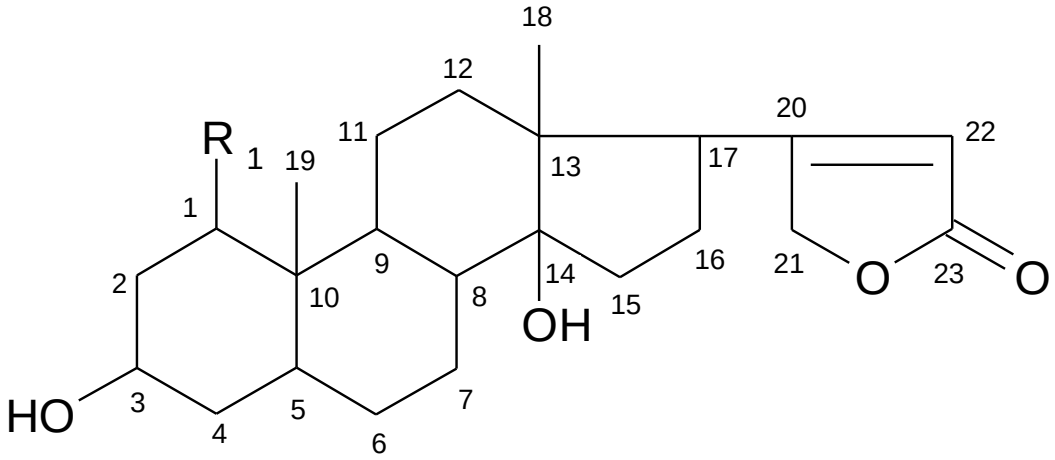


Steroidal Cardiac (cardioactive) Glycosides

1. General characteristic
2. Medicinal plants and plant materials

Steroidal cardioactive glycosides

- Cardiac glycosides are a group of natural products characterized by their specific effect on myocardial contraction and atrioventricular conduction.
- 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. Since, the improved circulation tends to improve renal secretion, which relieves the edema often associated with heart failure.

Distribution in nature

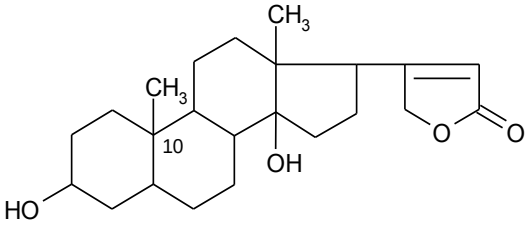
- **Cardiac glycosides** occur in small amounts in the seeds, leaves, stems, roots or barks of plants of wide geographical distribution, particularly of the Fam. *Apocyanaceae* (e.g. seeds of *Strophanthus,* roots of *Apocynum* and fruits of *Acokanthera);* others are found in the *Scrophulariaceae* (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*).

- **Cardiac glycosides** are a group of natural products, the structure of which comprise a steroidal aglycone having an unsaturated lactone at C-17, characterized by their specific effect on myocardial contraction

According to radical at C-17

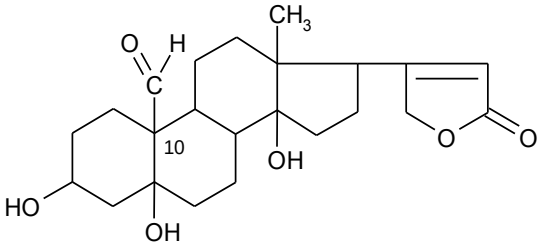
CARDENOLIDE

Group of *Digitalis*



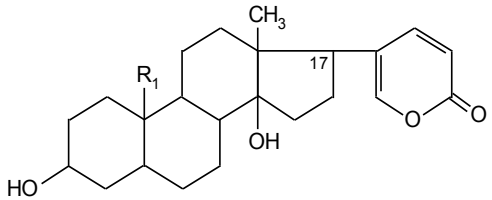
Folia Digitalis
Folia Digitalis lanatae
Folia Digitalis ferrugineae
Folia Digitalis ciliatae

Group of *Strofanthus*



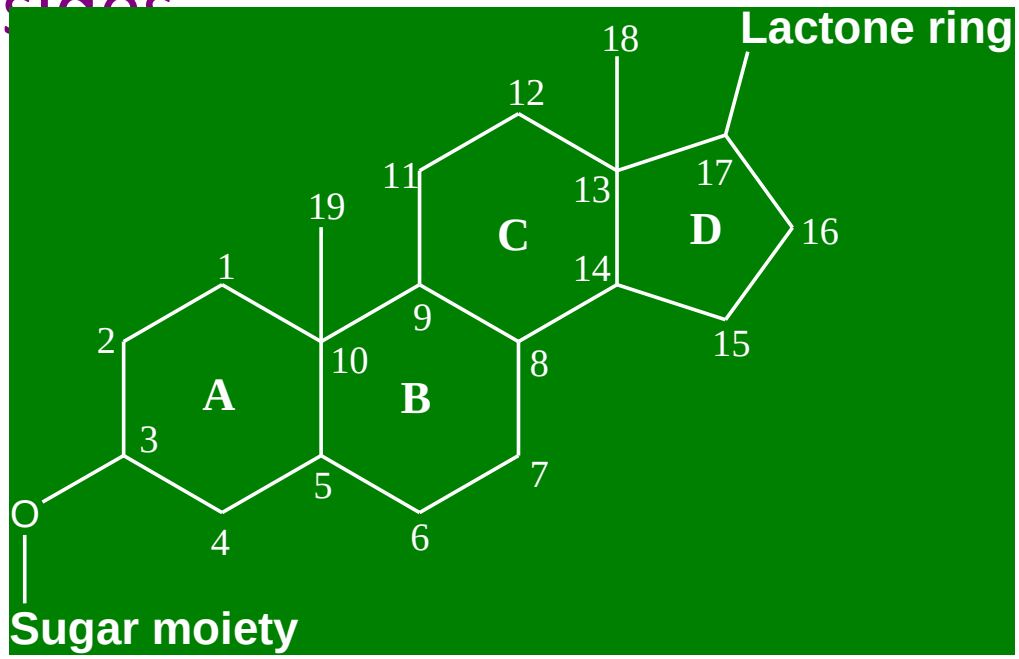
Semina Strophanthi
Herba Adonidis vernalis
Folia Convallariae
Herba Erysimi

