

# CARDIAC GLYCOSIDES

1. General characteristic
2. Medicinal plants and plant material containing cardiac glycosides

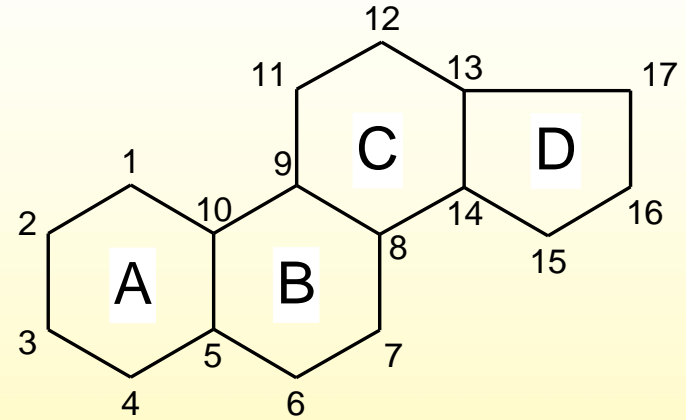


# Cardiac glycosides

**A group of biologically active compounds, cyclopentane perhydro phenanthrene derivatives, which have high specific action on heart muscle.**



- A/B rings: *cis*-/*trans*
- B/C rings: *trans*
- C/D rings: *cis* (while the majority of other steroids have *trans*-configuration)



## Activity of steroids:

- Development and control of reproduction;
- Vitamin D precursors;
- Oral contraceptives;
- Anti-inflammatory
- Anabolic etc.



# Cardioactive glycosides

- In large doses they are toxic and bring about cardiac arrest in systole, but in lower doses they are important drugs in the treatment of *congestive heart failure*.
- They have a diuretic activity. The improved circulation tends to improve renal secretion, which relieves the edema often associated with heart failure.



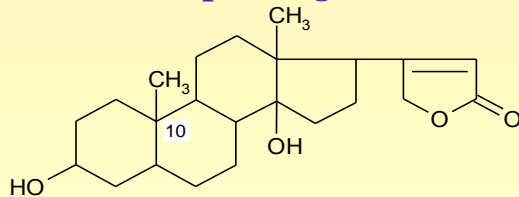
- **Cardiac glycosides** comprise a steroidal aglycone having an unsaturated lactone ring at C-17

According to radical at C-17

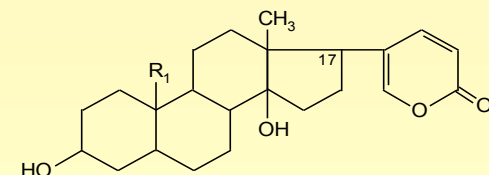
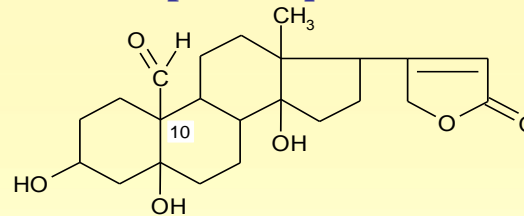
**CARDENOLIDES (C<sub>23</sub>)**

**BUFADIENOLIDES (C<sub>24</sub>)**

**Group of Digitalis**



**Group of Strophanthus**



*Folia Digitalis*  
*Folia Digitalis lanatae*  
*Folia Digitalis ferrugineae*  
*Folia Digitalis ciliatae*

*Semina Strophanthi*  
*Herba Adonidis vernalis*  
*Folia Convallariae*  
*Herba Erysimi*

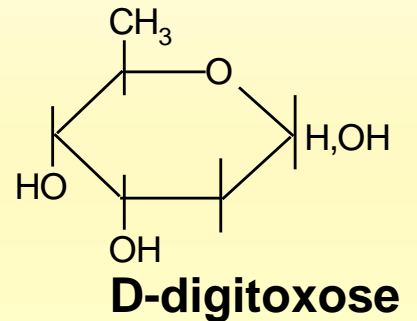
*Bulbus Scillae*  
*Rhizomata cum radicibus*  
*Hellebori*

## A. Structure of the aglycones

- All the aglycones have in common the classic, tetracyclic, **steroidal** nucleus.
- The A, B, C and D rings normally have a ***cis-trans-cis*** configuration or less often, a ***trans-trans-cis*** configuration.
- Also common to all the aglycones is the presence of two hydroxyl groups: one is a **3 $\beta$**  secondary alcohol, the other is a **14 $\beta$**  tertiary alcohol.
- All of the aglycones have a  $\beta$  constituent at **C<sub>17</sub>**: an  $\alpha,\beta$ -unsaturated **lactone**.

## B. Structure of the sugar moiety

- The **sugar moiety** is generally linked to the aglycone through the hydroxyl group at **C<sub>3</sub>**.
- The majority of the **saccharides** found in cardiac glycosides are **highly specific**:
  1. 2,6-dideoxyhexoses, e.g. **D-digitoxose**
  2. 2,6-dideoxy-3-methylhexoses, e.g. **L-oleandrose**
  3. 6-deoxyhexoses, e.g. **L-rhamnose**
  4. 6-deoxy-3-methylhexoses, e.g. **D-digitalose**
  5. Hexose, e.g. glucose (when this is a glucose unit, it is always the terminal one).
- The sugars can modify the activity (potency, toxicity), the solubility, the diffusion through membranes, the rate of absorption and transportation of the glycosides.



