FACULTY OF PHARMACY

Cardiac Glycosides

Pharmacognosy & Phytochemistry

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Cardiac Glycosides

- Therapeutically, this group of compounds may be considered as one of the most important of all natural occurring products.
- Cardioactive glycosides are steroids having the ability to exert specific powerful action on the cardiac muscle on injection into man or animal.
- A very small amount can exert a beneficial stimulation on diseased heart, but an excessive dose may cause death.
- Drugs containing these glycosides are used in medicine primarily to increase the tone, excitability and the contractility of the cardiac muscle.
- Secondarily, most of them exert a diuretic action, due principally to the increased renal circulation.

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- Cardiac glycosdies occurs in small amounts in the seeds, leaves, stems, roots or barks of wide geographical distribution, particularly of the Families:

1. Apocynaceae الفصيلة الدفلية
2. Scrophulariaceae الفصيلة الغدبية فصيلة نباتية تتبع رتبة الشفويات
3. Liliaceae الفصيلة الزَّنبقية
4. Ranunculaceae الفصيلة الحَوْذانية

- **Aglycone:** The aglycones of these cardioactive glycosides are chemically related to bile acids and sterols and possess the steroidal structure with the tetracyclic carbon skeleton which is largely saturated,
- The steroidal carbon skeleton is overall composed of 17 carbon atoms.
- The basic structure of the steroidal part is cyclopentano perhydrorphenanthrene nucleus, to which a lactone ring is attached.

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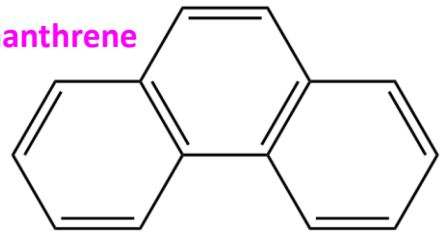
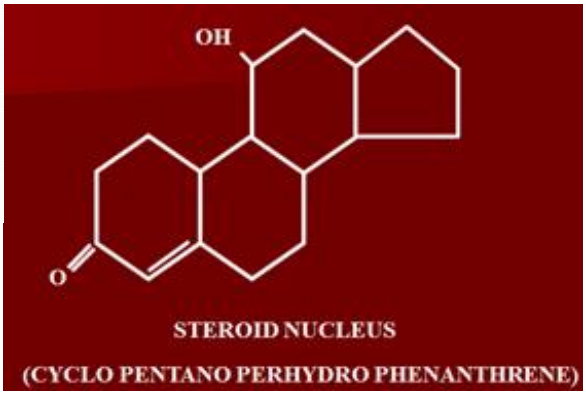
Phenanthrene



cyclopentanoperhydrophenanthrene ring i.e. consisting of 3 six membered fully hydrogenated (perhydro) phenanthrene rings & 1 five membered cyclo pentane ring.



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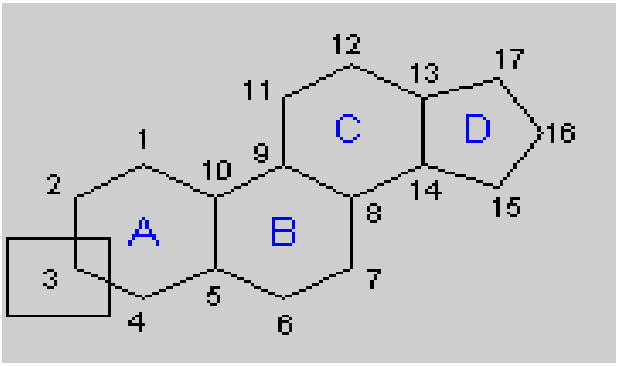

Lactone rings of the glycosides:

The lactone ring of these glycosides is either **5-membered** ring i.e **cardenolide** or **6-membered** ring = **bufadenolide,** and these are called either γ **lactone** or δ **lactone.**