BUFADIENOLIDES



Bulbus Scillae
Rhizomata cum radicibus Hellebori caucasici

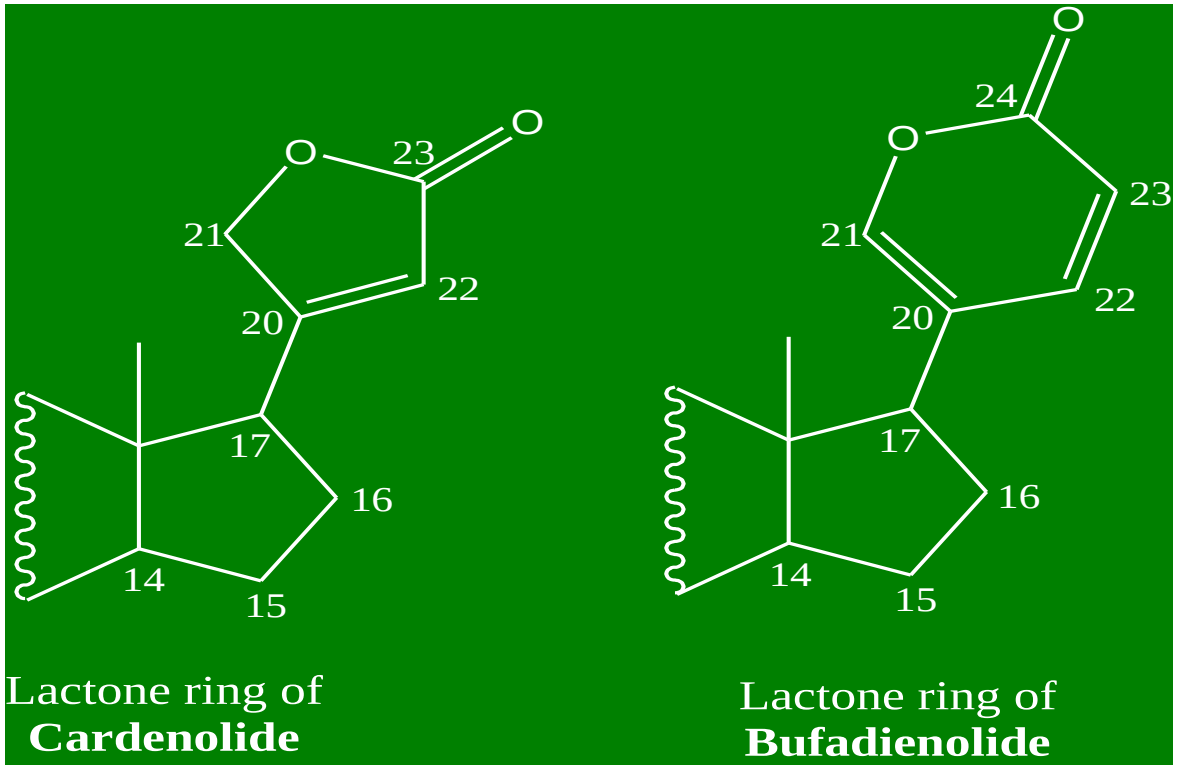
Structure of glycosides



- The structure comprise a steroidal aglycone of the (C_{23}) **cardenolide** type or of the (C_{24}) **bufadienolide** type, and a sugar moiety, most often an oligosaccharide.

A. Structure of the aglycones

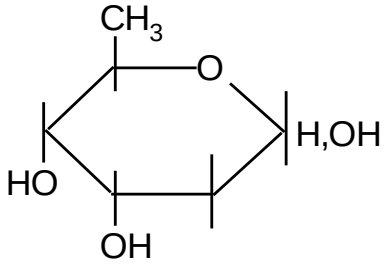
- All of the aglycones have in common the classic, tetracyclic, steroidal nucleus.
- The A, B, C and D rings normally have a *cis-trans-cis* configuration or less often, a *trans-trans-cis* configuration.
- Also common to all the aglycones is the presence of two hydroxyl groups: one is a 3β secondary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



- The size of the lactone ring distinguishes two groups of aglycones: the **C23** cardenolides with an α,β-unsaturated γ-lactone (= butenolide) and the **C24** bufadienolides with a di-unsaturated δ-lactone (= pentadienolide).

B. Structure of the sugar moiety

- The sugar moiety is generally linked to the aglycone through the hydroxyl group at C-3.
- The majority of the saccharides found in cardiac glycosides are highly specific:



D-digitoxose

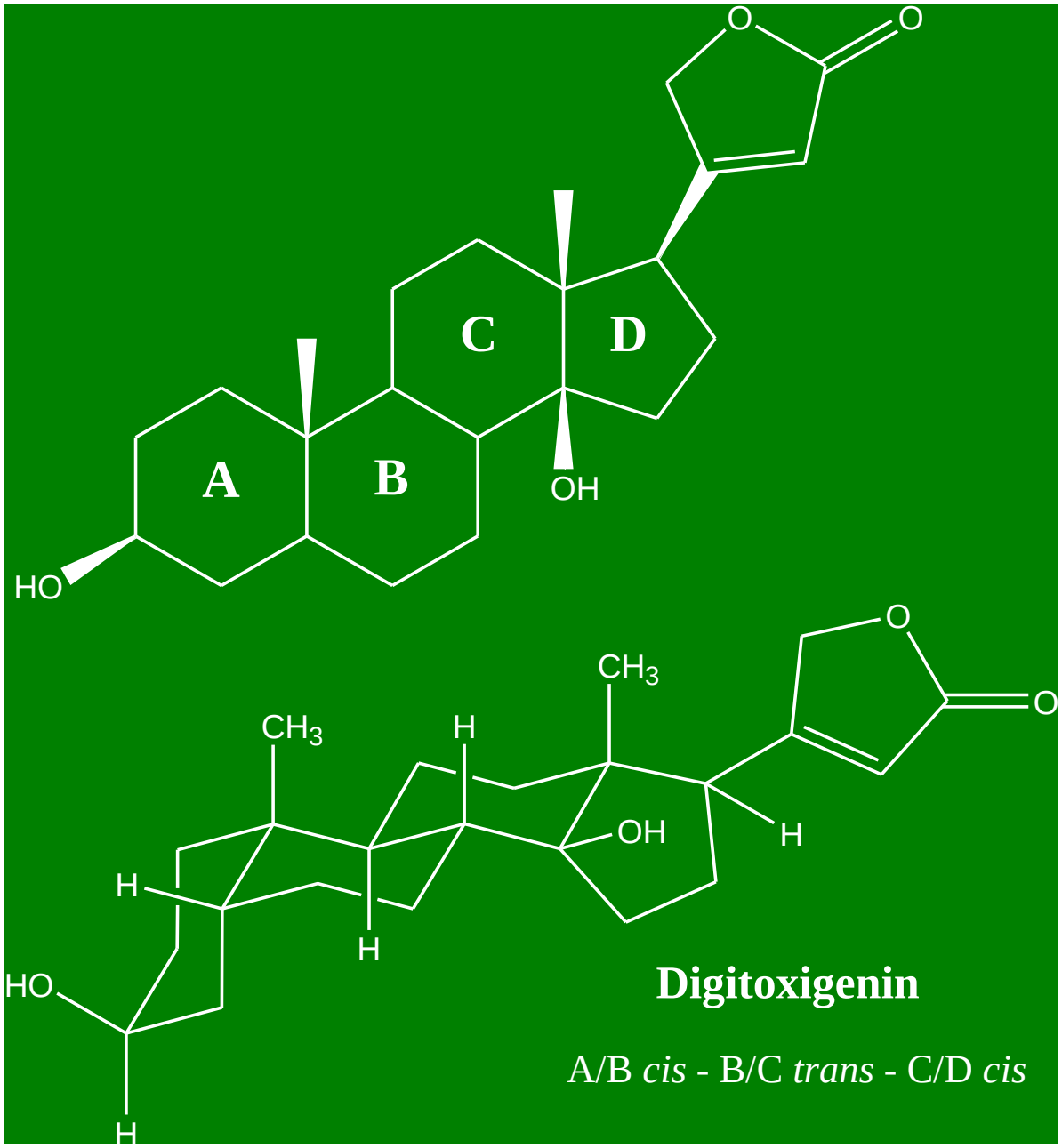
1. 2,6-dideoxyhexoses, e.g. D-digitoxose
2. 2,6-dideoxy-3-methylhexoses, e.g. D-diginose
3. 6-deoxyhexoses, e.g. L-rhamnose
4. 6-deoxy-3-methylhexoses, e.g. D-digitalose
5. Hexose, e.g. glucose (*when these is a glucose unit, it is always terminal*).

- 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, and it must be in the β 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.



Digitoxigenin

A/B *cis* - B/C *trans* - C/D *cis*

Biosynthetic origin

- Aglycone of the cardiac glycosides are derived from mevalonic acid but the final molecules arise from a condensation of a C_{21} steroid with a C_2 unit (the source of C-22 and C-23). Bufadienolides are condensation products of a C_{21} steroid and a C_3 unit.

👁 Color reactions

- They can be due to the sugars or to the aglycone:

A. ***Color reactions of the sugars***. The only color reactions of the sugars that are of interest are those specific to 2-deoxyhexoses. e.g. ***Keller-Kiliani test***.

B. ***Color reactions of the aglycones*** (steroidal nucleus). These are positive with any compound containing a steroidal nucleus including cardenolides or bufadienolide:

1) Antimony trichloride ($SbCl_3$)

2) Liebermann's test (for bufadienolides)

c. ***Color reactions of the aglycones*** (lactone ring).

These are characteristic for cardenolides having a five-membered lactone ring:

1. Legal's test
2. Raymond's test
3. Kedde's test
4. Baljet's test

Pharmacological properties

- Cardiac glycosides increase the force and speed of contraction of the heart. In patients with cardiac insufficiency, this positive inotropic effect translates into [1]an increase in cardiac output, [2]an increase in cardiac work capacity without any increase in oxygen consumption, [3]a decrease in heart rate, and, indirectly, [4]a decrease in arterial resistance. The glycosides are thought to act at the membrane level, by inhibition of the *Na-K ATPase*, which would result in an increase of the intracellular calcium ion concentration.

Despite numerous experimental investigations, the mechanism of action of the cardiac glycosides is still not completely known; however, observations have implicated Na^+, K^+-ATPas as the receptor enzyme. This enzyme catalyzes the active transport of Na^+ out of the cell and the subsequent transport of K^+ into the cell.

Na^+, K^+-ATPas operates in all cell membranes to maintain the unequal distribution of Na^+ and K^+ ions across the membrane. However, in the myocardium the ion exchange is rapid because it is required after each heart beat; therefore, an inhibition of Na^+, K^+-ATPas has a greater effect on heart tissue than on other cells of the body. When the heart beats, a wave of depolarization passes through it, changing the permeability of the cell membranes. Na^+ moves into the cell by passive diffusion and K^+ moves out. Na^+, K^+-ATPas supplies the energy from ATP to reverse this process and to pump the Na^+ out of the cell and the K^+ into the cell against a concentration gradient.

Inhibition of Na^+, K^+-ATPase by the cardiac glycoside results in an increase in Na^+ and a decrease K^+ within the cell which, in turn, stimulates a secondary Na^+ Ca^{2+} exchange mechanism that functions to remove intracellular Na^+ with a subsequent increase in intracellular Ca^{2+}. The positive inotropic action or muscle contraction enhancement of cardiac glycosides is mediated through the increase in Ca^{2+}. Ca^{2+} interacts with troponin which then, through its action on tropomyosin, unmasks the binding sites on actin that bind myosin, allowing for the formation of the contractile protein actomyosin.

Therapeutic indications

- Cardiac glycosides are currently indicated for:

1. Cardiac insufficiency with low output (generally in combination with diuretics), particularly when there is atrial fibrillation.