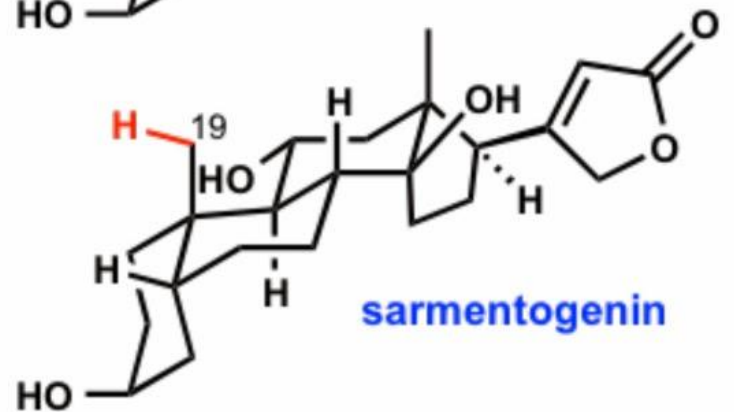
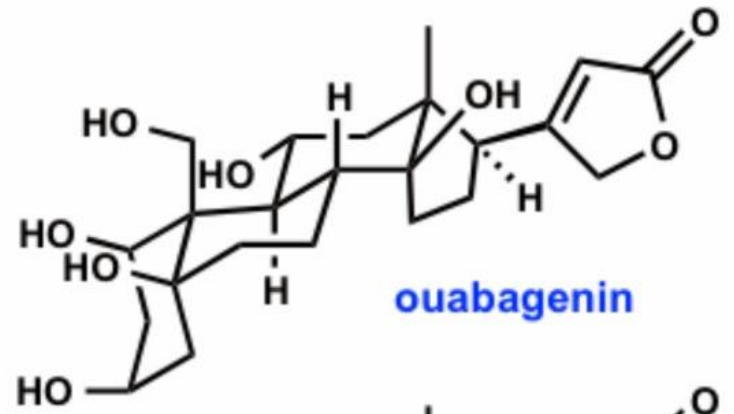
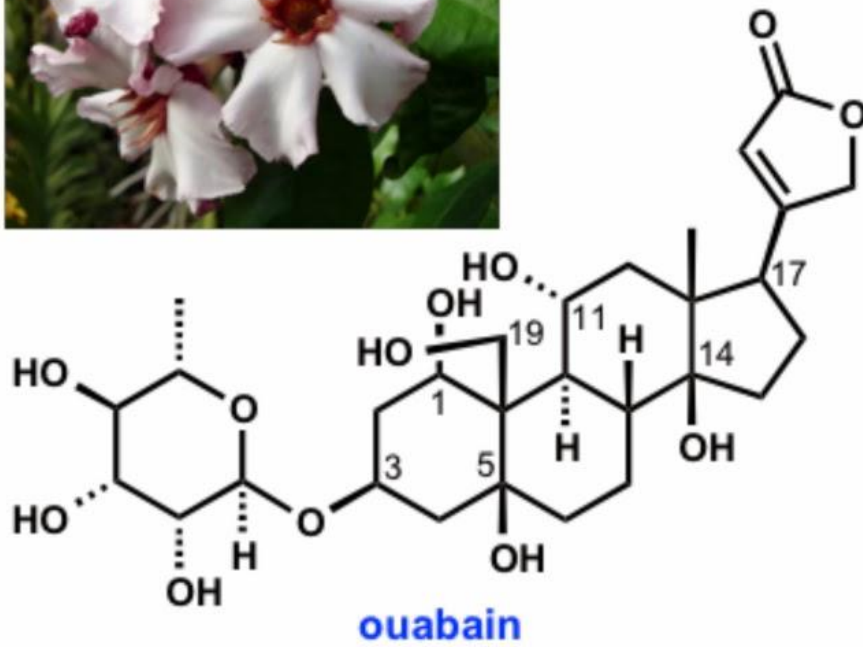
## C. Structure-Activity Relationships (SAR)

- The **cardiac activity** is linked to the **aglycone**.
- The **sugar moiety** does not participate directly in the activity, but its presence **enhances the activity** and modulates it by modifying the polarity of the compound.
- The presence of a certain number of **structural elements** is **required** for, or at least favorable, to the activity:
  1. The *lactone at C-17* must be in the  $\beta$  configuration.
  2. The *configuration of the rings*. The activity is maximized when the A, B, C and D rings are in the *cis, trans, cis* configuration. **The C and D rings must be *cis* fused.**
  3. The *substituents*. The inversion of the configuration at C-3 diminishes the activity, but 3-deoxy compounds are not completely inactive.





*Strophanthus  
gratus*



## **Distribution in nature**

- **Cardiac glycosides** occur in small amounts in the seeds, leaves, stems, roots or barks of plants of wide geographical distribution, particularly of the Fam. Apocynaceae (e.g. *Strophanthus* seeds, *Apocynum* roots and *Acokanthera* fruits); others are found in the Scrophulariaceae (e.g. leaves of *Digitalis sp.*), Liliaceae (e.g. scales of the bulbs of *Urginea* and *Convallaria*), and Ranunculaceae (*Adonis*).
- Cardiac glycosides are also found in animals only in exceptional cases: Bufadienolides occur in toads (*Bufo*).

# Physical and chemical properties

- Colourless or white crystals (rarely amorphous)
- Solubility is determined by the number of sugar moieties; *aglycones* – soluble in organic solvents, insoluble in water; *glycosides* – soluble in water and slightly soluble in ethanol and chloroform
- Optically active compounds
- Undergo hydrolysis (acid, enzymatic and alkaline)



