrrhizin content.

## Topically:

1. Inflammatory skin disorders.
2. Mouth ulcers.

## Chemical tests:

1. froth test.
2. Powder + H<sub>2</sub>SO<sub>4</sub> → orange red colour

# VI- Coumarin containing drugs

## 1-Ammi visnaga Fruit (Fructus Ammi Visnagae)

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

### **Active constituents:**

1. furanochromone bitter principle: khellin and visnagin.
2. Pyranocoumarin bitter principle: visnadin (a potent vasodialator).

### **Uses:**

1. relax smooth muscle of the ureter, so used to ease the passage of renal caculi.
2. Khellin is antispasmodic given in renal and biliary colic, in bronchial asthma and in angina pectoris attacks.

### **Chemical tests:**

Boil the powder with water for 1 min., add 1-2 drops of decoction to 1 cc solution of NaOH (1 in 1), shake, rose red colour is produced within 2 min.

## 2- *A. majus* (Fructus *Ammi majus*)

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

**Active constituents:**

Furanocoumarin bitter principles: xanthotoxin, ammoidin and imperatorin.

**Uses:** Treatment of leukoderma and alopecia and in combination herbal therapy for psoriasis.

# VII- Tannin containing drugs Galls

(Blue Galls, Aleppo Galls, Turkish Galls)

**Origin:** Dried excrescence (pathological outgrowth) resulting from the deposition of the eggs of *Cynips gallae tinctoria* F. Cynipidae on the young twigs of *Quercus infectoria* F. Fagaceae. Collected before the escape of the insect and known as blue galls.

**Active constituents:** 50-70% pyrogallol tannin: gallotannic acid, gallic acid and ellagic acid.

**Uses:** Medicinally: astringent, haemostatic used in treatment of hemorrhoids in form of supp. or oint.

Industrially: 1- in manufacture of ink and paints  
2- in tanning of leather.

**Chemical test:**  $\text{FeCl}_3 \rightarrow$  bluish black colour.

*Thank you  
for  
Your Kind  
Attention*

