CARDIOVASCULAR DISEASES

Diseases of cardiovascular system (CVS) belong to most serious worldwide health problems.

Ischemic heart disease (IHD) is in prevalence caused by atherosclerosis of coronary arteries (ischemia is local disorder of blood supply, atherosclerosis is a form of hardening of coronary arteries) *ischó – hold; haima – blood*

Chronic cardiac insufficiency

Hypertension (high blood pressure) is most often occurring CVS disease of adult persons (≥ 20 % of inhabitants)

- accelerates development of atherosclerosis
- accelerates IHD
- induces brain vascular disorders

Diseases of blood vessels – most often, varicose veins at cca 15 % of population above 18 years, mainly women

- Venous inflammations approx. 2 % of population (complications – streptococcal and fungal infections)

CARDIOVASCULAR DISEASES

Activity of Health Care

PREVENTION

THERAPY

CARDIOVASCULAR DISEASES

PREVENTION

Affection of risk factors

- Change of lifestyle
- High level of blood cholesterol
- High blood pressure
- Addiction to cigarettes smoking („paper tube filled with weed, which possesses from one side fire and from opposite lunatic“)
- Sedentary way of life („kinetic crises“)
- Overeating
- Diabetes
- Excessive stress

CARDIOVASCULAR DISEASES

THERAPY

To hit the certain level of disease which shows very complex character – therefore in maximal rate to use complex approach to therapy

- Drugs affecting heart
  - cardiotonics
  - antidysrytmics (antiarhytmics)
- Drugs affecting blood vessels
  - vasodilatants
  - vasoconstringents
- Antihypertensives
- Venopharmacs
- Drugs affecting hyperlipoproteinemia
- Sedatives

DRUGS AFFECTING HEART

Heart action is possible therapeutically affect by drugs targeting:

- directly heart muscle
- cardiac conduction system
- coronary arteries
- CNS
- VNS

Traditional division

- Cardiotonics
- Antidysrytmics (antiarhytmics)

DRUGS AFFECTING HEART

CARDIOTONICS

- Increase tonus of decompenzed myocardium
- Increase the force of contraction
- Improve energetic balance
- Show indirect diuretic effect
- In therapeutic doses do not affect healthy heart

DRUGS AFFECTING HEART

Cardiotonics

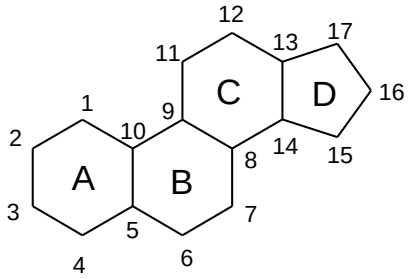
Cardioactive glycosides

- Native biogenic compounds
- Products of their hydrolysis
- Semisyntethic analogues

Present especially in plants of family

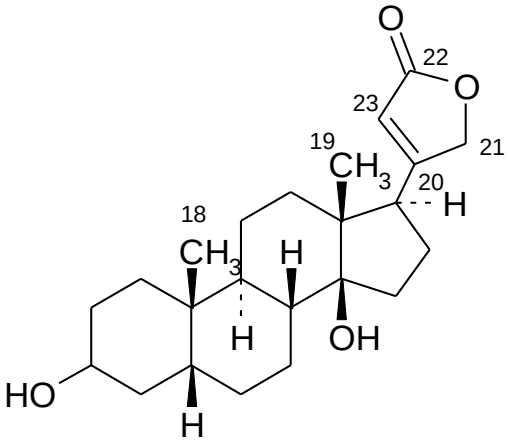
- Scrophulariaceae – *Digitalis* spp.
- Apocynaceae – *Strophantus* spp., *Nerium oleander, Thevetia* spp.
- Liliaceae – *Convallaria majalis*, *Urginea maritima*
- Ranunculaceae – *Adonis vernalis*, *Helleborus niger*
- Brassicaceae – *Erysimum* spp., *Cheiranthus* spp.

CLASSIFICATION OF CARDIOACTIVE GLYCOSIDES

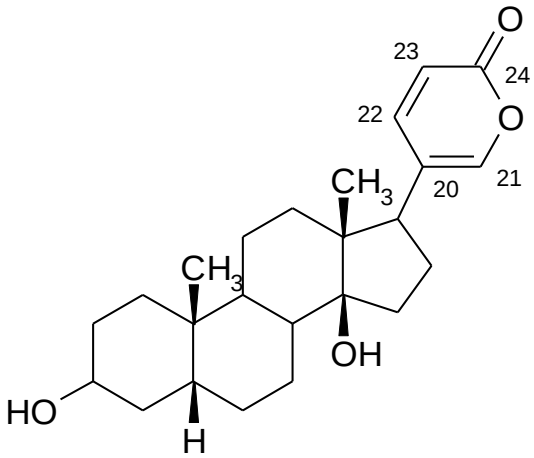


cyklopentanoperhydrophenanthrene

Relationship with sterols, sex hormons, hormons of adrenal gland, with bile acids and steroidal saponins

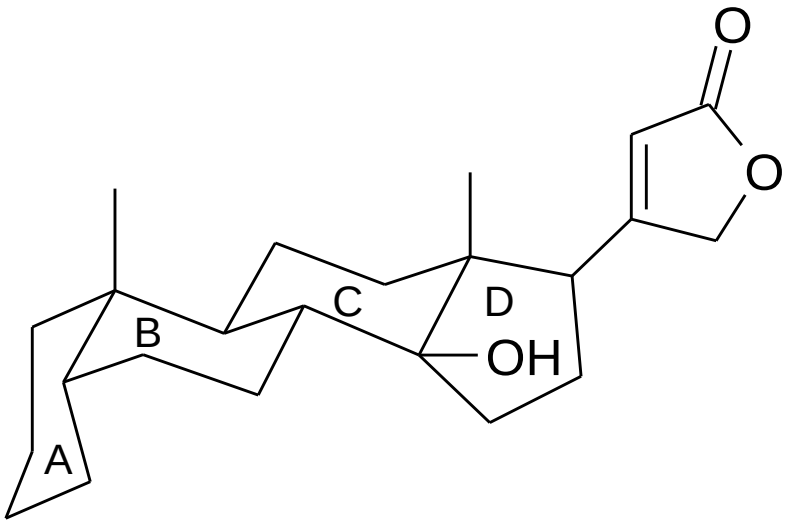


C23 cardenolide

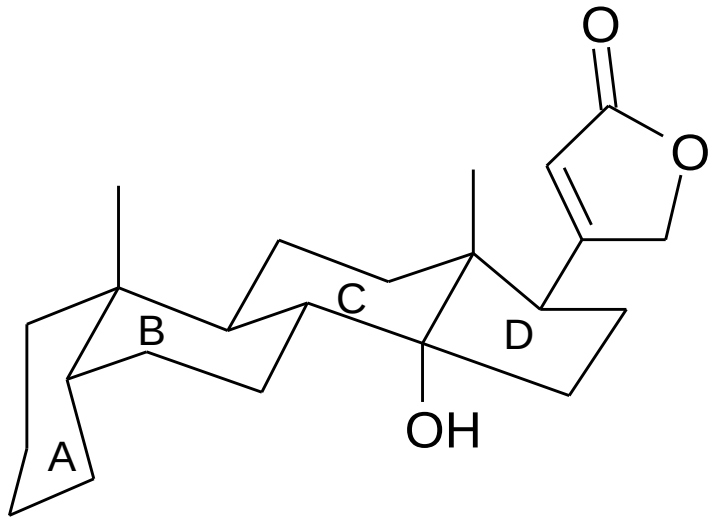


C24 bufadienolide

CARDENOLIDES



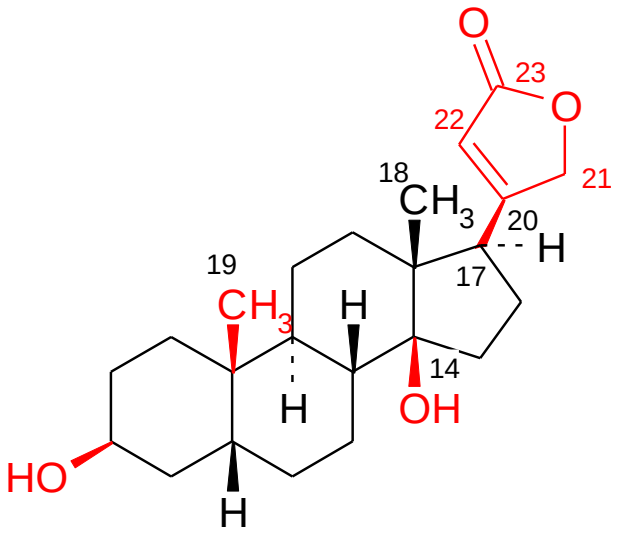
anelation C/D-*cis* (active)



C/D-*trans* (non-active)

CARDENOLIDES

C_{23} type; *Digitalis*, *Strophanthus*



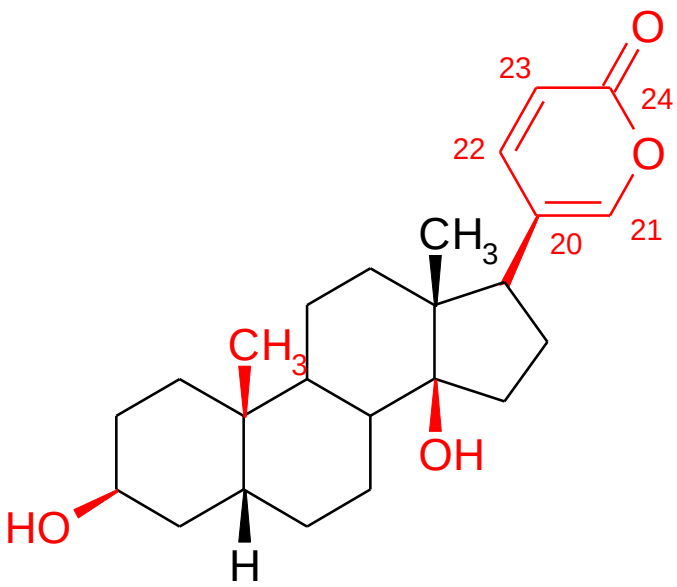
card-20(22)-enolide

Structure activity conditions

1. at C17 α,β-unsatturated γ-lactone (butenolide) ring β-oriented
2. hydroxyl group at C3 β-oriented
3. hydroxyl group at C14 β-oriented
4. anelation of rings A,B – *cis*
5. anelation of rings C,D - *cis*

BUFADIENOLIDY

C_{24} typ Scilla, Buffo

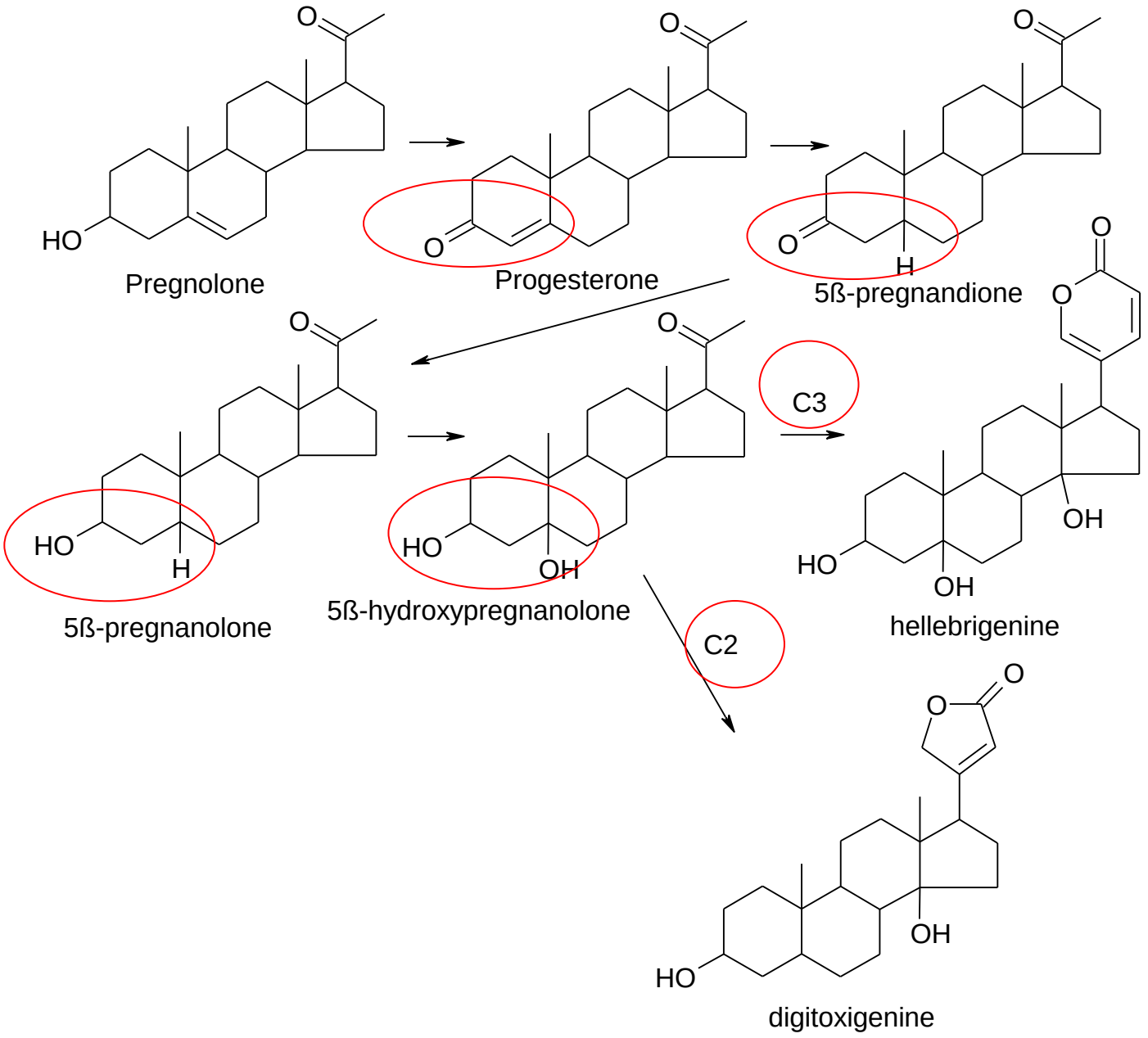


bufa-20,22-dienolide

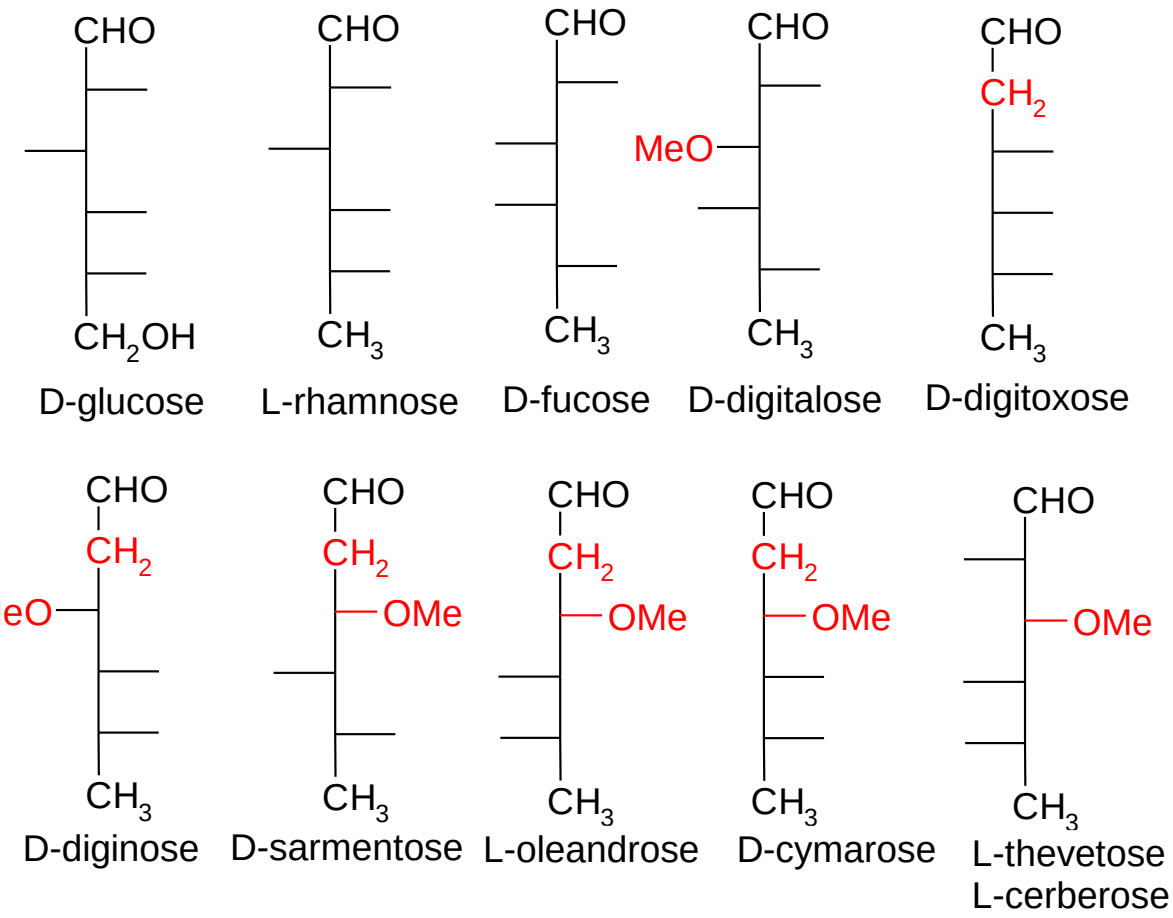
Structure activity conditions

1. at C17 α-pyrone lactone (cumaline) ring β-oriented
2. hydroxyl group at C3 β-oriented
3. hydroxyl group at C14 β-oriented
4. anelation of rings A,B – *cis*
5. anelation of rings C,D - *cis*

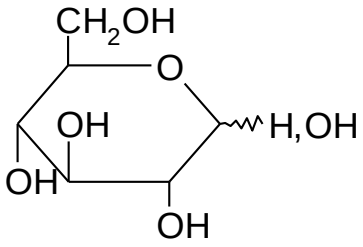
Cardiotonics



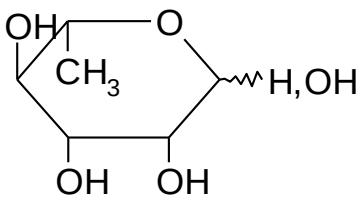
SUGAR COMPONENTS OF CARDIOACTIVNE GLYCOSIDES



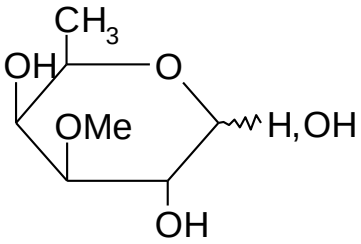
SUGAR COMPONENTS OF CARDIOACTIVNE GLYCOSIDES



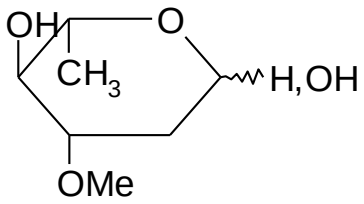
D-glucose



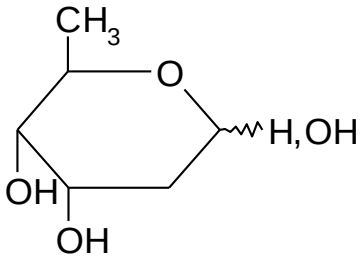
L-rhamnose



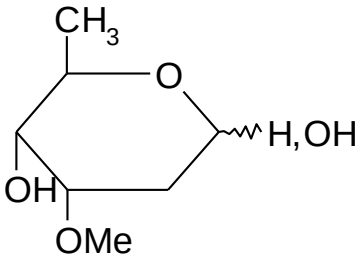
D-digitalose



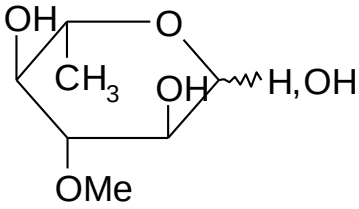
L-oleandrose



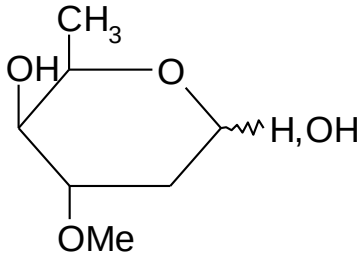
D-digitoxose



D-cymarose



L-thevetosa



D-sarmentose

CARDIOACTIVNE GLYCOSIDES

Influence on myocardium by effect on membrane bounded **Na^+, K^+-ATPase** connected with sodium pump

- provides quiescent potential in excitable cells.
- inhibition of this enzyme - following depolarization of membrane and further processes

1. Mechanical effect of sodium pump inhibition:
   - Decrease of sodium concentration triggers influx of Ca^{2+} into cell and it also increase deliberation of Ca^{2+} from cell internal storage
   - High level of Ca^{2+} causes action myosin + actin
   - Strengthened contraction
   - Improvement of ventricular function, limitation of pathological feedback mechanisms
   - Vasodilatation, decrease of peripheral resistance

2. Electrophysiological effect:
   - Indirect
     - Stimulation of *nervus vagus*
     - Senzibilization of baroreceptores
     - Negative chronotropic effect
   - Direct
     - Change of action potential, Ca accumulation
     - Possibility of rise of extrasystols
     - Bigeminia and trigeminia

Intoxication:

- **Extracardial symptoms**: nonspecific, nausea and vomiting, headache, fatigue, diarrhea, colored vision, neuropsychic disorders.
- **Cardiac symptoms:** Slowering of conductivity - AV block I.-III. Of grade. Increasing of automacy is manifested often by tachycardia, nodal tachykardia and ventricular tachyarhytmia (bigeminia, trigeminia).
- Inhibition of sodium pump affects all excitable tissues including CNS, striated muscles and GIT. Depolarization and spontaneous activity in neurons and muscular fibers is started.

