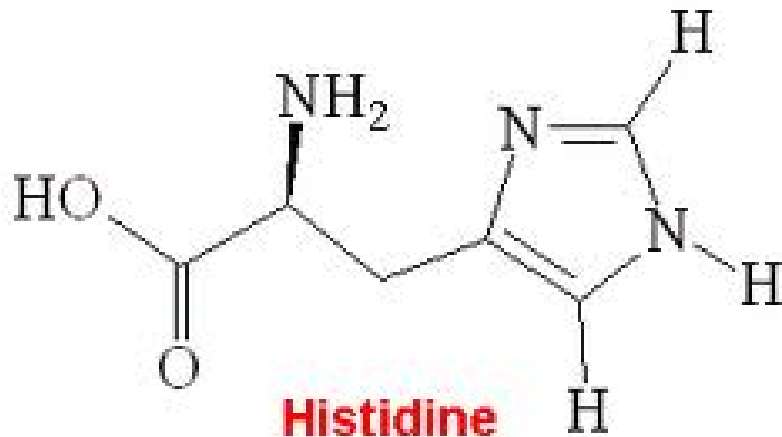


# **Alkaloids Derived from Histidine**

## **Imidazole Alkaloids**

Prof. Dr. Ali Hikmet Meriçli

Although histidine and histamine are ubiquitous, alkaloids that possess an imidazole nucleus are very rare. They are found in some Rutaceae, especially in the leaves of *Pilocarpus* of South America.



**Jaborandi**

**Jaborandi folium**

***Pilocarpus microphyllus***

**Rutaceae**

In South America, the term jaborandi designates miscellaneous drugs that belong to various species of Rutaceae of the genus *Pilocarpus*.

Maranhão jaborandi : *Pilocarpus microphyllus*

Pernambuco jaborandi : *Pilocarpus jaborandi*

Paraguay jaborandi : *Pilocarpus pennatifolius*

Ceara jaborandi : *Pilocarpus trachylophus*

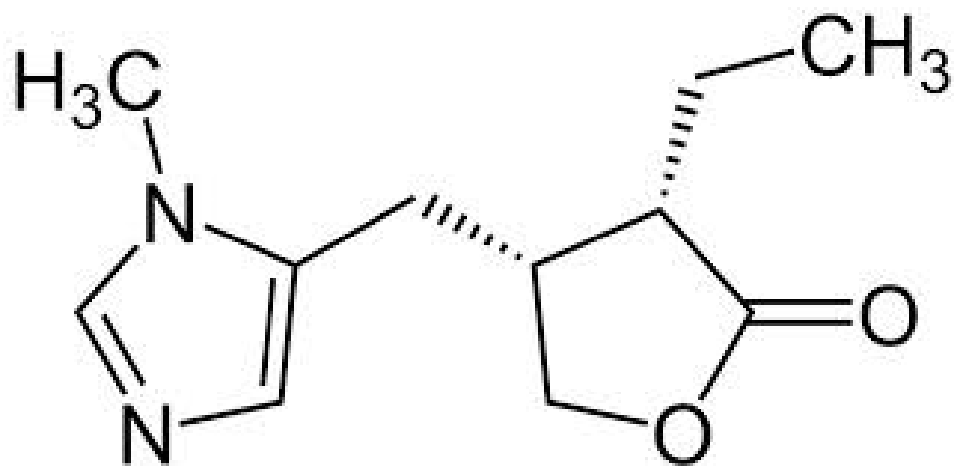
Guadeloupe jaborandi : *Pilocarpus racemosus*

**Chemical Composition** :The concentration of total alkaloids is nearly 0.7-0.8%; the chief constituent is (3S,4R)-(+)-pilocarpine. This is a lactone and it is fragile : in aqueous medium, it is readily hydrolyzed to pilocarpic acid and isomerized to isopilocarpine (3R,4R). The epimerization is very rapid in alkaline conditions, and involves an enolate that is stabilized by mesomerization.

**Pharmacological Activity and Uses** : Pilocarpine is a parasympathomimetic. It induces salivary, gastric, and sweat hypersecretion; it increases intestinal motility, induces bronchoconstriction, and bradycardia.

In the eyes, pilocarpine causes the iris sphincter to contract and causes myosis, which leads to the opening of the space between the iris and cornea, which in turn is expected to relieve narrow angle glaucoma; the contraction of the ciliary muscle, on the other hand, facilitates the flow of aqueous humor in case of wide angle glaucoma.

