Steroidal (Cardiac glycoside)

Definition

Cardiac glycosides constitute a well-defined and highly homogeneous group from a structure, as well as pharmacological, standpoint.

Structure of cardiac glycosides:  

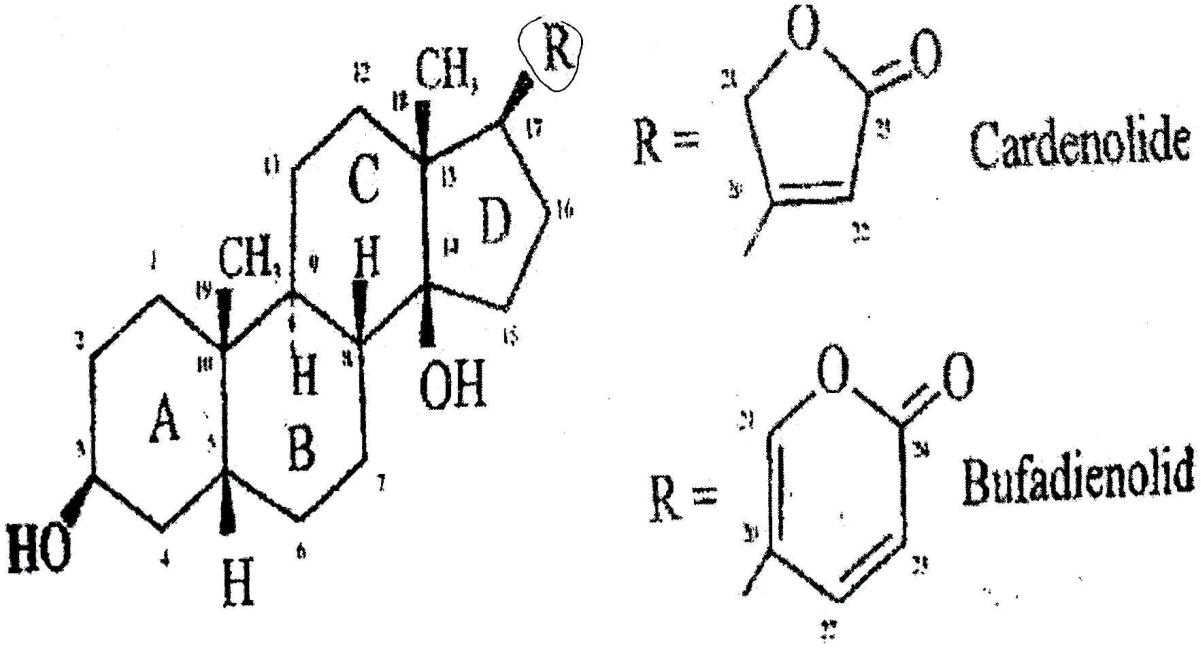
Steroidal aglycone of the (C23) cardenolide or the (C24) Bufadienolide, and a sugar moiety.

I. Structure of the aglycones:

All of the a glycones, tetracyclic, steroidal nucleus the A,B,C, and D rings normally have a cis-trans-cis configuration (digitoxigenin) or, less often , a trans-cis-trans configuration (Uziragenin) all of the aglycones is the presence of a β substitute at C-17. at C-17 an unsaturated lactone ring distinguishes into 2 groups are:

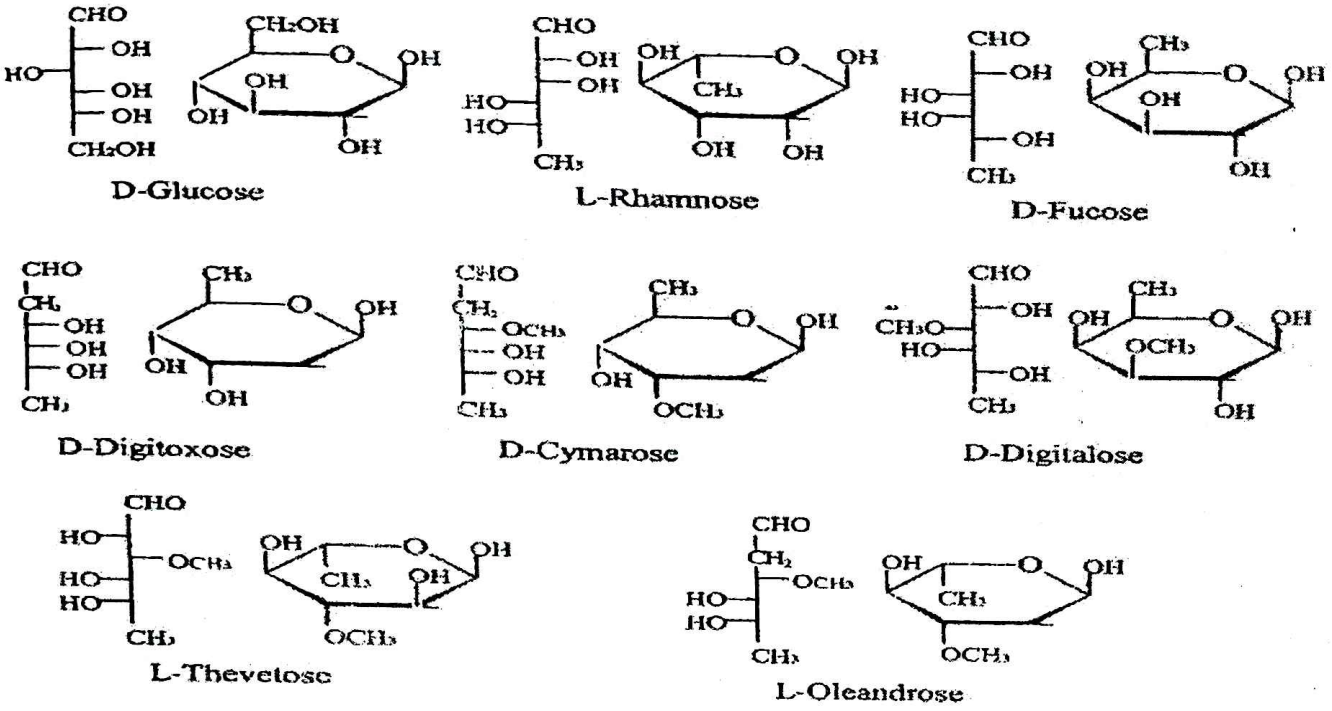
1. Cardenolide with an α,β-unsaturated γ-lactone (Butenolide).

2. Bufadienolides with a di-unsaturated δ-lactone (Pentadienolide).



II. Structure of the sugar moiety:

L-rhamnose, D-fucose, L-thevetose, D-digitalose, D-digitoxose, L-oleandeose, Dglucose.



Structure–activity Relationships:

The cardiac activity is linked to the a glycone. The sugar moiety does not participate directly and modulates it by modifying the polarity of the compound.

1. The lactone ring:

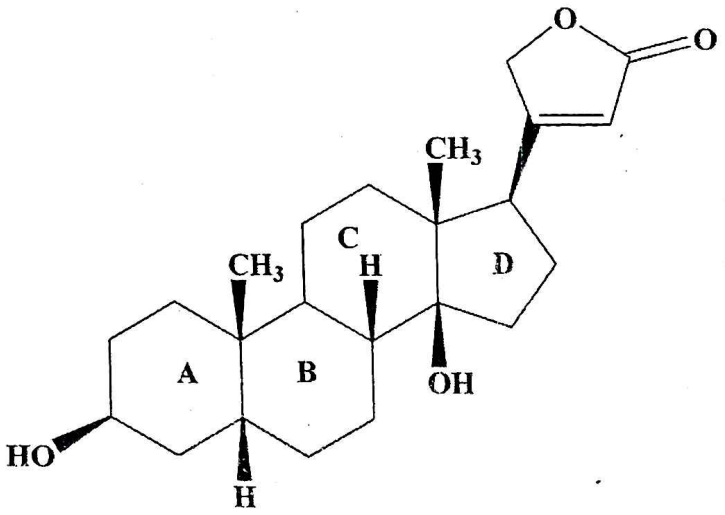
- ✓ Unsaturated lactone ring at C-17.
- ✓ Lactone must be in the β-configuration.

2. The configuration of the cycles:

- ✓ The activity maximized when the A,B,C, and D rings are in cis-tans-cis configuration
- ✓ The activity is greatly diminished when the A and B rings are trans fused (Uzarigenin).
- ✓ The C and D rings must be cis fused.

3. The substituents:

- ✓ The OH group at C-3 and C-14 must be in the β-configuration. α-configuration at C-3 diminishes the activity, but 3-deoxy compounds are nor completely inactive.
- ✓ α-C-14 configuration is inactive.



Digitoxigenin (H-5 beta)
Uzarigenin (H-5 alpha)

Distribution

Cardenolides are most common in Apocynaceae, Asclepiadaceae, Liliaceae, Scrophulariaceae, Ranunculaceae, Moraceae, Euphorbiaceae and Tiliaceae. The bufadienolides occur in Liliaceae and Ranunculaceae.

Physico-chemical properties:

1. Glycosides are fairly soluble in water and slightly soluble in ethanol and chloroform.
2. Sparingly soluble in ethyl acetate.
3. Digitoxin is more soluble in chloroform than digoxin.
4. Lactone ring is labile to open in an alkaline medium.

Hydrolysis of cardiac glycosides:

1. Acid hydrolysis:

The glycosidic linkages in these glycosides are cleaved by dilute acid hydrolysis breaking them down to sugar and aglycones, but the condition of conc. Acid damage the structure of the aglycone.

2. Reaction with alkaline: in the presence of the solution of alkali, the compound become inactive.

3. Enzyme hydrolysis: the present enzymes in many plants split the glycosides into a free sugar and secondary glycoside which contain less sugar.

General procedure for extraction of cardiac glycoside

Dried powdered drug

- Extraction with 50% ethanol
- Add 10% lead acetate.
- Boil then cool.
- Filter.

Residue

Filtrate

- Evaporate under vaccum.
- Extract the residue with $CHCl_3$ or CH_2Cl_2 in separating funnel.

Chloroform phase

TLC, HPLC

Non-Glu

Aqueous phase

Glucose

Mechanism of action:

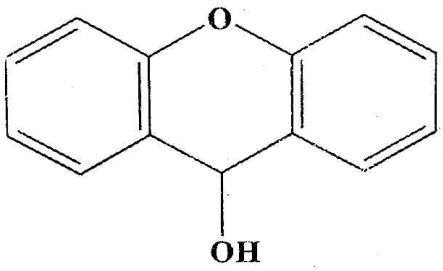
Act by inhibiting the Na+/K+ ATPase of the membrane of the myocard cells which increase Ca+2 cause increase force of contraction.

- **Chemical Identification of cardiac glycoside.**

A. color reaction of the sugar:

- Reaction with a xanthydrol (Pesez reaction)

Add xanthydrol to a glycoside solution in concentrated acetic acid, and heat in a water bath, of a red color is developed.



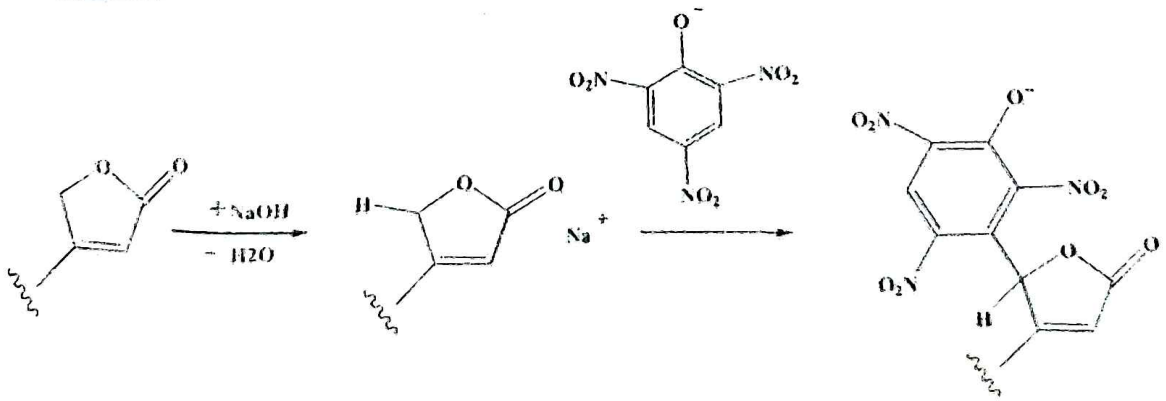
Xanthydrol

- Keller-kilani-reaction:

Dissolve the glycoside solution in concentrated acetic acid containing 2 drop of 5% ferric chloride solution. Carefully transfer sulfuric acid, a reddish-brown layer or ring forms at the junction of the liquids and the upper layer slowly becomes blue-green; darkening with standing.

B. Color reaction of the aglycones:

- Baljet reaction (uses picric acid and yields an orangey color).



- Kedde reaction (use 3,5,-dinitrobenzoic acid and yields a radishviolet color).

- Raymond reaction: (use m-dinitrobenzene and yields a blue color).