	Digoxine	Digitoxine	Strophantine
Absorption from GIT	40-100%	90-100%	0
Binding to plasmatic proteins	20-30%	> 90%	< 5 %
$t_{0,5}$	40 h	4-6 days	21 h
Enterohepat. circulation	6,8	26	0
Penetration through placenta	+	+	-

DIGITALIS LANATAE FOLIUM
WOOLY FOXGLOVE LEAVES

Digitalis lanata Ehrh., woolly foxglove, Grecian foxglove

(Scrophulariaceae/Plantaginaceae). Biennial herb, for pharmaceutical purposes cultivated as one-year winter-crop.

Drug: lanceolated *integerrimus* leaf, immediately after harvest dried up to 60 ^{0}C.

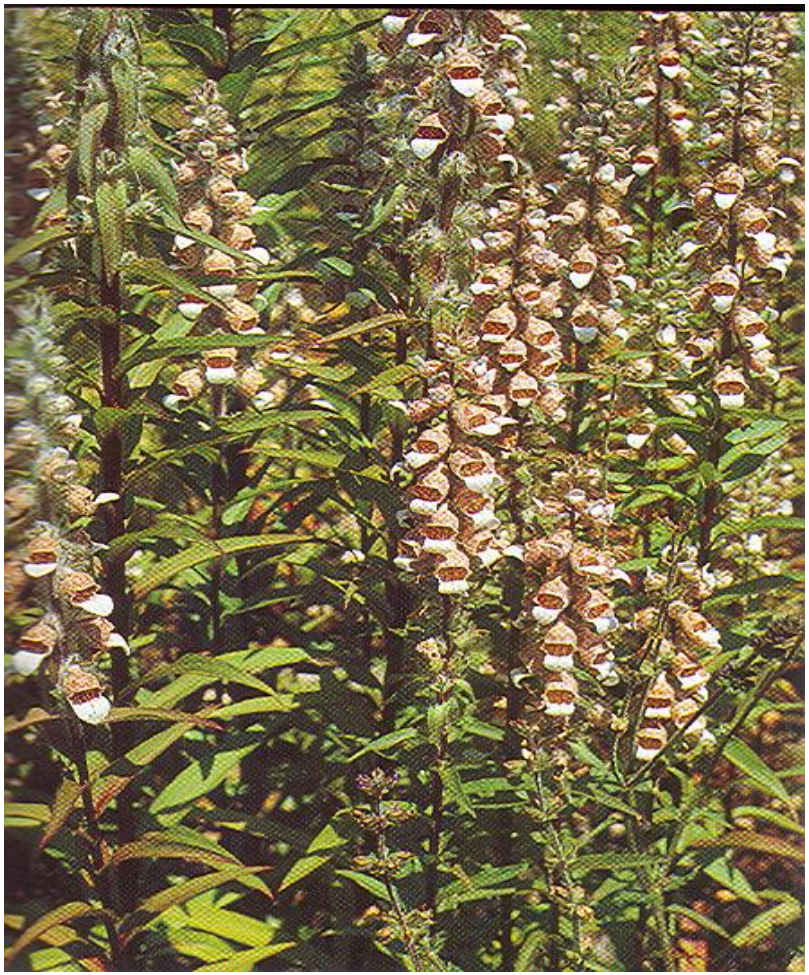
CC: approx. 1 % of mixture of more than 60 glycosides;

half of them are lanatosides A and C, furthermore B, D and E; minor glycosides. Lanatosides possess acetyled hydroxyl at C-3 of third molecule of digitoxose.

Usage: material for isolation of digoxine, digitoxine and lanatoside C.

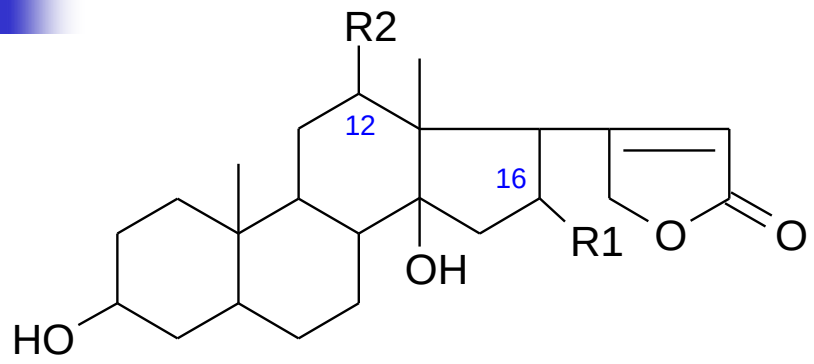
Cardiotonic for treatment of cardiac insufficiency.

Digitoxine/digoxine also as antidysrytmic.



Digitalis lanata EHRH. (Scrophulariaceae/Plantaginaceae)

MAIN GLYCOSIDES *DIGITALIS LANATA*

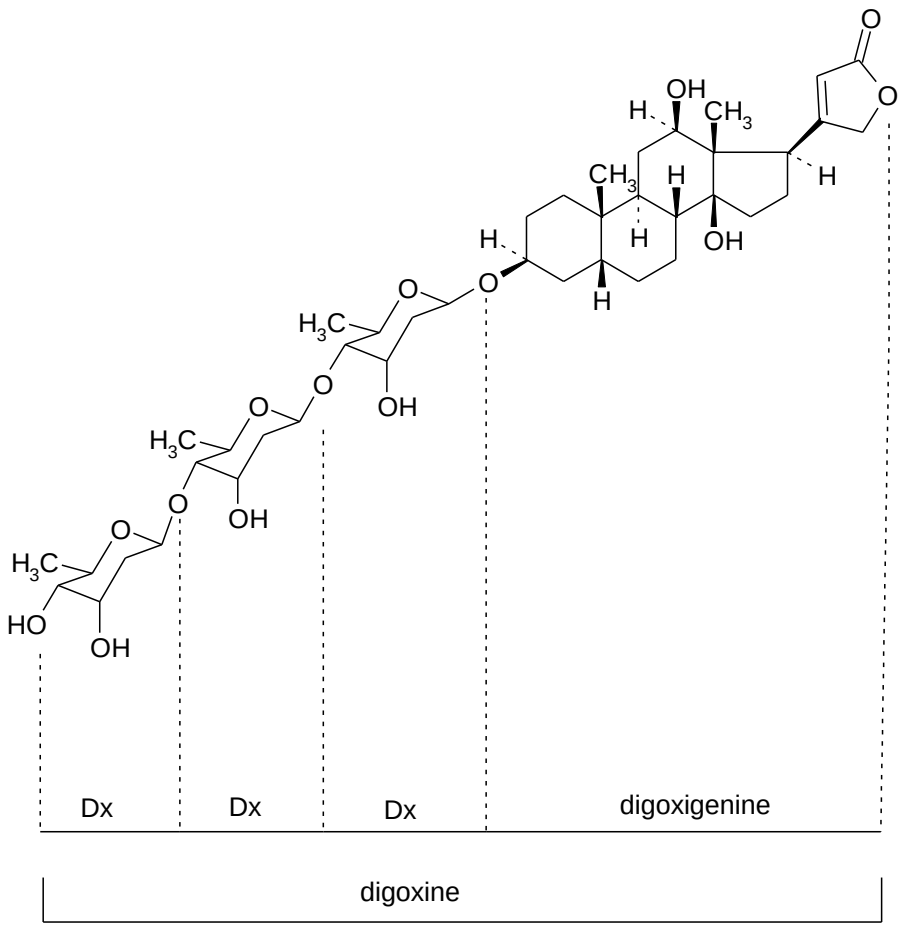


digitoxigenine R1=R2= H
gitoxigenine R1=OH, R2= H
gitaloxigenine R1=O-CHO, R2=H
digoxigenine R1=H, R2=OH
diginatigenine R1=R2=OH

SUGAR PART	**AGLYCONE**				
	DIGITOXIGENINE	GITOXIGENINE	GITALOXIGENINE	DIGOXIGENINE	DIGINATIGENINE
Glc-Dx(Ac)-Dx-Dx-	lanatoside A	lanatoside B	lanatoside E	lanatoside C	lanatoside D
Dx(Ac)-Dx-Dx-	acetyldigitoxine	acetylgitoxine	acetylgitaloxine	acetyldigoxine	acetyldiginatine
Dx-Dx-Dx-	**digitoxine**	gitoxine	gitaloxine	**digoxine**	diginatine

Glc = glukose; Dx = digitoxose; Dx(Ac) = 3-acetyldigitoxose

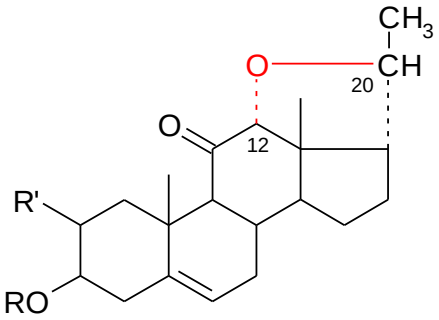
DIGOXINUM – DIGOXINE (ČL 2005)



DIGOXINE

- The mostly often used foxglove preparation
- Possibility of elevation of plasmatic concentration
  - Control of plasmatic level
- High intra-individual differences in pharmacokinetics
- Should be set in range of 0,5-0,8 ng/ml
- For this the dose 0,125 to 0,25 mg *per die* is enough
- Importance of pharmacogenomics for estimation of dose (phenotypes TT, CC, CT)

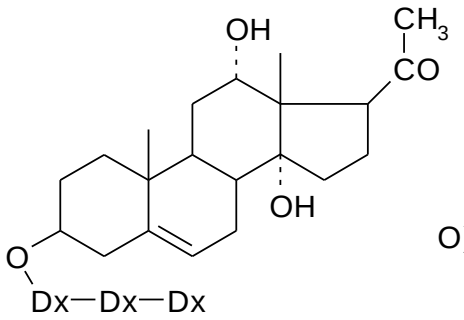
MINOR CONTENT COMPOUNDS OF *DIGITALIS LANATA*



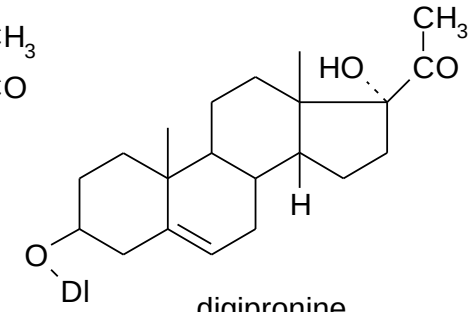
DIGITANOLY

	R	R'
diginine	diginose	H
digitalonine	digitalose	H
digofoleine	diginose	OH

DERIVATIVES OF PREGNANE

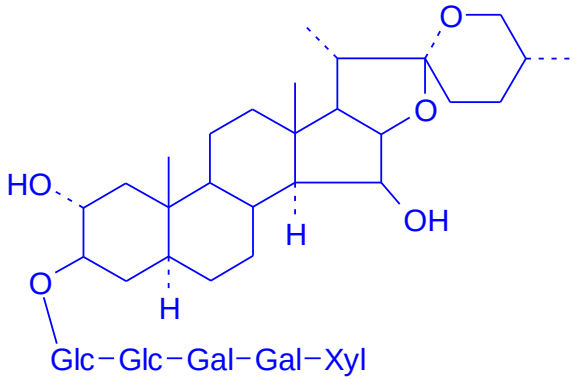


digipurpurine

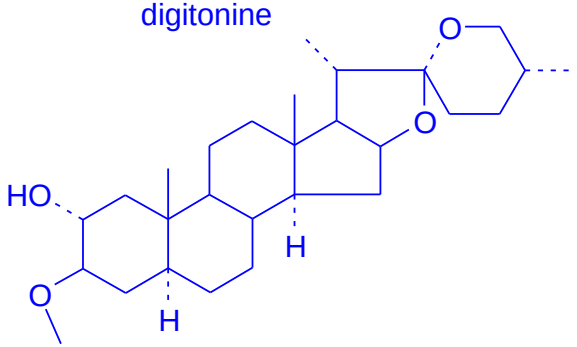


digipronine

STEROIDAL SAPONINS



digitonine



gitonine

DIGITALIS PURPUREAE FOLIUM (ČL 2002)
Common foxglove leaves

Digitalis purpurea L., common foxglove (Scrophulariaceae/Plantaginaceae); Europe, North America. Biennial plant, for pharmaceutical purposes is cultivated.

Drug: leaves dried up to 60 ^{0}C

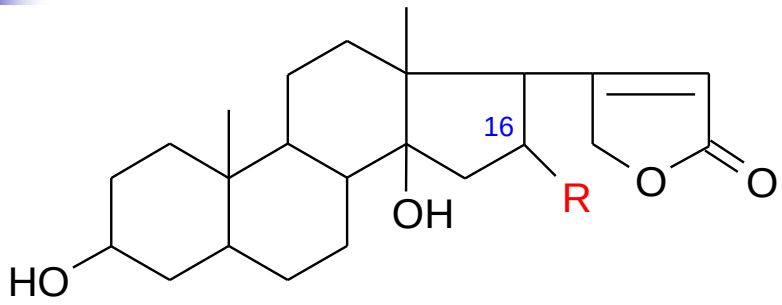
CC: ČL demands at least 0,3 % of cardenolides, calculated as digitoxine. More than 30 cardenolides. Further content compounds steroid saponins, flavonoids, anthraquinones, mucilage

Usage: material for isolation of digitoxine and further cardenolides, used for preparation of semisynthetic derivatives.

Cardiotonic for treatment cardiac insufficiency.

Digitoxine also as antidysrytmic.

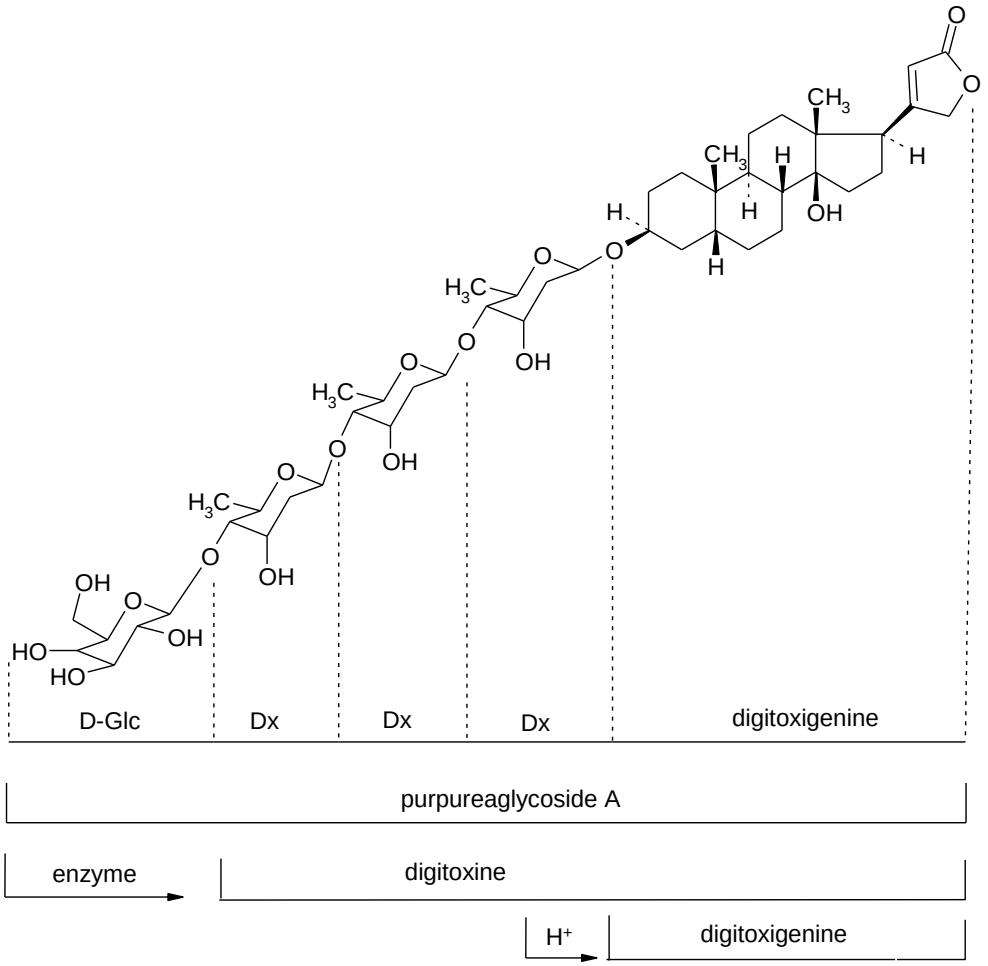
MAIN GLYCOSIDES OF *DIGITALIS PURPUREA*



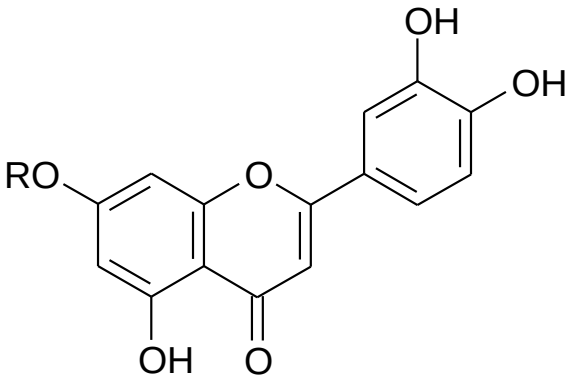
R = H digitoxigenine
R = OH gitoxigenine
R = OCHO gitaloxigenine