2. Supraventricular rhythm abnormalities: to slow down or decrease atrial fibrillation or flutter.

Examples

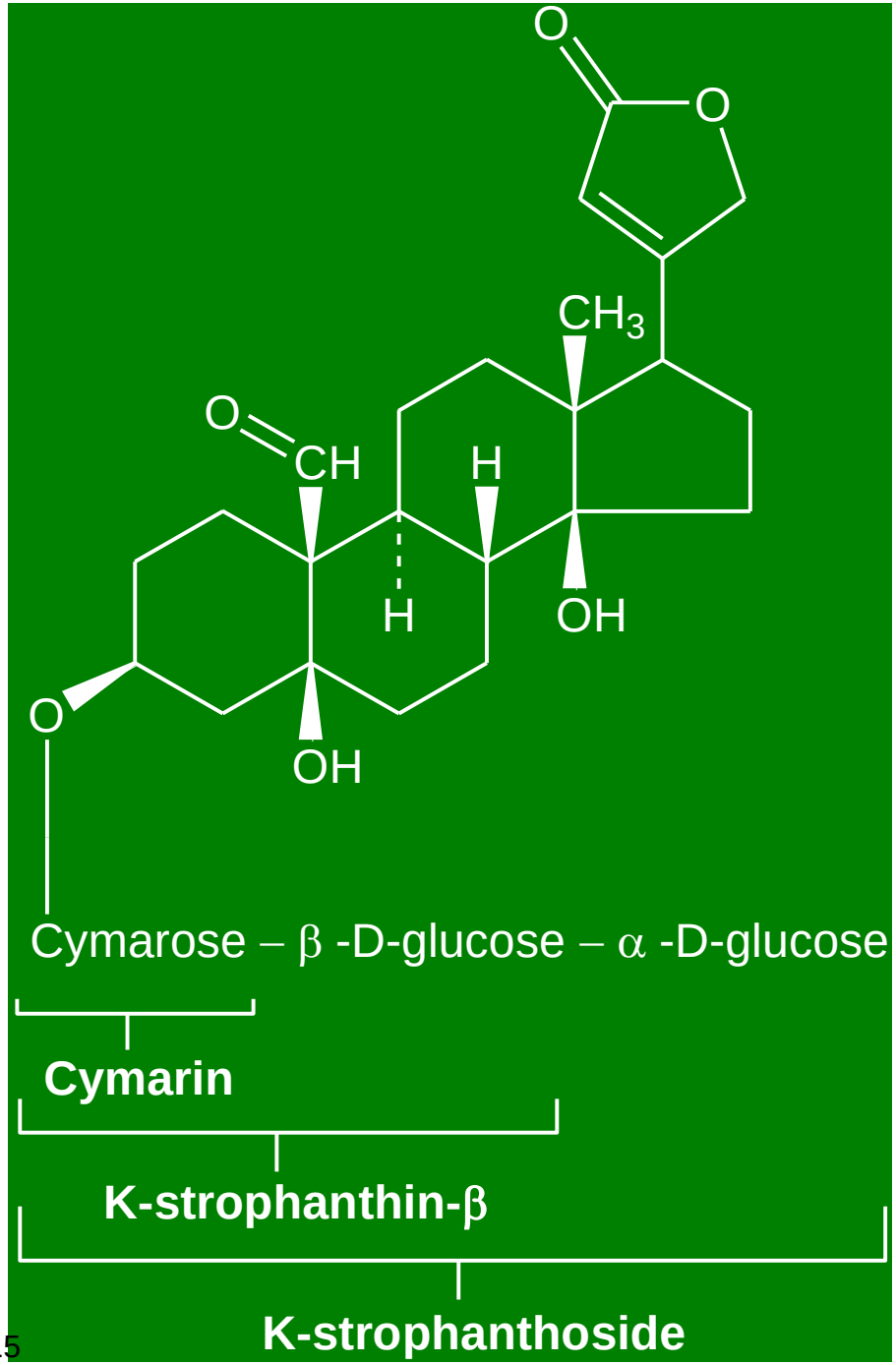
- **<u>Strophanthus glycosides</u>**

  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-β**
3. **Cymarin**



- **Squill glycosides**

  Urginea maritima (L.)

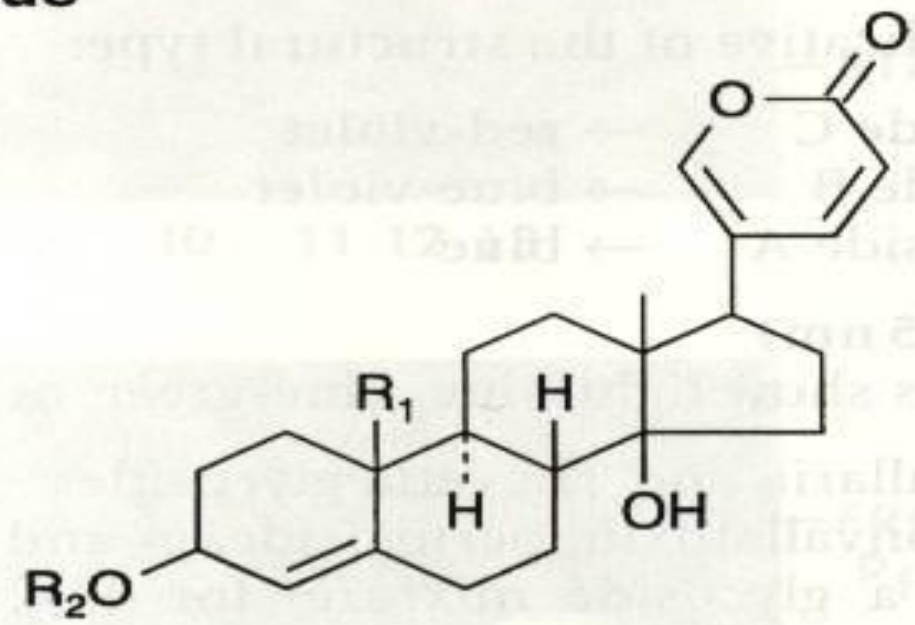
  0.1% – 2.4% total bufadienolides, ~15 glycosides
- **White variety:** average 0.2%-0.4%

  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

Scillae bulbus



	R_1	R_2
Scillarenin	CH_3	H (Aglycon)
Proscillaridin A	CH_3	Rham
Scilliphaeoside	H	Rham
Scillaren A	CH_3	Gluc-Rham
Glucoscillaren A	CH_3	Gluc-Gluc-Rham