Jaborandi leaves are used for the extractions of pilocarpine. This compound is used as its nitrate (eye drops at 1, 2, and 3%) or as its hydrochloride (eye drops at 1, 2, 3, and 4%), alone or in combination with phenylephrine. The normal indications are chronic simple (wide angle) glaucoma, acute congestive (narrow angle) glaucoma, and the diagnostic of the causes of mydriasis.



pilocarpine

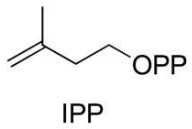


# **TERPENOID ALKALOIDS**

**Prof. Dr. Ali H. Meriçli**

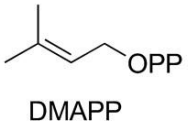
In some rare cases, the alkaloid does not arise from the metabolism of an amino acid, and is in fact a terpenoid (mono-, sesqui-, di-, triterpenoid, or a steroid) which incorporates a nitrogen atom late in the biosynthesis.

Because of their isoprene-type origin, some authors see in these compounds no more than “pseudoalkaloids”, however, they are still widely considered alkaloids.

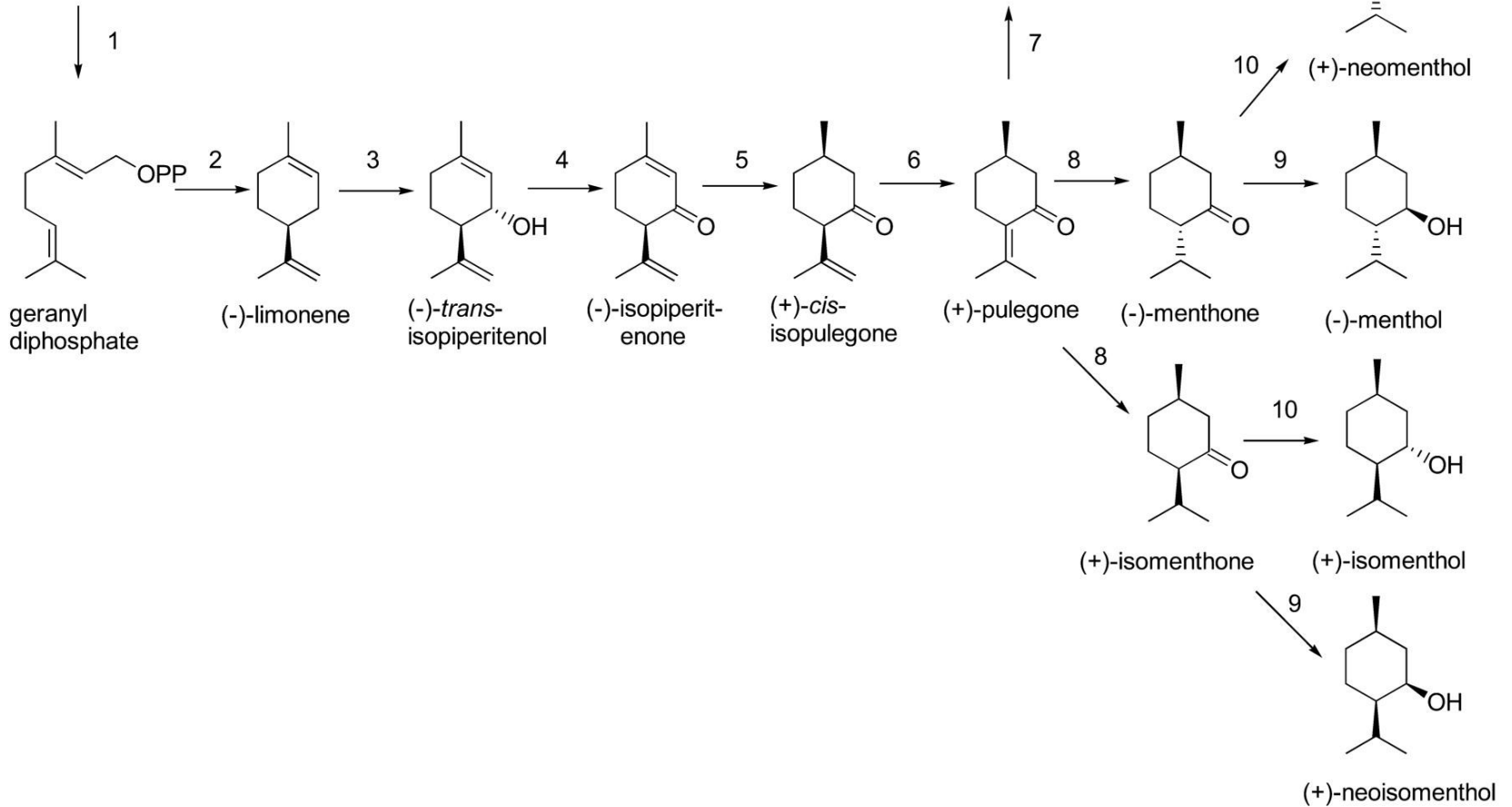


Isopentenyl pyrophosphate

+



Dimethylallyl pyrophosphate



# MONO- AND SESQUITERPENOID ALKALOIDS

There are a few drugs containing monoterpenoid alkaloids and their pharmacological interest is very limited.

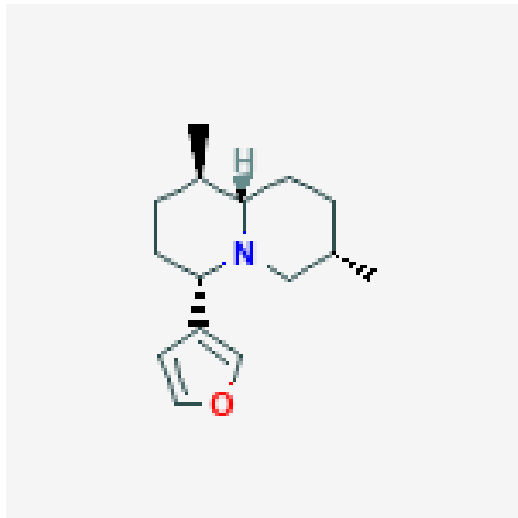
!!! The action of aqueous ammonia on an iridoid readily leads to nitrogen-containing structures (**ARTEFACTS**)