SUGAR PART	AGLYCON		
	DIGITOXIGENINE	GITOXIGENINE	GITALOXIGENINE
Glc-Dx-Dx-Dx-	purpureaglycoside A	purpureaglycoside B	glucogitaloxigenine
Dx-Dx-Dx-	**digitoxine**	gitoxine	gitaloxine
Gl-Dl-	glucoodoroside H	digitalinum verum	glucoverodoxine
Dl-	odoroside H	strospeside	verodoxine

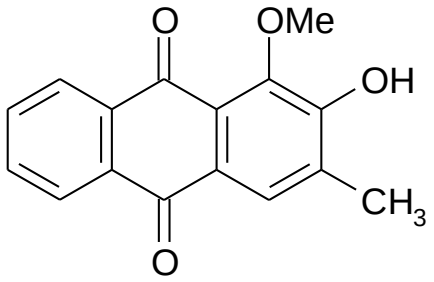
PURPUREAGLYKOSIDE A AND DIGITOXINE (ČL 2005)



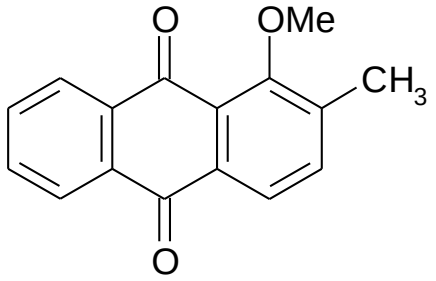
MINOR CONTENT COMPOUNDS OF *DIGITALIS PURPUREA*



luteoline R = H
luteoline-7-glucoside R = Glc

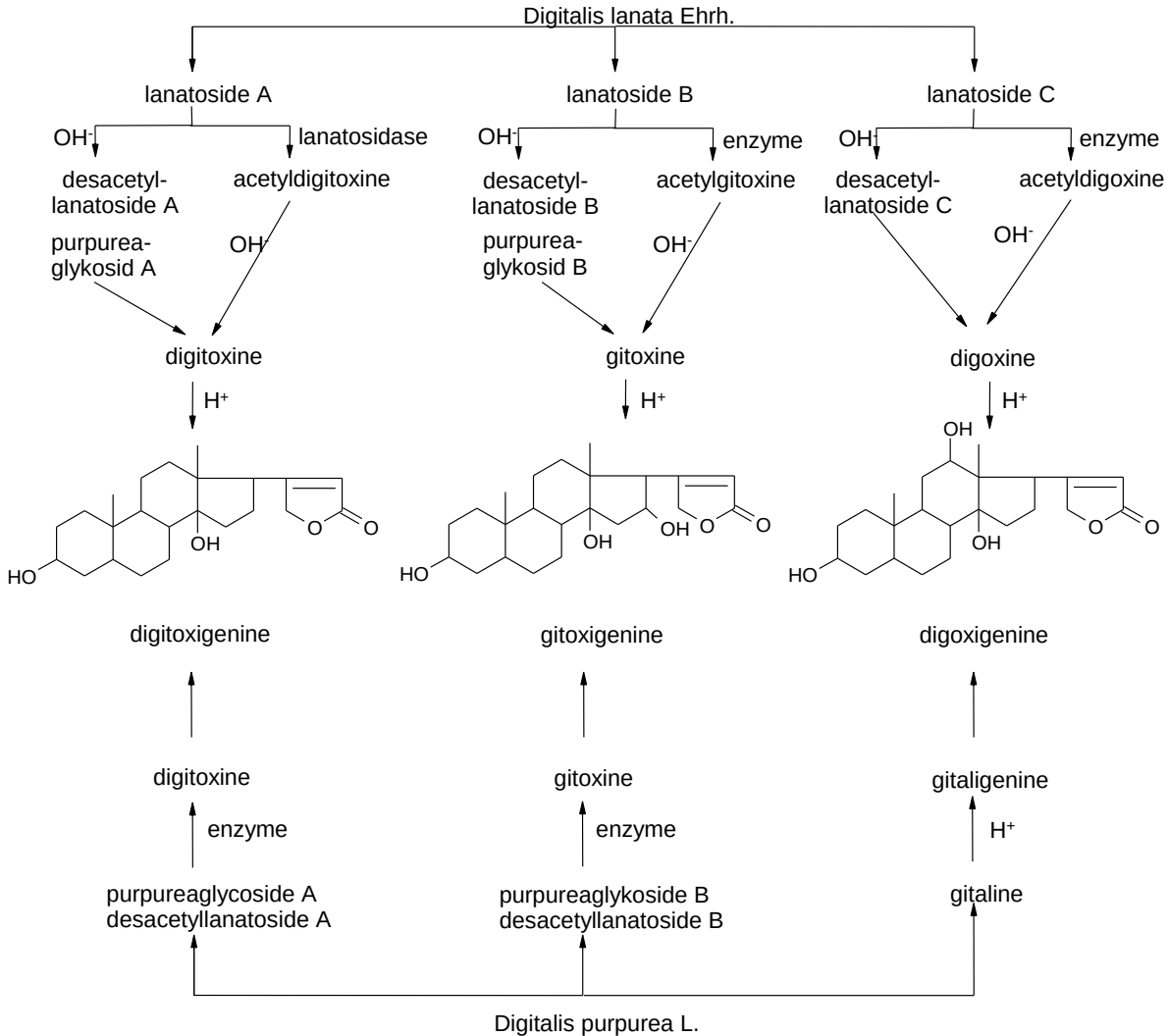


digitoluteine
3-methylalizarine-1-methylether



1-methoxy-2-methylantraquinone

MAIN GLYCOSIDES OF *DIGITALIS PURPUREA* AND *DIGITALIS LANATA*



OUABAINE (STROPHANTIN-G)

Strophanthi semen

Strophanthus gratus BAILL. (Apocynaceae), climbing liane of tropic Africa. Fruit – follicle conaining many seeds.

Acokanthera ouabaio – tree, from which was firstly isolated

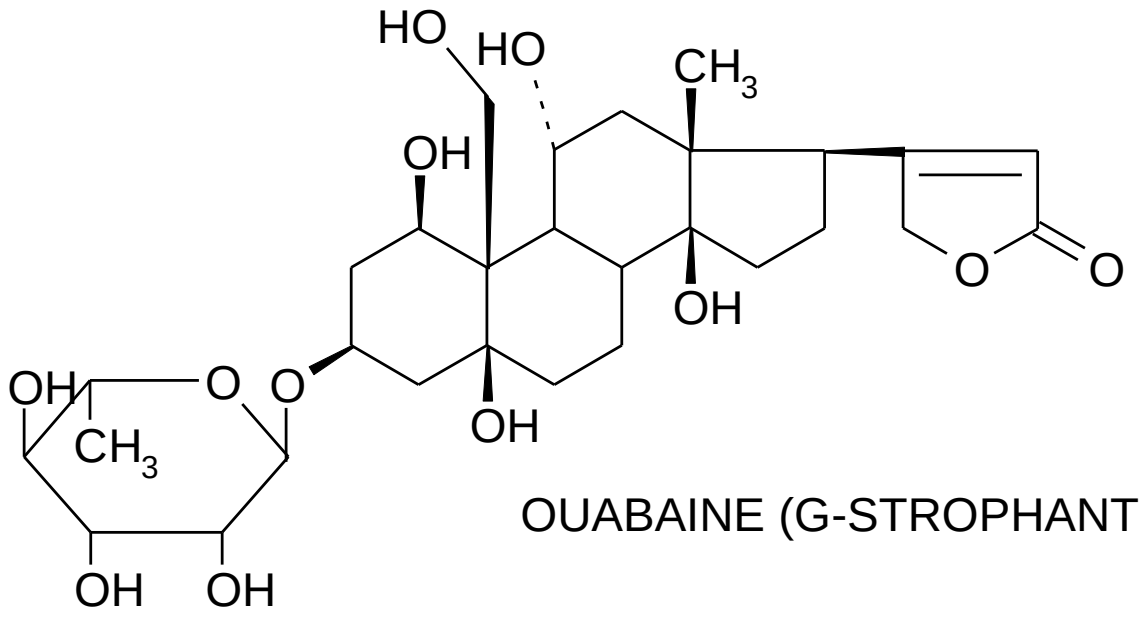
- Seeds contain up to 8 % of cardenolides, up to 35 % of oil, proteins
- Extracts from seeds → arrow poisons

++ Ouabainum octahydricum ČL 2002

STROPHANTHIN-g injections

- Fastly acting crdiotonic
- Low accumulation

OUABAINE (STROPHANTINE-G)

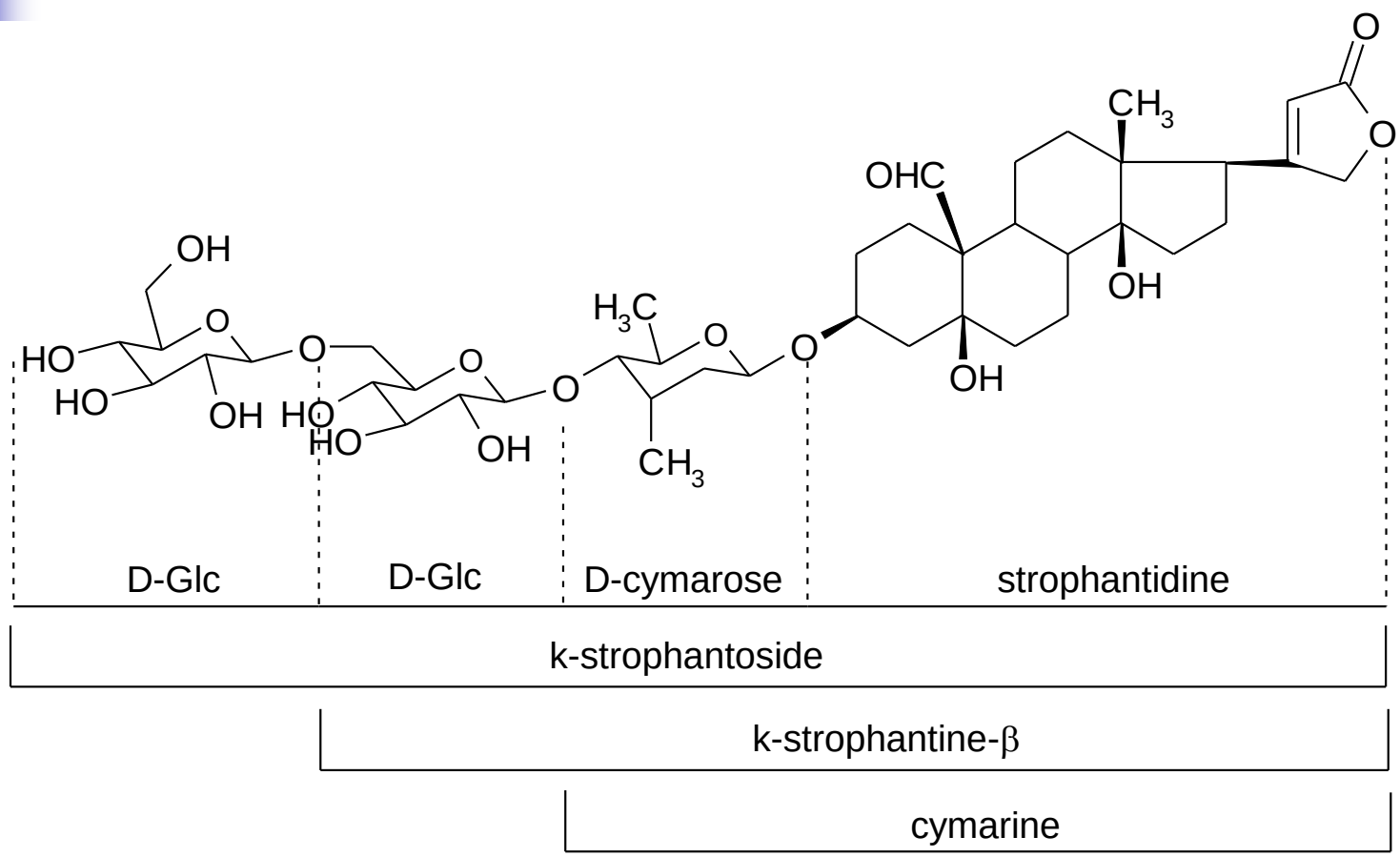


OUABAINE (G-STROPHANTINE)

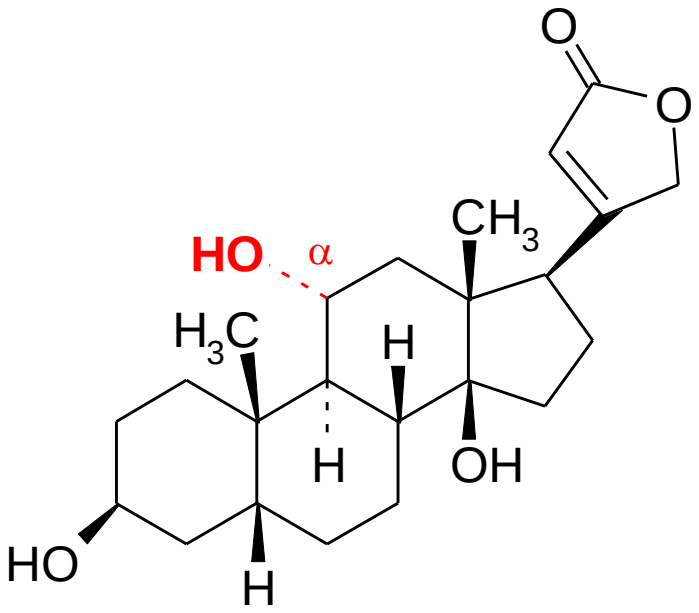
L-rhamnose

Strophanthi kombé and *Strophanthi hispidi semen*

(up to 10 % of cardenolides expressed as K-strophantine)



SARMENTOGENINE – steroide with OH at C-11
suitable for semisynthetic preparation of corticoids
Strophanthi sarmentosi DC. var. *senegambiae* semen



Sarmentogenine - aglycone of sarmentocymarine
(3β,5β,11α)-3,11,14-trihydroxy-card-20(22)-enolide

Adonidis vernalis herba – pheasant's eye herba

Adonis vernalis L. – pheasant's eye (Ranunculaceae).

Perennial herb native to Europe, Asia and North America.

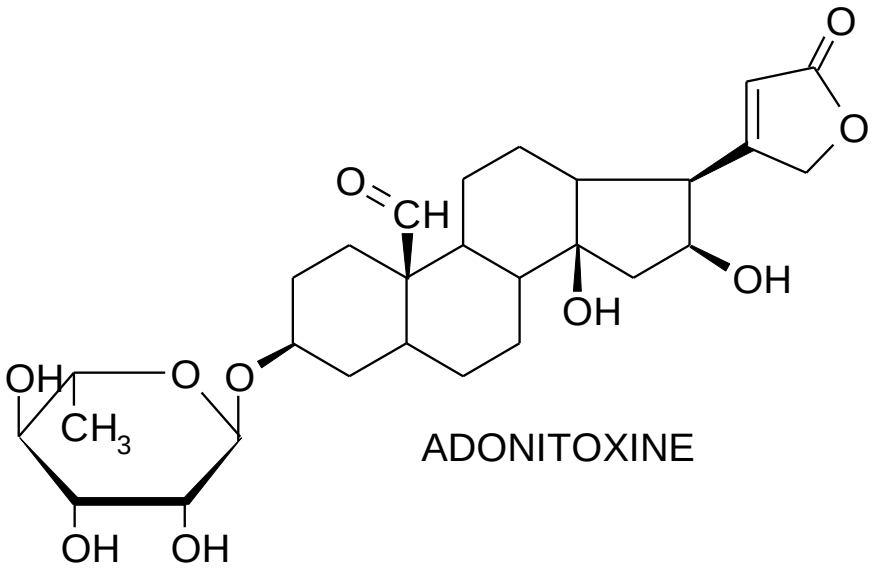
Leaves divided into narrow short line- like sections. Flowers (April, May) Ø 4 cm lemon-like yellow colour, shiny.

Drug: up to 60 ^{0}C dried flowering haulm

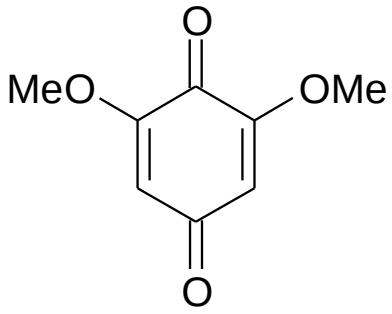
CC: 0,2-0,25 % of cardenolides with prevalence of adonitoxine; furthermore 20 minor glycosides. Antibacterial 2,6-dimethoxybenzoquinone

Usage: Cardiotonic with sedative and diuretic effect

Content compounds of *Adonis vernalis* L.



ADONITOXINE



2,6-dimethoxybenzoquinone

Convallariae herba – Lily of the Valley herba

Convallaria majalis L., Lily of the Valley (Liliaceae)

Perennial plant of Europe, Asia and North America

Lanceolated leaves and white smelling flowers (V-VI) formatting unilateral cluster

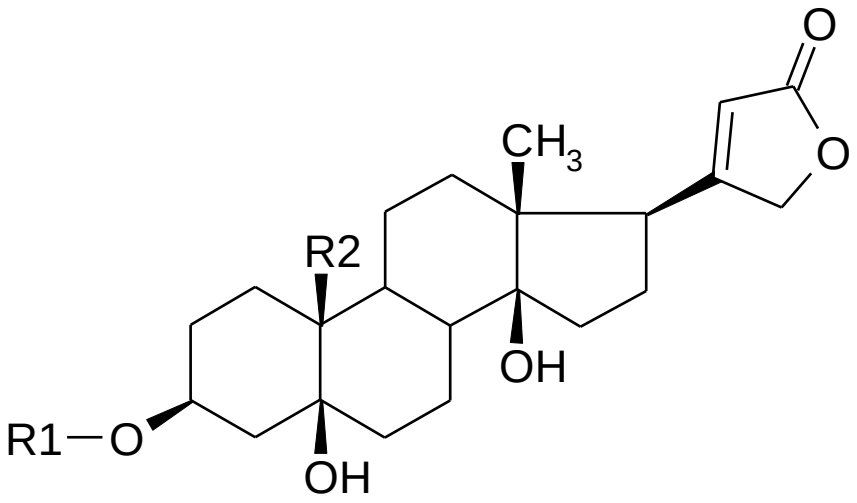
Drug: herb harvested during flowering period

CC: 0,2-0,3 % of mixture of 30 cardenolides, mainly convallatoxine and convalatoxol. Further compounds – GIT irritating saponins

Usage: Reserve cardiotonic with diuretic effect

Comment: flowers contain up to 0,45 % of cardenolides

Cardenolides of *Convallariae herba*



	R1	R2
convallatoxine	-Rha	-CHO
convalloside	-Rha-Glc	-CHO
convallatoxol	-R	-CH_2OH

Oleandri folium – oleander leaves

Nerium oleander L., oleander (Apocynaceae). Shrub or low tree native in Mediterranean.