Cardiac glycosides chief drugs

- **Cardenolide**

A- Purple foxglove (Digitalis purpura):

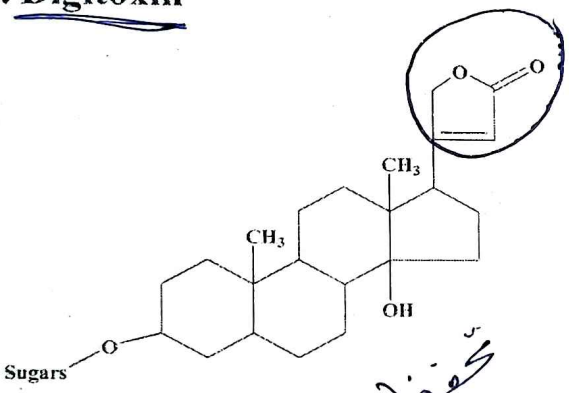
The drug consists of the dried leaves

B.N.: ***Digitalis purpurea***

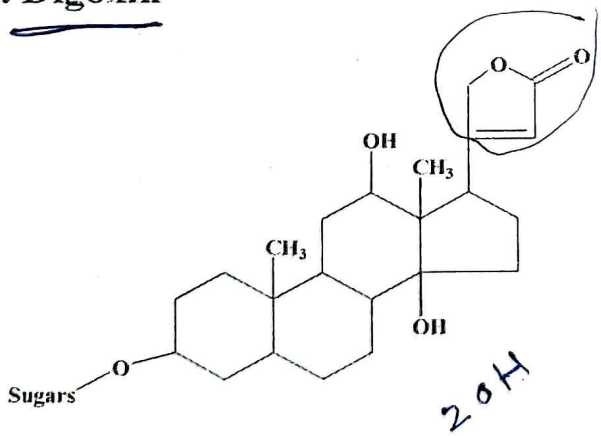
Family: Scrophulariaceae.

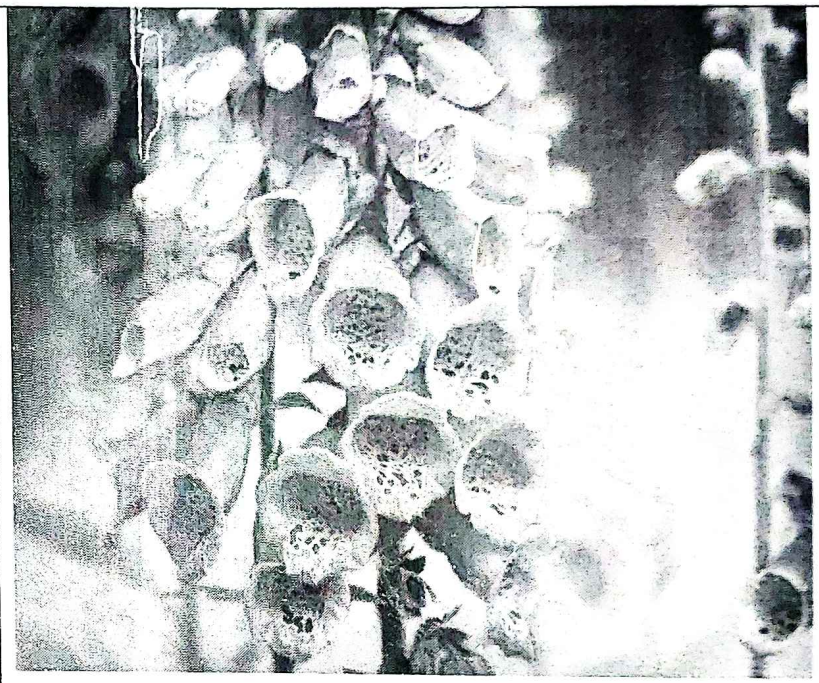
Active constituents:

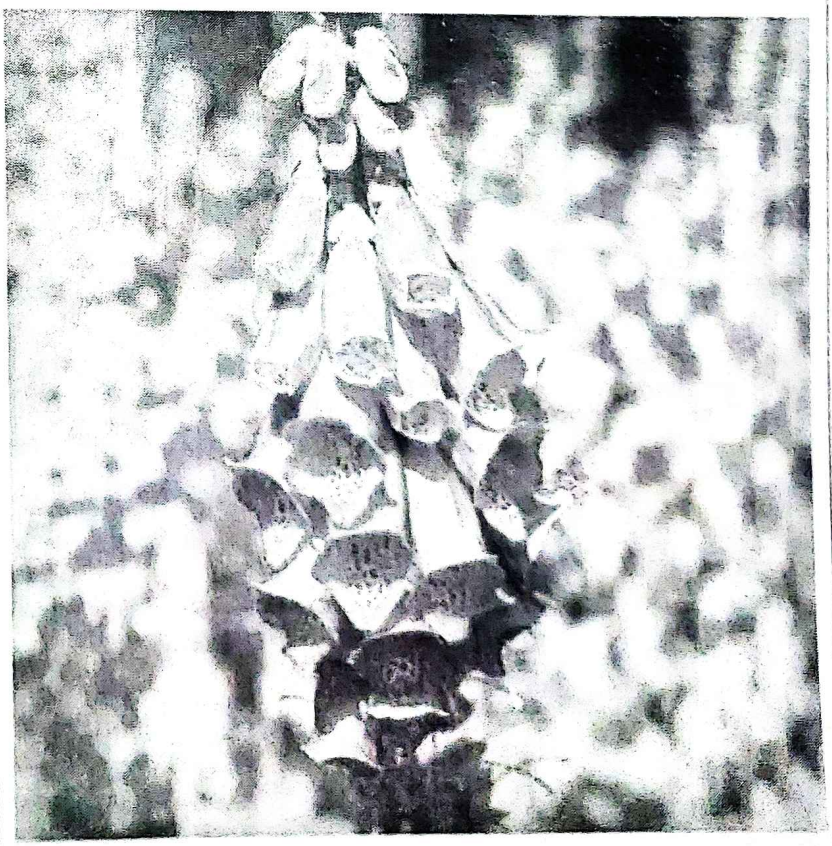
. Digitoxin



. Digoxin







Uses:

1. Congestive heart failure.
2. Diuretic.

B- Grecian foxglove:

The drug consists of the dried leaves

B.N.: ***Digitalis lanata***

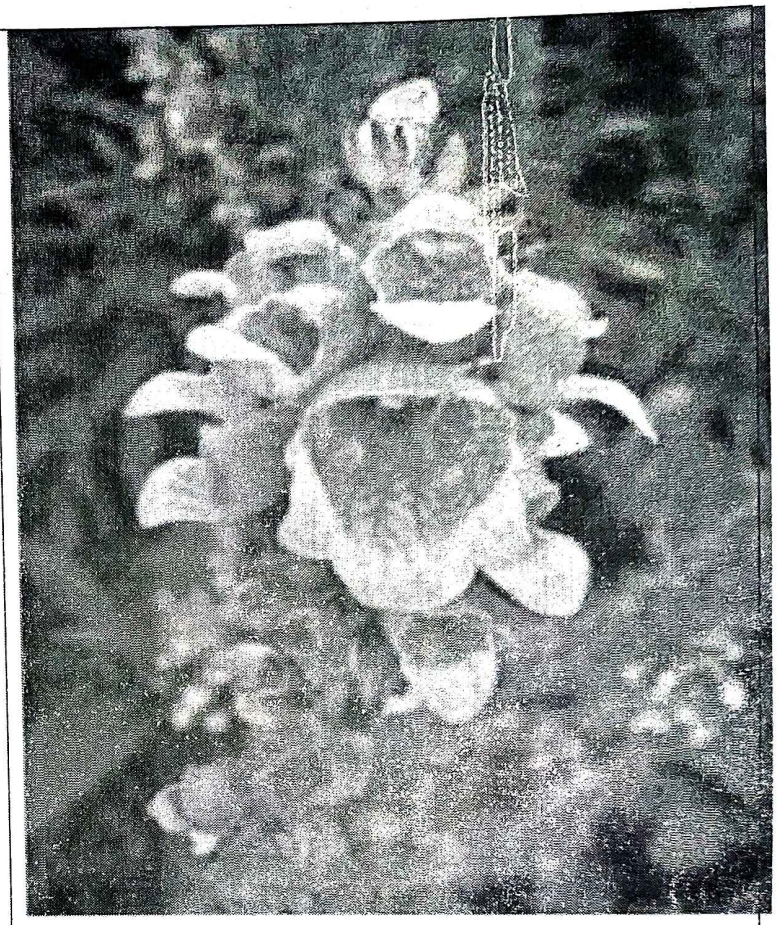
Family: Scrophularlaceae).

Active constituents:

Lanatoside A, B, C, D, E.

Uses:

1. Congestive heart failure.
2. Diuretic.



C- Strophanthus

i- Strophanthus kombe

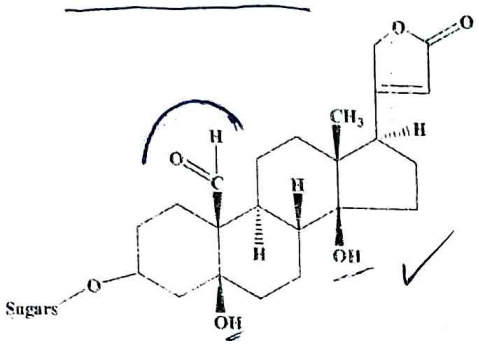
The drug consists of the seeds

B.N.: ***Strophanthus kombe***

Family: Apocynaceae).

Active constituents:

k- Strophanthoside,



k- Strophanthin-β and cymarin.

Uses:

1. Congestive heart failure.
2. Diuretic.

ii- **Strophanthus gratus**

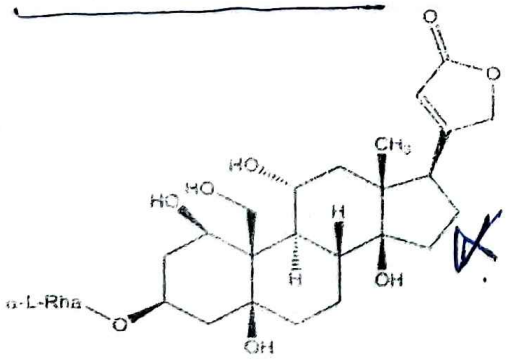
The drug consists of the seeds

B.N.: ***Strophanthus gratus***

Family: Apocynaceae).

Active constituents:

g-Strophanthin (Ouabain)



Uses:

1. Congestive heart failure.
2. Heart tonic.

D- Convallaria

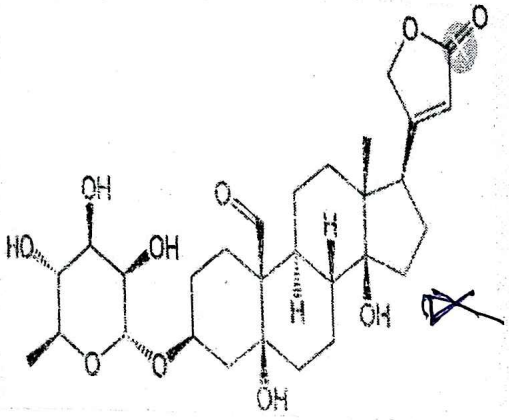
The drug consists of the herb.

B.N.: ***Convallaria majalis***

Family: Liliaceae.

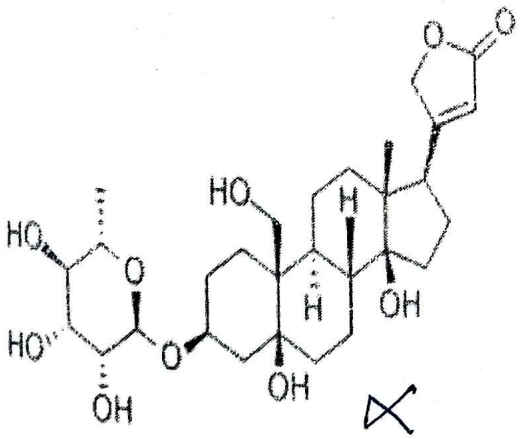
Active constituents:

Convallatoxin,



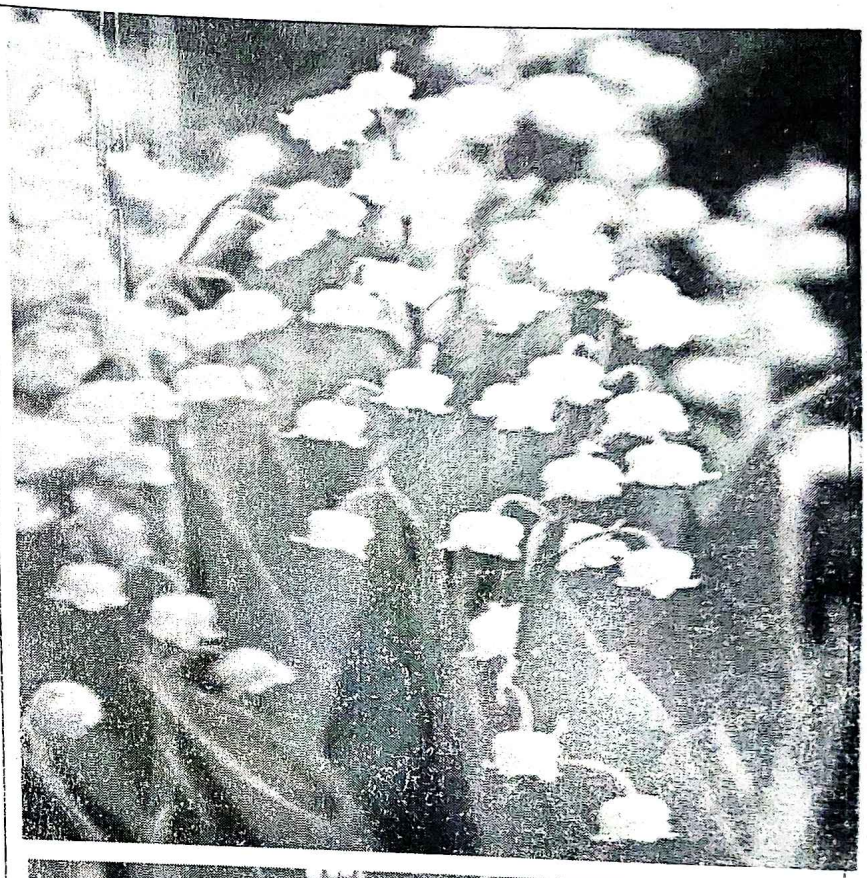
Convalloside

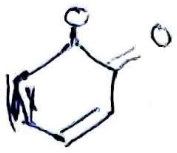
and Convallatoxol.