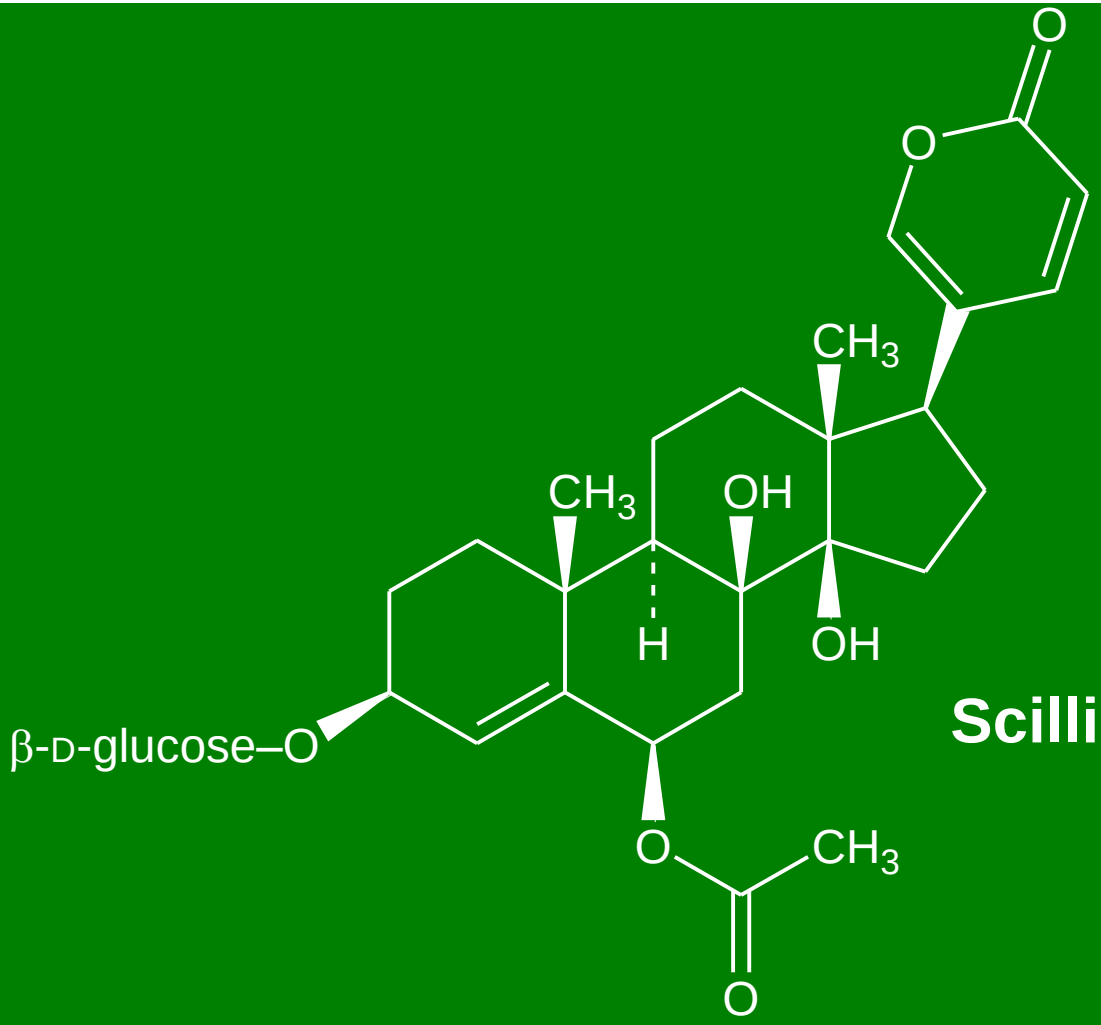
Pharmacological properties of squill

- **White squill:**

  it is an expectorant, but it also possesses emetic, cardiotonic (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.



Scilliroside

(3β,6β)-6-(Acetyloxy)-3-(β-D-glucopyranosyloxy)-8,14-dihydroxybufa-4,20,22-trienolide

- **Digitalis glycosides**

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

1. Digitalis purpurea folium (Red foxglove leaves)

   0.15% – 0.4% total cardenolides, ~ 30 glycosides

   Purpurea glycosides A and B (~60%), digitoxin (~12%), gitoxin (~10%) and gitaloxin (~10%).

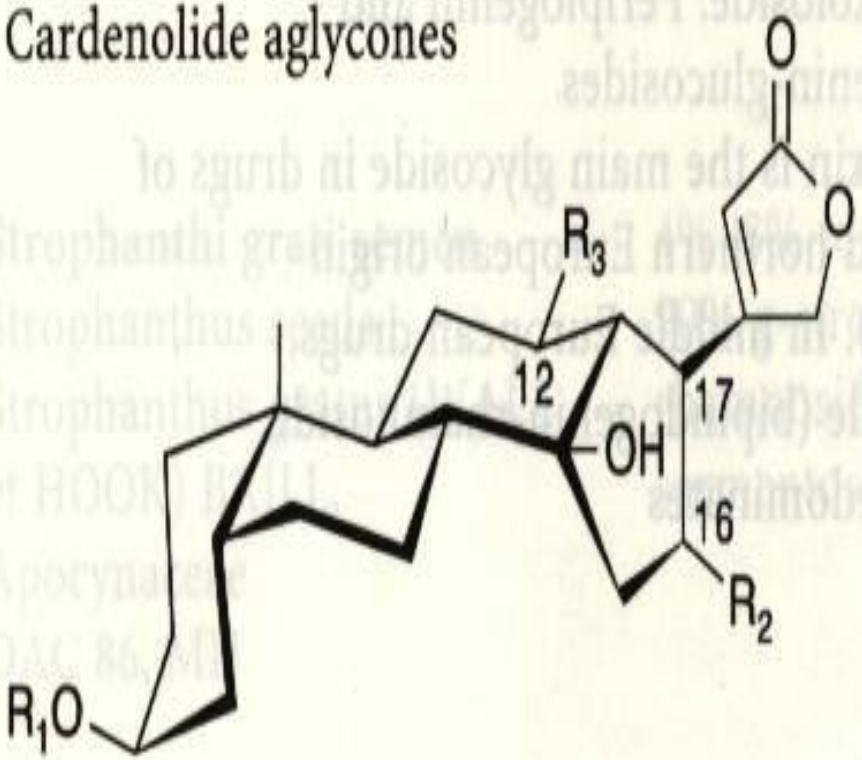
2. Digitalis lanata folium (White foxglove leaves)

   0.5% – 1.5% total cardenolides, ~ 60 glycosides

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

Digitalis lanatae and Digitalis purpureae folium

	R_1	R_2	R_3
Cardenolide aglycones			
Digitoxigenin	H	H	H
Gitoxigenin	H	OH	H
Digoxigenin	H	H	OH
Diginatigenin	H	OH	OH
Gitaloxigenin	H	O-CHO	H



- **Digitoxin** is a cardiotonic glycoside obtained from *D. purpurea*, *D. lanata*.
- It is the most lipid-soluble 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.