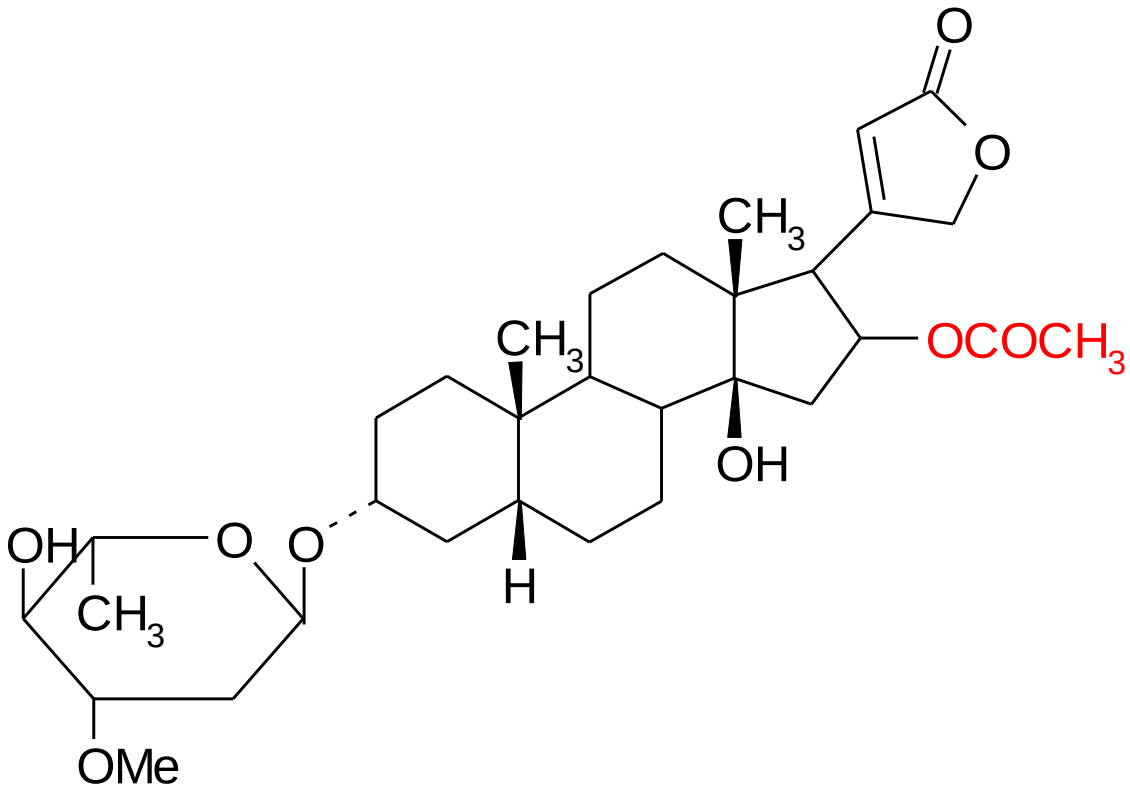
Drug: dried, lanceolated, leathery, integerrimus leaves, harvested in VII-VIII during flowering period.

CC: cardenolides derived from oleandrigenine, digitoxigenine and oleagenine. Main component is oleandrine.

Usage: highly effective cardiotonic with diuretic effect. Slow elimination (1 -2 weeks)

Comment: some glycosides of oleander show antimitotic activity.

OLEANDRINE



Thevetiae semen –thevetia seed

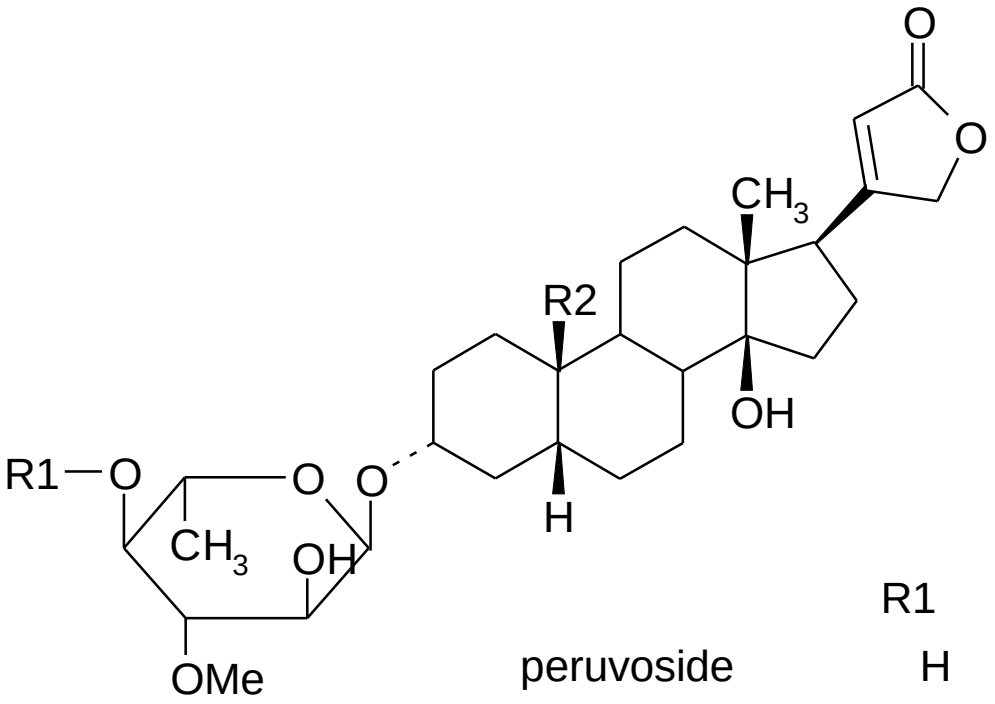
Thevetia neriifolia JUSSIEU, (Apocynaceae). Shrub or low tree native in Middle and South America.

Drug: dried bright-yellow seeds, button-shaped

CC: up to 10 % of cardenolides derived from digitoxigenine and canogenine. Main component is peruvoside. It is obtained from fermented seeds or by enzymatic hydrolysis of triglycoside thevetine A.

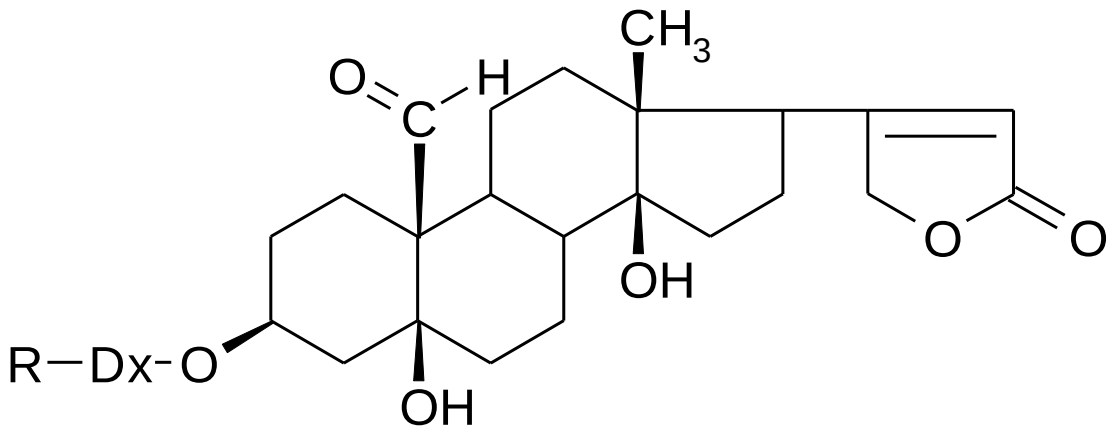
Usage: peroraly active cardiotonic, easy dosage. Resorption from GIT about 50 %.

Cardenolides of Thevetiae semen



	R1	R2
peruvoside	H	CHO
thevetine A	-Glc-Glc	CHO
neriifoline	H	CH_3
thevetin Be	-Glc-Glc	CH_3

Erysimi herba – cardioactive glycosides



erysimine R = H

erysimoside R = Glc

Erysimi herba – Nať trýzele

Source: *Erysimum diffusum* EHRH., trýzel rozvětvený (Brassicaceae). Biennial, 30-90 cm tall plant covered with grey trichomes. Leaves shortlined, integerrimus, yellow flowers in bunches.

Drug: dried herb collected during flowering period.

CC: 0,8-1,5 % of cardioactive glycosides.

Usage: cardiotonic for treatment of rheumatic heart diseases and hypertension.

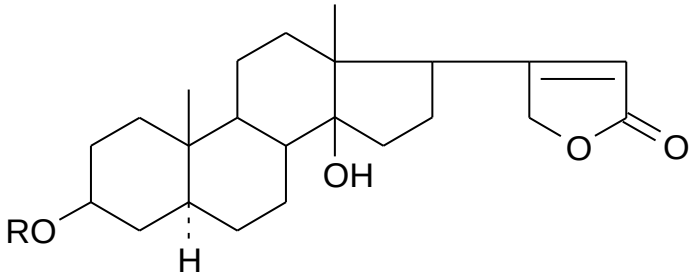
UZARA, UZARAE RADIX

Source: Gomphocarpus fruticosus – ostnoplod, Xysmalobium undulatum (Asclepiadaceae), r. Pachycarpus.
Shrubs or low trees native in South Africa.

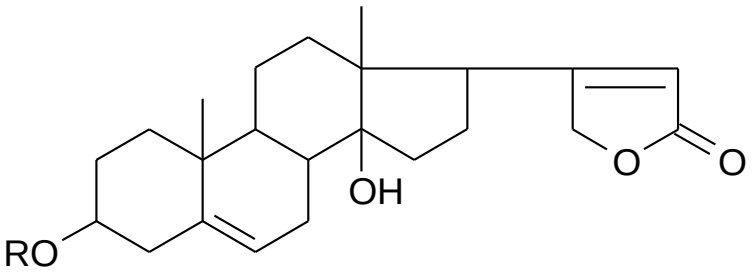
Effect:

- minute effect on heart muscle (1/100 of oubaine effect)
- markedly spasmolytic effect on guts and uterus, decreases the gut motility

Usage: antidiarrhoic, dysmenorrhoeic, enuresis

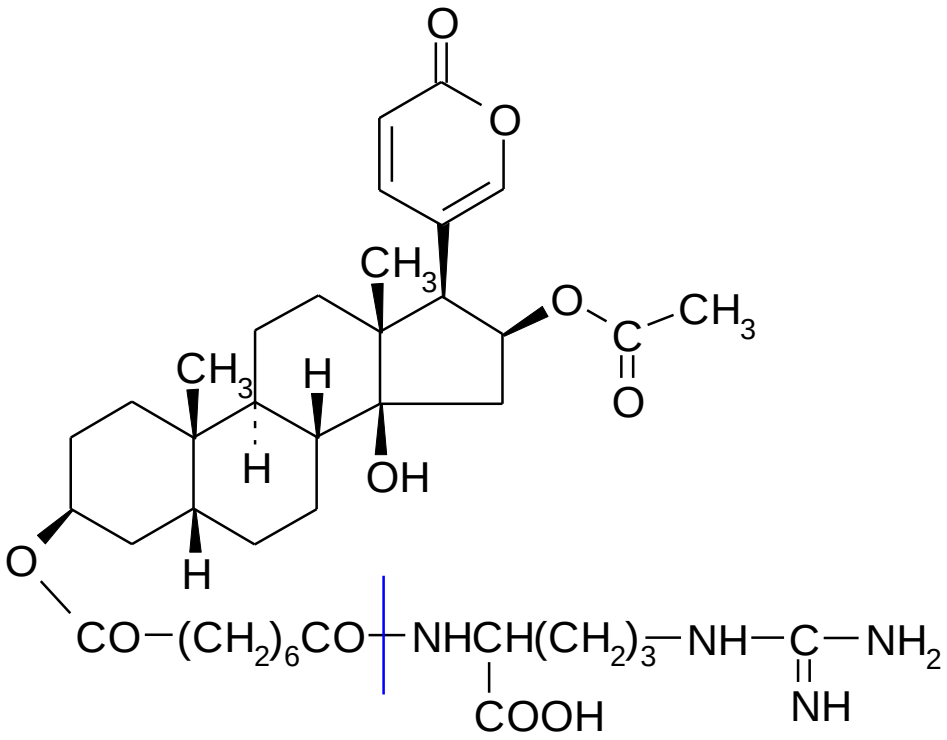


uzarigenine R = H
uzarine R = -Glc-Glc
uzaroside R = -Glc-Glc-Glc



xysmalogenine R = H
xysmalorine R = -Glc-Glc

CARDIOTONICS OF SCILLOID (BUFO) TYPE



bufotoxine = bufotaline-3-suberoylarginine

Scillae albae bulbus – cibule mořská bílá

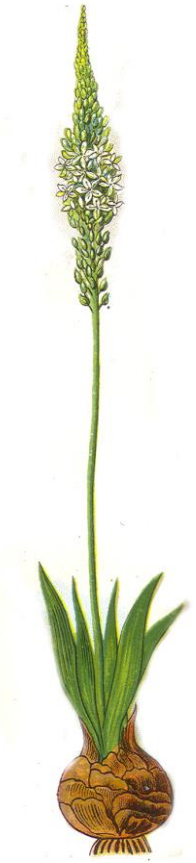
Zdroj: *Urginea maritima* (L.) BAK., urginea mořská (Liliaceae). Coast of Mediterranean. Cultivated in Italy, USA and India. Harvested after withering the leaves up (VIII-IX). Transversal cuts, drying.

Drug: dried, internal part of fleshy bulb.

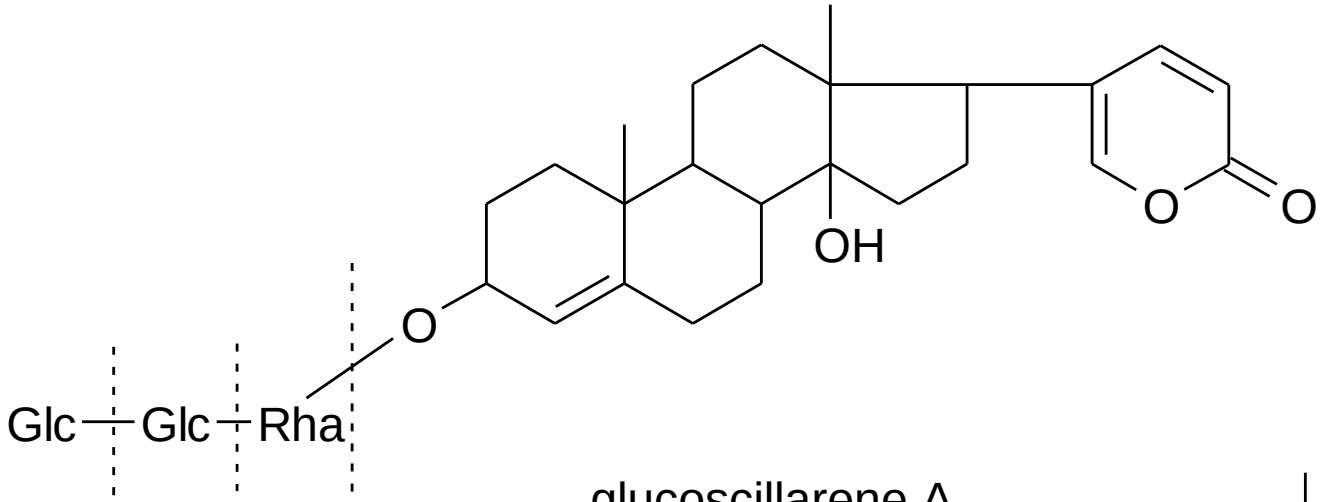
CC: 0,2-0,4 % of mixture of cca 15 glykosides. Main are glucoscillarene A and proscillaridine A (CARADRIN drg.); fructosans, sterols.

Usage of proscillaridine A:

- cardiotonic with effect faster than digitalis
- very low accumulation
- diuretic



Scillae albae bulbus – bufadienolides



glucoscillarene A

scillarene A (majority)

proscillaridine A

scillarenine = scillaridine

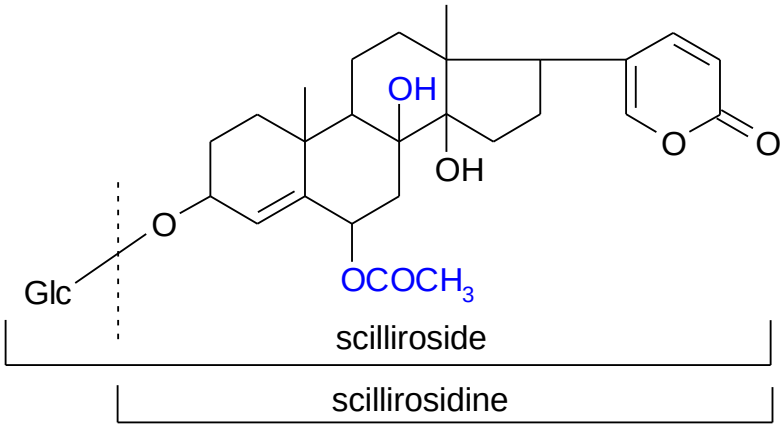
Scillae rubrae bulbus – cibule mořská červená

Source: *Urginea maritima var. rubra,* urginea mořská červená.

Occuerence: as white variety

CC: scilliroside, scillirubroside and glycosides same as at white variety.

Usage: rhodenticide (killing of rats), toxic is scilliroside. Acting on CNS. LD for adult rat is 0,3 mg.



Hellebori nigri radix – kořen čemeřice černé

Zdroj: *Helleborus niger* L. – čemeřice černá (Ranunculaceae). Perennial plant native in Europe. Ornamental „Christmas rose".

Drug: dried rgizome with roots.

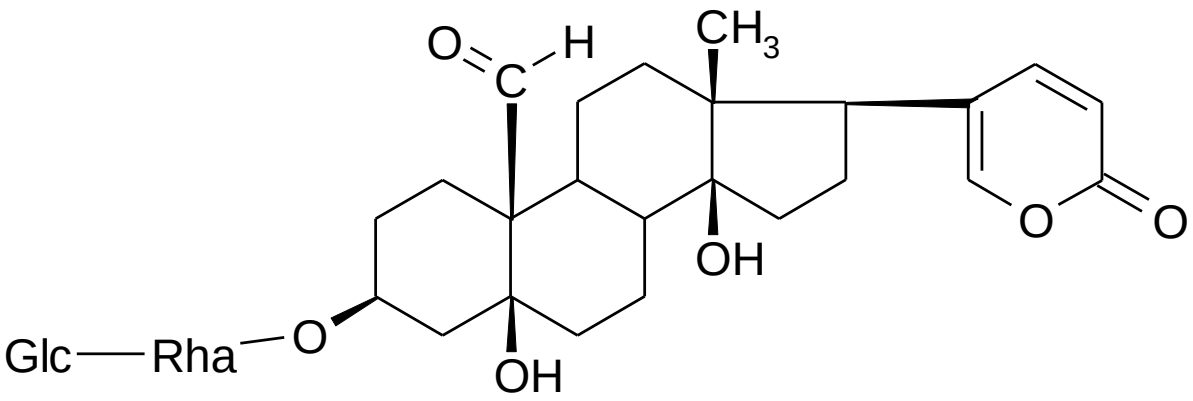
CC: 0,3 % of hellebrine (glucorhamnoside of hellebrigenine) – in exception of cumaline ring the same structure as strophantidine. Saponin helleborine.

Usage: deglucohellebrine as cardiotonic

Semisynthetic derivatives:

- deglucohellebrigenine-acetate is the most active compound.
- 3-(3-methylcrotonate)-hellebrigenine (Acrihellin).

Hellebori nigri radix – bufadienolides



hellebrine

desglucohellebrine (highly active)

hellebrigenine

FURTHER EFFECTS OF CARDIOACTIVE GLYCOSIDES

- in non-toxic concentration digitoxine and digoxine inhibit growth and induce apoptosis of different lines of human malignant cells, and do not affect normal proliferating cells

- oleandrine, ouabaine and digoxine induce apoptosis at cancer cells of prostate gland independent on androgen *in vitro*

ANTIDYSRYTMICS

- Affect disorders of heart rate.
- Affect in prevalence heart automacy, conductivity and often also excitability.