Uses:

1. Congestive heart failure.
2. Diuretic.





❖ **Bafadienolides**

They are less widely distributed in nature than are the cardenolides. They are found in some Liliaceae and Rananculaceae and in the toad venom.

They are little use as cardio active drugs because of their low therapeutic index and their production of side effects.

Squill (white squill)

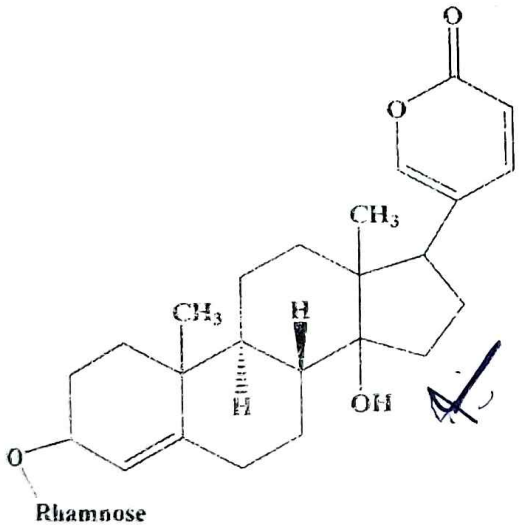
Squill consists of the dried sliced bulbs

B.N.: ***Urginea martitime***

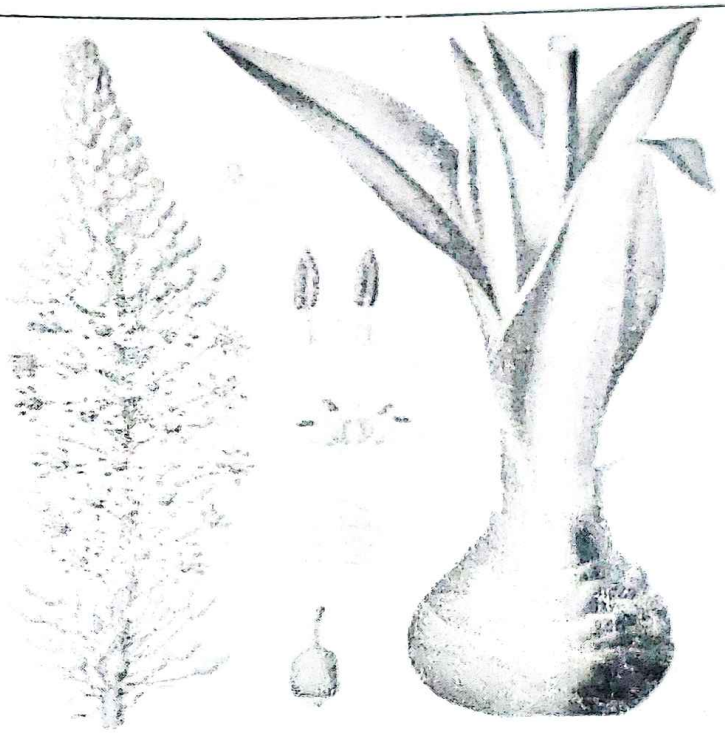
Family: Liliaceae.

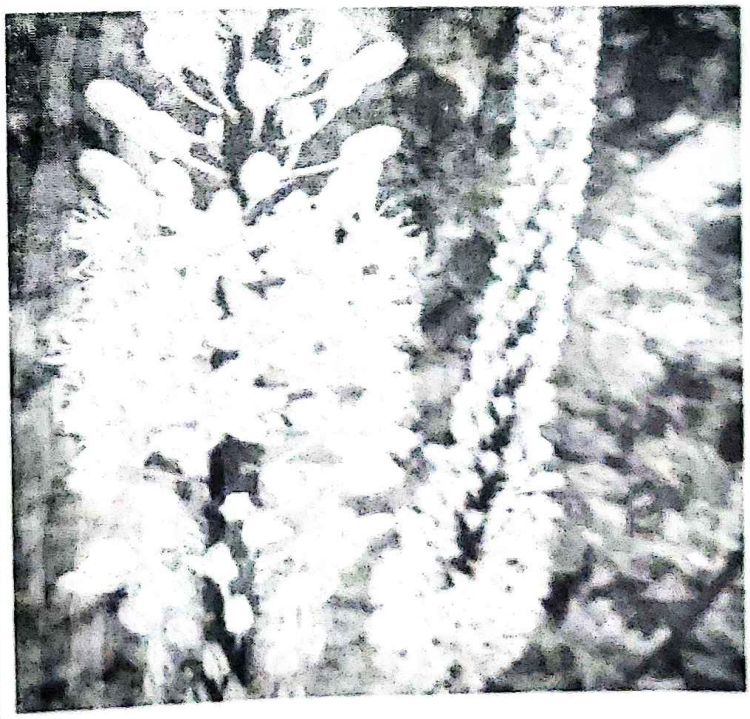
Active constituents:

Glucoscillaren A, scillaren A and proscillaridin A.



Proscillaridin A



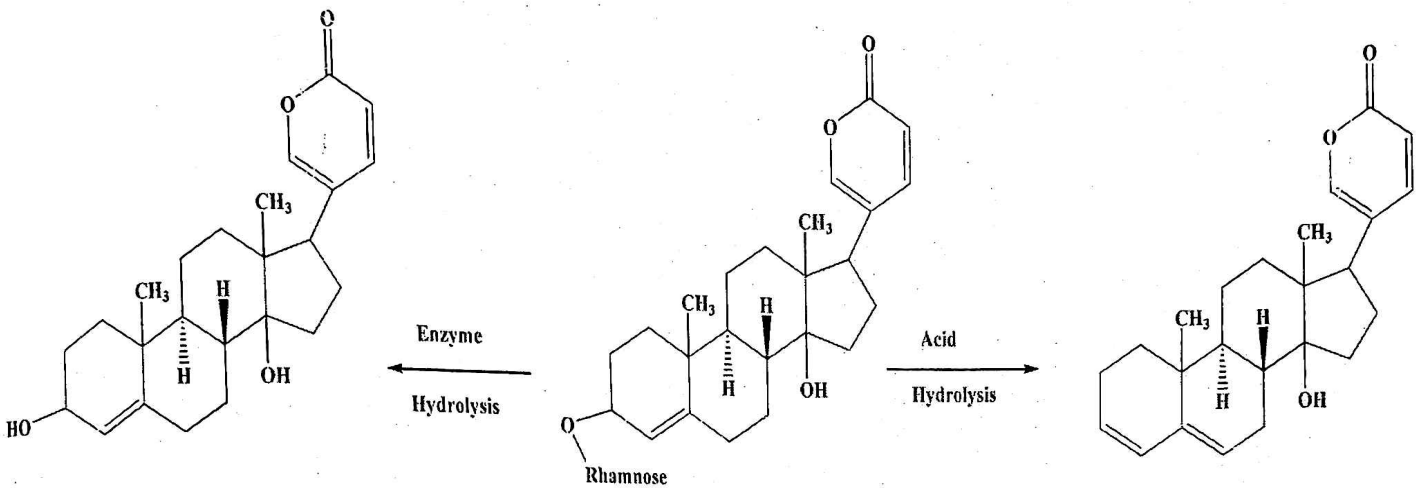


Uses:

1. Congestive heart failure.
2. Herat tonic.

Hydrolysis

- **Acid hydrolysis of** proscillaridin A give scillaridin A
- **Enzyme hydrolysis of** proscillaridin A give scillarenin.



Scillarenin Proscillaridin A Scillaridin A

Chemical test:

Scillaren A with acetic anhydride and H_2SO_4 develop a blood red color changing gradually to blue and finally bluish green.

Saponins glycosides

Definition

Saponins are glycosidic compounds. They are characterized by their surface-active properties and are generally soluble in water, giving stable foams. They name saponin comes from the Latin word sapo (soap) which explain the centuries-old use of saponin-containing plants such as ***Saponaria officinalis*** for their detergent action. Saponins have the ability to haemolyse red blood cells.

Classification of saponins:

1. Steroidal saponins.
2. Triterpenoid saponins.
3. Steroidal alkaloidal saponins.

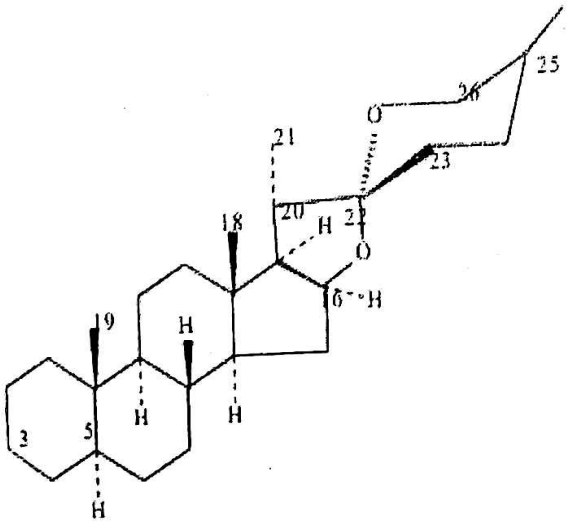
Steroidal saponins.

Structure of Steroidal saponins:

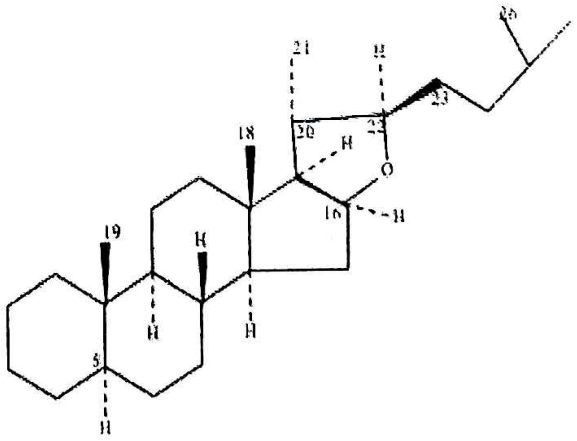
Structure of aglycone

1. Steroidal glycosides:

Steroidal a glycones all possess a skeleton of 27 C-atom, which generally comprises sex rings.

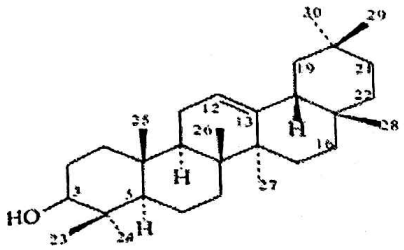


5α-spirostane

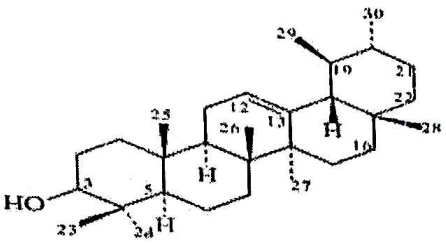


5β-furostane

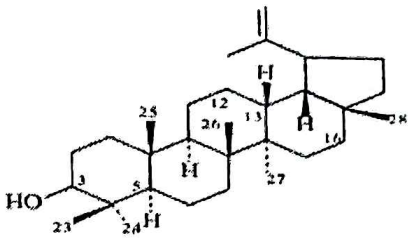
2. Triterpene glycosides:



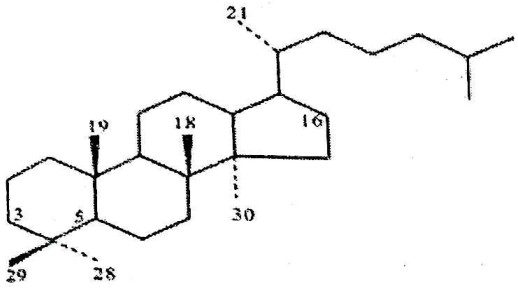
Oleananes



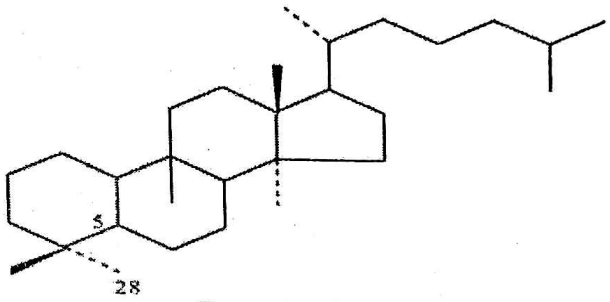
ursanes



lupanes



Dammarane



Cucurbitane

Structure of the glycosides

Aglycone attached to one or more sugar chains. The chains may be linear or branched. The sugar is D-glucose, D-galactose, D-glucuronic acid, Larabinose, L-rhamnose, D-xylose, D-fucose.

Characterization:

1. Haemolysis:

Saponins have ability to rupture erythrocytes.

2. Forth test:

Drugs containing saponins give persistent froth (foam) when shaken with water.

3. Color reaction and thin layer chromatography:

Use vanillin or anisaldehyde in the presence sulfuric acid reagent.

Physico-chemical properties:

- High polarity.
- Relative fragility.
- Soluble in water.

General procedure for extraction of saponins

Dried powdered plant material

① Defat with hexane or petroleum ether

Hexane or petroleum ether extract contains fats, waxes and chlorophylls.

Marc

② Extract withe methanol or ethanol or Eth.OH/H_2O.