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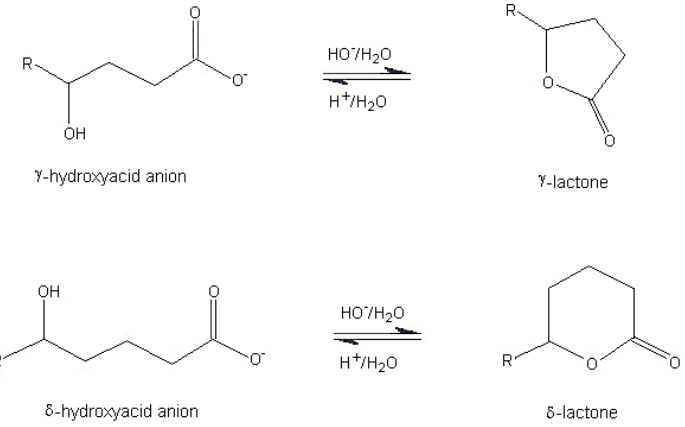

γ lactone (cardenolides)

δ lactone (bufadenolides)

- **Origin of termination γ (gamma) δ (delta):** The lactone is a cyclic ester which is formed from acid and alcohol:

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$$R - \underset{\underset{O}{||}}{C} - OH + R^{-} - OH \rightarrow R - \underset{\underset{O}{||}}{C} - O\text{-}R^{-}$$

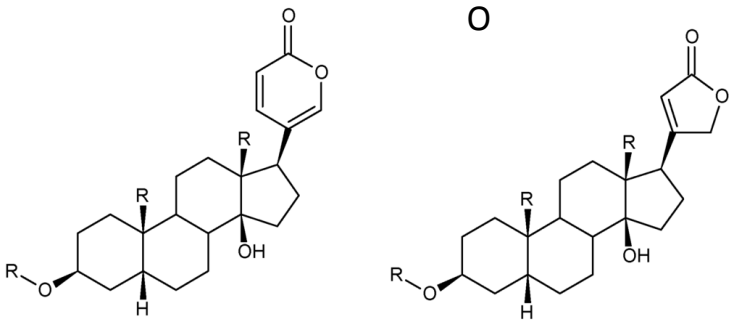
Formation of the lactone ring from an acid and an alcohol.

- The lactone ring atoms are derived from the following acid atoms:

C - C - C - C - C - OH

δ γ β α ||

O



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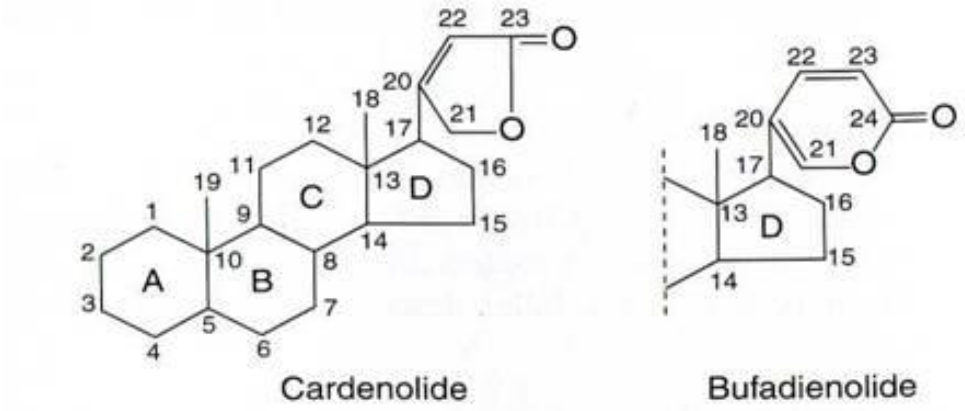
Bufadienolide

Cardenolide



Stereochemistry of the steroidal structure of cardiac glycosides:

1. The asymmetric centers (chiral) of the structure are:

5, 10, 9, 8, 14, 13, 17, also if we have OH at 3, they will be **8 centers**.

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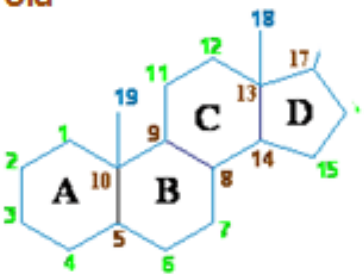
Asymmetrical centers in steroid structure

- Number of sterioisomers = 2^n, n: number of chiral centers.