Biogenic therapeutics – structurally different compounds

Quinidine
Ajmaline
Sparteine
Digitoxine

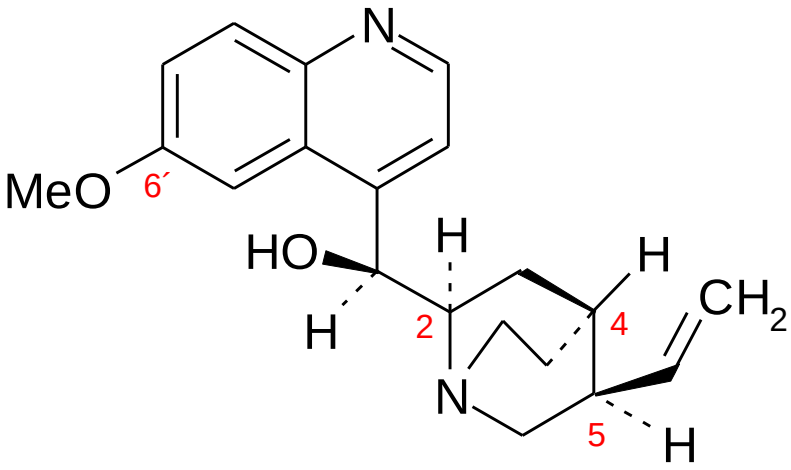
Qinidini sulfas dihydricus – Quinidine sulphate dihydrate (ČL 2002)

Source: Chinae cortex – *Cinchona succirubra* (Rubiaceae)

Ppreparation: isolation, isomerisation of quinine

Usage: Antidysrytmic

- in general induce myocardial depression
- slowering of excitement conduction, slowering of its formation
- decreasing of contractility
- decreasing of heart rate



steric line (+)

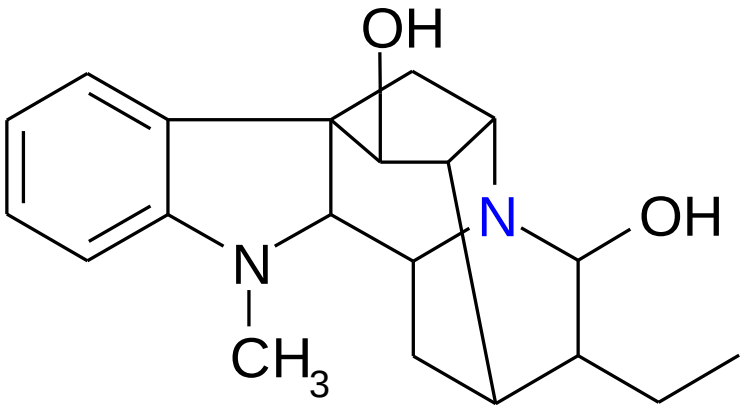
Ajmaline – Aimalinum (ČsL 4)

Source: Rauwolfiae radix,
Rauwolfia serpentina
(Apocynaceae)

Usage: Antidysrytmic separately or in combination

- decreases conductivity
- Used mainly during tachysystolic dysrytmias

Comment: from ajmaline are prepared derivatives prajmalinium and detajmium by the qurternization of N at position 4



Sparteinum sulfuricum – Sparteine sulphate

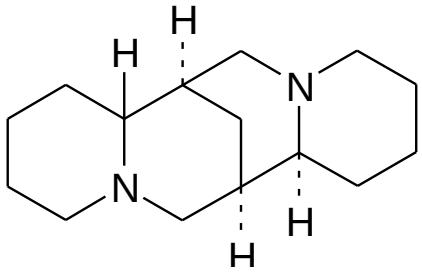
Source: *Sarothamnus scoparius* – janovec metlatý. A semi shrub with trifoliate leaves and yellow flowers.

Drug: dried flowering tips of branches; for alkaloid isolation harvested in the yearly spring.

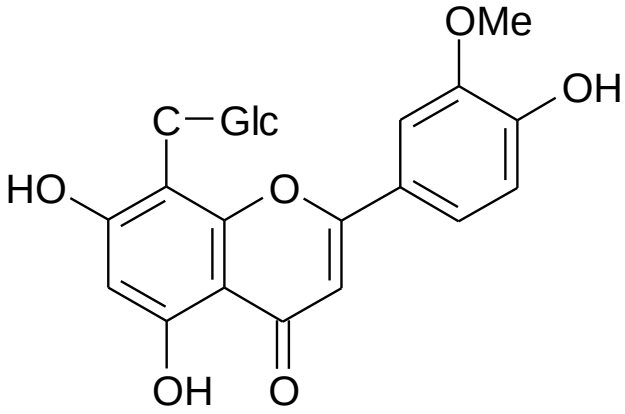
CC: 1 – 1,5 % of quinolizidine alkaloids with prevalent sparteine

Usage: prophylaxis of atrial dysrythmias and sinus tachycardia

Sarothamni flos – contains diuretic scoparoside – component of diuretic herbal teas.



sparteine



scoparoside

DRUGS AFFECTING BLOOD VESSELS

VASODILATANTS

- dilatate veins
- eliminate vascular spasms, what makes better blood supplies of organs
- some of them lower blood pressure

VASOCONSTRINGENTS

- reduce lumen of veins

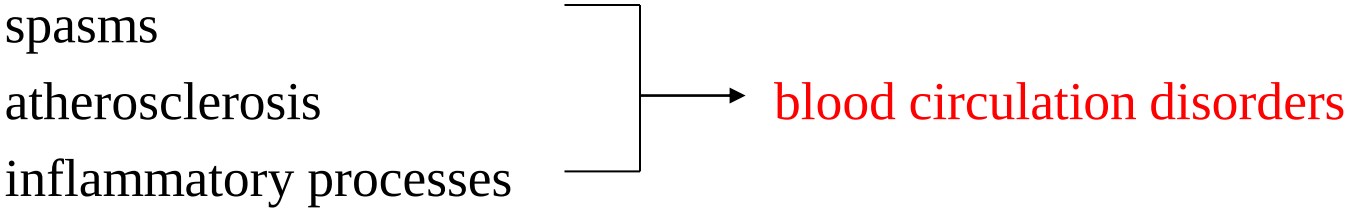
VENOPHARMACS

- affect durability of vascular wall
- affect metabolism of vascular wall

VASODILATANTS

Used for treatment of blood circulation disorders

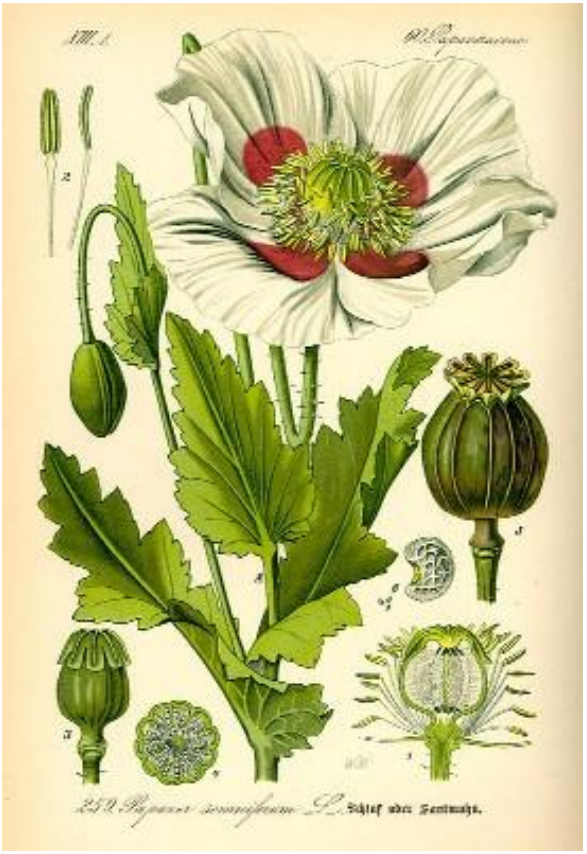
- coronary and brain blood vessels
- muscular and skin blood vessels



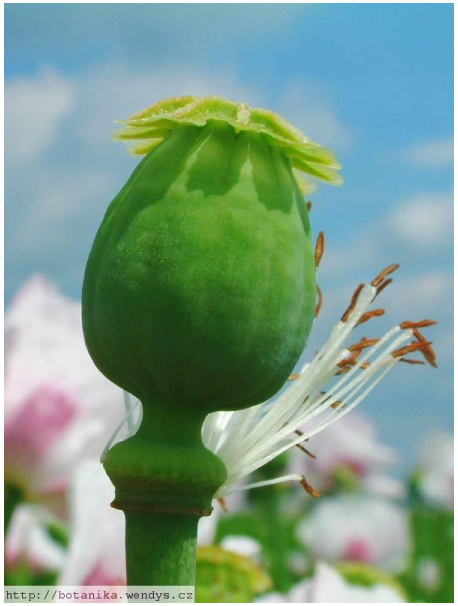
VASODILATANTS

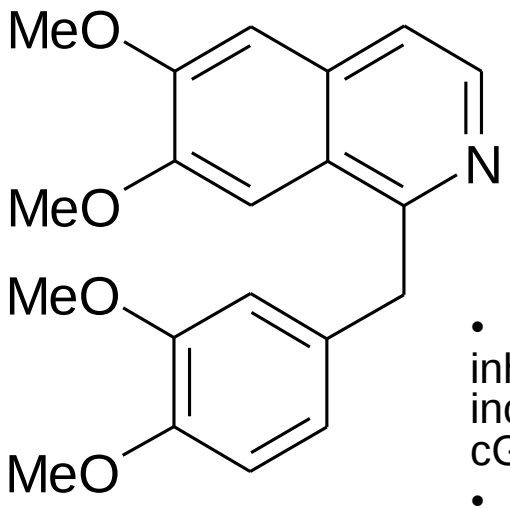
1. METHYLDERIVATIVES OF XANTHINE (theophylline, theobromine, aminophylline (complex of theophylline with ethylendiamine) OXYPHYLLIN
2. PAPAVERINE (dilatates big veins, into them can be directly administered; also for treatment of central and coronary blood circulation disorders - angina pectoris) PANERGON
3. DH-ERGOT ALKALOIDS (mainly dihydroergotoxine together with etophylline – cerebral vasodilatant, separately for peripheral circulation disorders) SECATOXIN, ERSILAN
4. KHELLINE – furanochromone derivative and VISNADINE – pyranocoumarin derivative (coronary vasodilatants and spasmolytics)
5. VINKAMINE (cerebral vasodilatant, affects cognotive functions) CAVINTON
6. *GINKGO BILOBA* content compounds (cerebral and peripheral vasodilatant) TEBOKAN
7. RAUBASINE = AJMALICINE, *Rauwolfia serpentina* – snake root (improves blood circulation during cerebral and peripheral disorders) LAMURAN

Papaverine



- *Papaver somniferum* Papaveraceae
- Benzylisoquinoline alkaloid
- Up to 1% in opium.
- Releases smooth muscles tonus in internal organs
  - Effect on smooth muscles induce dilatation of veinds and improvement of blood supplies
- Passes into mother milk, metabolized in liver, excreted by kidneys, biological halftime is 1-2 hours.
- **Indications:** Gut, gallbladder colic, vascular spastic states (increased tonus of smooth muscles of veins), states during local insufficiency of blood supplies in tissue of eye, inner ear, spastic states during emboli

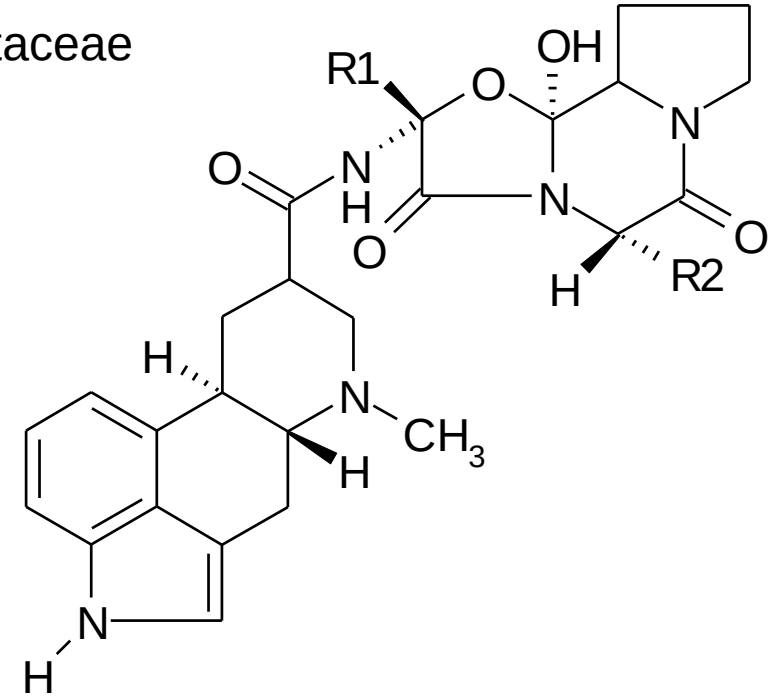




- Erectile impotency – non-specific inhibitor of phosphodiesterase, increasing the level of cAMP and cGMP
- Lead for semisynthetic derivatives

Dihydrogenated ergot alkaloids

Secale cornum, *Claviceps purpurea* Clavicipitaceae

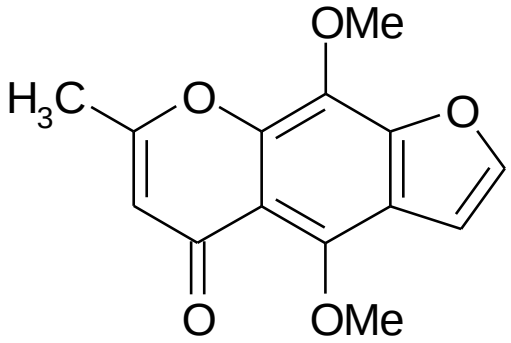


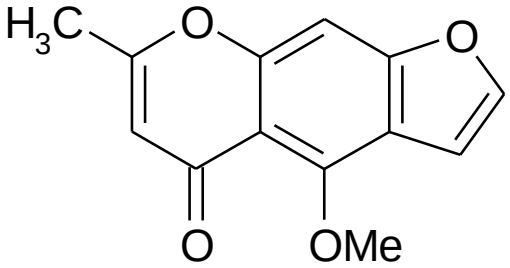
- **DH-ergotoxine** – hydergine
- sympatolytic, vazodilatant
- dilatation of veins in brain and extremities, improvement of blood supplies
- disorders of brain blood supplies, mild psychic disorders of older people
- disorders of function of peripheral blood vessels, troubles connected with high pressure (especially headaches and vertigoes).
- Ocular diseases (some disorders of blood supplies of retina and choroid).
- Menière syndrome (disease characterized by vertigo, sounds in ears, nausea and vomitus)

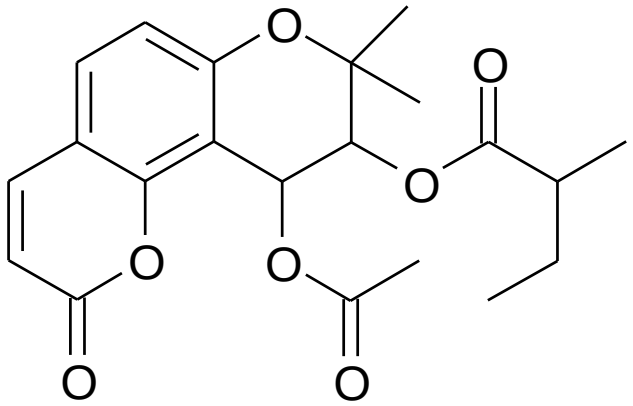
	R1	R2
DH-ergocrystine	iPr	CH_2Ph
DH-ergocornine	iPr	iPr
DH-α-ergocryptine	iPr	iBu
DH-β-ergocryptine	iPr	secBu

Khelline and visnadine

- *Ammi visnagae fructus*, *Ammi visnaga* Apiaceae
  - Khelline, visnagine – furanochromones
  - Visnadine – pyranocoumarin
  - Dilatation of coronary arterias – improvment of heart supplies
  - Spasmolytic on smooth muscles – antagonist of Ca entry into cell
  - Againsti psoriasis
  - Indication
    - Ischemic heard disease
    - Mild forms of CHOPD
- Antispastic of GIT (gallbladder) and urinary tract

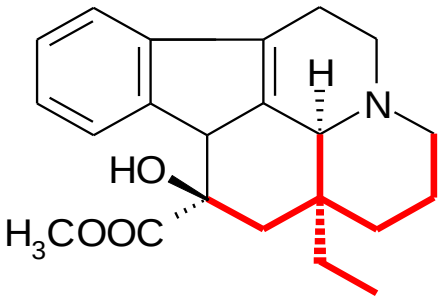


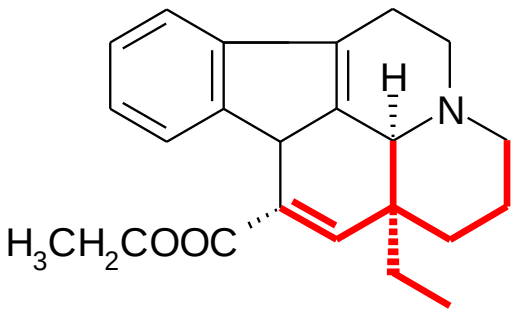


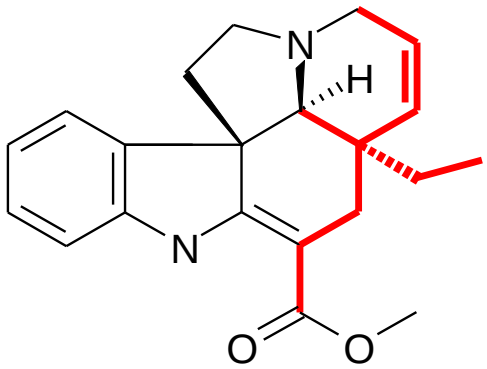


Vincamine

- *Vinacae herba*, *Vinca minor*
  Apocynaceae
  - Indol alkaloid of aspidospermine type
  - Vinka contains about 50 alkaloids (vincamine, vincamidine, vincaminoreine, isovincamine, pervincine), 0,1-0,7 %.
  - Drug decrease blood pressure, it is also used for suppression of irritation during dry caught, it acts also as sedative, it is used during diabetes. During hemorrhagic states.
  - Vincamine: V*oaconga* and *Crioceras*
    - **Blood vessels dilatation**
    - **Passes through BBB**
    - **Improvement of supplies of brain by oxygen, ATP and glucose**
    - **Redistribution of blood into ischemic parts**
    - **Nootropic effect**
    - **Produced from tabersonine (voakanga seeds)**