# Hydrolysis of cardiac glycosides

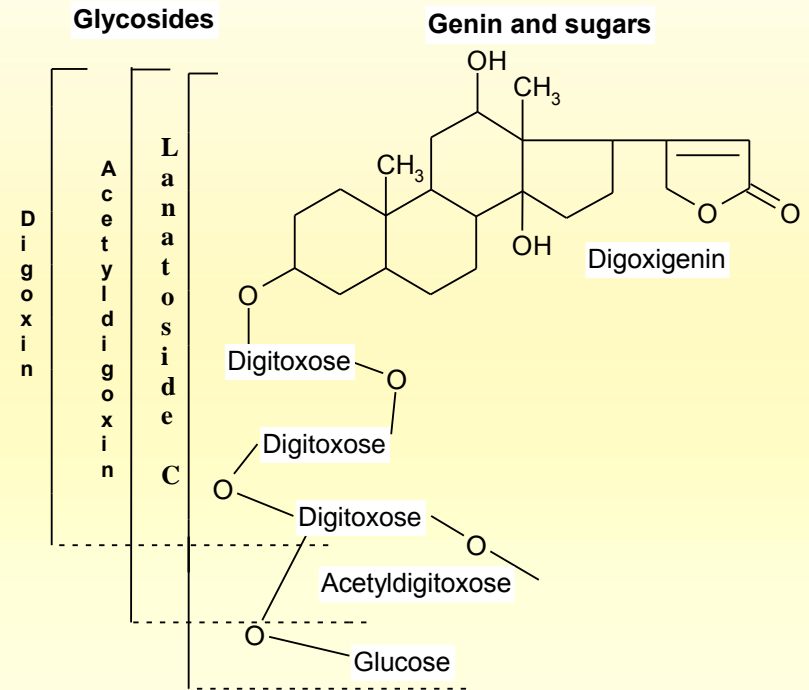
## Acid hydrolysis

Glycoside linkage is cleaved → sugar part is separated from the aglycone

## Alkaline hydrolysis

- Mild hydrolysis – cleavage of acetyl groups of sugars
- The lactone ring is cleaved

## Enzymatic hydrolysis



# Extraction of cardiac glycosides

Defatting with petrol or petroleum ether

Extraction with organic extragent (ethanol, acetone)

Concentration of the extract, transfer of glycosides to the water or water-alcohol solution

Sedimentation of resins, chlorophylls (using metal salts, e.g. aluminum sulfata)

Extraction of the glycosides from the water solution using organic solvents with further evaporation

Treatment of the water-alcohol solution with lead hydroxide or aluminum oxide

Extraction of the glycosides from the water solution using organic solvents with different polarity

Chromatographic division of the glycosides' mixture

Crystallization

# Identification of cardiac glycosides

## • *Tests for steroidal core*

- Liebermann-Burchard test: with acetic anhydride+sulphuric acid conc. (50:1) → purple colour changing to greenish-blue;
- Rosenheim test: with trichloroacetic acid → pink colour changing to purple or blue (for cardenolides with a diene functional group);

## • *Tests for unsaturated lactone ring*

- Kedde test: with 3,5-dinitrobenzoic acid → red-violet colour;
- Legal's test: with sodium nitroprusside → red colour;
- Raymond test: with *m*-dinitrobenzene in benzene → violet colour (for cardenolides with substituents at C<sub>21</sub>);
- Baljet test: picric acid → red-orange colour of cardenolides;
- The lactone ring of bufadienolides is identified using UV-spectroscopy at  $\lambda=300$  nm;

# Identification of cardiac glycosides

- ***Tests for sugar part***

- *Keller-Kiliani test*: with glacial acetic acid with traces of ferric (III) chloride + sulphuric acid conc. with traces of ferric (III) chloride → reddish-brown colour which turns blue on standing (for specific desoxysugars);
- *Xanthydol test*: with xanthydol in glacial acetic acid in the presence of 1% HCl → red colour (for specific desoxysugars);
- Tests for carbohydrates (with Fehling reagent, “silver mirror” test with Tollens reagent).





# Quantitative determination of cardiac glycosides

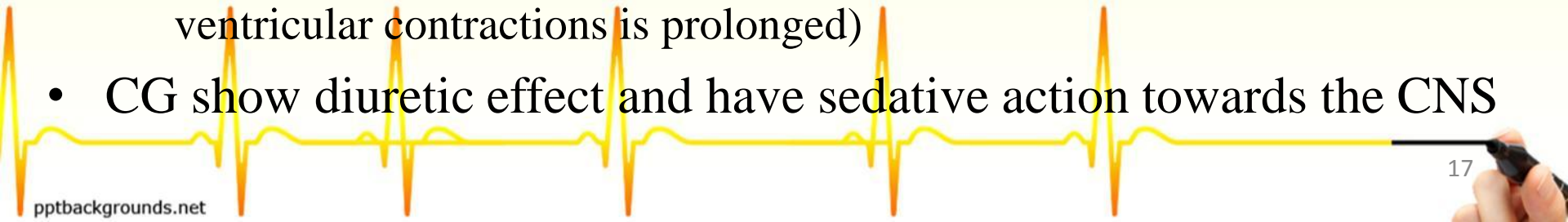
- Biological standardization (**specific**) – determined on cats, frogs, pigeons – 1 International Unit is the smallest amount of the object studied (1 mg of a substance or 1 ml of an extract) causing systolic arrest of the ventricle in an animal within 1 hour.
- UV-spectrophotometry after formation of coloured products of the reactions with acid-containing reagents.
- Fluorimetry
- Polarography
- Chromatography (TLC with further fluorimetric assay, GC, HPLC)
- Immunoassay





# Pharmacological properties

- Cardiac glycosides show selective cardiotoxic effect, increasing myocardial contractility and eliminating the signs of cardiac insufficiency
- Major effects:
  - Positive inotropic: increase the force and speed of myocardial contraction;
  - Positive tonotropic: increase of the tone of cardiac muscle;
  - Negative chronotropic: prolongation of the diastole (fast relaxation of the cardiac muscle leads to the increase of blood volume in the heart during the diastole which results in the decrease of demand in oxygen of myocardium and its energetic resources renewal);
  - Negative dromotropic: decrease the rate of electrical impulses in the heart;
  - Positive bathmotropic: increase the response of cardiac muscle to stimulation, thus, increasing the excitability (the time between atrial and ventricular contractions is prolonged)
- CG show diuretic effect and have sedative action towards the CNS



# Mechanism of action

Cardiac glycosides suppress the  $\text{Na}^+/\text{K}^+$ -ATPase of the membranes of cardiomyocytes. By inhibiting the  $\text{Na}^+/\text{K}^+$ -ATPase, cardiac glycosides cause intracellular sodium concentration to increase. This then leads to an accumulation of intracellular calcium via the  $\text{Na}^+-\text{Ca}^{2+}$  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*).