For the steroid nucleus number of sterioisomers = 2^8=256



2. If there is any group on any carbon atom of the above structure, it will be either **above** or **under** the plane of the structure and usually, the symbols α & β are used to denote to them.
3. For any steroidal structure to be considered a cardiac glycoside, it must have the following requirements:

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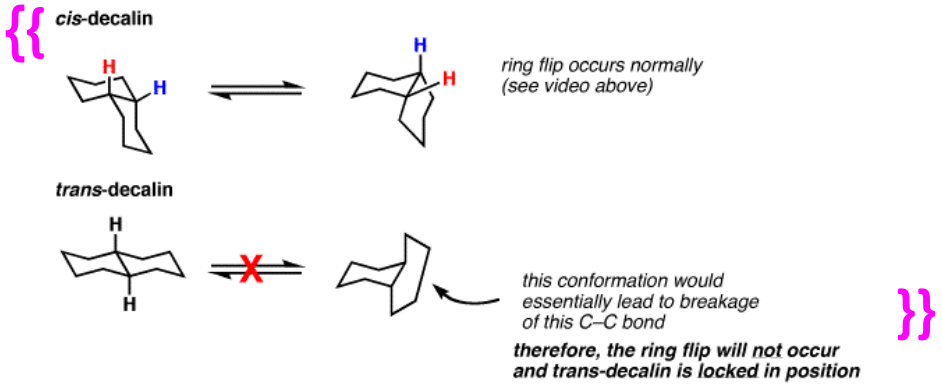
1. 3 β OH
2. 14 β OH
3. 17 β-unsaturated lactone ring.
4. Also, usually for maximum activity of cardiac glycoside structure the rings must comply with CATSC rule, that is:

- Rings A & B are cis to each other.
- Rings C & D are cis.
- Rings B and C in trans.



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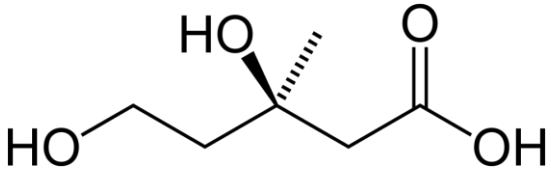
- **Biosynthesis of cardiac glycosides:**

❖ From mevalonic acid:



➢3,3-dimethylally pyrophosphate (DMAPP) or its isomer isopentenyl-pyrophosphate (IPP) which are the active forms are formed from **mevalonic acid** which is the precursor of all terpenes.

➢ The joining of **isoprene units** will end up in formation of cardiac glycosides from cholesterol.

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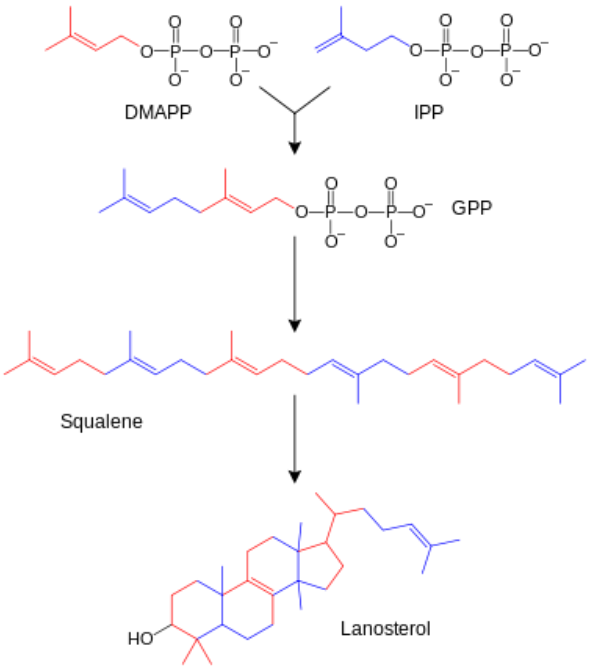

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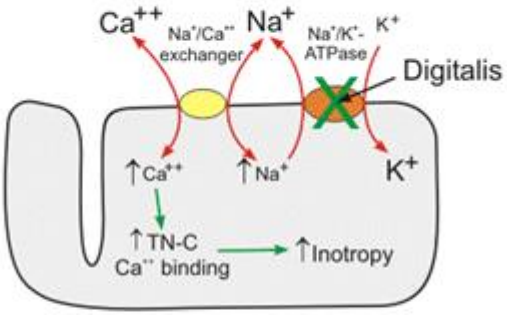
Mechanism of action



** Digitalis compounds are potent inhibitors of cellular Na^+/K^+-ATPase. This ion transport system moves sodium ions **out** of the cell and brings potassium ions **into** the cell.