Methanol extracts

Marc (discard)

- **Concentrate with rotary evaporator at 40-30 C°.**
- **Partition with H_2O and butanol.**

③

Aqueous phase

④

Butanol phase

Addition of Diethyl ether

Precipitation of crud saponin

TLC, HPLC

Chief saponins containing drugs:

1- Saponin-containing drugs as expectorant and anti-tussive

A- Liquorice لیکوریس

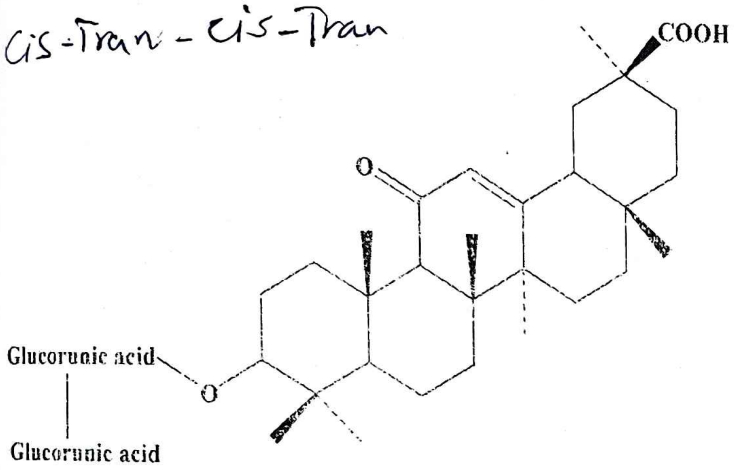
B.N. *Glycyrrhiza glabra*

Family: Leguminosae

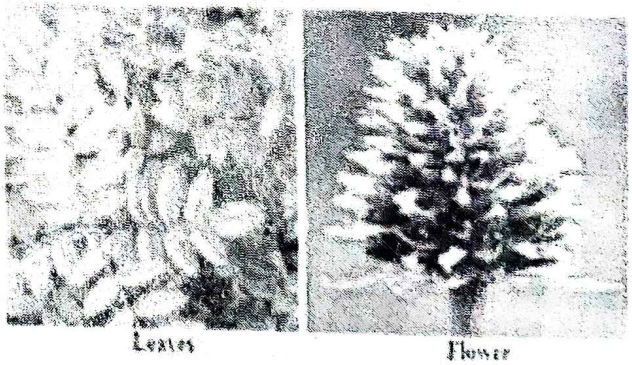
Active constituent:

Glycyrrhizin and Glycyrrhizinic acid

Cis-Tran - Cis-Tran



Glycyrrhizin



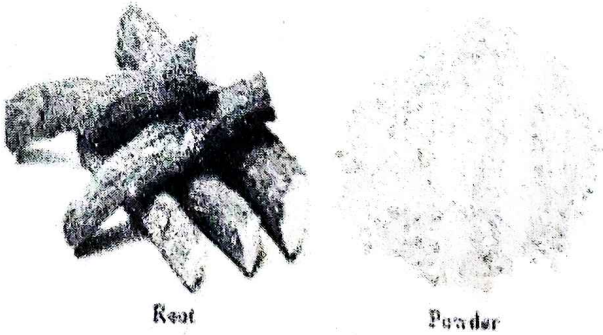


Figure 1: Leaves, flower, root and powder of *Glycyrrhiza glabra*

Main uses:

1. Mild expectorant.
2. Rheumatoid arthritis.
3. Addison's disease.
4. Inflammatory condition.
5. Spasmolytic.
6. Anti-ulcer activity.

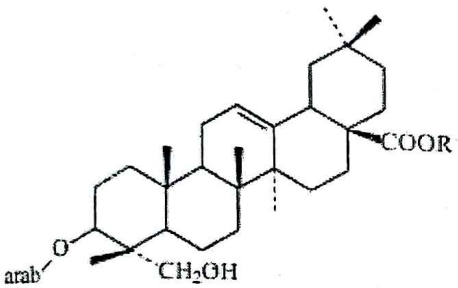
B- Leaves of Ivy

B.N. *Hedera helix*

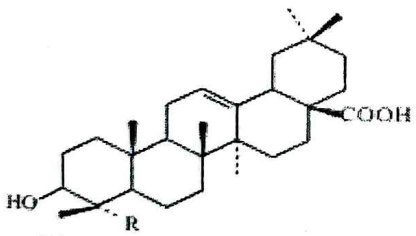
Family: Araliaceae

Active constituent:

1. Oleanolic acid.
2. Hederagenin.
3. Hederacoside C.
4. α-hederin.



Hederacoside C: R= Glu-Glu-Rham
α-hederin: R= H



Oleanolic acid: R= CH_3
Hederagenin.: R= CH_2OH

Uses:

- Treatment of cough.
- Acute benign bronchial disease
- Use in cosmetic products, creams, lotion and shampoos and to treatment of skin disorder.

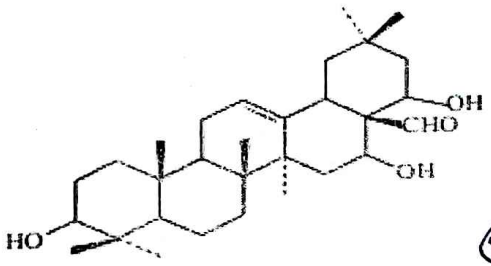
C- Primrose زهرة الربيع

B.N. ***Primula veris***

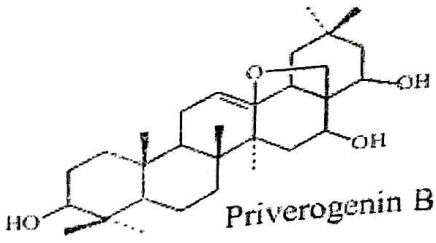
Family: Primulaceae

Active constituent:

Priverogenin A and B.



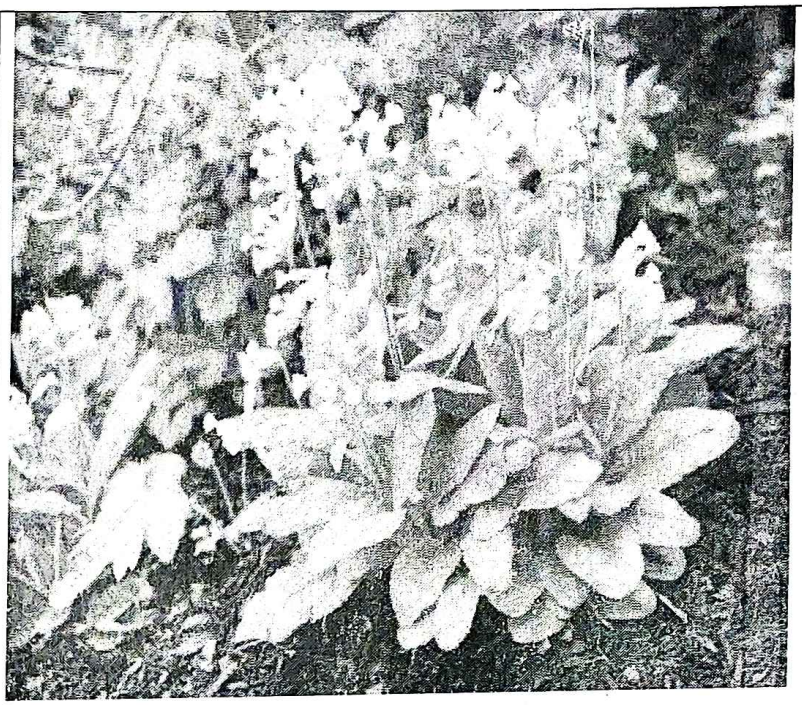
Priverogenin A



Priverogenin B

Uses:

Treatment of cough.



2- Saponin-containing drugs as Adaptogens

A- Ginsing

B.N. ***Panax ginseng***

Family: Araliaceae

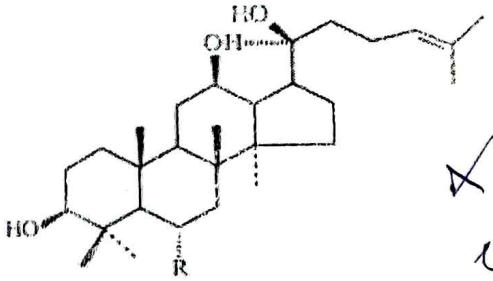
Active constituent:

Protopanaxadiol

Panaxadiol

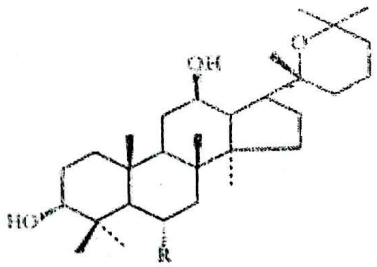
Protopanaxatriol.

Panaxatriol.



R= H: Panaxadiol

R= OH: Panaxatriol

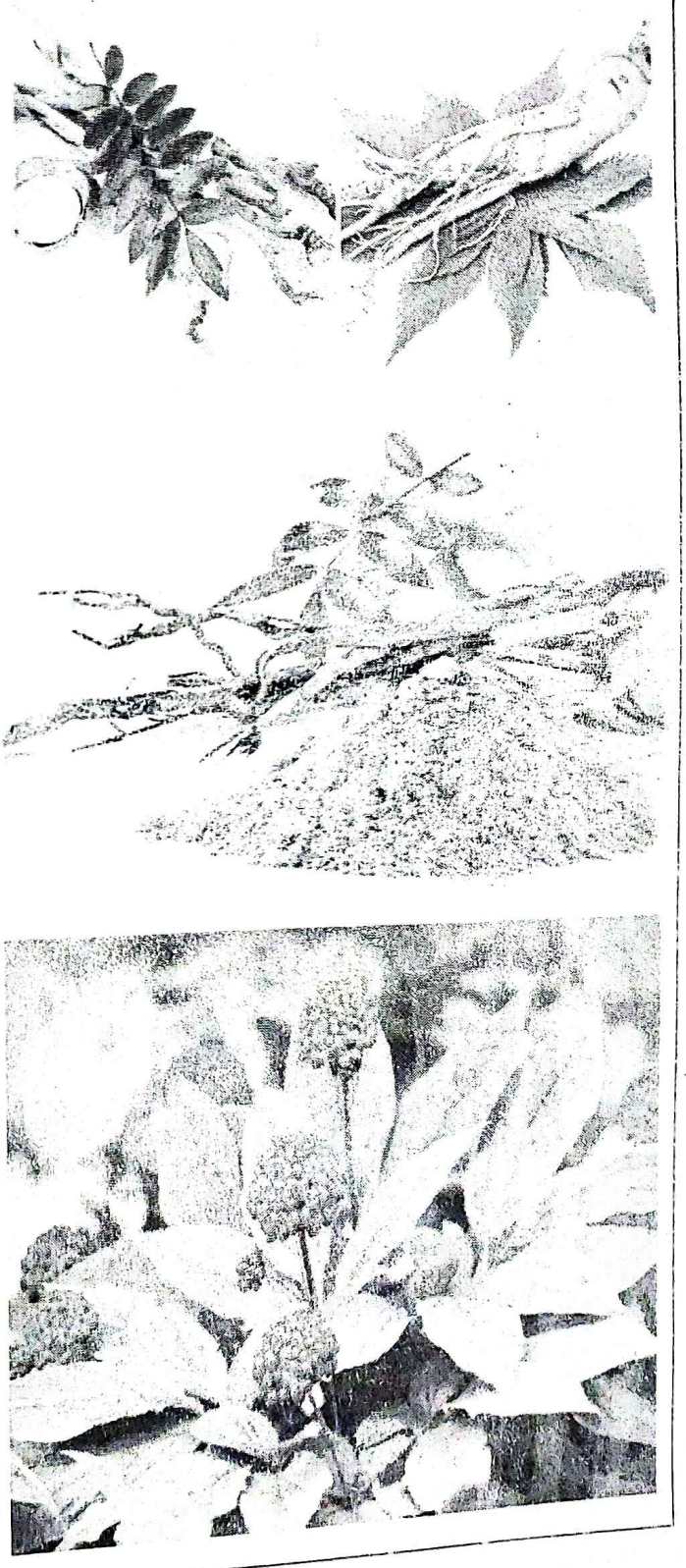


R=H: Protopanaxadiol

R=OH: Protopanaxatriol

Uses:

- CNS stimulant to increase resistance to fatigue and stress.
- Improve memory (use as adaptogen).
- Treatment of functional asthenia.
- Treatment of anemia, diabetes and sexual impotence.



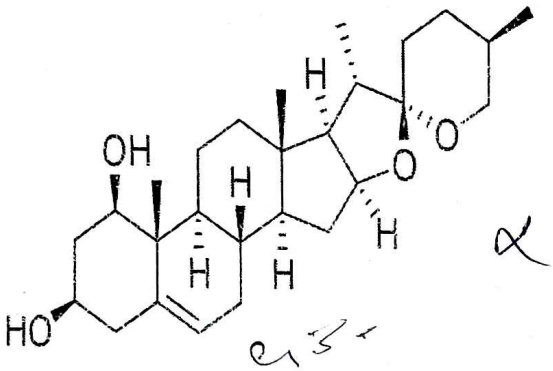
B- Butcher's Broom

B.N. *Ruscus aculeatus*

Family: Liliaceae

Active constituent:

Ruscogenin



Uses:

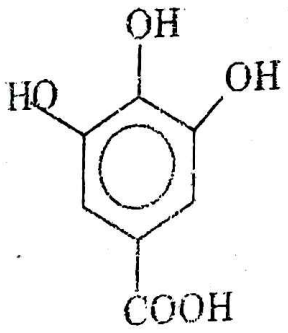
- Anti-inflammatory activity.
- Produce diminished capillary permeability.
- Vasoconstriction effect in the peripheral blood vessels.