Inhibition of the  $\text{Na}^+/\text{K}^+$ -ATPase in vascular smooth muscle causes depolarization, which causes smooth muscle contraction and vasoconstriction.



# Indications

- Cardiac glycosides are currently indicated for:
  1. Heart failure - The initial dosage, generally high and called loading dosage, is followed by a lower dosage, called maintenance dosage.
  2. Atrial fibrillation or flutter
  3. Supraventricular tachycardia



# Adverse effects

- **Accumulation**
- *Digitalis glycosides* have a **narrow therapeutic range** and changes in digitalis pharmacokinetics and/or pharmacodynamics caused by a digitalis-drug interaction can result in toxicity or underdigitalization
- *Digitalis glycosides* cause cardiac arrhythmia, especially atrial tachycardias and atrioventricular block



# HEART FAILURE

- Heart failure is characterized by the heart's inability to pump an adequate supply of blood.
- In **acute heart** failure, the symptoms appear suddenly but go away fairly quickly. This condition often occurs after a heart attack. It may also be a result of a problem with the heart valves that control the flow of blood in the heart.
- In **chronic heart** failure, however, symptoms are continuous and don't improve over time. The vast majority of heart failure cases are chronic.
- The combination of digoxin and a beta-blocker is more effective than a beta-blocker alone in controlling the ventricular rate at rest.

# ACUTE HEART FAILURE

- Acute heart failure (AHF) is the term used to describe the rapid onset of, or change in, symptoms and signs of HF. It is a lifethreatening condition that requires immediate medical attention and usually leads to urgent admission to hospital.
- Often treatment must be administered in parallel with the diagnostic work-up. The key drugs are oxygen, diuretics, and vasodilators. Opiates and inotropes are used more selectively (with Blood pressure  $<85\text{mmHg}$ )



- **Strophanthus glycosides**

*The name Strophanthus is derived from the Greek strophos (a twisted cord or rope) and anthos (a flower).*

*e.g. Strophanthus kombe*

The principle glycosides are:

1. **K-strophanthoside**
2. **K-strophanthin- $\beta$**
3. **Cymarin**

**Indications:** Atrial fibrillation, Atrial flutter, Cardiac arrhythmia, Left ventricular failure, Ventricular arrhythmias





- **Squill glycosides**

*Urginea maritima* (L.)

0.1% – 2.4% total bufadienolides,  
~15 glycosides

- **White variety:** average 0.2%-0.4%

proscillaridin A, scillaren A,  
glucoscillaren A (aglycone:  
scillarenin)

scilliphaeoside, scilliglaucoside

- **Red variety:** < 0.1%

scilliroside and glucoscilliroside  
(aglycone: scillirosidin);

proscillaridin A and scillaren A as in  
the white variety





# CHRONIC HEART FAILURE

- ‘Congestive HF’ is a term that is sometimes still used, particularly in the USA, and may describe acute or chronic HF with evidence of congestion (i.e. sodium and water retention).
- Digitalis glycosides are mainly used in patients with atrial fibrillation at any HF degree
- Narrow therapeutic window, arrhythmias and GIT side effects are the most common clinical problems in using digoxin

(Chronic Heart Failure: National Clinical Guideline for Diagnosis )



- **Digitalis glycosides**

Several species of *Digitalis* yield pharmacologically active principles. The most important of these species are *Digitalis purpurea* and *Digitalis lanata*.

1. *Digitalis purpureae folium* (Purple foxglove leaves)

0.15% – 0.4% total cardenolides, ~ 30 glycosides

Purpureaglycosides A and B (~60%), digitoxin (~12%), gitoxin (~10%) and gitalotoxin (~10%).

2. *Digitalis lanatae folium* (Grecian foxglove leaves)

0.5% – 1.5% total cardenolides, ~ 60 glycosides

Lanatosides A and C (~50%), lanatosides B, D, E as well as **digoxin** and **digitoxin**.



- **Digitoxin** is a cardiotonic glycoside obtained from *D. purpurea*, *D. lanata*.
- It is the most lipophylic of the cardiac glycosides used in therapeutics.
- The major pharmacokinetic parameters for digitoxin include complete oral absorption, which distinguishes it from other cardiac glycosides.
- Digitoxin may be indicated in patients with impaired renal function.
- **Digoxin** is the most widely used of the cardiotonic glycosides, and it is obtained from the leaves of *D. lanata*.
- It is a highly potent drug and should be handled with exceptional care.
- Digoxin tablets are 60 to 80% absorbed.
- Digoxin is indicated when the risk of digitalis intoxication is great, since it is relatively short-acting and rapidly eliminated when compared with digitoxin.



# Digitalis leaf (Purple Foxglove leaf) – *Folium Digitalis*

**Digitalis (Purple Foxglove ) - *Digitalis purpurea* L.**

**Family - *Scrophulariaceae***

Foxglove is very common in England and the Continent and is naturalized in North America. It is widely cultivated in many countries.

**Collect.** Either first or second year leaves are permitted by the pharmacopoeias. The second year leaves are collected in the phase of flowering. After collection the leaves should be dried as rapidly as possible at a temperature of about 60°C.

**Descript.** The leaf is brittle and often occurs broken. The upper surface is green and the lower surface is greyish-green. The apex is subacute and the margin is dentate or serrate. The base is decurrent. The venation is pinnate, the lateral veins being prominent especially on the lower surface, leaving the midrib at about 45° and anastomosing near the margin; a veinlet terminates in each tooth of the margin.