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Mechanism of action

** Cardiac myocytes, as well as many other cells, have a Na^{+}-Ca^{++} exchanger (not an active energy-requiring pump) that is essential for maintaining sodium and calcium homeostasis {any self-regulating process by which biological systems tend to maintain stability while adjusting to conditions that are optimal for survival}.

** Calcium and sodium can move in either direction across the sarcolemma {the fine transparent tubular sheath which envelops the fibers of skeletal muscles}.

** Increase in intracellular sodium concentration competes for calcium through this exchange mechanism leading to an increase in intracellular calcium concentration.

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Mechanism of action

** As intracellular sodium increases, the concentration gradient driving sodium into the cell across the exchanger is reduced, thereby reducing the activity of the exchanger, which decreases the movement of calcium out of the cell.

** Therefore, mechanisms that lead to an accumulation of intracellular sodium cause a subsequent accumulation of intracellular calcium because of decreased exchange pump activity.

** This then leads to an accumulation of intracellular calcium via the Na^{+}-Ca^{++} exchange system.

** In the heart, increased intracellular calcium causes more calcium to be released by the sarcoplasmic reticulum, thereby making more calcium available to bind to troponin-C, which increases contractility (inotropy).

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Mechanism of action

** **Or:** As 3 molecules of Na are exchanged for each 1 ion of Ca, the accumulation of Na ions in the cell will increase the rate of the Ca ions transported **into** the cell which will result in accumulation of Ca ions.

** In other words, upon build-up of Na ions in the cell, more Ca ions will **enter** the cell as the amount of Na ions available for exchange has become more.

** Accordingly, the exchanger is not inhibited anymore, and it continues to work without any cessation.

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❖Drugs Containing Cardioactive Glycosides:

1. Digitalis:

- Several species of Digitalis yield physiologically active principles.
- The most important of these are ***Digitalis purpurea*** القِمَعية الأرجوانية and ***D. lanata*** القِمَعية الصوفية.
- Both species belong to the family **Scrophulariaceae** الفصيلة الغدبية.

D. lanata

D. purpurea

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- The part used is the **leaves** and the common name of the plant is **foxglove**.
- The main active constituents are the **primary** and **secondary cardiac glycosides**.
- Each 100 mgs of the official drug are equivalent to not less than 1 U.S.P. digitalis unit.
- ***Digitalis purpurea*:** The cardioactive glycosides classified into **3** main groups:

1.Digitoxin (purpurea glycoside A).

aglycone (digitoxigenin) + sugar part (glycone: digitoxose)

- **Digitoxin:** digitoxigenin + 3 molecules of digitoxose.

2. Gitoxin.
3. Gitaloxin.

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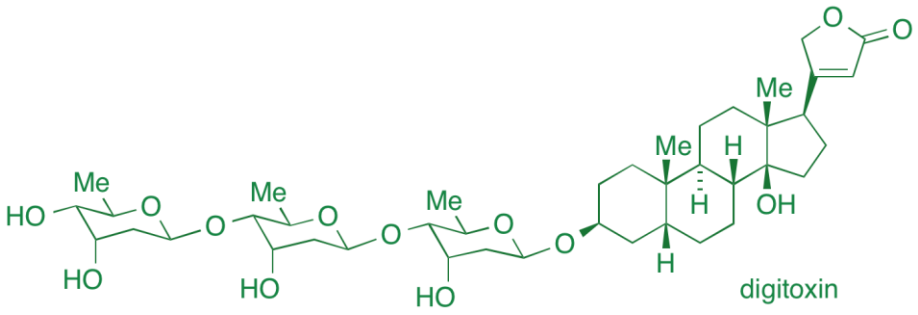