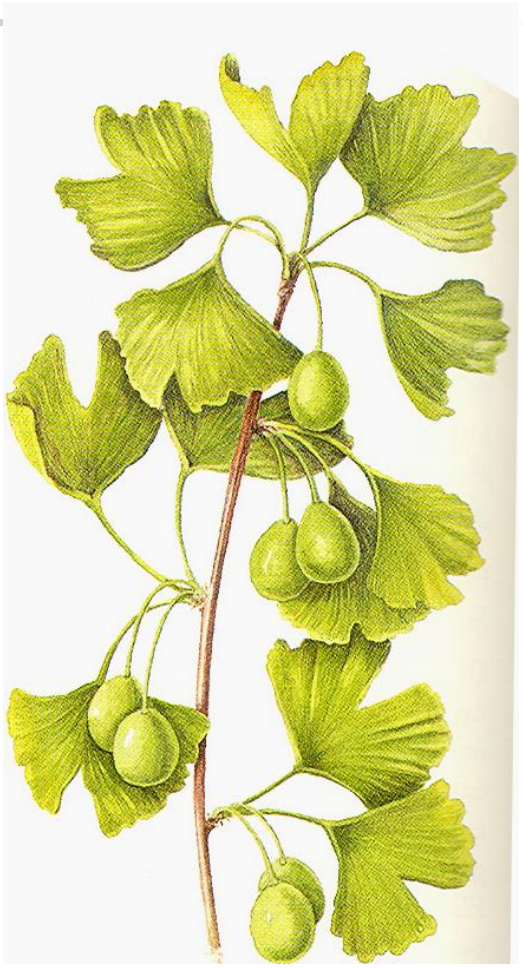


Ginkgo folium – Jinanový list (ČL 2002)

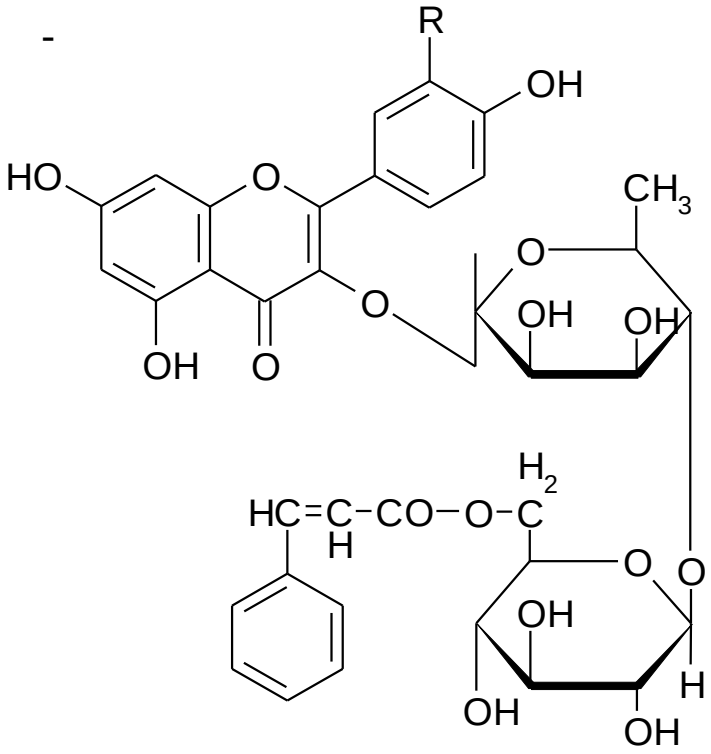
GINKGO FOLIUM

Ginkgo biloba L. – jinan dvoulaločnatý (Ginkgoaceae)

- dioecious gymnosperm tree
- Leaves wide wedge bilobar, veil-shaped vasculature
- Native to eastern Asia
- Cultivated in Asia, Europe and USA
- From leaves are prepared extracts with complex of active compounds
  - flavonoids
  - ginkgolides
- Application peroral and parenteral
- Usage during disorders of blood supplies of brain and peripheral parts, mainly atherosclerotic origin
- Antiedematic effect

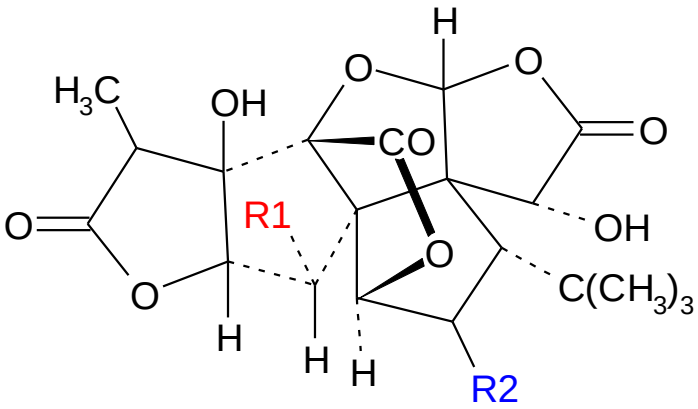


Content compounds of *Ginkgo folium*



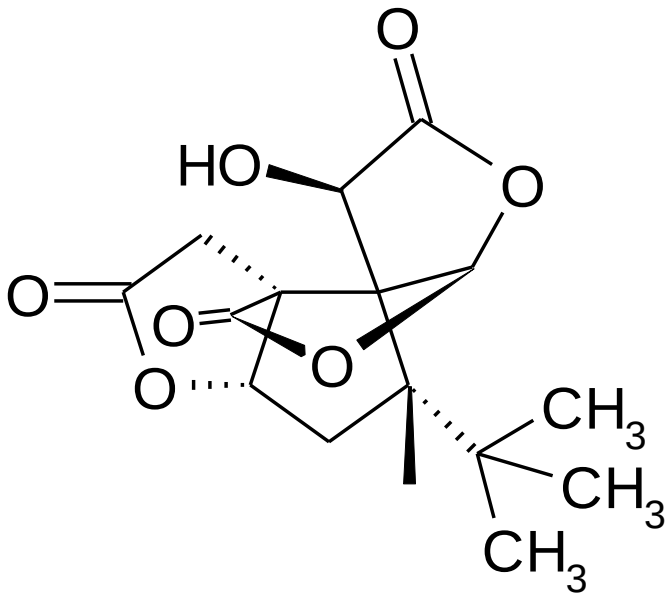
aglycone

R=H, kaempferol
R=OH, quercetine



ginkgolide	R1	R2
A	H	H
B	OH	H
C	OH	OH

(diterpenes with 6 rings, 3 of them are lactones)



Pharmacologic effects:

- Neuroprotective
- Antioxidant, scavenger
- Membranes stabilizing effect
- Inhibitor of PAF
- Inhibition of β-amyloid deposition into tissue (Alzheimer disease)
- Protection against the age-dependent loss of acetylcholinergic and adrenergic receptors
- Inhibition of cGMP phosphodiesterase
    - Relaxation of veins

0,2 % of gingkolides (diterpenes)
0,05 % of bilobalide (sesquiterpene)
2 % of flavonoid glykosides
2 % of biflavonoids
Proanthocyanidines, triterpenes and further

Standardized extracts:
24 % of flavonoids
6 % of terpenoids

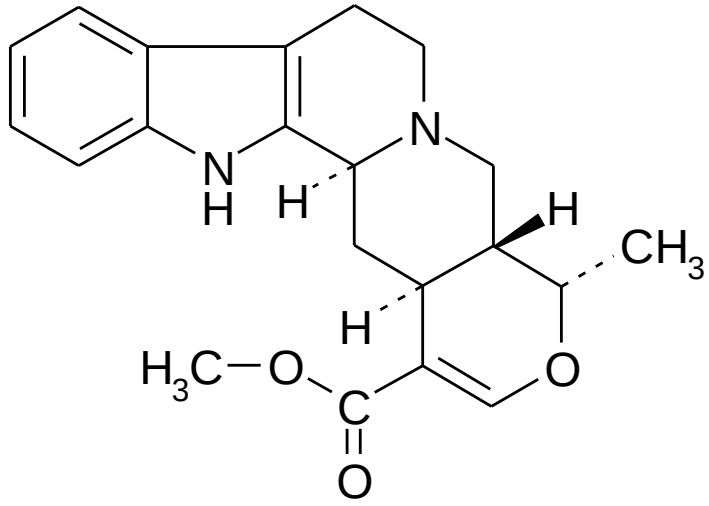
RAUBASINE (syn. AJMALICINE)

Source: *Rauwolfia serpentina* (L.) BENTH. (Apocynaceae), especially roots of Chinese variety

Characteristics: weakly basic monoterpenic indol alkaloid

Usage:

- Cerebrovascular vasodilatant
- Blood supplies of peripheral tissues during varicose complex.
- Disorders of ocular blood supplies.
- Lamuran, Circolene, Isoarteril



ANTIHYPERTENSIVES

REMEDIES AGAINST INCREASED ARTERIAL BLOOD PRESSURE

HYPERTENSION – mostly often occurring cardiovascular disease of adult, but today described often also in children

- It is one of main factors playing role in ethipathogenesis of atherosclerosis and its complications:

  - IHD

  - cerebrovascular incidents

- Needs permanent treatment

ANTIHYPERTENSIVES

REMEDIES AGAINST INCREASED ARTERIAL BLOOD PRESSURE

- Alkaloids from Rauwolfiae radix – snake root, mainly reserpine
- Alkaloids from Veratri albi radix – kořen kýchavíce bílé, protoveratrines A and B

Antihypertensives – vasodilatants

- Content ocmpounds from Crataegi folium cum flore – list hlohu s květem
- Visci albi herba – nať jmelí (limited use becouse of side effects)

Folk medicine

- Oleae folium – olive leaves
- Allii sativi bulbus – garlic bulbs

RESERPINUM – RESERPINE (ČL 2002)

Source: different species of *Rauwolfia*, especially *Rauwolfia serpentina* – snake root (Apocynaceae). Small shrub with evergreen leaves, white or pinkish flowers. For pharmaceutical purposes is cultivated. Main producers: India, Thailand.

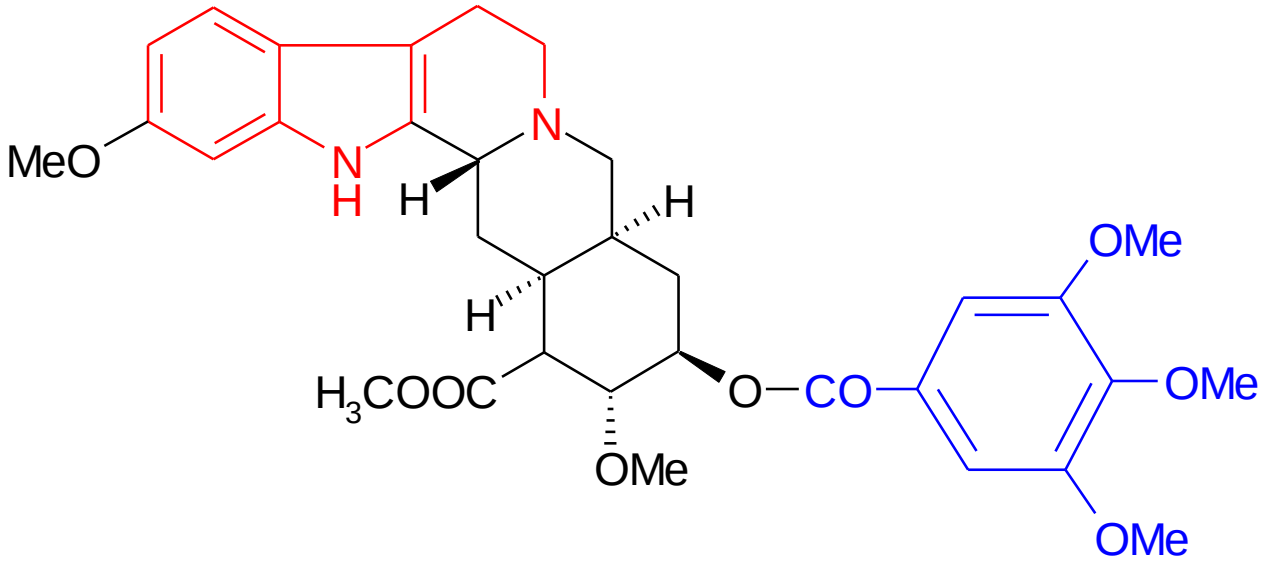
Drug: dried root - Rauwolfiae radix, bark is more rich on alkaloidal content than wood.

CC: 1-2,5 % of mixture of more than 50 indol alkaloids. Reserpine is monoterpenic alkaloid of yohimbane type. Obtained only by isolation.

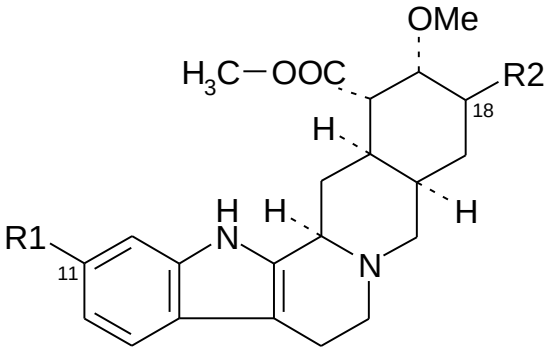
Dosage: Antihypertensive 0,1 – 0,25 mg *pro die*

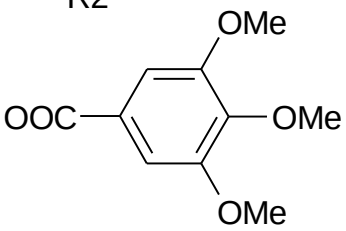
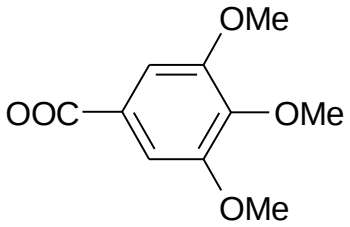
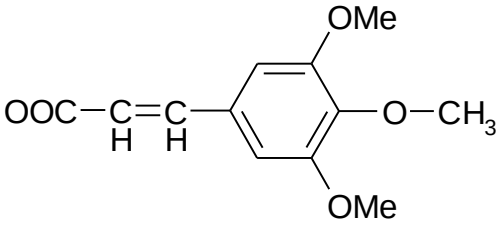
Comment: also used mixture of alkaloids: reserpine, deserpidine, rescinnamine and syrosingopine

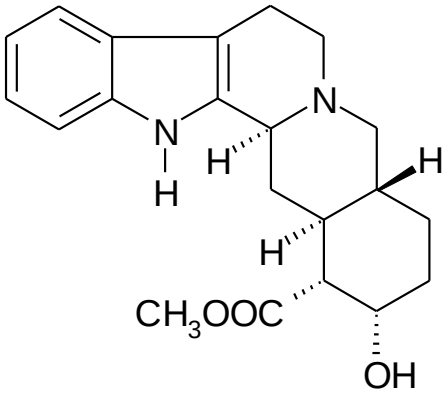
RESERPINUM – RESERPINE (ČL 2002)



Alkaloids of *Rauwolfiae radix* with antihypertensive effect

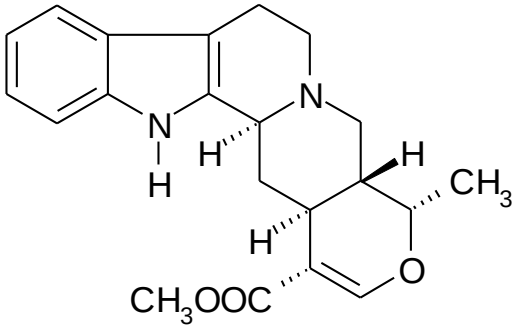


	R1	R2
reserpine	O·CH3	
deserpidine	H	
rescinnamine	O·CH3	



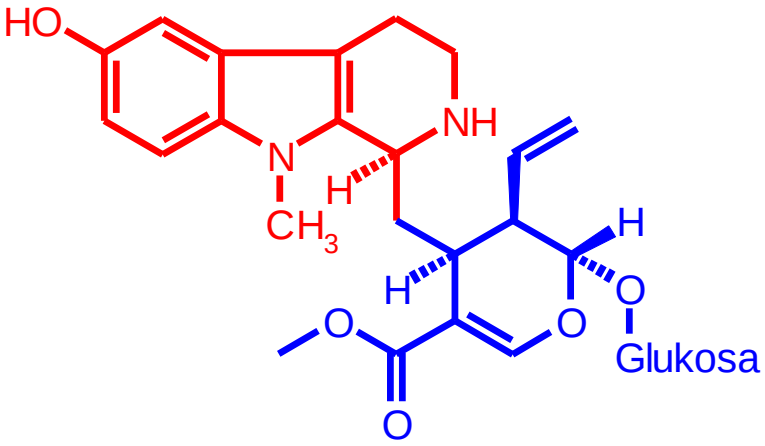
Yohimbin

- Sympatolytic (peripheral vasodilatation)
- Erectile dysfunction

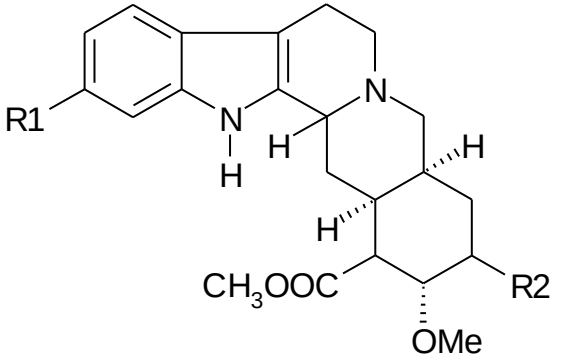


Ajmalicine (raubasine)

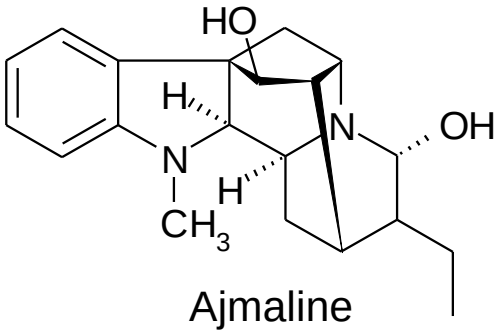
- Vasodilatation



strictosidine

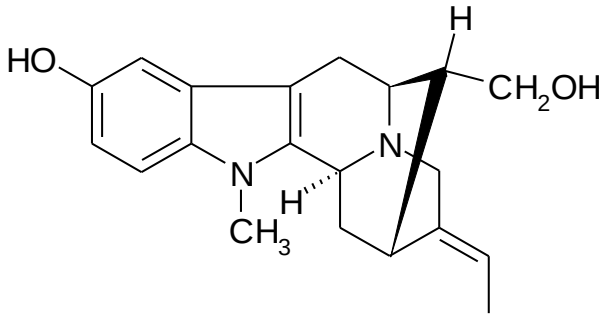


Reserpine



Ajmaline

- Antiarhytmic



Sarpagine

- Sympatolytic (peripheral vasodilatation)

Veratri albi radix – Kořen kýchavice bílé (ČsL 4)

Zdroj: *Veratrum album* L. – kýchavice bílá (Liliaceae). Perennial plant, large elipsoid leaves with parallel nervature. Flowers in panicle (VII-VIII). Krkonoše, Nízké Tatry.

Drug: dried cylindric rhisomes with numerous roots. Harvest in X.

CC: 1-1,5 % of alkaloid mixture (type of cholestane, cevanine, jervanine, veratramine and solanidanine).