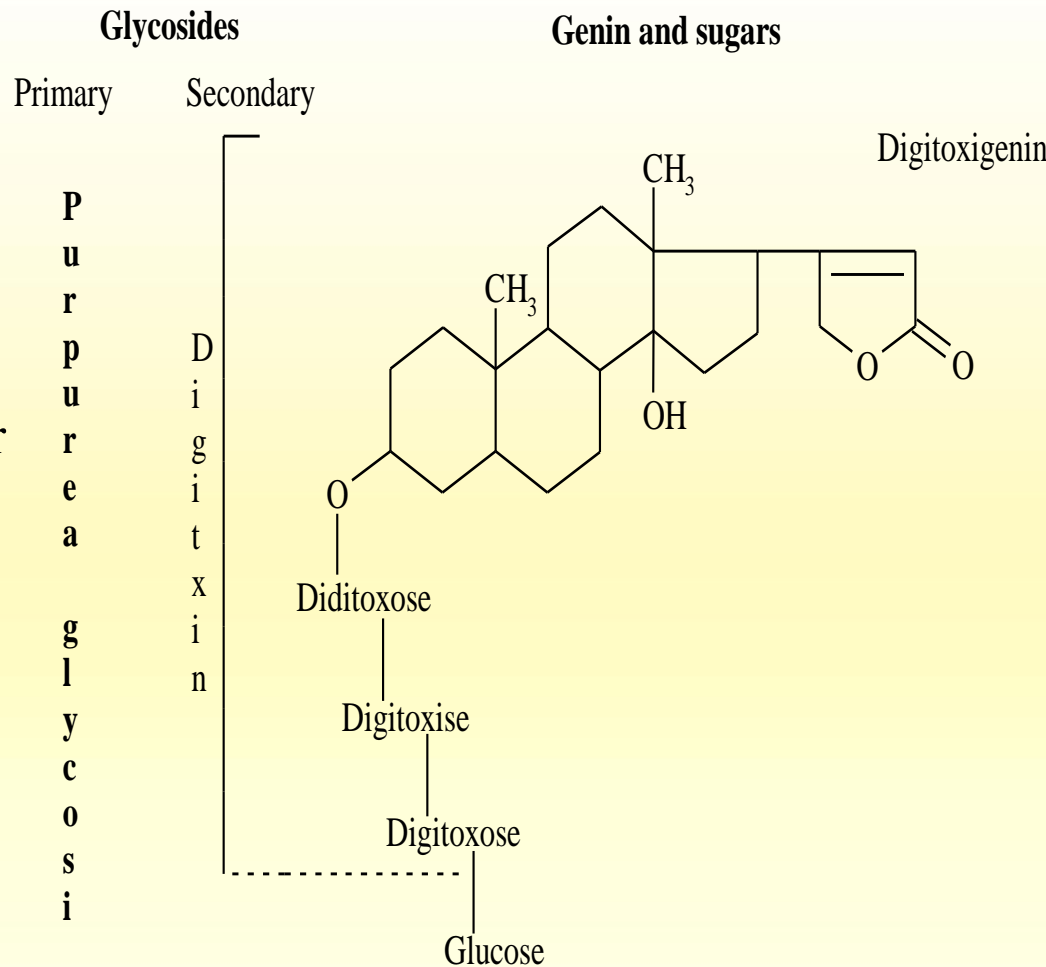


Joël Reynaud

The upper surface is rugose and pubescent; the lower surface shows a network of raised veinlets and is densely pubescent. The drug has no marked odour, but a distinctly bitter taste.

## Chemical constituents.

The leaves contain cardiac glycosides it is primary glycosides: purpurea glycoside A, purpurea glycoside B and glucogitaloxin (Table 1, Fig. 4). They possess at C-3 of the genin a linear chain of three digitoxose sugar moieties terminated by glucose. Their aglycones are digitoxigenin, gitoxigenin and gitoloxigenin. Leaves also contain steroidal saponins, flavonoids and anthraquinone derivatives.



## Uses.

Digitalis preparations are mainly used for their action on cardiac muscle. Digitalis glycosides are used for treatment of all stages of heart failure of different origin: disturbances of circulation of the second and third stages; valve heart diseases, flickering arrhythmia and high blood pressure. When prolonged uses of digitalis take place it is necessary to foresee the possibility of their accumulation in the body.



# **Digitalis lanata leaf – *Folium Digitalis lanatae***

**Woolly Foxglove, Grecian Foxglove - *Digitalis lanata* Ehrh.**

**Family - *Scrophulariaceae***

**Distribution.** The plant is indigenous to central and southeastern Europe. It is also cultivated in Holland, Ecuador, USA and other countries.

**Collection.** The leaves are collected in the second year before the flowering; the radical leaves are collected in the first year. The leaves are dried at a temperature of about 60°C as soon as possible.

**Description.** The leaves are linear-lanceolate to oblong-lanceolate in shape, sessile, slightly leather-like and up to about 30 cm long and 4 cm broad. The margin in entire, rare wavy. The apex is acuminate and the veins leave the midrib at a very acute angle. The surface of leaves is naked, the colour of the upper surface is green, the lower one is light-green. The odor is weak, peculiar, the taste is bitter.