Definition

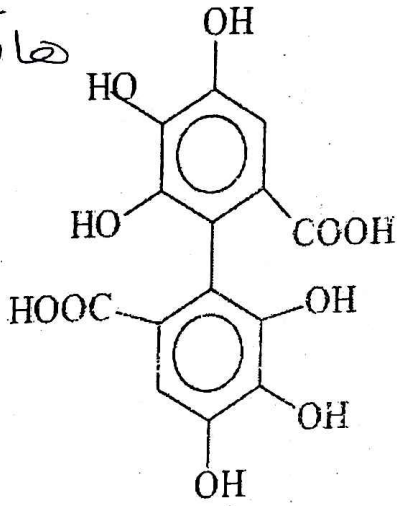
Tannins are phenolic compound of high molecular weight. They are able to combine with protein of animal hide, prevent their putrefaction and convert them into leather.

Classification of Tannins: -

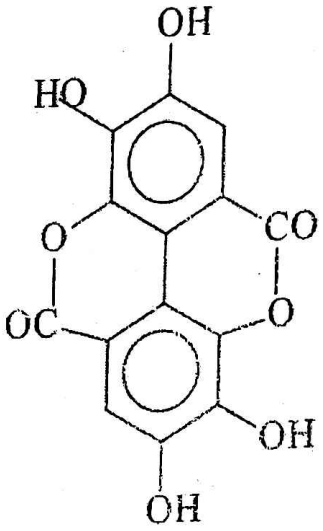
1. Hydrolysable tannins: They may be hydrolyzed by acids or enzymes such as tannase. e.g. gallic acid and ellagic acid.



Gallic acid

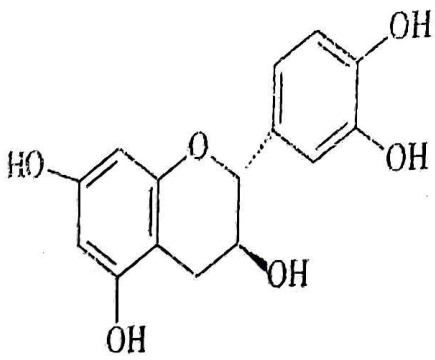


Hexahydroxydiphenic

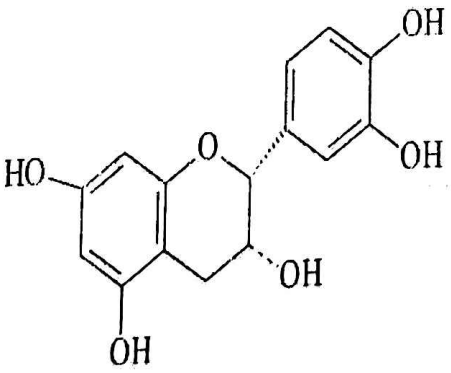


Ellagic acid

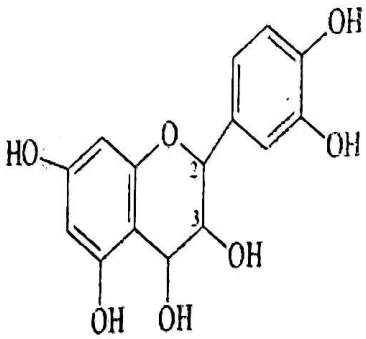
2. Condensed tannins (proanthocyanidins): unlike hydrolysable tannins these are not readily hydrolyzed to simpler molecules and they do not contain sugar moiety.



(+)-Catechine



(-)-Epocatechine



Falvan-3,4-diol

3. **Complex tannins:** this group of tannins is biosynthesized from both hydrolysable tannin and condensed tannins.

4. **Pseudo tannins:** they are compounds of lower molecular weight than true tannins and they do not respond to the goldbeater's skin test.

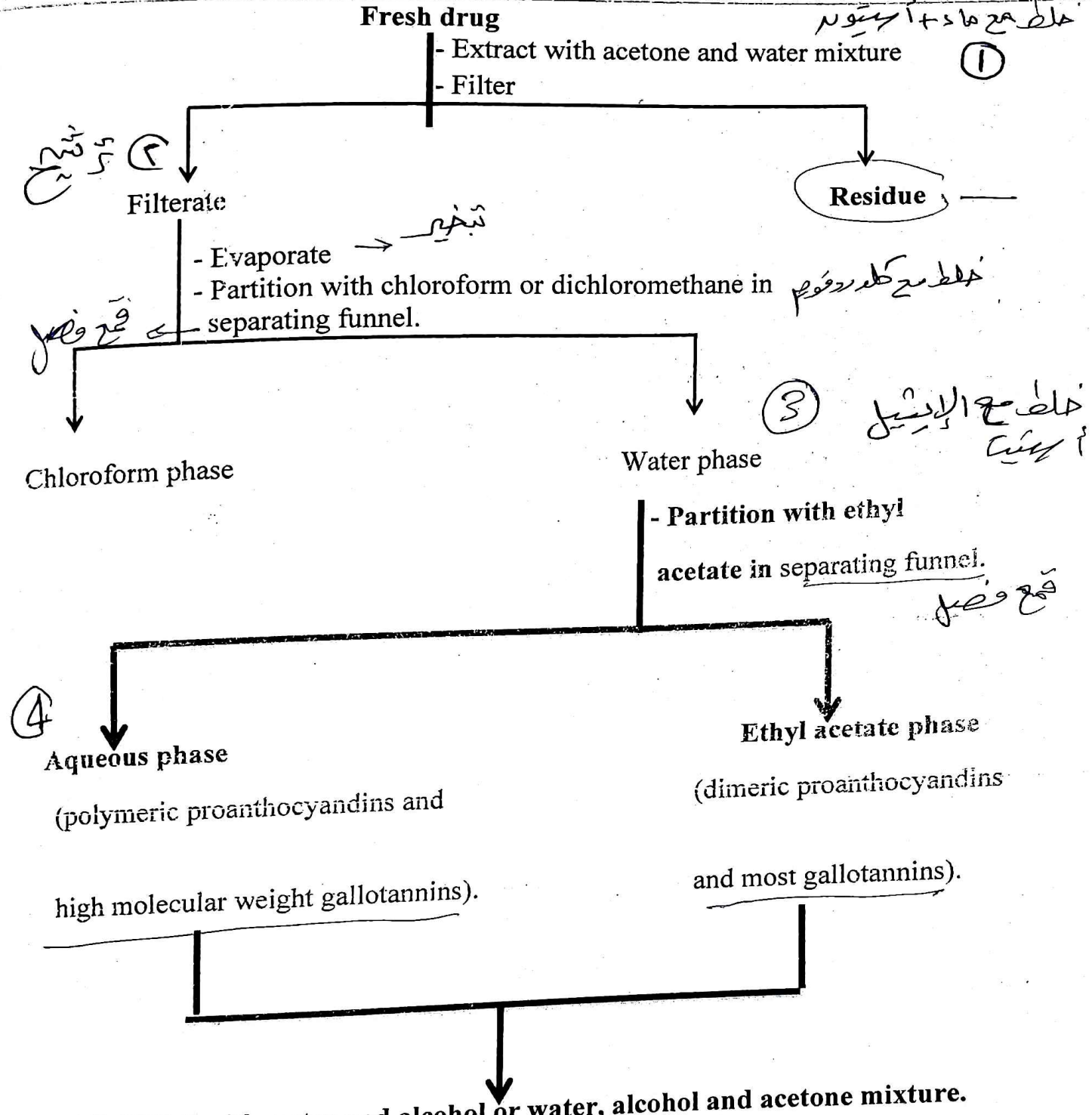
Physico-chemical properties:

1. Soluble in water, dilute alkalis, alcohols, glycerol and acetone but their solubility varies with their degree of polymerization.
2. Sparingly soluble in other organic solvent.
3. Solutions of tannins precipitate heavy metals, alkaloids and gelatin.
4. React with ferric chloride.
5. Precipitated by lead acetate solution and salt of copper and tin.

Chemical characterization

1. **with ferric chloride:** hydrolysable tannins give bluish-black color or precipitate, and condensed tannins give greenish-brown precipitate.
2. **Goldbeater's skin test.**
3. **Gelatin test:** solution of tannins precipitate gelatin.
4. **Phenazone test:** all tannins are precipitated, the precipitate being bulky and often colored.
5. **Potassium iodate:** gallotannins give a pink color and free gallic acid gives an orange color with this reagent.
6. Ellagitannins are colored by nitrous acid in the presence of acetic acid (pink at first, the color turns purple, then blue).
7. **Condensed tannins** trun red with vanillin and HCl acid.

General procedure for extraction of tannins



Biological properties:

1. **Antidiarrhoeal activity.**
2. **Antidotes in poisoning by heavy metals, alkaloids and glycosides.**
3. **Antioxidants.**

Drugs containing tannins

1- Galls الحفص

B.N. *Qurecus infectoria*

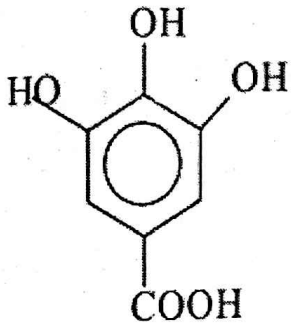
Family: Fagaceae

Active constituent:

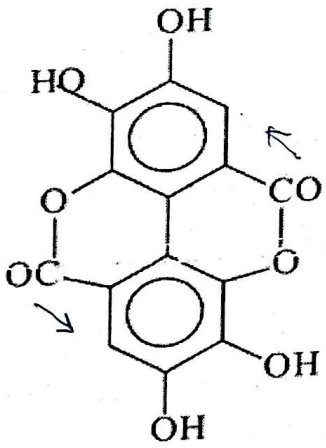
Hydrolysable tannins:

1 - Gallotannic acid.

2- Gallic acid

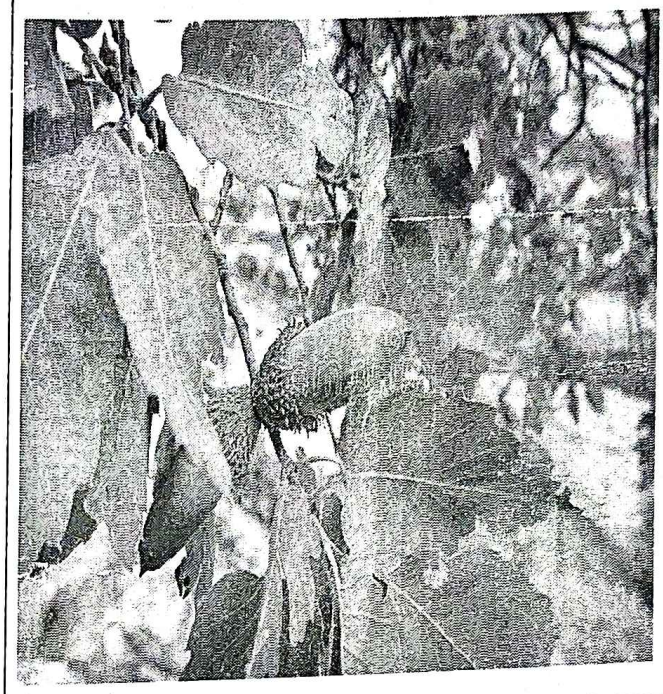


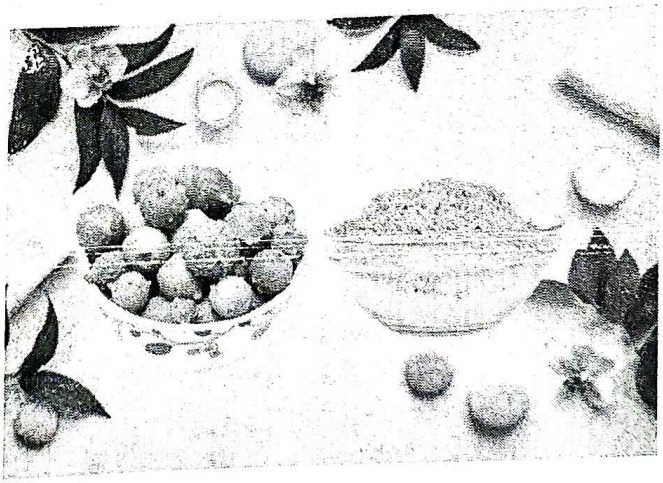
3- Ellagic acid.

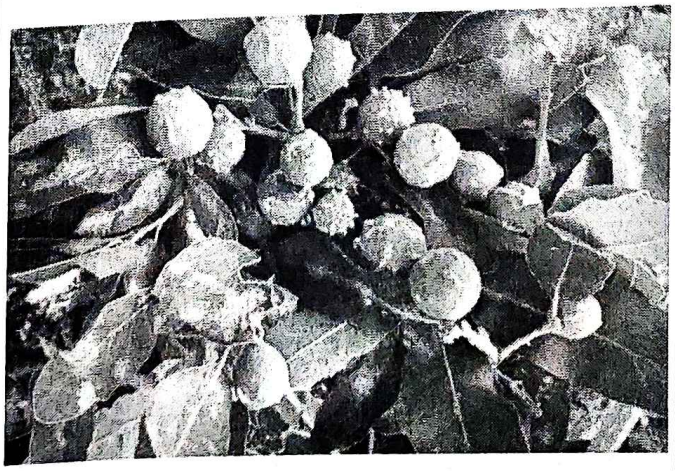


Uses: إيقاف النزيف

1. Hemostatic agents (boil one spoonful of powder in 200ml of water for 30 min, take 50ml/1).
2. In the manufacture of ink.
3. Astringent used for burns and dermatitis.
4. Source of tannic acid.