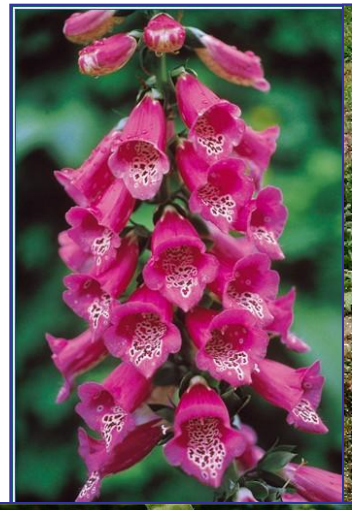
- **Digoxin** is the most widely used of the cardiotonic glycosides, and it is obtained from the leaves of *D. lanata*.
- It is a highly potent drug and should be handled with exceptional care.
- Digoxin tablets are 60 to 80% absorbed.
- Digoxin is indicated when the risk of digitalis intoxication is 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.

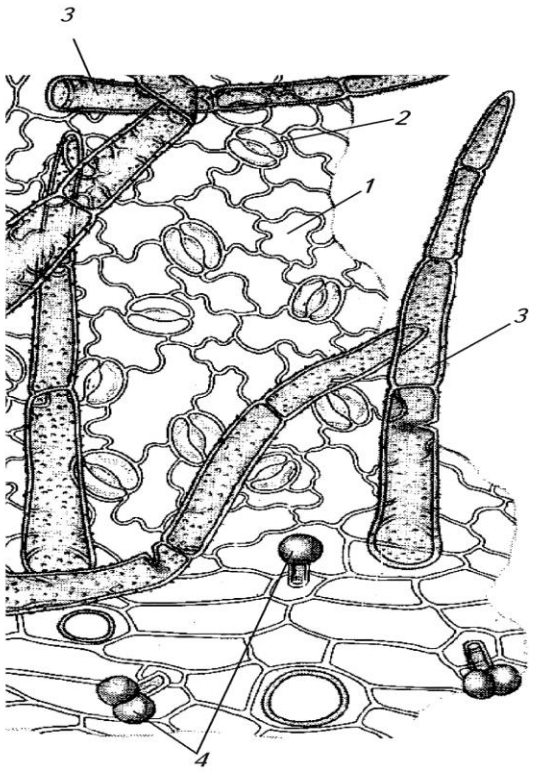
Descript. The leaf is brittle and often occurs broken. The upper surface is green and the lower surface is greyish-green. The apex is subacute and the margin is dentate or serrate. The base is decurrent. The venation is pinnate, the lateral veins being prominent especially on the lower surface, leaving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



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.

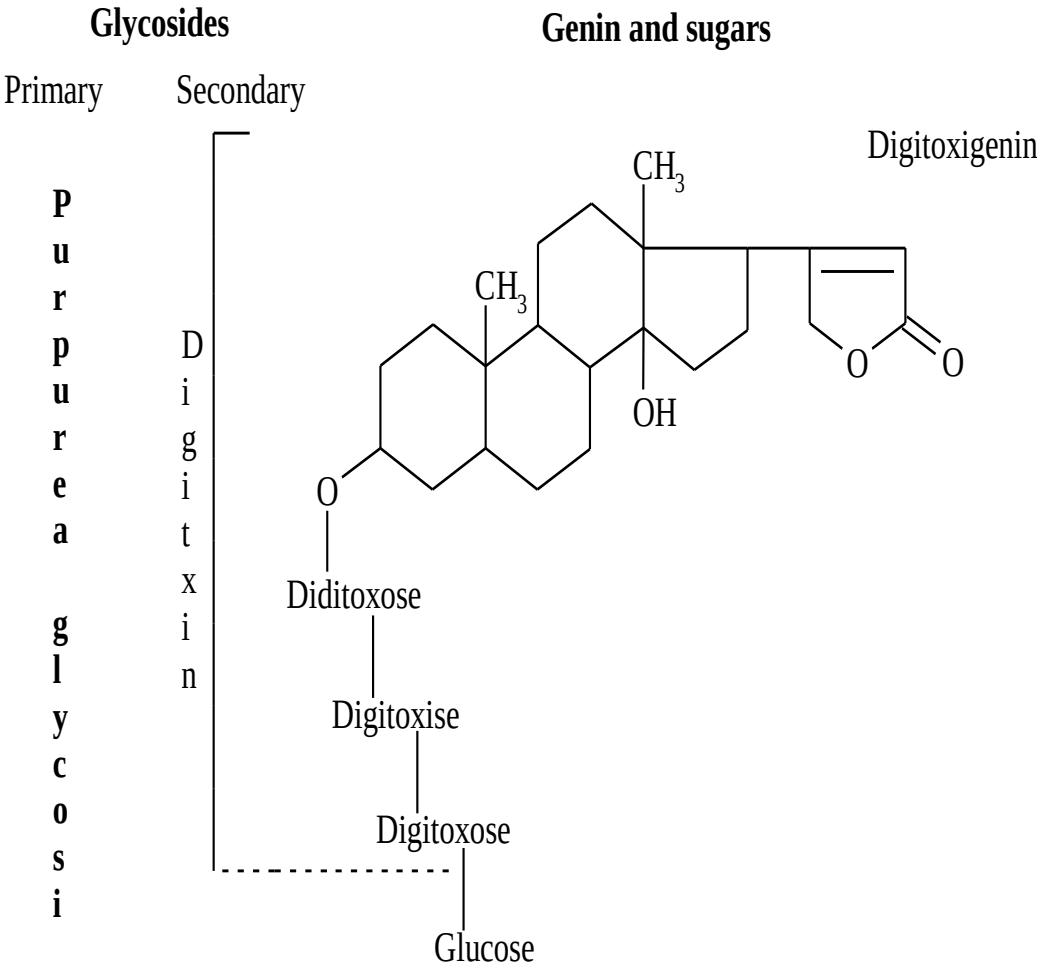
Diagnostic characters:

Epidermal cells (1) walls are straight or slightly sinuous on the upper surface and markedly sinuous on the lower surface; the cuticle is smooth. Trichomes are of two types: uniseriate, bluntly pointed non-glandular, usually of three to five cells, often with one or more collapsed cells, walls mostly finely warty or faintly striated (3); glandular trichomes usually with a unicellular, sometimes a multicellular uniseriate stalk and a unicellular or bicellular head. Anomocytic stomata are absent or very rare on the upper surface, numerous on the lower surface.