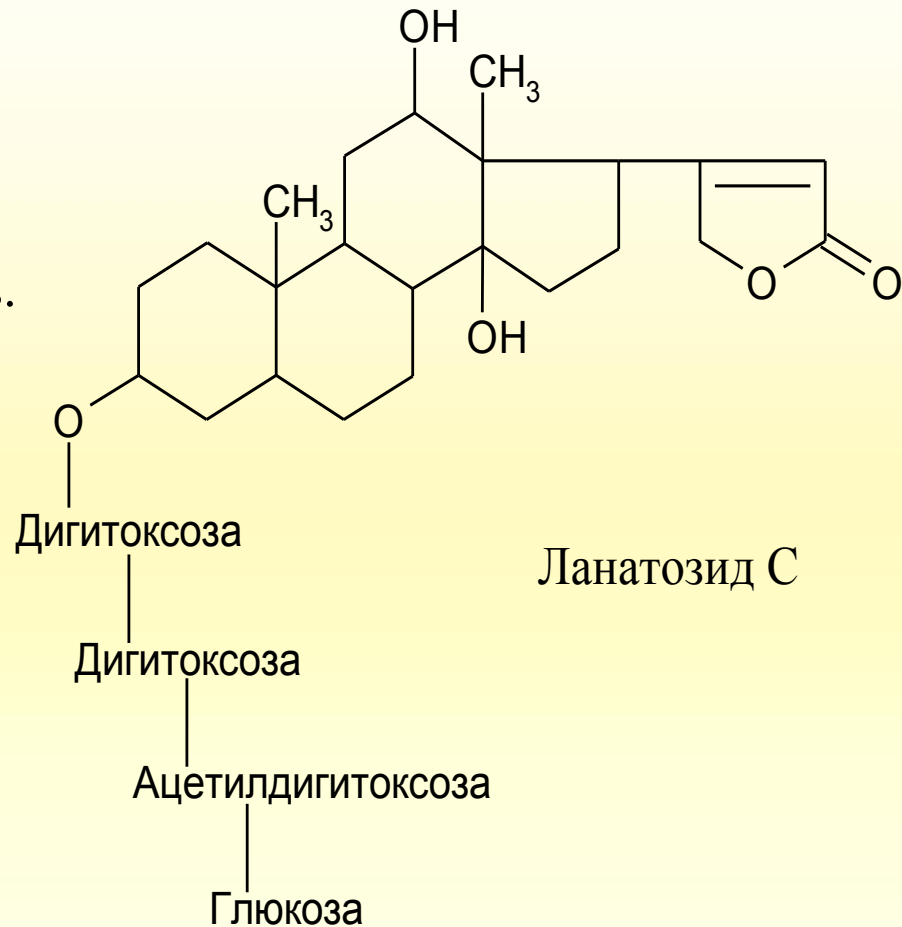


## Chemical constituents.

The leaves contain cardiac glycosides: lanatosides A, B, C, D, E, based on digitoxigenin and digoxigenin. Besides, they contain steroidal saponins, flavonoids, anthraquinone derivatives and phenolic acids.

## Uses.

The leaves are used almost exclusively for the preparation of the lanatosides and digoxin. Over the past decades digoxin has become the most widely used drug in the treatment of congestive heart failure and disturbances of circulation.



**Phytomedicine:** «Digoxin», «Celanid», «Lanatoside», «Lanatoside C», «Acetyldigoxin» - cardiotonic in the treatment of congestive heart failure and disturbances of circulation.

**Strophanhtus seed – *Semen Sthrophanthi***  
**Strophanthus - *Strophanthus Kombe Oliv.***  
**Family - *Apocynaceae***

**Distribution.** Strophanthus Kombe is distributed in the Eastern Africa, it is widely cultivated in Africa and India.

**Description.** The seeds are lanceolate or linear-lanceolate in shape, somewhat flattened, 12 to 18 mm long, 3 to 5 mm broad. The testa is densely covered with greyish-green or fawny silky hairs, which are directed towards the acuminate apex. On the ventral surface a small ridge, the raphe, runs from a point near the centre of the seed to its apex.

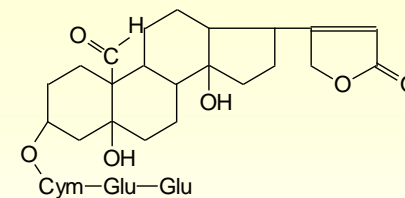
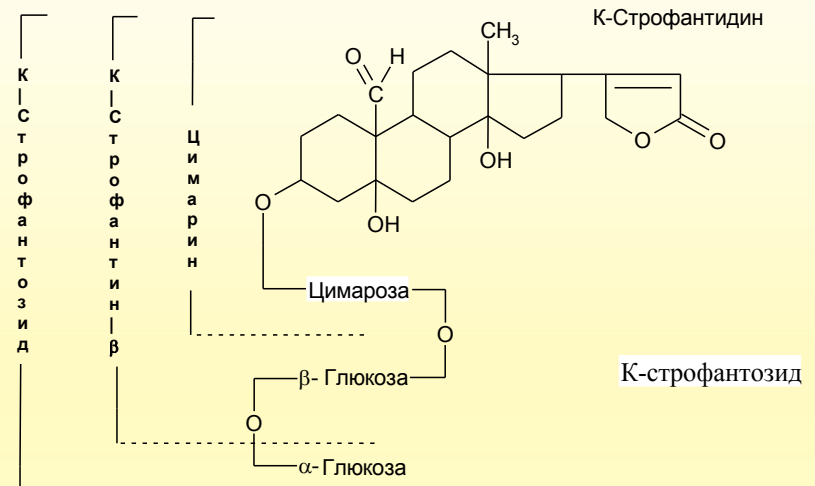
Ripe seeds are collected and dried at a temperature of about 60°C.





## Chemical constituents.

Strophanthus contains cardiac glycosides: K-strophanthoside, K-strophanthin- $\beta$  and cymarine; all of them based on the genin strophanthidin. The seeds also contain about 30% of fixed oil, the nitrogenous bases trigonelline and choline, resin and mucilage, saponins.



## Uses.

Strophanthus resembles digitalis in its action. Strophanthus **does not possess cumulative action.**

«*Strphanthin-K*», «*Strphanthin -G*», «*Strphanthidin acetate*» - cardiotoxic

# Adonis herb (Spring Pheasant's eye herb) – *Herba Adonidis vernalis*

**Spring Pheasant's eye - *Adonis vernalis* L.**

**Family - *Ranunculaceae***

The herbs are collected at the phase from the end of flowering to fruit-bearing and dried at the temperature of about 60°C.

**Description.** Raw material is represented by densely-leaved shoots about 35 cm in length, with flowers or without them, sometimes with flower-buds or fruits of various stage of development. The leaves are naked, green, alternate, sessile, wide-ovate in shape, palmately-lobed in 5 linear segments; two lower of them are shorter than the others.