# WATER LILIES

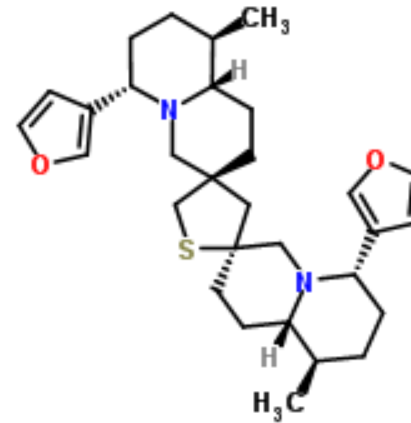
*Nuphar luteum*,      *Nymphaea alba*  
(Nymphaeaceae)

nilüfer

The rhizome of these species (*Nymphaeae* rhizoma) contains sesquiterpenoid alkaloids



**Deoxynupharidine**

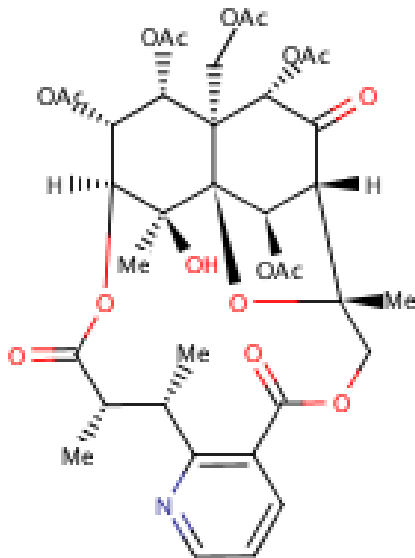


**Thiobinupharidine**

# Spindle tree, (*Euonymi semen*)

## *Euonymus europaeus* (Celesteraceae)

The fruits are toxic. The seeds contain a small quantity (0.1%) of alkaloids and cardiac glycosides. The alkaloids are polyesters of sesquiterpenoid polyols.



**Evonine**

***Euonymus europaeus***

# **DITERPENOID ALKALOIDS**



The nitrogen-containing diterpenoid bases known to date have been, for the most part, isolated from various Ranunculaceae ( *Aconitum*, *Delphinium*, *Consolida* ).

Their structure is always complex and their skeletons can comprise 19 or 20 carbon atoms; they are referred to as norditerpenoid and diterpenoid alkaloids, respectively. Especially norditerpenoid alkaloids are very toxic compounds.

*Aconitum*

*Consolida*

*Delphinium*

*Aconitum*, *Consolida* and *Delphinium* species are important plants due to the diterpenoid alkaloidal contents. These alkaloids are neurotoxic agents, causing bradycardia, muscle system spasms, hypotension and death by arrest of respiration.