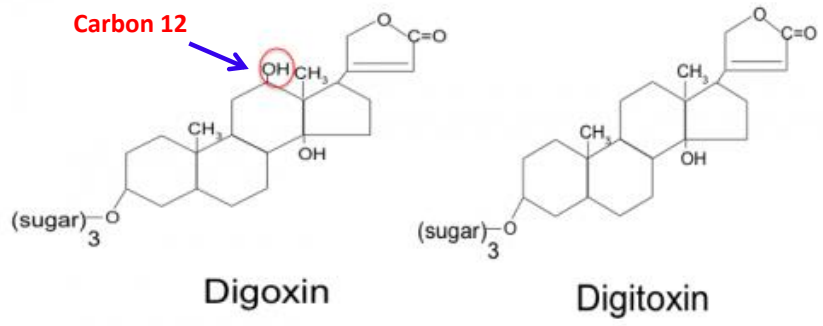

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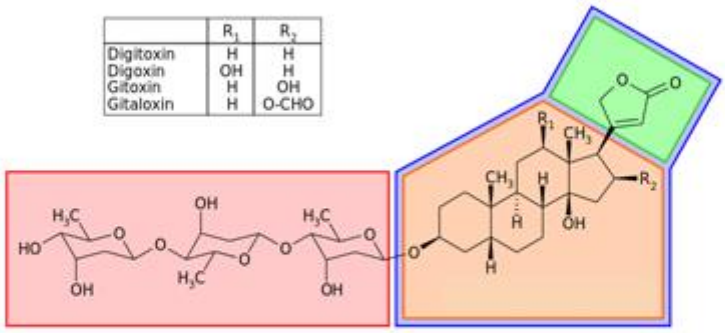

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Lanatoside C:

- Is one of the main constituents in *Digitalis lanata*.
- Its chemical structure is:

Digitoxigenin (aglycone)+2 digitoxose+acetyldigitoxose+β-D-glucose.

Digitonin:

- The plant [*Digitalis purpurea*] also contains a steroidal saponine glycoside called digitonin which is **used for blood test of cholesterol.**

➢ Actions and uses of cardioactive glycosides:

- Mainly, they are used for congestive heart failure (CHF), and for different cardiac arrhythmias (particularly, **atrial fibrillation**).
- Small doses of cardiac drugs slower **heart beat**, and increase **blood volume** pumped through the heart, so the heart chambers are filled more completely during the diastolic phase which now lasts longer.

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- During the systolic phase the contraction is stronger, so heart chambers empty more completely.
- Also, these glycosides cause more blood passing through kidneys (more effective circulation), and thus are effective diuretics.
- Digoxin: tablets, lanoxin® ampoules (manufacturer: Sandoz) and syrup.

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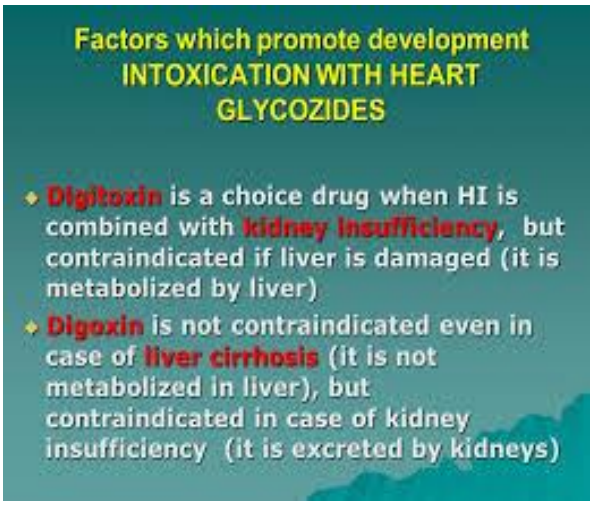
- **Loading dose** : is divided through the first 24 hrs and the patient is monitored by taking blood samples.
- **Maintenance dose**: to maintain digitalis effect, the following parameters should be considered:

1. Body weight.
2. Renal / hepatic function.
3. Electrolytes in the body.
4. Presence of other diseases.



Reasons of digitalis toxicity :

1. Admisnstration of larger maintenance dose.
2. Too rapid digitalisation.
3. Presence of other drugs like: amiodarone, verapamil,

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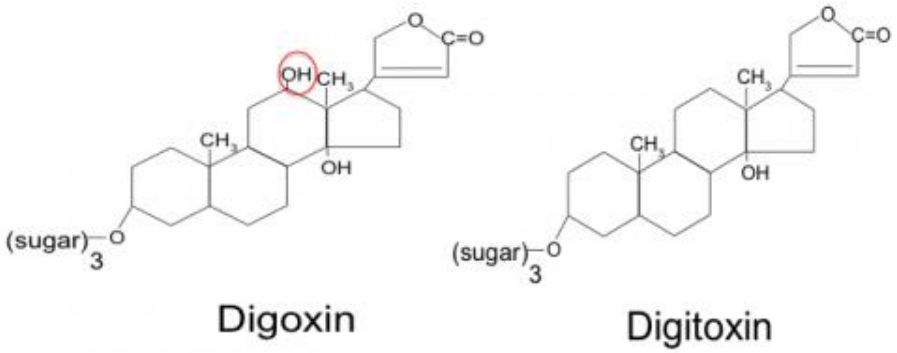
..... quinidine, erythromycine.