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 theree 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 prolongated uses of digitalis take place it is necessary to foresee the possibility of their accumulation in the body.

Digitalis lanata leaf – *Folium Digitalis lanatae*
Wooly Foxglove, Grecian Foxglove - *Digitalis lanata Ehrh.*
Family - *Scrophulariaceae*

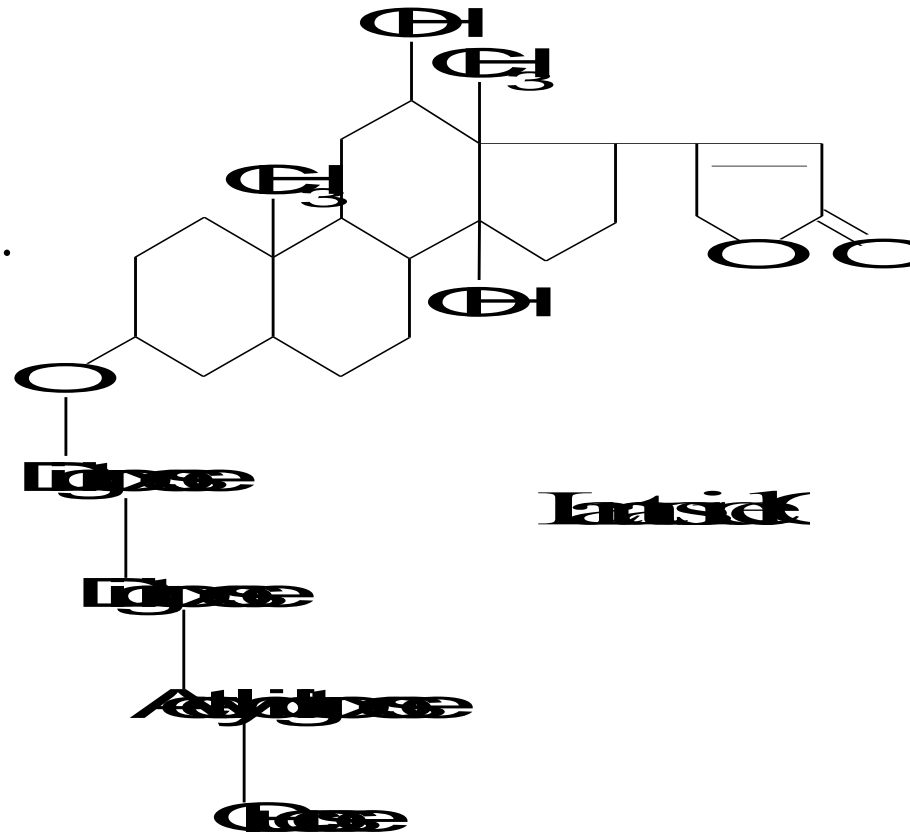
Distribution. The plant is indigenous to central and southeastern Europe. It is also cultivated in Holland, Ecuador, USA and other countries.

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^{o}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.

PHARMACOLOGICAL EFFECT

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

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

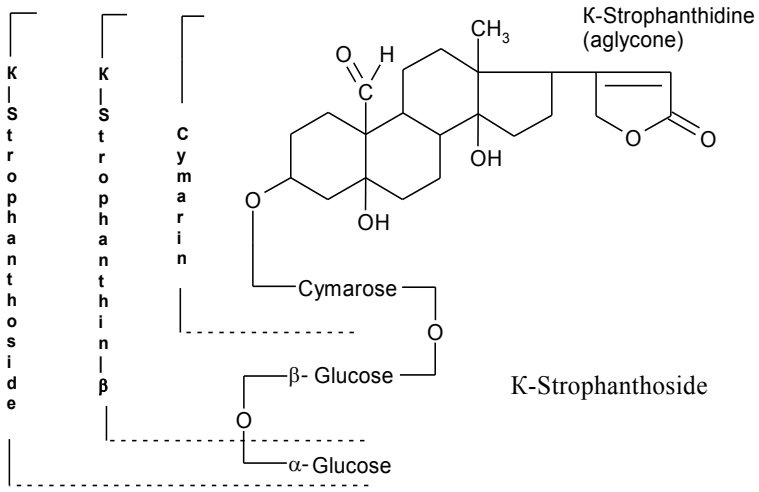
Distribution. Strophanthus Kombe is distributed in the Eastern Africa, it is widely cultivated in Africa and India.

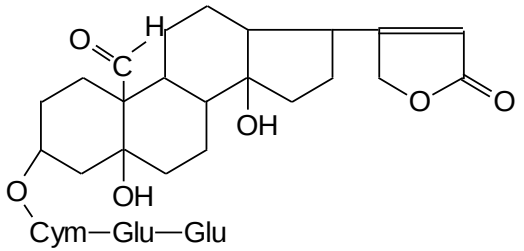
Description. The seeds are lanceolate or linear-lanceolate in shape, somewhat flattened, 12 to 18 mm long, 3 to 5 mm broad. The testa is densely covered with greyish-green or fawny silky hairs, which are directed towards the acuminate apex. On the ventral surface a small ridge, the raphe, runs from a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

Ripe seeds are collected and dried at a temperature of about 60^{o}C.

Chemical constituents.

Strophanthus contains cardiac glycosides: K-strophanthoside, K-strophanthin-β and cymarin; 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.**

«*Strophanthin-K*», «*Strophanthin -G*», «*Strophanthidin acetate*» - cardiotonic

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 60ºC.

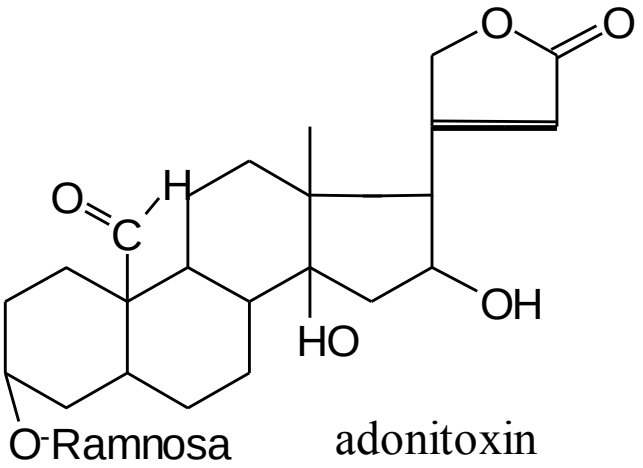
Description. Raw material is represented by densely-leaved shoots about 35 cm in length, with flowers or without them, sometimes with flower-buds or fruits of variousstage of development. The leaves are naked, green, alternate, sessile, wide-ovate in shape, palmati-sected in 5 linear segments; two lower 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, cymarin, K-strophanthin-β.