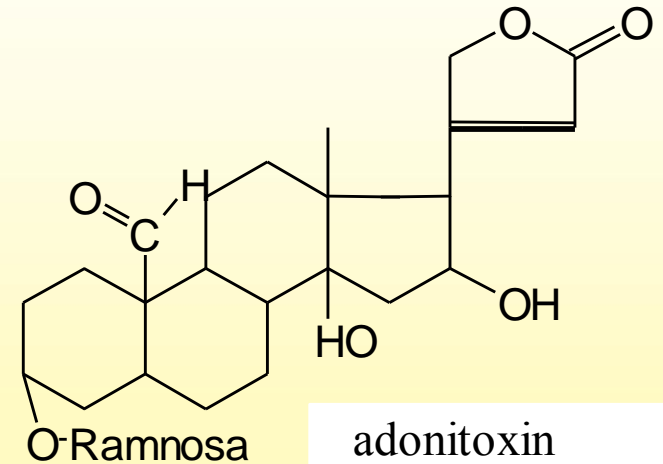
Flowers are arranged at the apex of the stem and branches; they have 10-20 oblong-elliptical goldish-yellow petals. Calyx is green, downy; it has 5-8 calyx lobes, ovate in shape. Fruit is oval in shape, consisting of numerous, fine greenish nutlets. The odour is weak, characteristic, the taste is bitter.



## Chemical constituents.

The herb contains cardiac glycosides: adonitoxin, cymarine, K-strophanthin- $\beta$ .

Flavonoids, saponins, tannins, carotenes, ascorbic acid are also found.



## Uses.

The preparations of Adonis are used when congestive heart failure takes place and as sedative agents. The preparations mainly increase of diuresis due to the flavonoid compounds.

«**Adonid**», tablet «**Adonis-bromine**» - cardiotoxic, sedative;



# **Convallaria (The lily-of-the-valley) herb, leaf, flowers – *Herba, Folium, Flores Convallariae***

**Lily-of-the-valley (Convallaria) - *Convallaria majalis* L.**

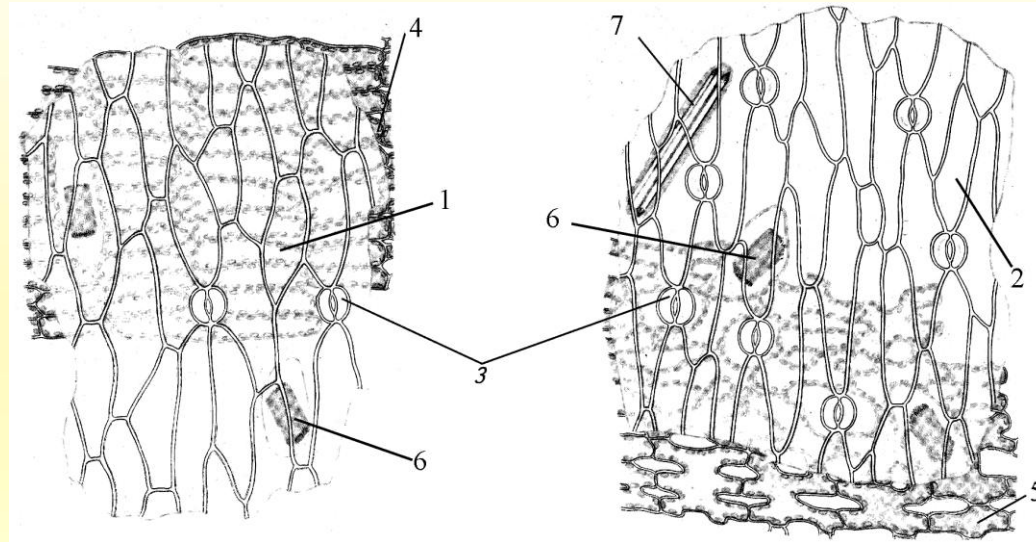
**Family - *Liliaceae***

**Collection.** The aerial parts collected, when the flowers are beginning to open and dried as rapidly as possible at a temperature of about 60°C.

**Description.** Three kinds of raw material are distinguished: flowers (inflorescence), leaves and herb. Leaves with long sheaths, separate or conjugate, oval or oblong-elliptical in shape; acuminate, entire, glabrous on both sides, with arching venation, green, petioles often yellowish. The leaf is 10-20 cm long, 3-8 cm wide. Flower scapes are naked, light green, triangular or half rounded in crosssection, terminating in a unilateral loose raceme. Flowers with a simple perianth are on bent flower stems. The corolla-like perianth is bell-shaped, 6 stamens on short filaments fixed at the base of the perianth. Odour is weak, faint.



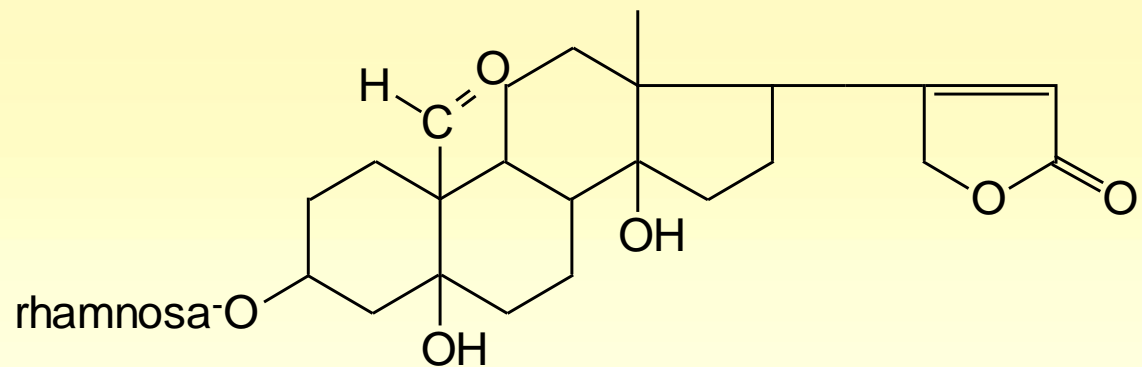
# Microscopical characters.