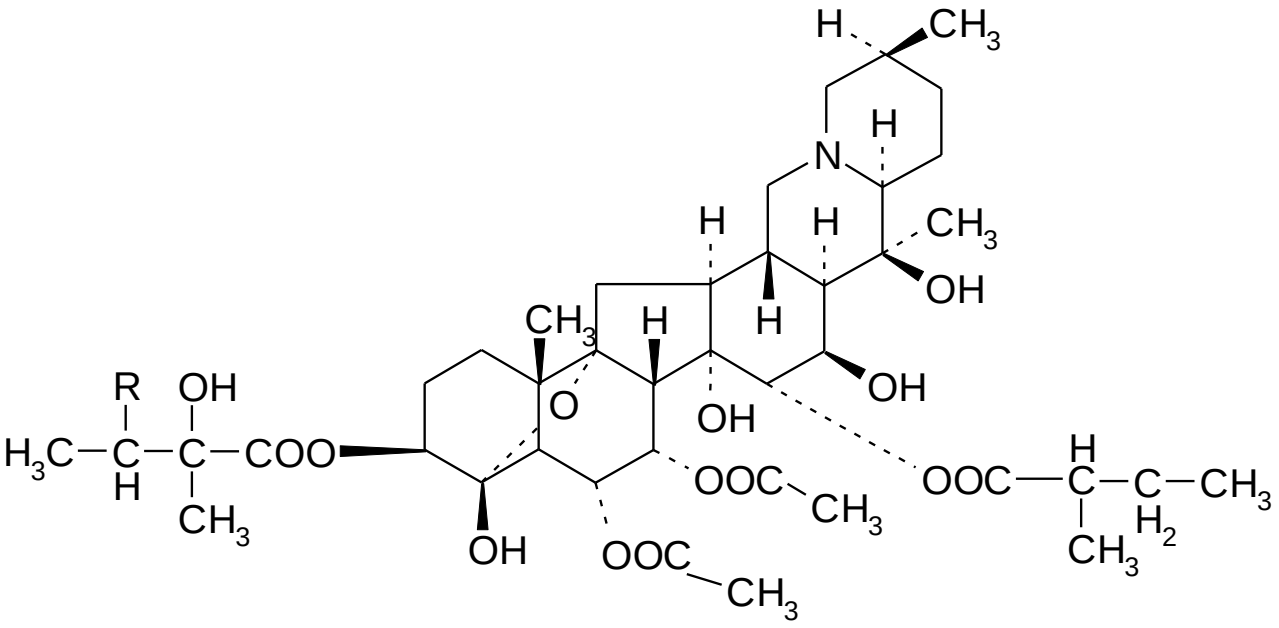
Therapeutic importance possess only ester C-nor-D-homo-cevanines: protoveratrine A and protoveratrine B.

Usage: antihypertensive, side effects, experimental compounds.

Veratri extractum – veterinary medicine – stomachic, laxative

Alkaloids possess insecticidal effect. Powdered root irritates to sneezing.

Veratri albi radix – antihypertensive active alkaloids



protoveratrine A, R = H
protoveratrine B, R = OH

Crataegi folium cum flore – Hlohový list s květem (ČL 2002)
Crataegi fructus – Hlohový plod (ČL 2002)

Source: different species of *Crataegus* – hloh, especially *C. monogyna, C. laevigata* or their hybrids

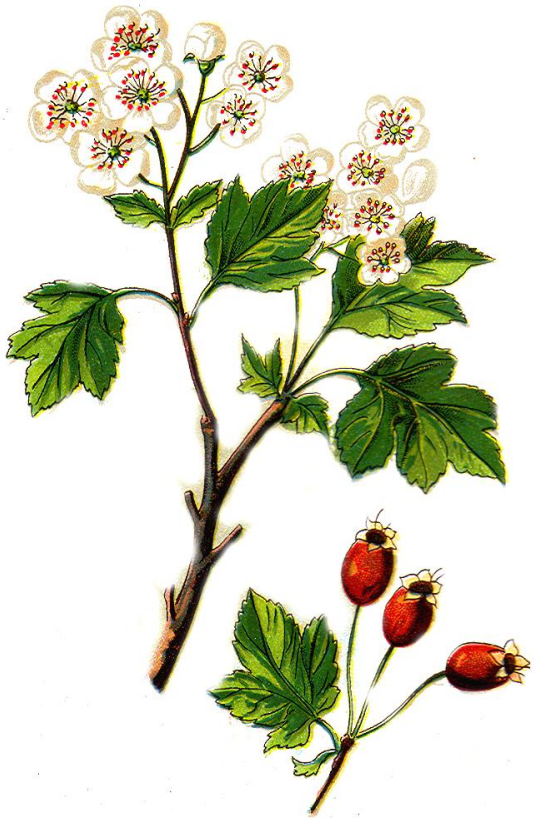
Drug: whole or cut dried flowering tips of branches, collected in spring from white flowering shrubs with simple flowers.

CC:

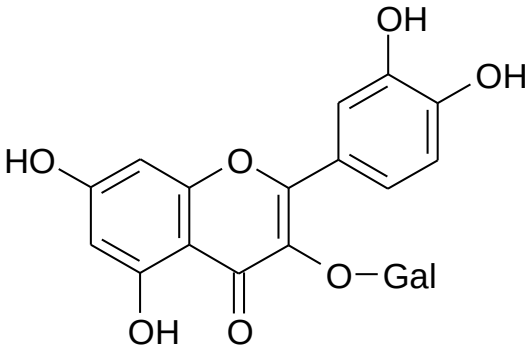
- At least 1,5 % of flavonoids expressed as hyperoside (further more rutoside, quercetine, vitexine)
- Epicatechine, procyanidine
- Triterpenic acids (oleanolic, ursolic and crataegolic)
- Adenosine

Usageí: Antihypertensive, coronary vasodilatant in form of herbal teas or standardized extracts.

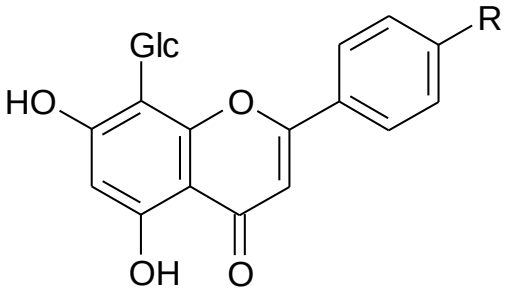
Crataegi fructus – dried pseudofruit (pome). Contains at least 1,0 % of procyanidines (expressed as cyanidine chloride).



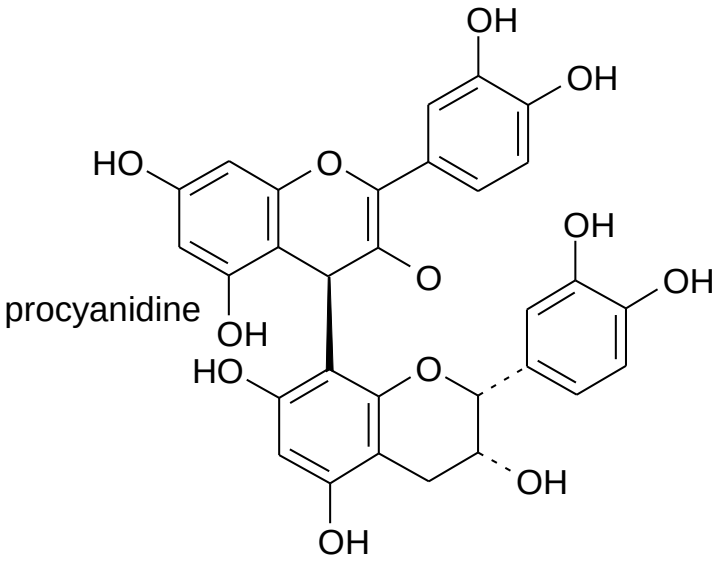
Crataegi folium cum flore – content compounds

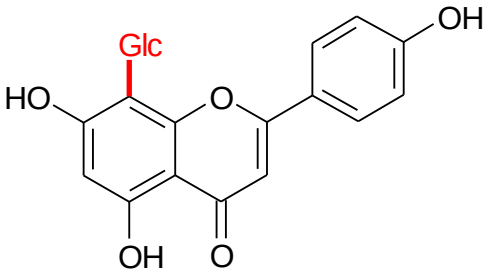


hyperoside

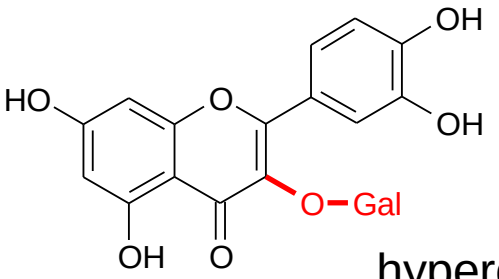


vitexine, R = OH
vitexine-4'-rhamnoside, R = O - Rha

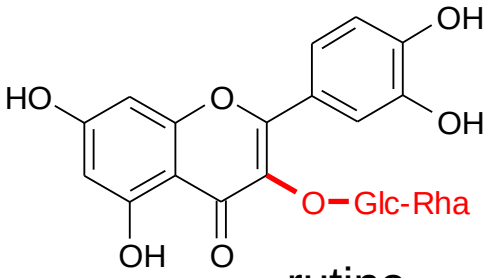




vitexine

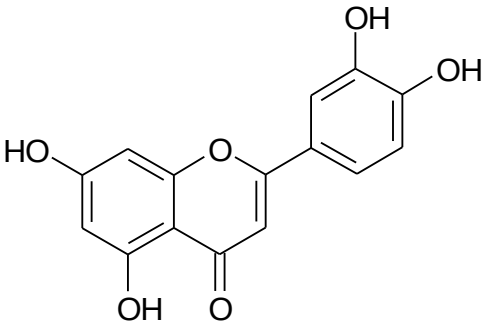


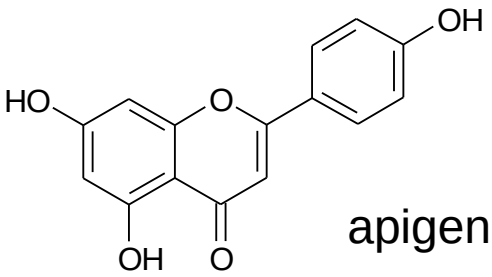
hyperoside



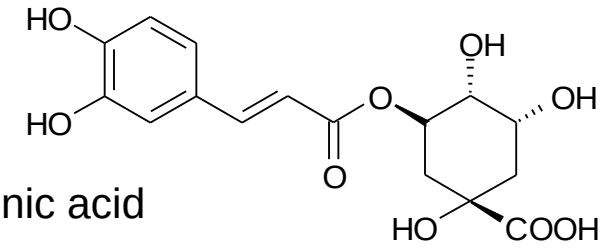
rutine

luteoline



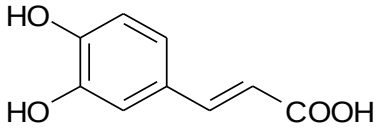


apigenine



Chlorogenic acid

Caffeic acid



Effect:

- Antiradical activity
- Inhibition of phosphodiesterase
- Increase of cAMP
- Relaxation of smooth muscles
- Lowering of blood pressure
- Antiarhytmic effect, improvement of energetic bilance of heart
- Improvemnt of oxygen supplies
- Hepatoprotective
- Prevention of neoplasia
- Lowering of cholesterol level

Visci albi herba – Nať jmelí

Source: *Viscum album* L. – jmelí bílé (Lorantha-ceae). Dioecious epiphytic shrub with furcated branched stems, semiparazitic on woody plants. Thick leathery ingerrimus leaves and small flowers, fruit - pseudo berry.

Drug: dried deciduous tips of young branches, yellow-green, without fruits

CC:

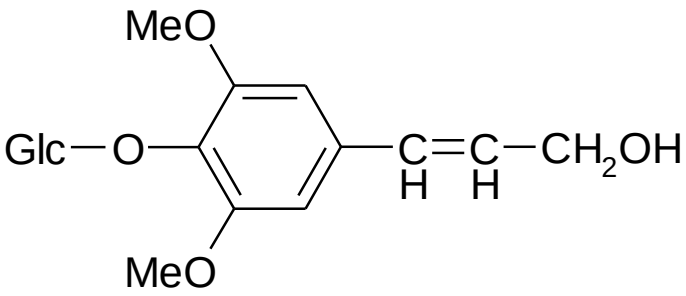
- Lectins – high molecular glycoproteins
- Viscotoxins – proteins
- Aminoacids (GABA, valin, arginin)
- Flavonoids
- Amines (choline, acetylcholine, tyramin, histamin)
- Triterpenes (amyrine, lupeol, oleanolic acid)
- Polysaccharides and cyclic sugars
- Lignans

Usage:

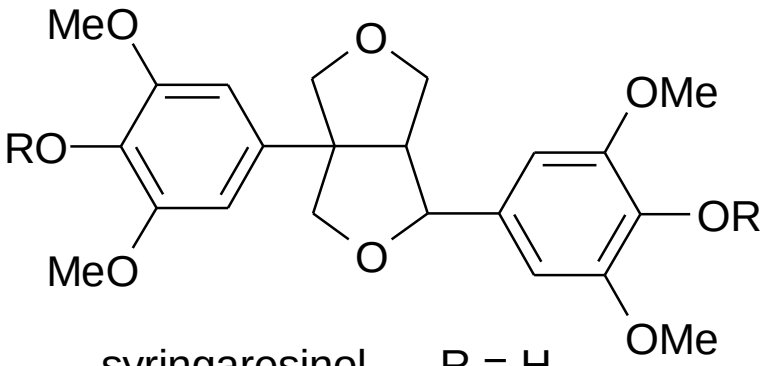
- Antihypertensive (GABA, flavonoids)

Cytotoxic (lectins – agglutination of human erythrocytes and toxic for tumor cells)

Visci albi herba – content compounds



syringine



syringaresinol, R = H
eleutheroside E, R = Glc

VENOPHARMACS – DRUGS FOR TREATMENT OF VASCULAR DISEASES

Vascular diseases – the most common diseases of blood circulation

- Varixes
- Vein inflammations
- Decreased elasticity of veins
- Increased permeability
- Increased fragility

- Local bleedings
- Inflammations, oedemas

Flavonoids as venopharmacs

Rusznyák L. and Szent Györgyi (1936): „Vitamin P, flavonols as vitamins“. **P**-vitamins – anti**P**ermeabile compounds.

Flavonoids (cca 6000) – biologic activity differs in dependence on:

- Oxidative degree of 2-phenyl-γ-benzopyrone
- Different number and position of hydroxyl and methoxyl (and other substituent) groups
- Different number, character and position of glykosidic residues

Flavonoids used as venopharmacs: rutoside, quercitrine, hesperidine, diosmine and astragaline

- normalize metabolism betwen blood and tissue – decrease permeability of capillary walls
- decrease fragility of capillaries
- inhibit hyaluronatelyase – decrease degradation of hyaluronidase, which cleavages proteoglycan component of intercellular cement and improve absorption of hematoms and oedemas.

RUTOSIDE

Source: *Sophora japonica* L. – Japanese Pagoda Tree (Fabaceae). Shrub or tree with green colored branches, and to *Robinia pseudoacacia* (Black Locust) similar leaves. Small pale yellow aromatic flowers in panicles. Producers: China, Japan.

Drug – not full-blown flower buds *Sophorae flos* with content up to 20 % of rutoside.

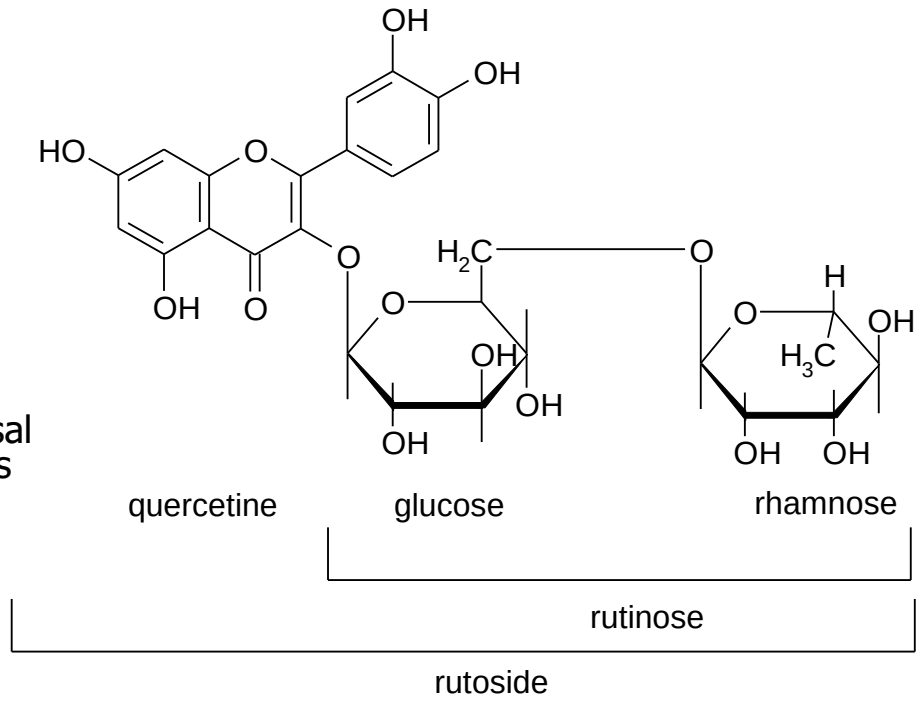
Semisynthetic derivative tris-β-hydroxy-ethyl = troxerutine, CILKANOL

Usage: increased fragility and permeability of capillaries, lack of vitamin C (scorbut), hemorhagias, hypertension, alergies, varicosal complex, surface phlebitis, infection diseases

Source: *Fagopyrum sagittatum* L. – buckwheat (Polygonaceae). One-year plant, for pharmaceutical purposes is cultivated.

Drug: dried herb harvested during flowering period.