4. Hypokalemia.
5. Hypercalcemia.
7. Hypomagnesia.

❖ **Digitalis has a small therapeutic window**



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For the batches containing the same glycosides content, differences in the proportions of the individual glycosides can give differences in the pharmacological effect i.e.:

Digitoxin is **more readily** absorbed than gitoxin when given orally, whereas the two glycosides are equilvalent when given intravenously. Therefore, these differences in pharmacokinetics should be regarded well.

Accordingly, (digitoxin > gitoxin) preparation is more effective than (gitoxin> digitoxin) preparation.

Why digitalis leaf is not used very much nowadays:

1. The preparations of crude drugs vary in the content of CG.
2. Heavily contaminated by bacteria, therefore leaves should be sterilized.
3. Contaminated with soil and dirt trapped by hairs on the leaves.

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Digitoxin: ❖

The main secondary glycoside in *Digitalis purpurea*.

Its effect starts very slowly after an oral dose, and reaches its maximum after 8-12 hours.

Also, its excretion is slow, therefore, the risk of overdose is very high due to cumulation of the drug.

Due to the low safety margin, dose should be determined individually.

To prevent overdose, drug should not be taken during 1-2 days a week.

Signs of overdose: nausea, vomiting, diarrhea, abdominal pain, headache, drowsiness, fatigue, malaise,backache, visual disturbances, convulsions, cardiac arrhythmias, ventricular tachycardia.

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Positive inotropic effect

Positive inotropic effect includes:

1- Increased cardiac output.

2- Decreased cardiac filling pressure.

3- Decreased venous and capillary pressure.

4- Decreased heart size-increased renal blood flow.

5- Deactivation of renin-angiotensin-aldosterone system. compensation, promoting diuresis

6- Decreased fluid volume.

7- Diminished edema.

➢ Have a negative chronotropic effect {decreased heart rate}.

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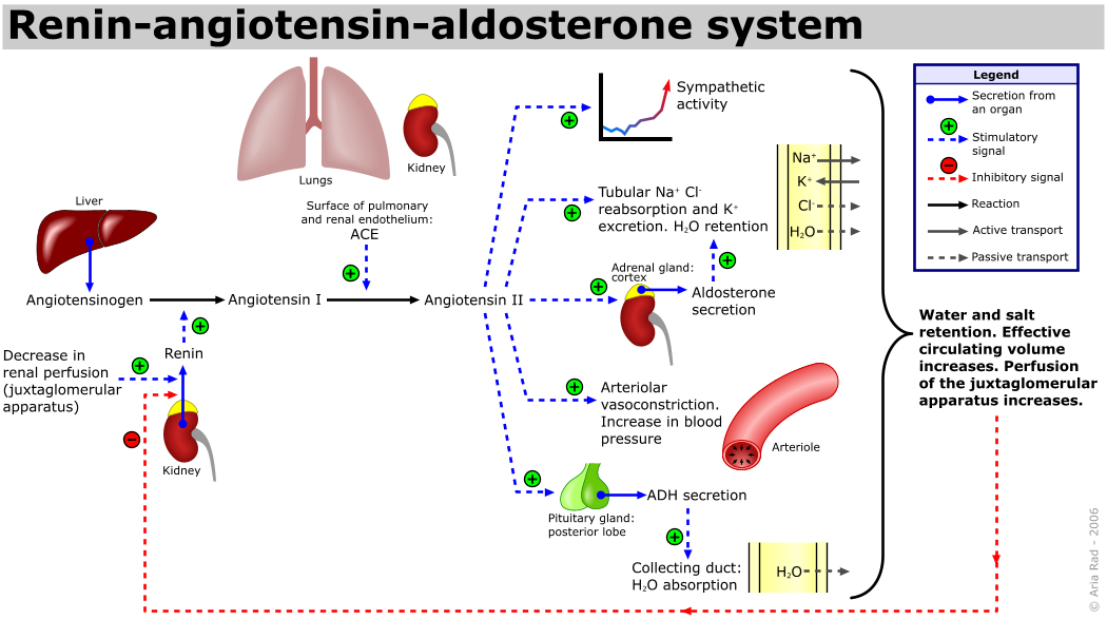

2. Strophanthus:

- The crude drug: the dry **seeds** of *Strophanthus kombe* (Apocynaceae).