***Aconitum*, *Delphinium* and *Consolida* species are among the zygomorphic flowered species of Ranunculaceae family.**

***Aconitum* species are usually bigger than *Delphinium* and *Consolida* species and have a more striking appearance. As a characteristic property, upper outer perianth segment of *Aconitum* species is hooded whereas upper outer perianth segments of *Consolida* and *Delphinium* species are spurred.**

The most important difference between *Delphinium* and *Consolida* species is that *Delphinium* fruits consist of 3 follicles but *Consolida* fruits have only 1 follicle.

Aconiti tuber (Aconiti radix)

Delphinii herba

Delphinii semen

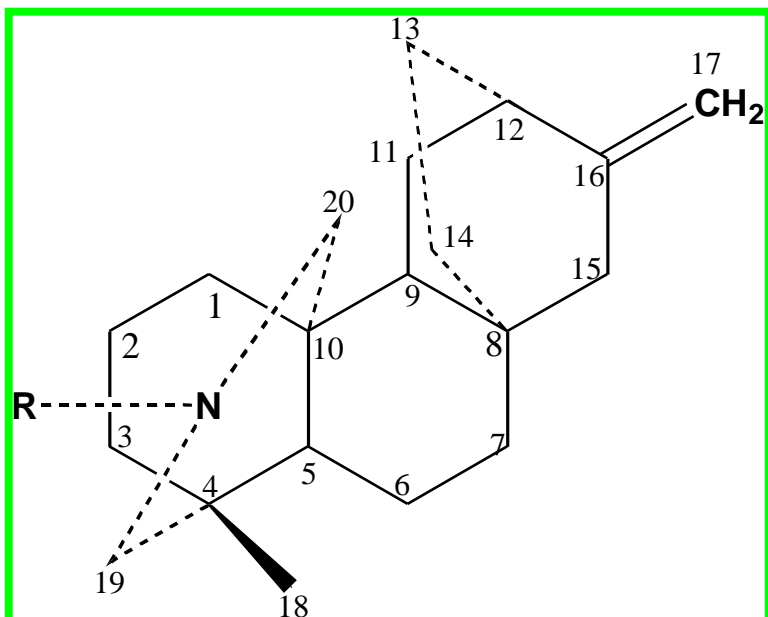
Consolidae herba

*Aconitum spec.* : Kurtboğan, kaplanboğan

*Delphinium spec.* : Bit otu, hezaren

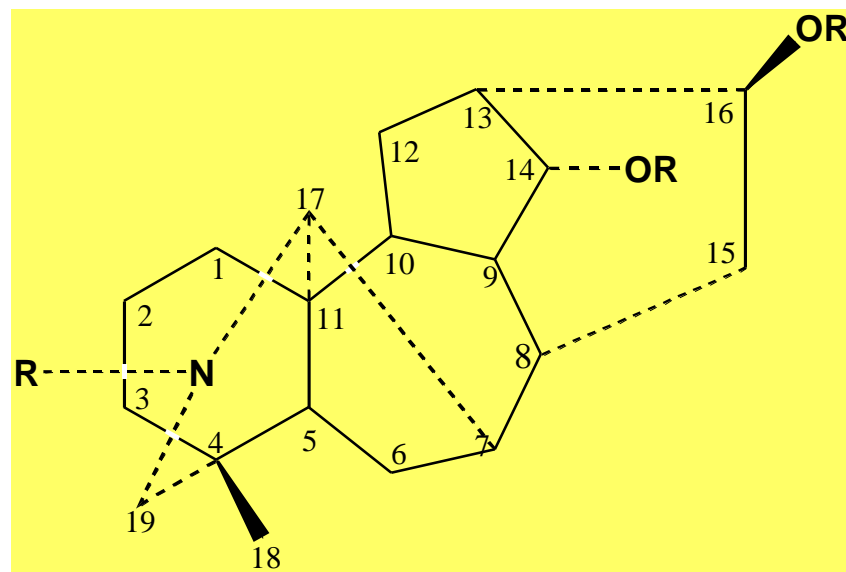
*Consolida spec.* : Ekin anası

# Main Skeletons of Diterpenoid and Norditerpenoid Alkaloids:



C-20 diterpenoid alkaloids have an ethylenic bond between C-16 and C-17

C-19 norditerpenoid alkaloids are characterized with the methoxy groups

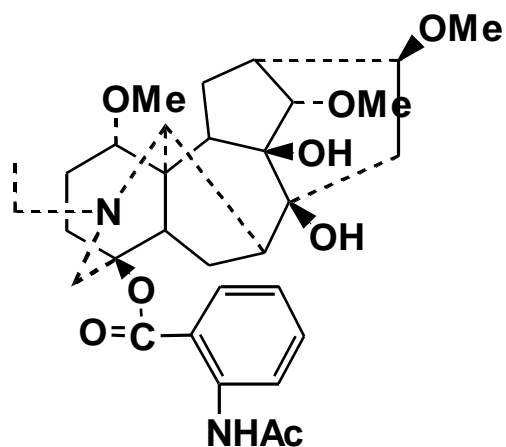


Norditerpenoid alkaloids have a complex structure and are generally classified under the aconitine type (unsubstituted at C-7) and lycoctonine type (7-substituted).

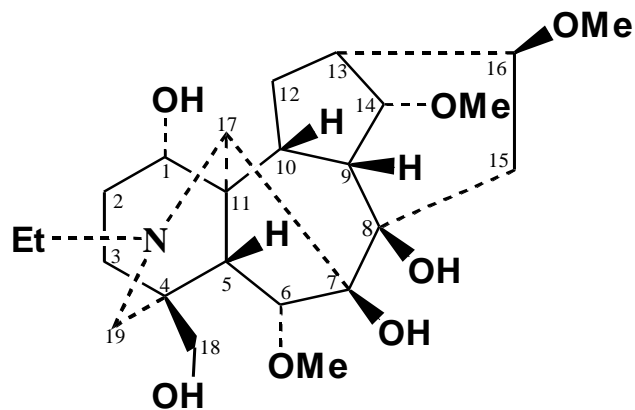
Diterpenoid alkaloids (  $C_{20}$  ) have subtypes like atisine, hetisine, veatchine groups.