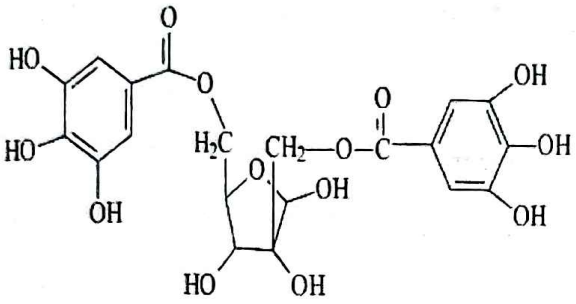
2- Hamamelis

B.N. *Hamamelis Virginia*

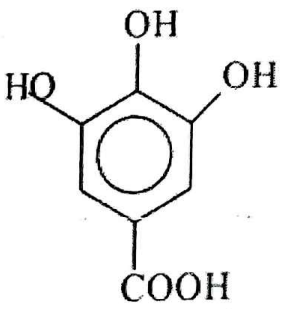
Family: Hamamelidaceae

Active constituent:

1- Hamamelitannin.

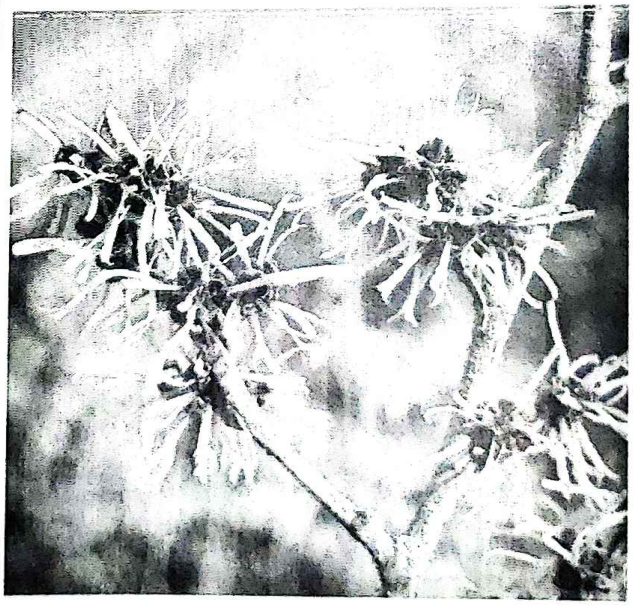


2- Gallic acid.



Uses:

1. Astringent. قابض
2. Homeostatic for nasal and rectal موقف نزيف bleeding (hemorrhoids).
3. Sprains, bruises and superficial الكدمات والإلتواءات wound. جرح سطحي



3- Guava

B.N. Psidium guajava

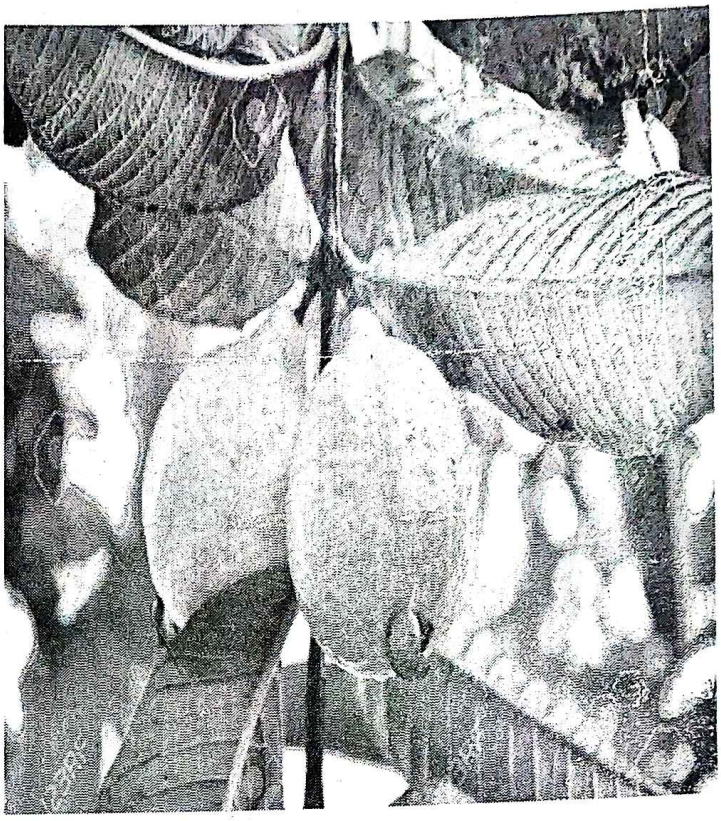
Family: Myrtacea

Activeconstituent:

Tannins, vitamins B and C.

Uses:

1. Anticough.
2. Antidiarrhoea.
3. Treatment toothaches by pounded, squeezed leaves in salt water and use solution.
4. Treat indigestion by use infusion of leaves and roots.



4- Tormentil

B.N. *Potentilla erecta*

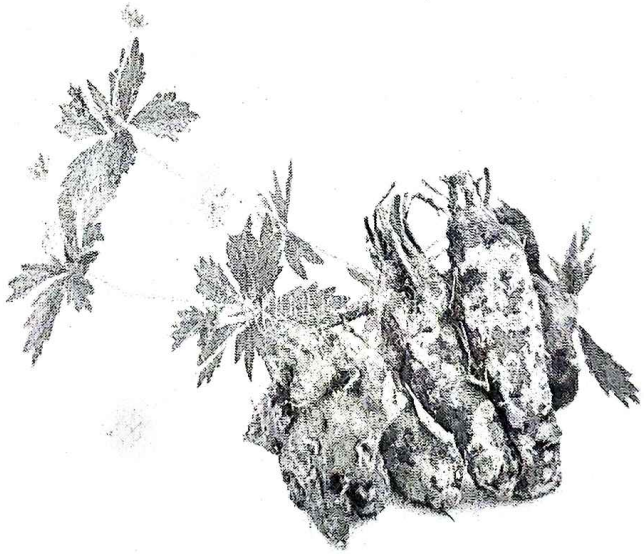
Family: Rosaceae

Active constituent:

Condensed tannins (agrimonin).

Uses:

1. **Astringent.**
2. Anti-diarrhea.
3. Antibacterial properties.
4. Gingivitis, stomatitis and angina.

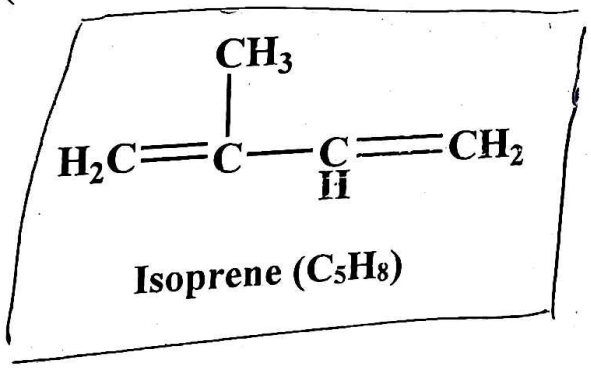


Terpenoids are diverse widely spread numerous classes of natural products, which are derived from a common biosynthetic pathway based on mevalonic acid as a parent.

The terpenoids were divided according to the number of isoprene units into eight classes:

التعريف
التقسيم

1. **Hemiterpenes** (1 - isoprene unit).
2. **Monoterpenes** (2- isoprene unit)
3. **Sesquiterpines** (3- isoprene unit).
4. **Diterpenes** (4- isoprene unit).
5. **Sesterterpenes** (5- isoprene unit).
6. **Triterpenes** (6- isoprene unit).
7. **Tetraterpenes** (8- isoprene unit).
8. **Polyterpenes** (more than 8- isoprene unit).



Isoprene (C_5H_8)

Monoterpenes

2 Isoprene

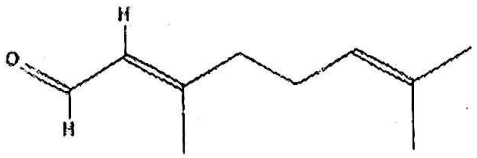
التعريف

Monoterpenes are **a class of terpenes that consist of two isoprene units and have the molecular formula $C_{10}H_{16}$.** Monoterpenes may be linear (acyclic) or contain rings (monocyclic and bicyclic). Modified terpenes, such as those containing oxygen functionality or missing a methyl group, are called monoterpenoids.

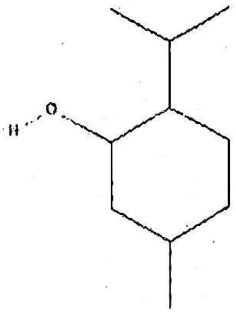
Some monoterpenes are **acyclic hydrocarbons (such as myrcene and ocimene) or their derivatives (such as linalool and geraniol)**, but cyclic monoterpenes and their derivatives (such as limonene, pinenes, camphor, alpha-terpineol, perillyl alcohol, carveol, carvone, and menthols) are more abundant in nature and have more.

- Monoterpenoids may be divided into three groups:

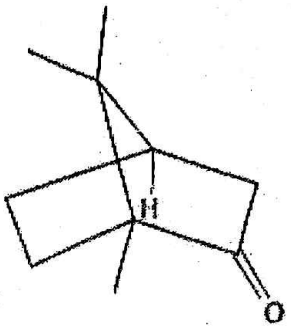
1. Acyclic monoterpenes. Example- citral.
2. Monocyclic monoterpenes. Example- menthol
3. Bicyclic monoterpenes. Example- camphor



Citral



Menthol



Camphor

Pharmacological properties:

Anti-bacterial, Anti-fungal, and Anti-cancer activities.

Extraction and characterization

1. The **extraction** is achieved with polar solvents (alcohols of various concentrations) and frequently an initial separation is obtained by partition water and other immiscible solvents.

2. The **fractionation** is done by chromatography on alumina or silica gel with polar eluents the purification is achieved using classic procedures (TLC and HPLC).

3. To **visualize** TLCs a non-specific reagent is used: vanillin in the presence of H_2SO_4.

Chief iridoid containing drugs

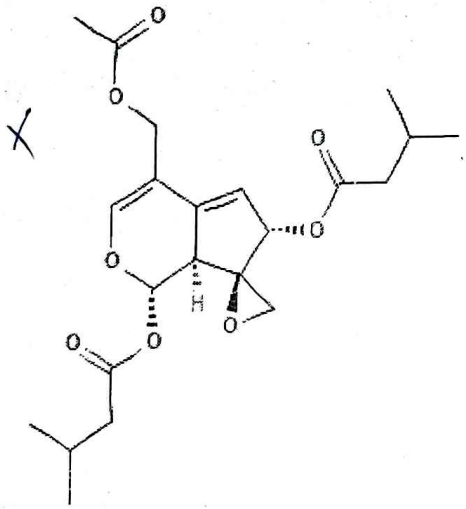
1- Valerian

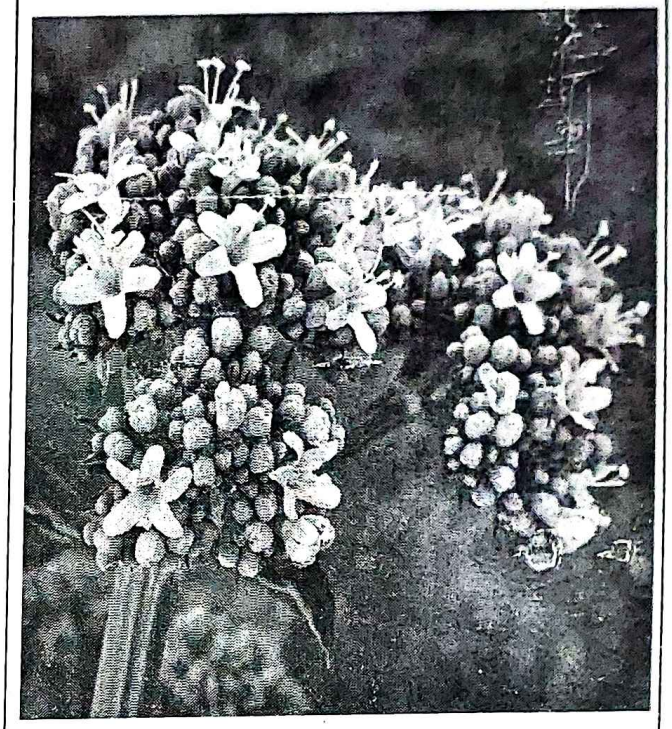
B.N. *Valeriana Officinalis*

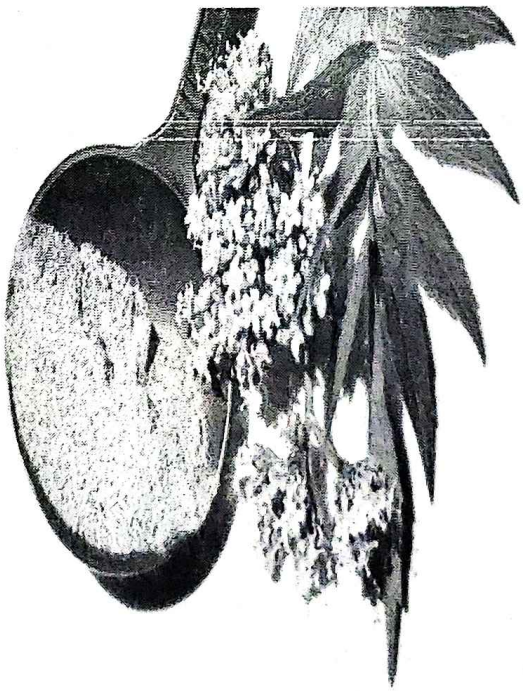
Family: Valerianaceae

Active constituents:

- Dihydrovaltrate
- Valtrate and acevaltrate







Action and uses:

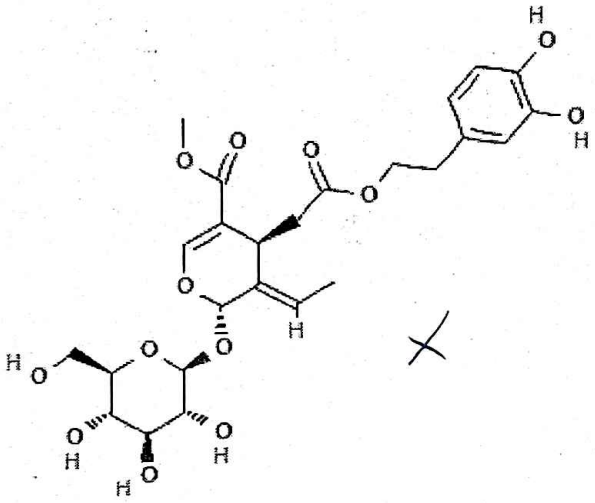
1. Hysteria and other nervous conditions.
2. Anxiety and restlessness.
3. Carminative.