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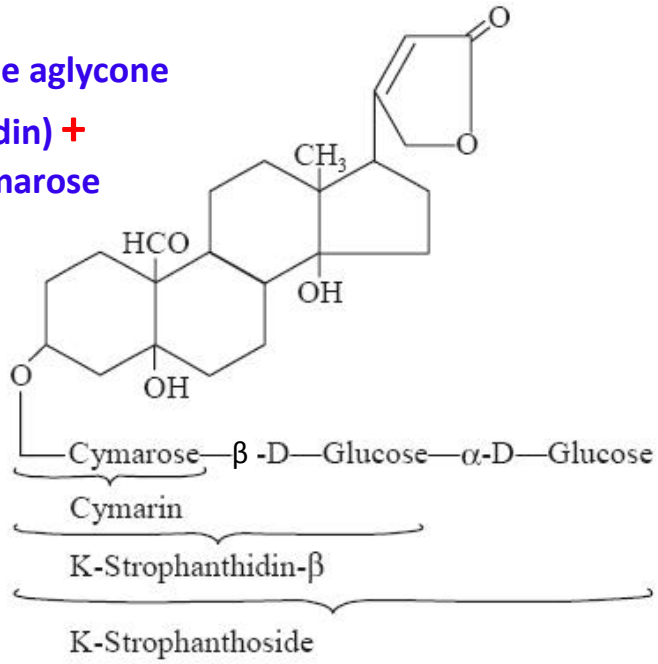
Strophanthus kombe

- Seeds contain:

❖ K-strophanthoside= [**Strophanthidin (is the aglycone)+ cymarose + β-D -Glucose + α-D-glucose**].

Cymarin = the aglycone (strophanthidin) + the sugar cymarose



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{{ **Primary glycoside** Constituents

- K-strophanthoside, also known as strophoside, is the primary glycoside in both strophanthus species.
- It is composed of genin (Strophanthidin), coupled to a trisachcaride consisting of cymarose, β-glucose, α-glucose.
- α-glucosidase removes the terminal α-glucose to yield K-strophanthin-β and the enzyme strophanthobiase (contained in the seed) converts this to cymarin plus glucose.
- A mixture of these glycosides, existing in the seed in concentrations up to 5 %, was formerly desihnated strophanthin or K-strophanthin.

NOTE:

Upon hydrolysis of the **primary glycoside** {e.g. here it is K-strophansoide}, we obtain SECONDARY GLYCOSIDES {e.g. here, K-strophanthin-β, cymarin}.

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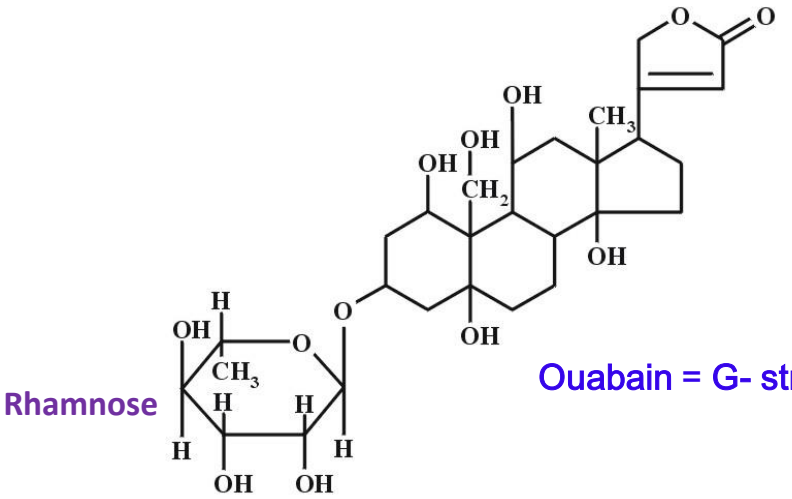
}}

- ***Strophanthus gratus:*** (Family: Apocynaceae).

➢ This species contains the cardioactive glycoside (**Ouabain**) or **G- strophanthin**.

➢ The **seeds** are the part used of the plant, which was used as **arrow poison** as it is extremely poisonous.



Rhamnose

Ouabain = G- strophanthin.