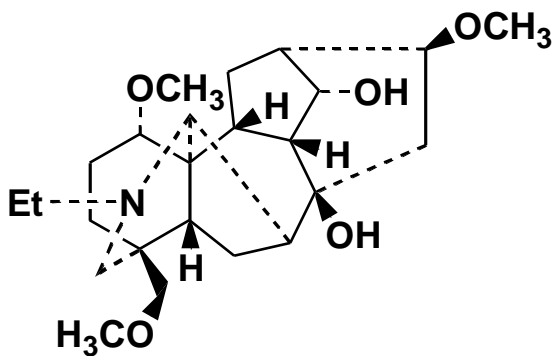
# Some norditerpenoid alkaloids



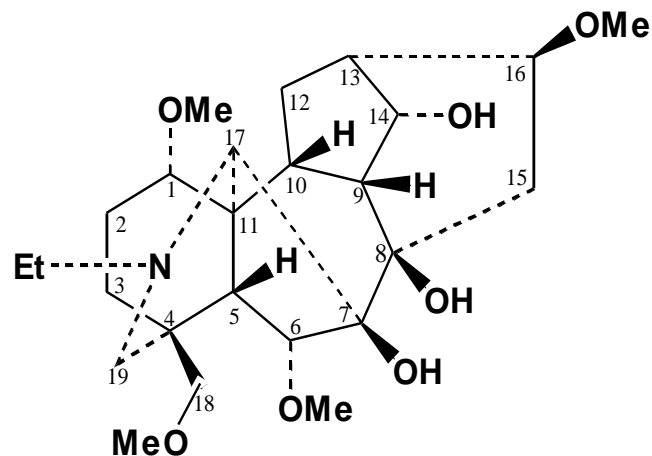
**lappaconitine**



**lycoctonine**

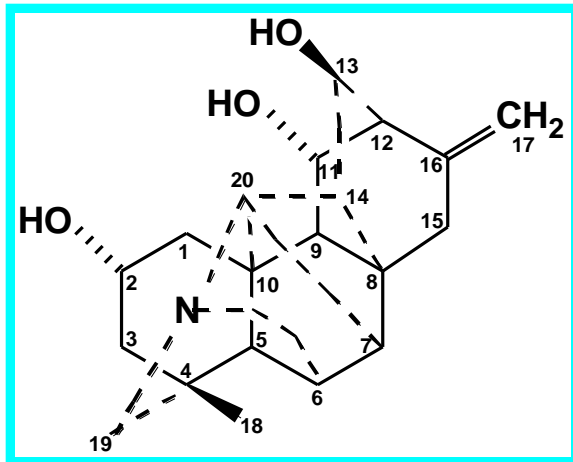


**talatisamine**

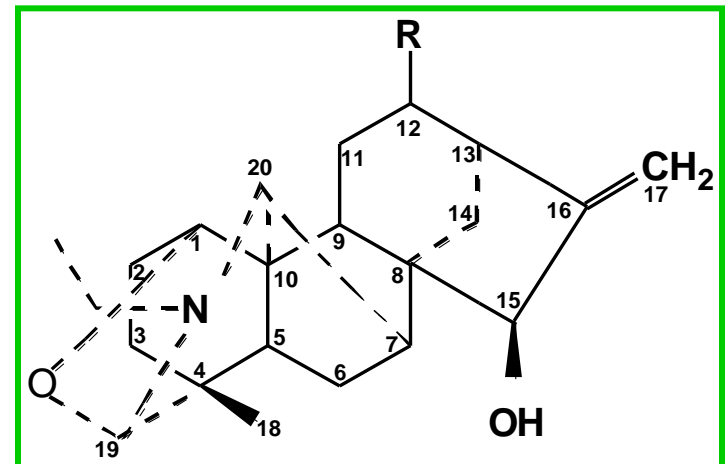


**browniine**

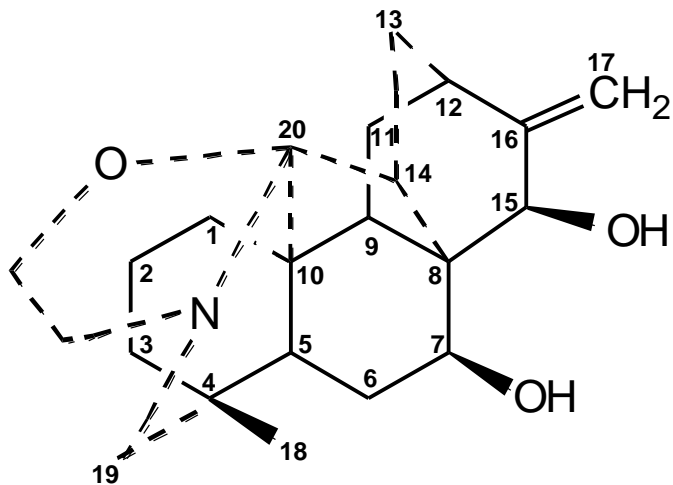
# Some diterpenoid alkaloids



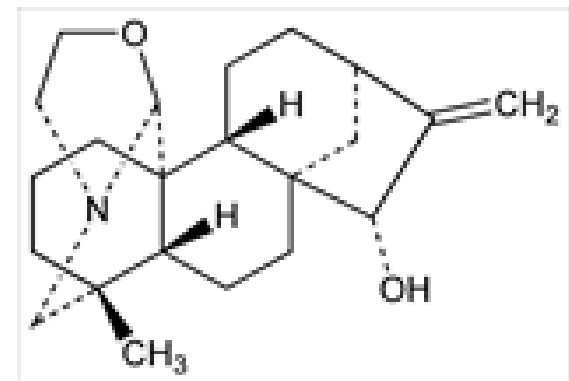
**hetisine**



**napelline**



**septatisine**



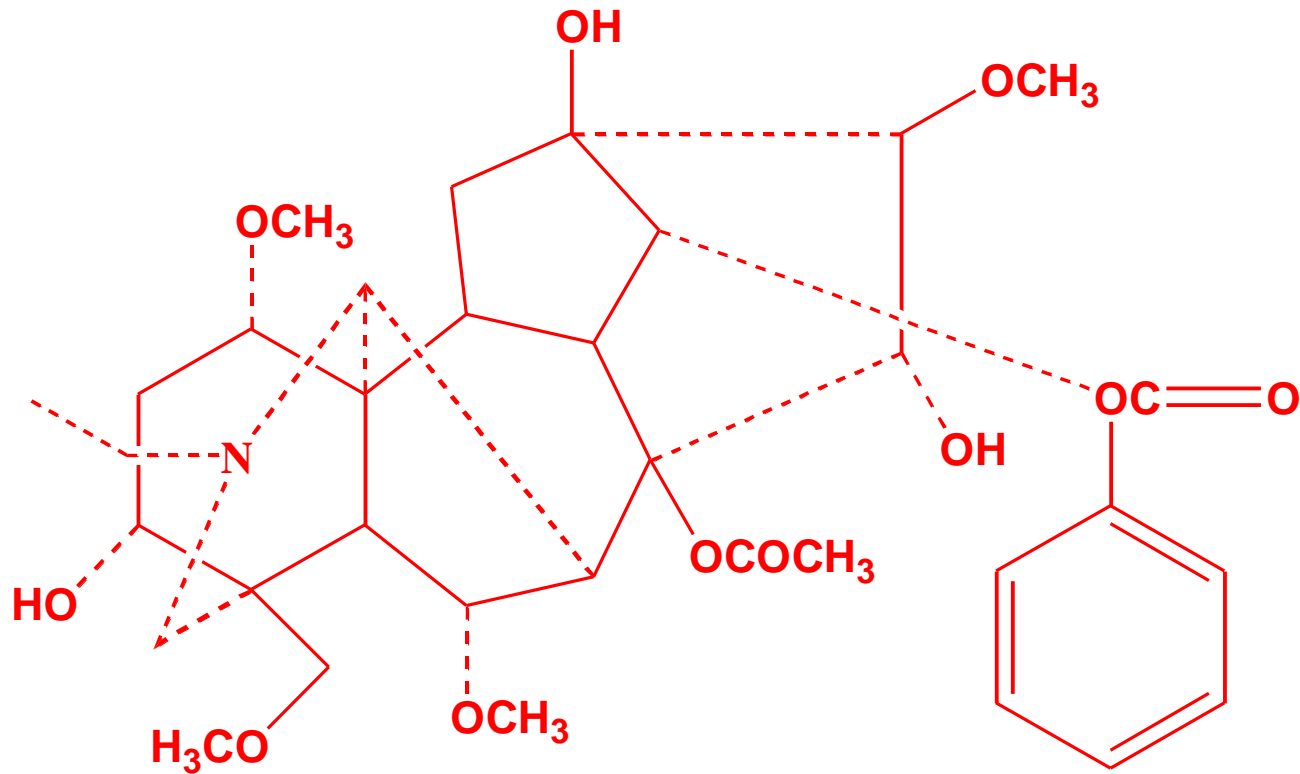
**veatchine**

**Especially the norditerpenoid alkaloids (aconitine and similar compounds) have a very high toxicity.**

**Manifestation of the toxicity begins with faster respiration and tachycardia, and is followed by a slight loss of consciousness, benumbation of lips and tongue and a strong headache. Feeling like ice is running in the veins occurs as the characteristic symptom of these compounds' toxicity because of the decrease in body temperature and death occurs in 2 - 3 hours with respiratory paralysis.