Surface preparation shows on both sides epidermal cells stretched along the leaf axis. Cells of the "lying" palisade tissue are seen under the upper epidermis stretched horizontally and situated cross-wisely in relation to the length of the leaf, which is characteristic of the lily-of-the-valley leaves. Stomata are present on both surfaces; they are surrounded, as a rule, by 4 epidermal cells and located along the length of the leaf. The needle crystals of calcium oxalate situated in groups of 2-4 and raphides are present in the mesophyll.

# Chemical constituents.

Herb contains cardiac glycosides, the main of them are the following: convallotoxin, which on hydrolysis gives strophanthidin and rhamnose and convalloside, when acted on by strophanthobiase yields convallotoxin and D-glucose. The herbs also contain saponins, flavonoids, coumarins.



## Uses.

Convallaria is used in medicine for its cardioactive properties, which are similar to those of digitalis, but much less cumulative. It is used for the treatment of neurosis of the heart and acute heart failure.

**Convallotoxin**

**Phytomedicines: Tincture, Corglycon,  
Convaflavin**



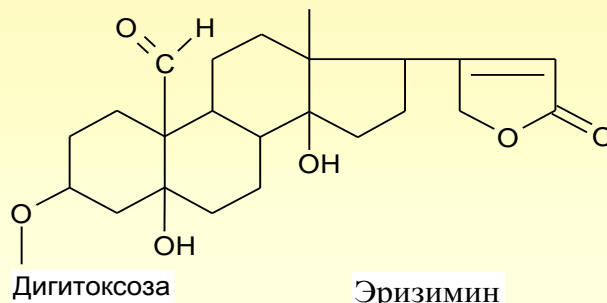
# Fresh Erisimum herb - *Herba Erysimi recens*

*Erysimum canescens* Roth and *Erysimum diffusum* Ehrh.

Family - *Brassicaceae (Cruciferae)*

**Plant.** Biannual herbaceous plant attaining a height of from 30 to 80 cm. In the first year's aerial growth consist of a rosette leaves. During the second year a stems is erect, branched with narrow linear-lanceolate leaves. The flowers are yellow and in terminal raceme. The fruit is a silique up to 7 cm in length, seeds are small, mostly reddish-brown.

**Distribution.** Siberia. Cultivated in Ukraine, Russia, Kazakhstan, Asia Minor.



**Constituents.** The cardiac tonic glycoside (up to 6 % in seeds and 1-1,5 % in leaves) The main glycosides are erysimin and erysimoside.

**Uses.** employed as cardiac stimulant. Pharmacological action similar to *Strophantus* preparations.

**Phytomedicine:** «*Cardiovalen*», «*Erysimin*» - cardiotoxic, diuretic, sedative



**Hellebore rhizome and root - *Rhizomata cum radicibus Hellebori***  
**Hellebore - *Helleborus caucasicus*,**  
***Helleborus purpurascens***  
***Ranunculaceae***

**Active const.**

- ✧ The cardiac tonic glycosides,
- ✧ steroidal saponines,
- ✧ resine,
- ✧ fatty oil.



Фармакологическое действие

Phytomedicin «**Corelborin**» - cardiotonic; antineoplastic action



# Squill Bulb – *Bulbus Scillae*

Squill (*Urginea maritima*) – *Scilla maritima* L.

Family - *Liliaceae*

**Collection.** The bulbs are collected in august, a month in which the plant has finished flowering and is without aerial leaves. After the dry outer scales have been removed, the bulbs are cut transversely into thin slices. These are dried in the sun or by stove heat, when they lose about 80% of their weight.

**Description.** The dried drug occurs in yellowish-white, translucent stripes about 0,5 - 5 cm length and tapering at both ends. The odour is slight; the taste is bitter and acrid.

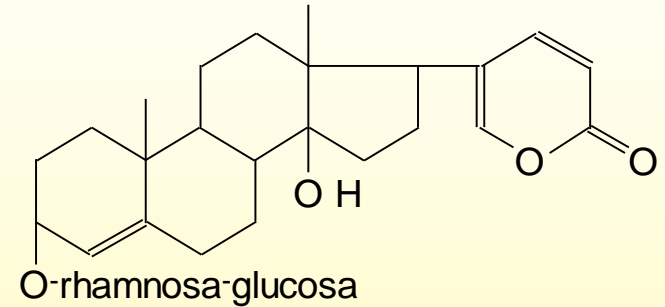


## Chemical constituents.

Squill contains cardioactive glycosides of which the principal one is scillaren A. On hydrolysis it yields the aglycone scillarenin, a bufadienolide, plus rhamnose and glucose. Other minor glycosides include glucoscillaren A (scillarenin + rhamnose + glucose + glucose) and proscillaridin A (scillarenin + rhamnose). The drug also contains flavonoids (they involve quercetin and kaempferol derivatives), sinistrin, a carbohydrate resembling inulin, mucilage, bitter substances (scillipicrine), the traces of volatile oil.

### Uses.

The glycosides are poorly absorbed from the gastrointestinal tract; they are of short-action duration and they are not cumulative. In small doses the drug promotes mild gastric irritation causing a reflex secretion from the bronchioles. It is for this expectorant action that it is widely used; in larger doses it causes vomiting.



**Scillaren A**

**Phytomedicine:**  
«Proscillaridin», «Talusin»

# Pharmacological properties of squill

- **White squill:**

it is an expectorant, but it also possesses emetic, cardiotoxic (proscillaridin A), and diuretic properties.

- **Red squill:**

it is used as a rat poison (scilliroside), because rodents lack the vomiting reflex, which makes red squill particularly lethal to these animals.