B.N. *Olea europea*

Family: Oleaceae

Active constituents:

- Oleuropein.

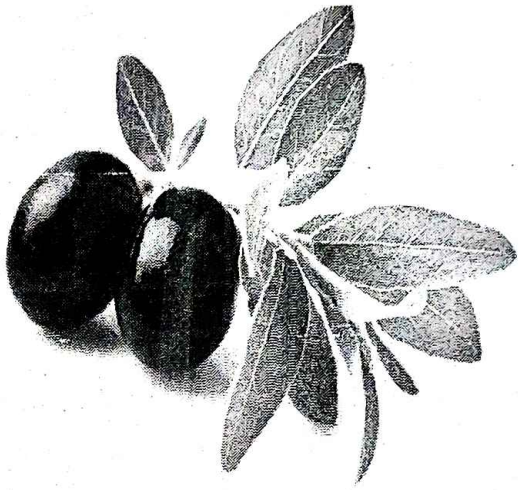


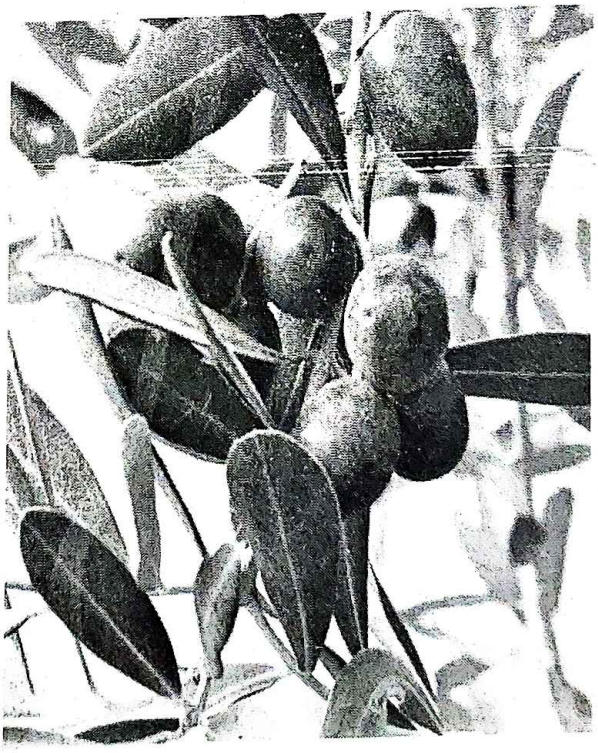
- Oleoside and **ligustroside.**

Action and uses:

1. Spasmolytic effect.
2. Causes dilating of blood vessels.

It supports the treatment of hypertension.





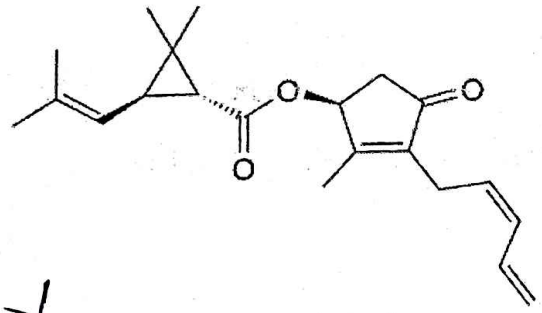
3- Pyrethrum (insect flower)

B.N. *Chrysanthemum cinerariifolium* and of *C. coccineum.*

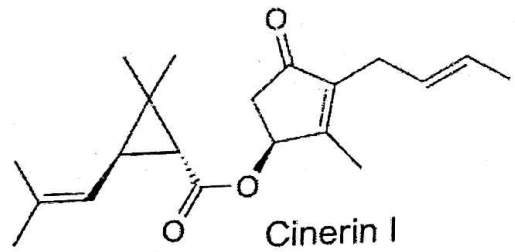
Family: Compositae

Active constituents:

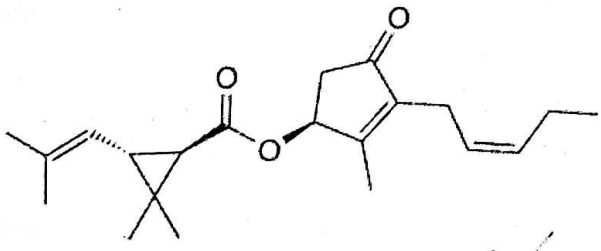
Monoterpene ester, the pyrethrins (pyrethrins I and II, cinerins I and II, and Jasmolins I and II).



Pyrethrin I



Cinerin I

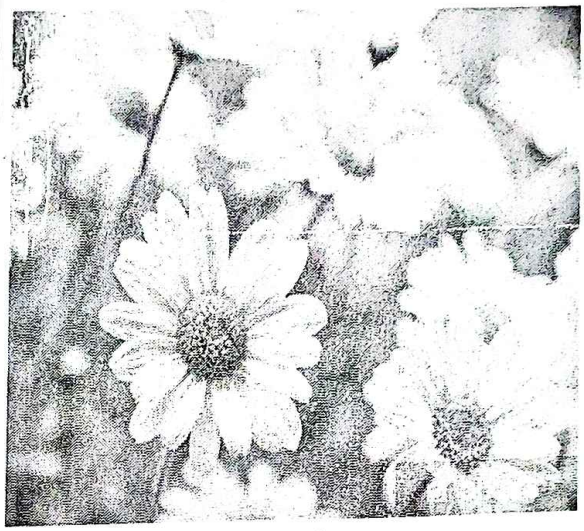


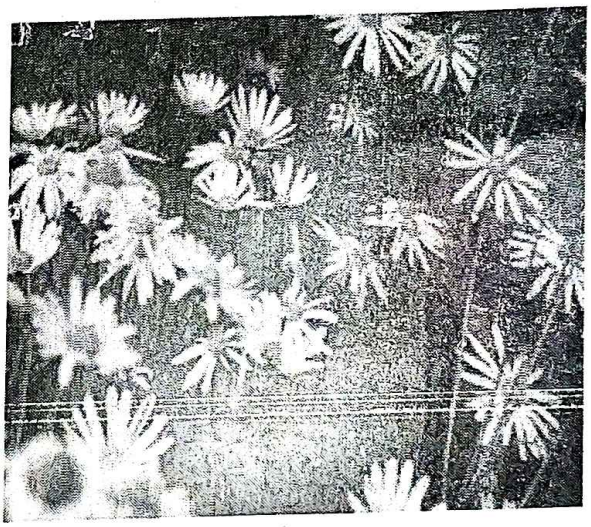
Jasmolin I

Action and uses:

- **Insecticidal.**

-They are also used in veterinary medicine to protect pets against parasites.





Sesquiterpenes

Sesquiterpenes are a class of terpenes that consist of three isoprene units and often have the molecular formula $C_{15}H_{24}$. Like monoterpenes, sesquiterpenes may be cyclic or contain rings, including many unique combinations. Biochemical modifications such as oxidation or rearrangement produce the related sesquiterpenoids

Sesquiterpenoids

Biosynthetic origin:

GPP + IPP ⇒ FPP

The Sesquiterpenes are formed by chain elongation of geranylpyrophosphate (GPP) with (IPP) unit isopentenylpyrophosphate to give Farnesylpyrophosphate (FPP), which represent the precursor of the **Sesquiterpenoids.** The biosynthesis of cyclic **Sesquiterpenoids** is based on the cyclization of FPP.

- Extraction and characterization

- There is no extraction method specific to sesquiterpenoid lactones. They can be extracted with **dichloromethane** or with of a mixture of **diethyl ether, petroleum ether** and **methanol** and the extraction can be fractionated by the appropriate chromatographic methods.

- Various reagents are available to visualize the TLC spots. Including **iodine vapors**, a **dilute solution of $KMnO_4$ and vanillin in the presence of HCl.**

The chief sesquiterpenes with potential activity

1-Gossypol

B.N. *Gossypum* species

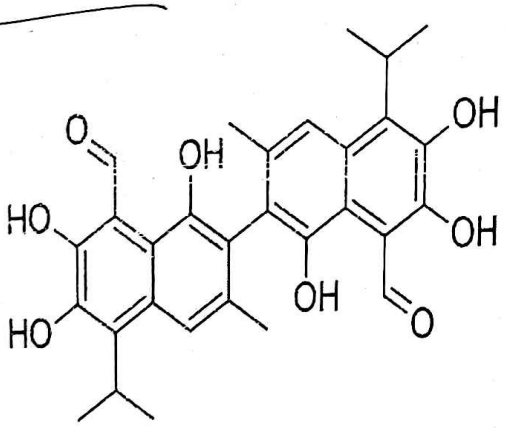
Family: Malvaceae

Geographical source:

Found on Tehamah, Lahj, Hujariyah, Hadiyah, Alujah, wadi Hari in the Haraz, Bayt alfaqih and Sana'.

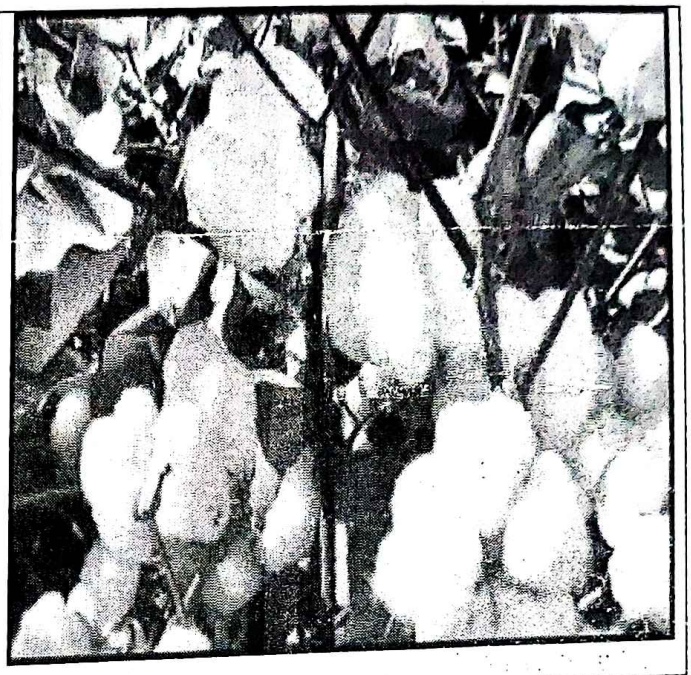
Active constituents:

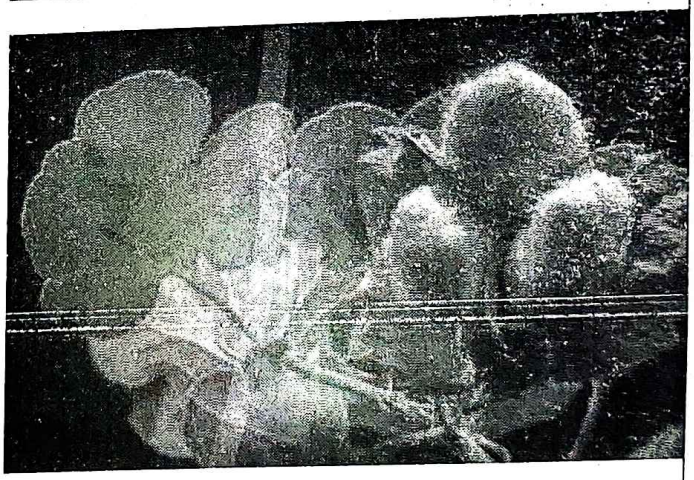
Gossypol.

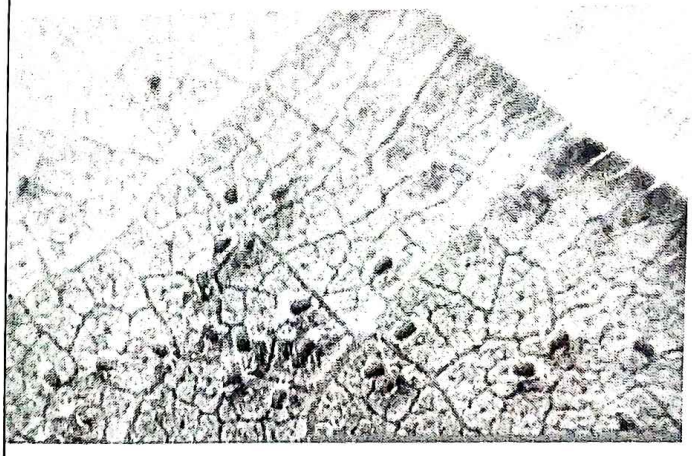


Uses:

—Anti-fertility agent.