**

“ These symptoms inspired the use of very dilute homeopathic *Aconitum* preparations for the treatment of influenza, rheumatism, headaches, toothaches and conjunctivitis ”

# Aconitine : The most known norditerpenoid alkaloid



# Method of preparing diterpenoid alkaloid extract

Powdered material

percolation

EtOH Extract

After evaporation  
dissolved in 0.5 N H<sub>2</sub>SO<sub>4</sub>

Separating funnel, CHCl<sub>3</sub>

Aqueous layer

% 10 NaOH

PH 10

PH 10

Separating funnel,  $\text{CHCl}_3$

$\text{CHCl}_3$  Extract

evaporation

Crude alkaloid extract

basic  $\text{Al}_2\text{O}_3$  column  
in a step gradient (100 ml each)  
PE and  $\text{CHCl}_3$  and MeOH

VLC



# VLC Fractions

were combined according to their TLC results

## Combined VLC Fractions

The logo for Chromatotron features a light blue circular gradient with two concentric red circles. A grey horizontal bar is superimposed across the center, containing the word "Chromatotron" in red text.

**Chromatotron**

Chromatographed on a silica or a  
basic alumina rotor  
hexane- $\text{CHCl}_3$ -MeOH mixtures



# Chromatotron-Fractions

Prep. TLC



diterpenoid or norditerpenoid compounds

The structures of the compounds were established by spectroscopic studies (1- D and 2-D NMR ; MS techniques)

# Pharmacological Activity and Uses of the Drugs:

Aconites are among the genera most often used as arrow poisons during at least three millennia, in Orient as well as in the western hemisphere. The names of certain species (wolfsbane) are reminiscent of their former use as poisons against wild animals : wolves, foxes, bears, and also rodents.

The use of aconite (*Aconitum*) as a medicinal plant is an ancient in India or China, and appeared a little later in the western world.

Both of groups (norditerpenoid and diterpenoid alkaloids) show also insecticidal activities (insect repellent and antifeedant activities).