OL: 1-2 % of rutoside, difficult isolation



VENOPHARMACS – DRUGS FOR TREATMENT OF VASCULAR DISEASES

FLAVONOIDS

DIOSMINE (Folium bucco, Cortex xanthoxylli)

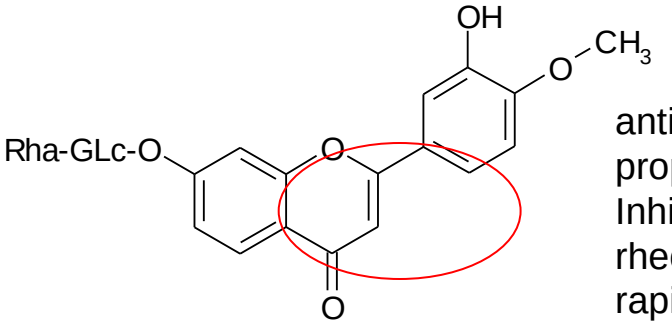
TOVENE, DAFLON, FLEBOSTEN, VENOTREX

HESPERIDINE (fruits of Citrus spp. plants)

HESPEROSIDE

QUERCITRINE (Quercus tinctoria)

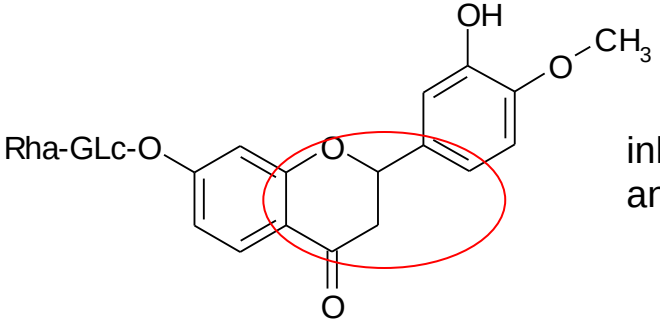
ARIVEN



diosmine

Xanthoxylli avicenae cortex, Rutaceae
Bucco folium

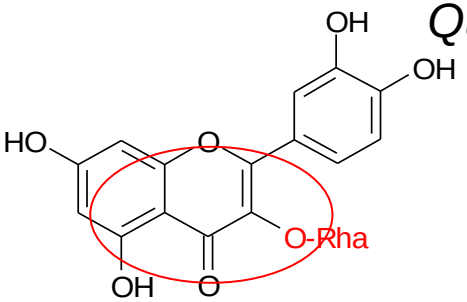
antiinflammatory, antimutagenic and antioxidative properties
Inhibition of prostaglandine and tromboxane – rheologic
rapid metabolisation to aglycon



hesperidine

Rutaceae fructi

inhibition of ACAT, HMG-CoA reductase
antihistamine effect



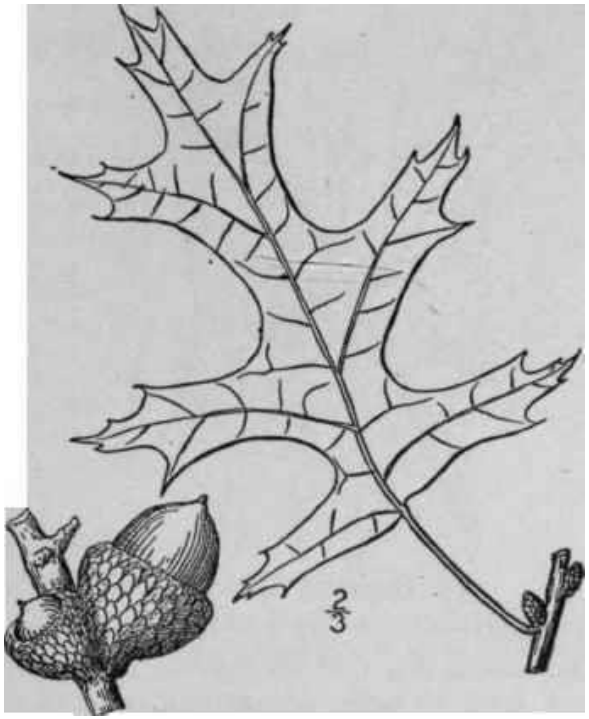
quercitrine

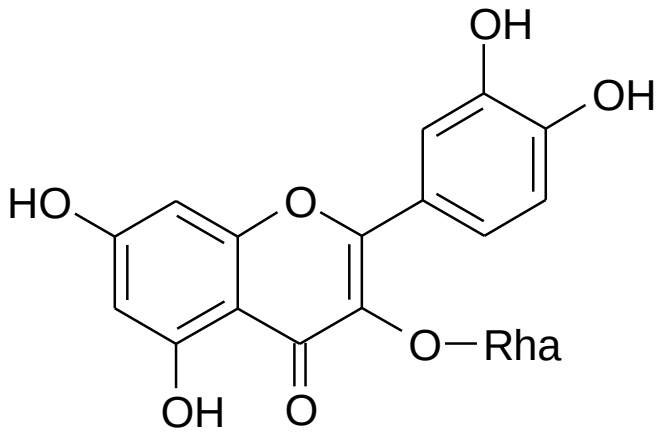
Quercus tinctorie cortex

KVERCITRINUM

Source: *Quercus tinctoriae cortex*

ARIVEN

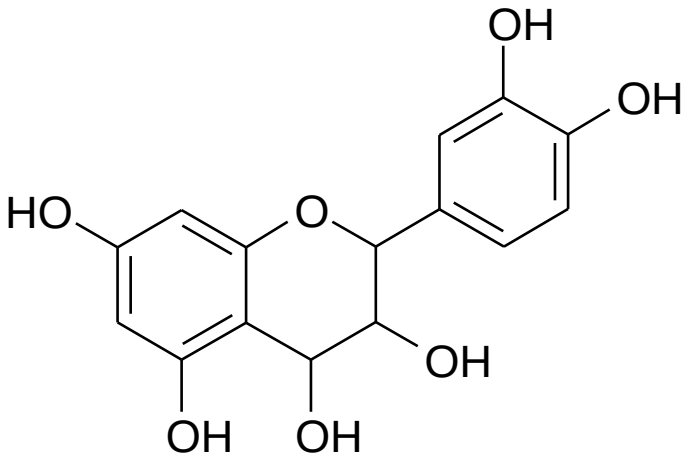




quercitrine

LEUKOCYANIDOL

Source: *Pini maritimae cortex* – maritime pine; *Cacao semen*; *Gossypii flos*; *Corylli avelanae fructus* – common hazel fruit

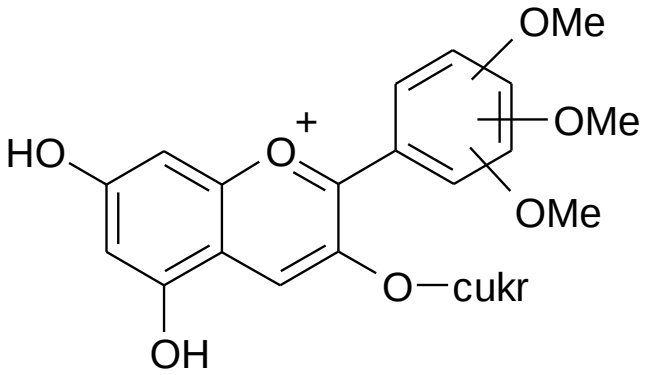


leucocyanidol

PYCNOGENOL

ANTHOCYANOSIDES – MIXTURE

Source: *Myrtilli fructus*



anthocyanosides

hemeralopia, xerophtalmia

DIFRAREL, MYRTOCYAN

Hippocastani semen – horse chestnut seed

Source: *Aesculus hippocastanum* L.– horse chestnut (Hippocastanaceae). Large tree with arched treetop. Fruit is rounded spinose capsule with 1-3 seeds with shiny brown testa.

Drug: frsh or dried seeds. Dried bark.

CC: Seeds contain at least 3 % o f mixture of triterpenic saponins, called as aescine (aglycons protoaescigenine and baringtogenol C).

Usage:

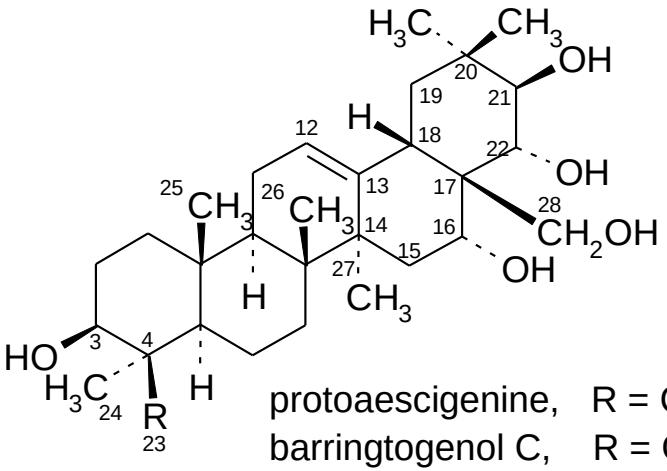
- decreases permeability of capillaries, suppresses development of oedemas
- used also during vascular brain accidents, comotion, contusion, encephalitis

YELLON, REPARIL, ANAVENOL

In testa and bark described presence of aesculine (coumarin derivative)

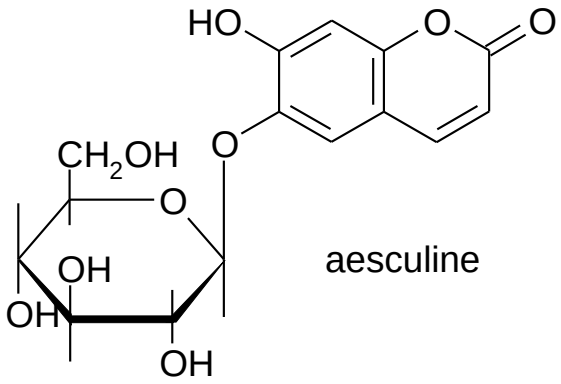
EVERCIL

Hippocastani semen – content compounds

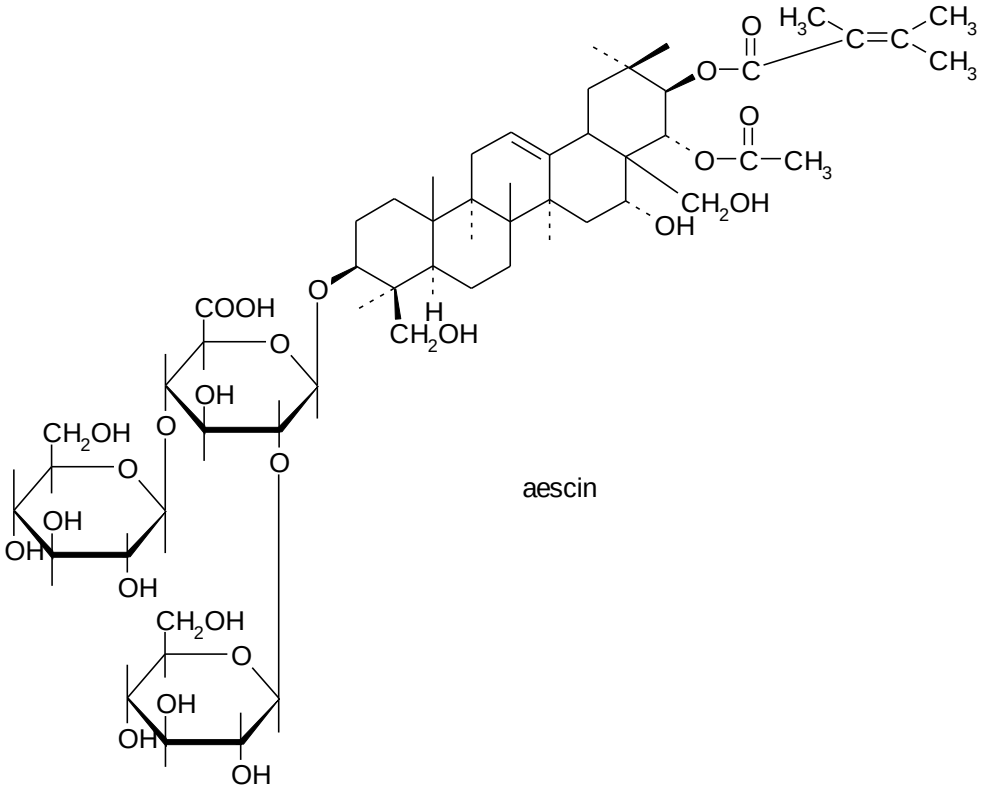


protoaescigenine, R = CH_2OH

barringtogenol C, R = CH_3



aesculine



aescin

COMPOUNDS AFFECTING DYSLIPIDEMIA (DLP) [HYPERLIPOPROTEINEMIA (HLP)]

Dyslipidemia – a panel of metabolic deviations leading to increase of proatherogenic, and procoagulative acting lipoproteins:

DLP – risk factor of development of atherosclerosis and its complications

DLP – in connection with pancreas, liver and billiard tract diseases

DLP – increased number of low density lipoproteins (LDL), lipoproteins (a) Lp(a), triglycerides together with total cholesterol in serum, or decreased number of antiaterogenic high density lipoprotein (HDL)

Prevention

- strict diet with limited amount of animal fat
- Increased energetic output

- Biogenic compounds
  - cellulose, lignin, pectins, gums – high molecular plant compounds vegetables, fruits
  - heparinoids activating lipoprotein lipases, splitting non-atherogenic fatty acids

COMPOUNDS AFFECTING DYSLIPIDEMIA

- Biogenic compounds - continued

  - **β-sitosterol** lowers the level of blood cholesterol; it is used also for treatment of benign hyperplasia of prostate gland

  - **soya lecithin** = side product of oil manufacturing from soya seeds, it contains phosphatidylcholine

  - **choleretics** (cynarine and others) and **compounds preventing resorption of bile acids**

  - **product blocking synthesis of cholesterol skeleton** – inhibitors of enzyme 3-OH-3-Me-glutaryl-CoA reductase (HMG-CoA reductase) – statins

  - **products blocking resorption of cholesterol** and its esterification: **inhibitors of acetylcoenzym-A-cholesterol acyltransferase** - ACAT

  - development of **inhibitors of squalene synthase**, inhibiting last stage of chlesterol synthesis

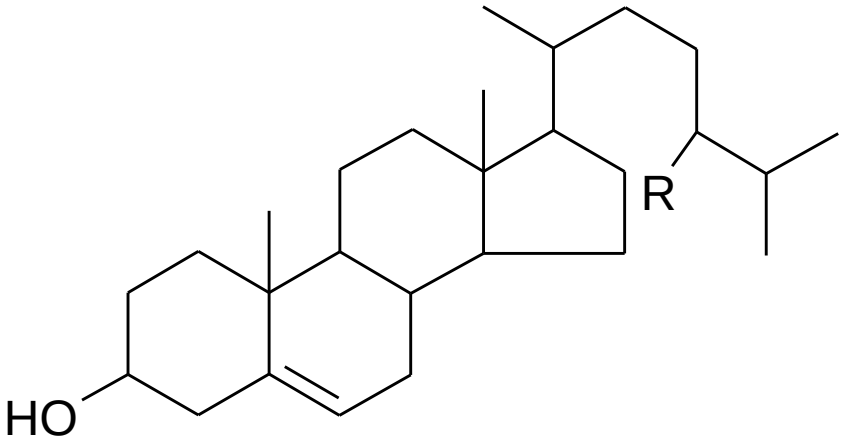
β-SITOSTEROL

Source: slices of sugar beet, defatted soya seeds, oil from cereal sprouts.

Plant sterols are absorbed by human in minimal rate.

High doses considerable inhibit cholesterol absorption

Usage: hypercholesterolemia, benign adenoma of prostate gland.



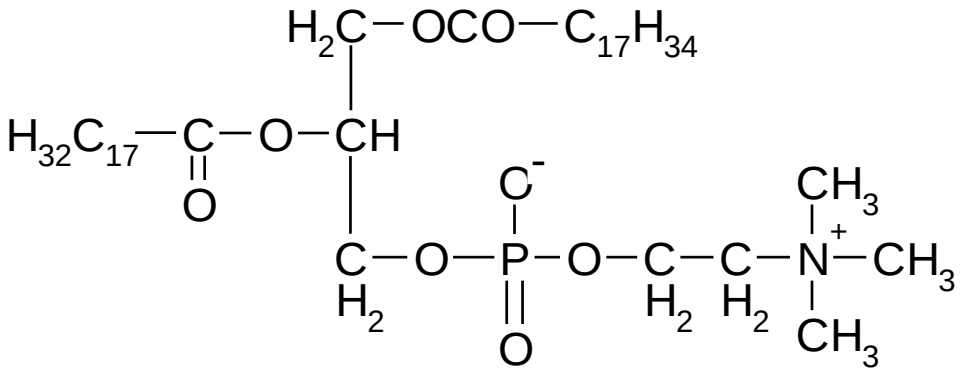
β-sitosterol	R = CH_2-CH_3
campesterol	R = CH_3
cholesterol	R = H

SOYA LECITHIN

Source: side product of manufacturing of soya oil from soya seeds. Purified on ion exchangers.

Yellowish hygroscopic mass containing 90-95 % of phosphatidylcholine. Linoleic acid content cca 70 %.

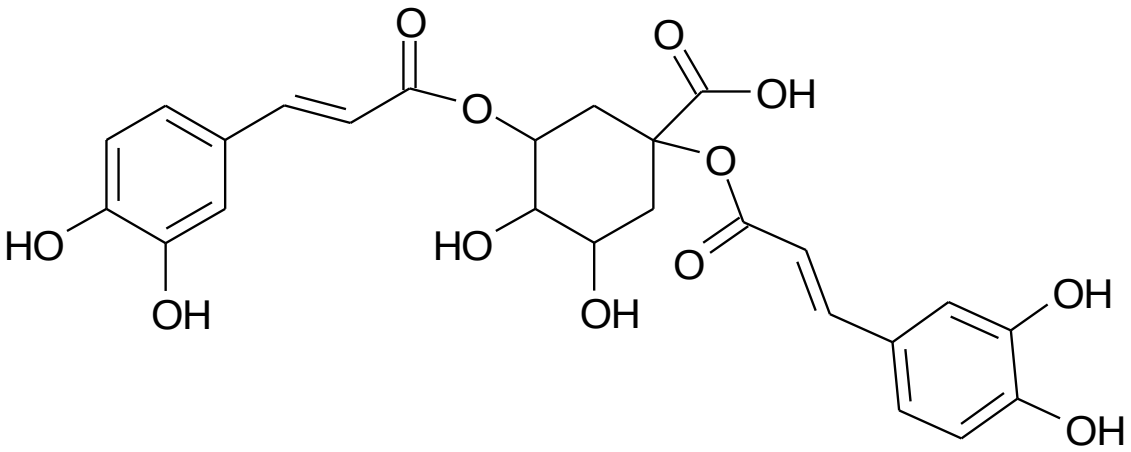
Usage: lowering of cholesterol level.



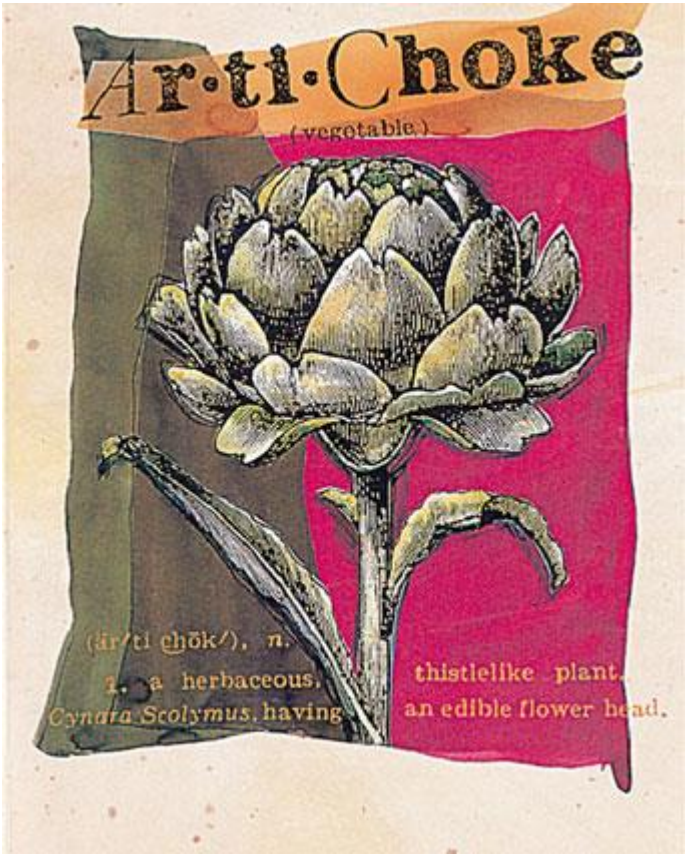
phosphatidylcholin

CHOLERETICS

Source: Cynara scolymus and others

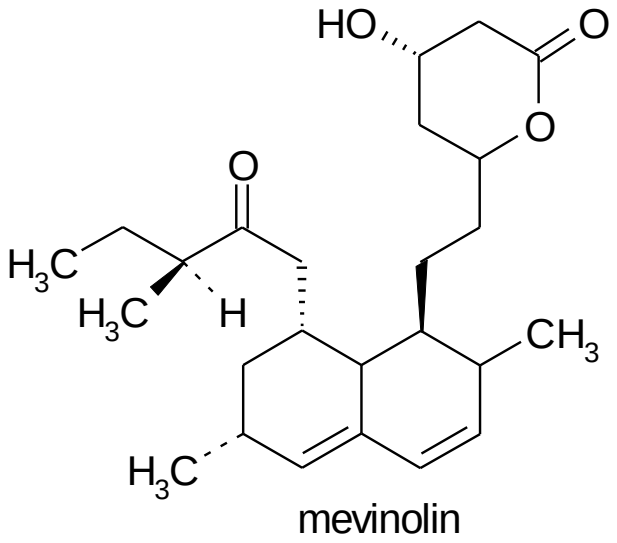


- cynarin



Products of moulds – originally antimycotics
MEVINOLIN

Source: *Aspergillus terreus*



mevinolin

- Lowers blood cholesterol about 18 – 34 %
- blocks key enzyme reductase of 3-OH-3-Me-glytarylCoA (HMG-CoA) which participates on cholesterol biosynthesis