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Strophanthus gratus (Family: Apcynaceae)

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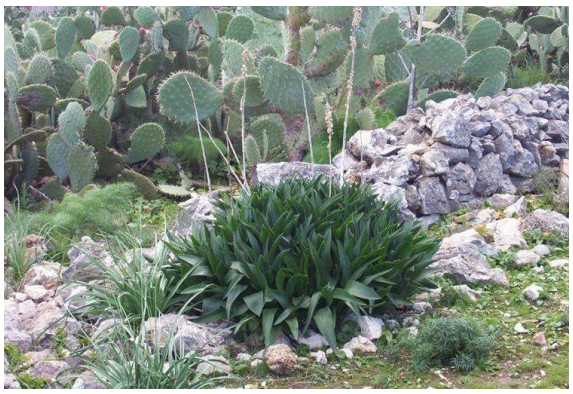
3. Squill:

- It is the dry fleshy inner scales of the bulb of the white variety of: *Urginea maritima* (synonymous to *Drimia maritima*) (Fam. **Liliaceae**)

العُنْصُل البَحْرِيّ أو البَاصُول أو العُنْصُلاَن أو بَصَل الفَأْر أو بَصَل الخِنْزِير أو بَصَل البَرّ أو البَصَل البَرِّيّ



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Drimia indica

Drimia maritima

- Commercially is known as: **Mediterranean squill.**
- Also, there is another variety which is known as the red variety which is used as rat poisoning and it is *Urgenia indica*.
- It is known commercially as: Indian squill.

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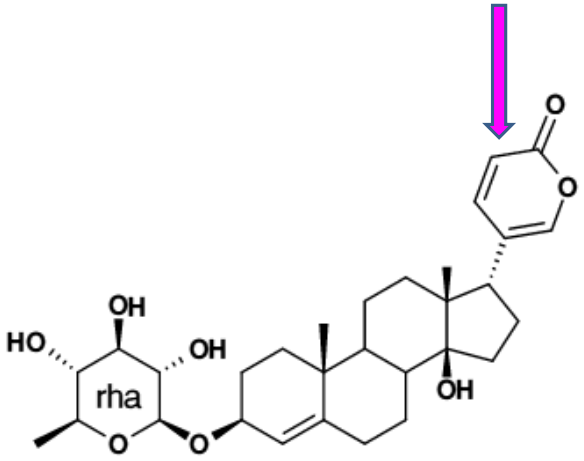
- The main active cardiac glycosides in *D. maritima*:
  - Proscillaridin A: is bufadienolide (6-membered lactone ring).



ProScillaridin A

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❖ Uses:

- Squill glycosides have 1. **similar** action to digitalis glycosides, but they have a, **more rapid action** (rapid onset of action), but **less used**.
- Also, they have 2. **diuretic** action and 3. expectorant.
- The **red bulb** is used as rat poison and not as cardiac glycoside.
- It kills rats only and not other animals. In fact other animals refuse to take the poison and for most animals, if they ingest some, they vomit it right away.
- Rats cannot vomit.
- Cats, dogs and pigs starve rather than eating food containing squill.
- Red squill is 100-500 times more toxic to rats than is the white variety.

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{{ 4. Nerium:

- Nerium oleander : الدفلى أو الدفلى الزيتية is an evergreen shrub or small tree in the dogbane family Apocynaceae, toxic in all its parts.
- It is the only species currently classified in the genus *Nerium*.
- It is most commonly known as oleander, from its superficial resemblance to the unrelated olive *Olea.*
- it is extensively used as an ornamental plant in landscapes, in parks, and along roadsides.
- *Oleander* has historically been considered a poisonous plant because some of its compounds may exhibit toxicity, especially to animals, when consumed in large amounts. Among these compounds are oleandrin and oleandrigenin, known as cardiac glycosides, which are known to have a narrow therapeutic index and can be toxic when ingested.}}

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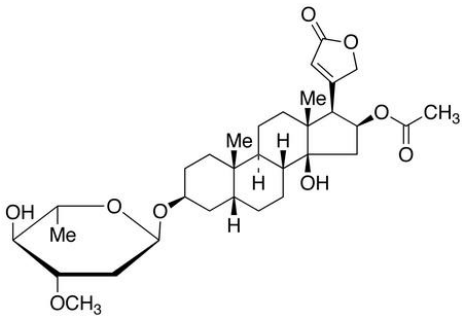

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