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



adonitoxin

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 compouds.

«*Adonisid*», tablet «*Adonis-bromine*» - cardiotonic, sedative;

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

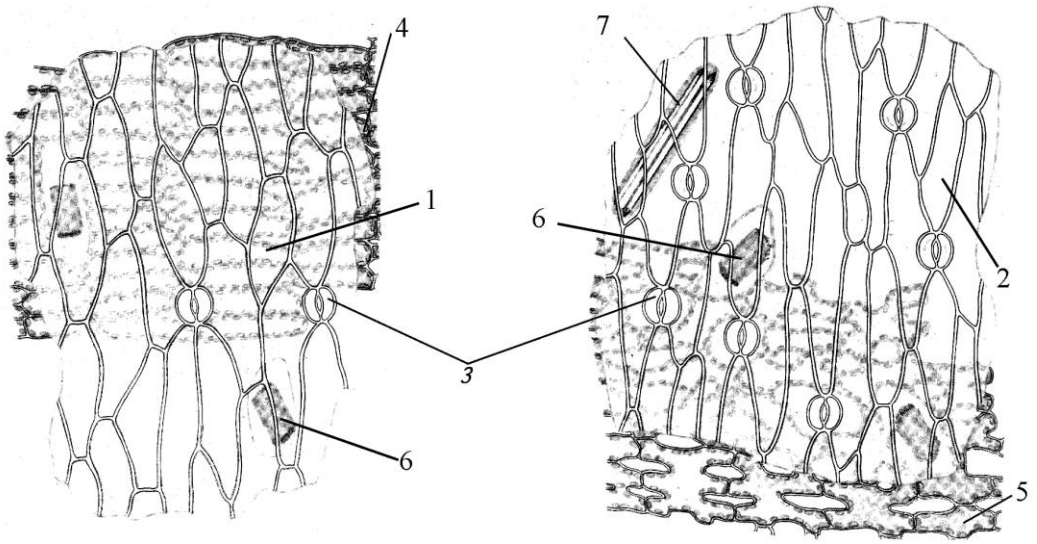
Lily-of-the-valley (Convallaria) - *Convallaria majalis L.*

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 distinquished: 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, trianglular or half rounded in crossection, 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.

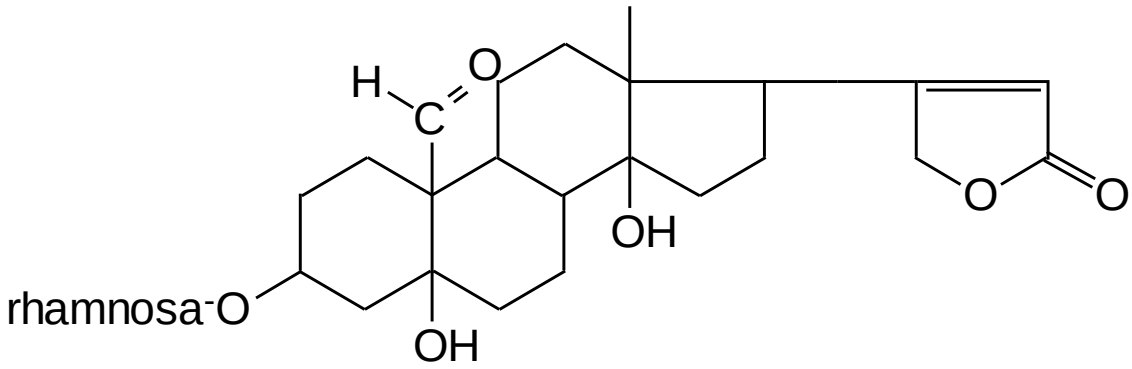
Microscopical characters.



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 inrelation 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 jields convallotoxin and D-glucose. The herbs also contain saponins, flavonoids, coumarins.



Convallotoxin

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.

Phytomedicines: Tincture, Corglycon, Convaflavin

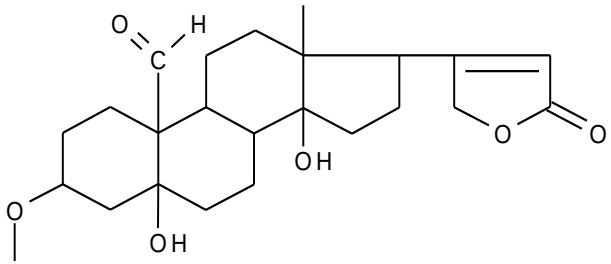
Fresh Erisimum herb - *Herba Erysimi recens*

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.



Digitoxose Erysimin

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*» - cardiotonic, diuretic, sedative

Anatomical characteristic.

Epidermis cells is small slightly wavy-walled (1). Stomata (3)cells is small.The stomatal apparatus is characteristic, the pair of guard cells (2) is surrounded by third neighboring cell, smaller than the other two. The main diagnostic significance have numerous non-glandular hairs (4). They unicellular, different form, branched, with 3-5 end. They have thick cuticle and papillose wall (see in figure).

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.

PHARMACOLOGICAL ACTIVITY

Phytomedicin «*Corelborin*» - cardiotonic; antineoplastic action

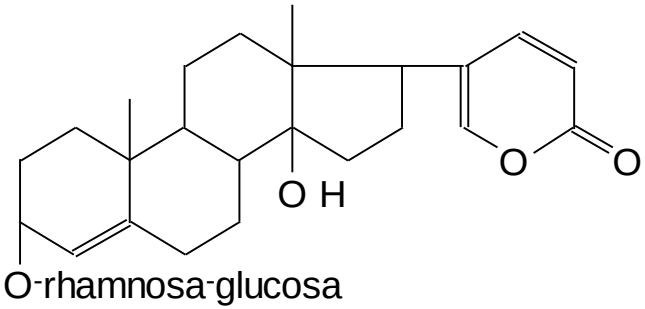
Squill Bulb – *Bulbus Scillae*
Squill (Urginea maritima) – *Scilla maritime L.*
Family - *Liliaceae*

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.



Scillaren A

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.

Phytomedicine: «Proscillaridin», «Talusin»