Chief drug containing sesquiterpenoid lactones

1- Sweet wormwood (Rand)

B.N. *Artimisia annua*

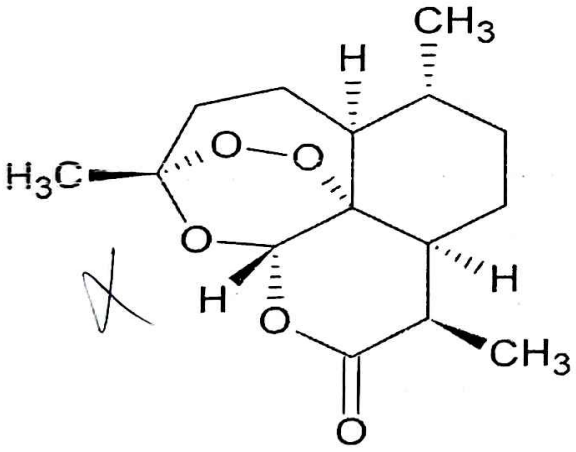
Family: Compositae

- Other species in Yemen:

Artimisia abyssinica: found in J. Nabi shu'ayb, J. Sabir, J. Ta'kar, J. Hubaysh, Manakhah and Shaharah

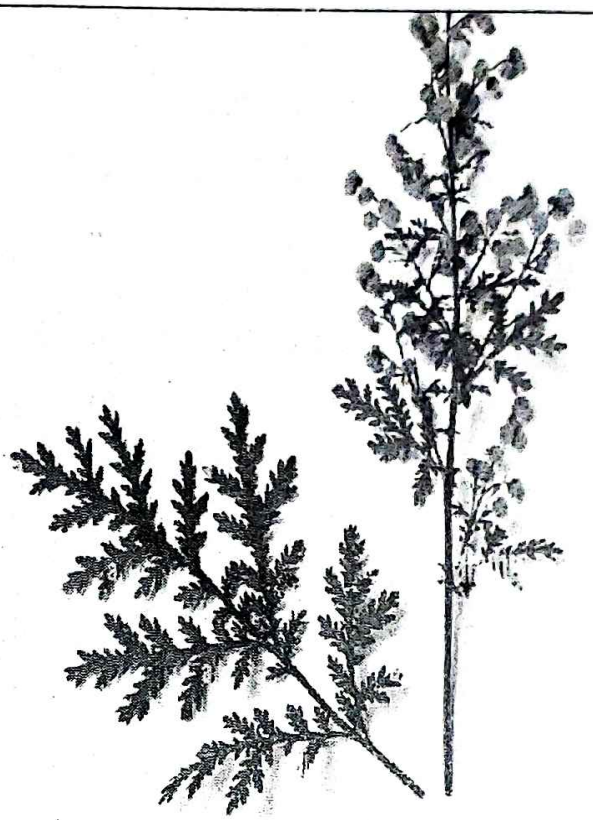
-Active constituents:

Artimisinin.



-Uses:

Anti-malarial activity.



Classification of diterpenes

Diterpenes can be classified into four main groups which are:

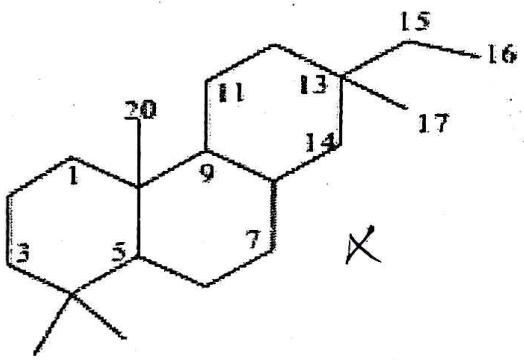
1-Aliphatic or acyclic diterpenes. Ex. The chain of phytol as unit in chlorophyll and as chain in vit.E.

2- Bicyclic diterpenes. Ex. Forskolin

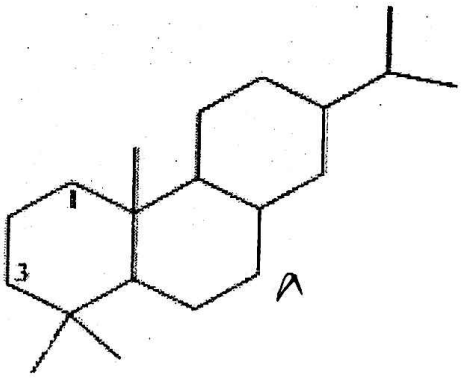
3-Tricyclic diterpenes which include two types

a- Pimarane type

b- Abietane type.



Pimaran-type

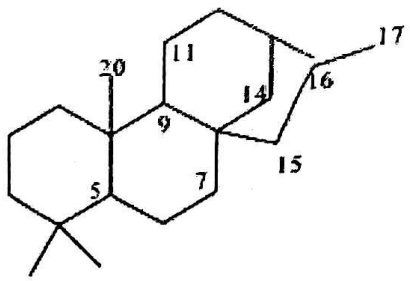


Abietan-type

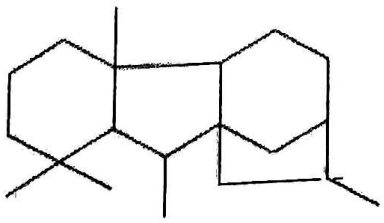
4-Tetracyclic diterpenes which include two types which are:

a- Kauran type.

b- Gibbane type.



Kauran-type



Gibbane-type

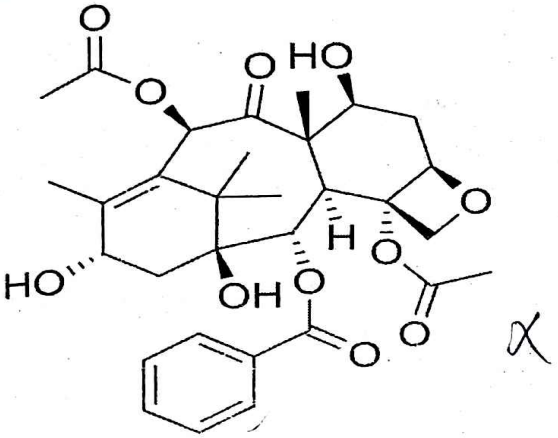
1- Yews

B.N. ***Taxus brevifolia***

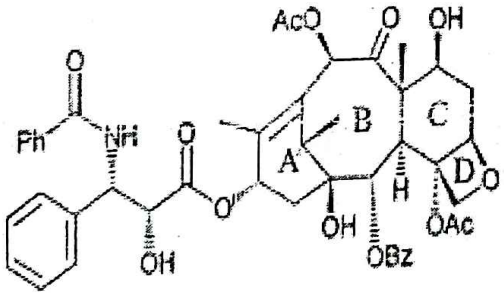
Family: *Taxaceae*

Active constituents:

Baccatin III, taxine A & B and taxol.



Baccatin III

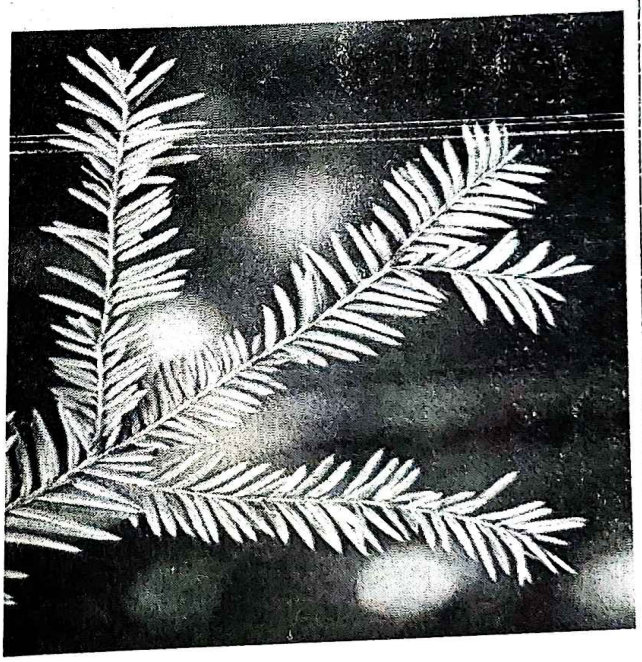


Taxol

Uses

1. Treatment of ovarian cancer.

2. Treatment of lung cancer and breast cancer



Triterpenoids

Pharmacological activities

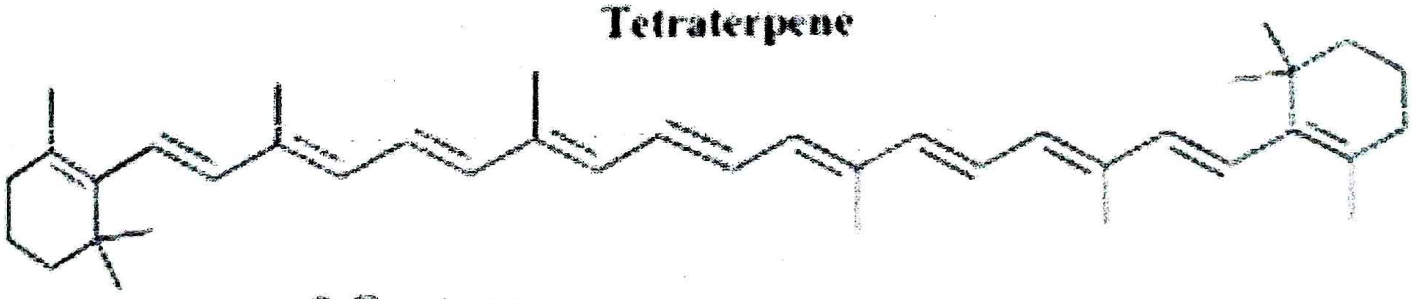
— Cytotoxic and anti-tumor activity. They are drastic laxative. In general, they have narrow therapeutic effect.

Tetraterpenes

Pharmacological activities

- Natural spice.
- β-caroten and other carotenoids are important as pro-vitamin A.
- The carotenoids can be converted into retinal and into vitamin A itself (retinol) by an intestinal cleavage enzyme.
- β-caroten is also important antioxidant which can afford protection against some form of cancer and other diseases.

Tetraterpene



β-Carotene
(Pigment, Provitamin A)

Chief carotenoids containing plants

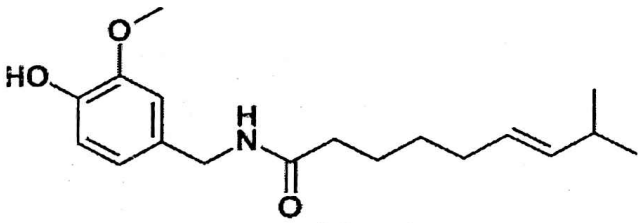
1- Capsicum

B.N. *Capsicum species*

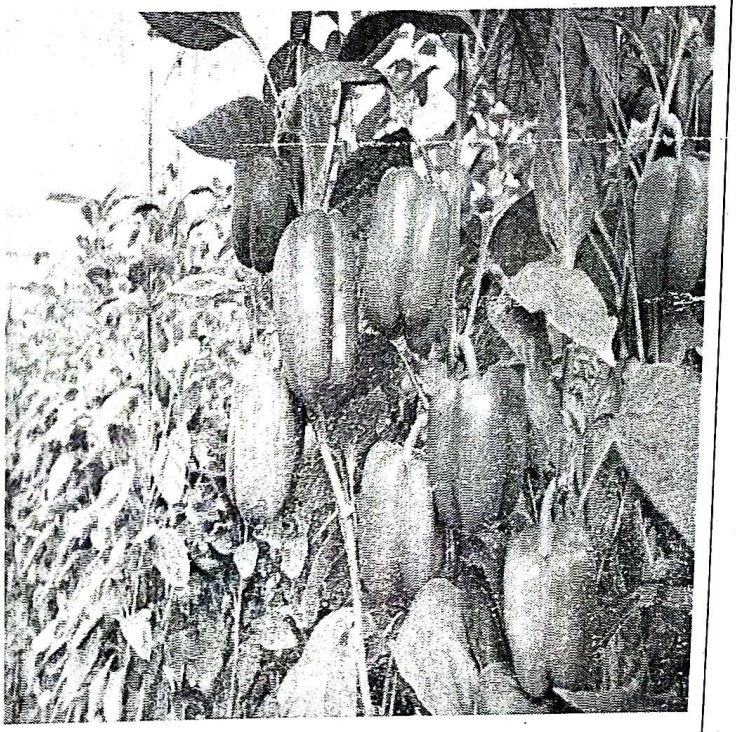
Family: Solanaceae

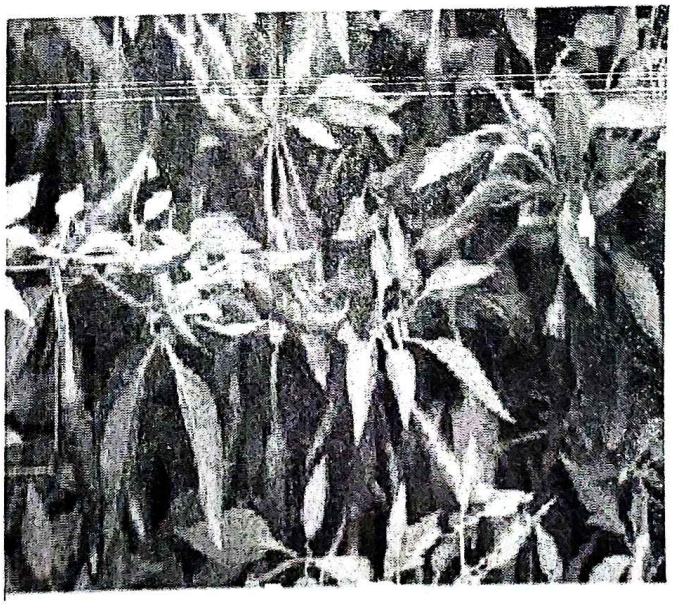
— **Active constituents:**

1. Capsicum is rich in ascorbic acid.
2. It also contains diterpene glycosides.
3. The color is due to the presence of carotenoids with terminal cyclopentane ring such as capsanthin and capsorubin.



Capsaicin





Uses:

1. Used as spices.

2. Counterirritant to relieve rheumatic pain and neuralgic pains in form plaster.

3. Carminative.

2- Saffron الزعفران

B.N. *Crocus sativus*

Family: Iridaceae

Active constituents:

Volatile

Glycosidal coloring matter (crocin).

Uses:

1. Coloring agent.

2. Stimulant and antispasmodic.