**Uses in the Western World :** Aconite tincture is the normal form which the aconite tuber (**Aconiti tuber**) is used. As a decongestant, it is an ingredient of medications, generally syrups, used to relieve unproductive coughs. It is used in many combinations with galenicals (ipecac syrup, eucalyptus syrup) as well as specific chemicals (bromoform, codeine, eucalyptol). *Aconitum* is widely used in homeopathy.

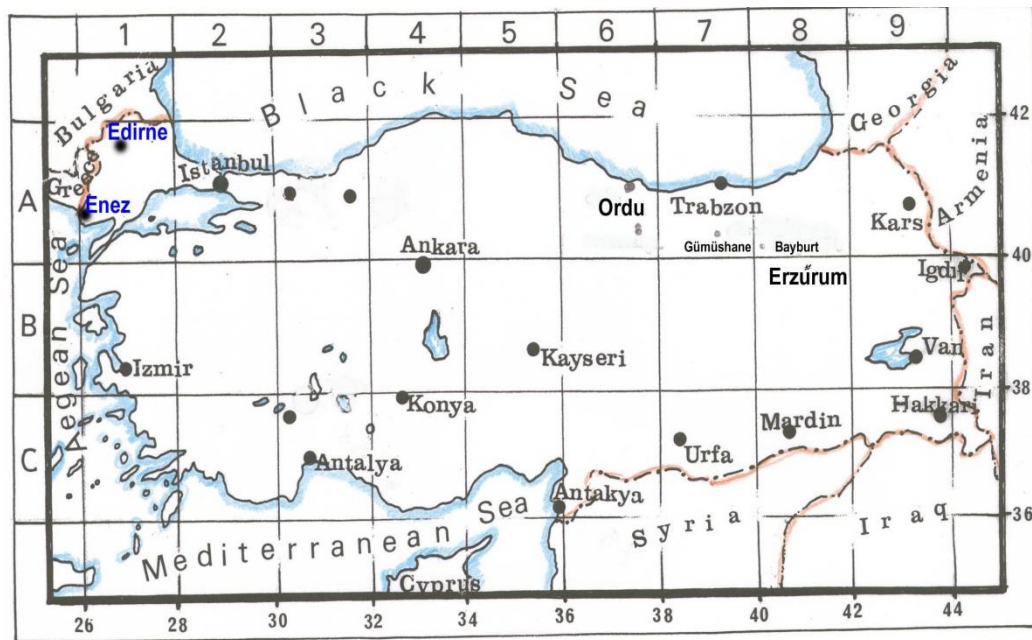
**Uses in the Orient :** Chinese medicine finds many uses for aconities, to which it attributes antirheumatic, analgesic, anesthetic, and antinevralgic properties.

Ration consist of soaking in water, then cooking for 4-6 hours or treating with steam for 6-8 hours. Only prepared root must be used.

In Europe two *Aconitum* species, *Aconitum napellus* and *Aconitum vulparia* are growing.

***Aconitum napellus***

***Aconitum vulparia***



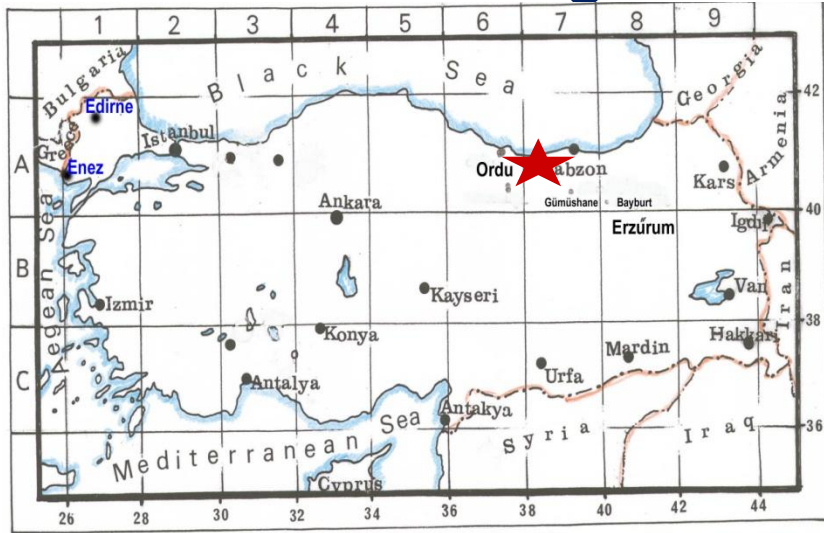
There are 4 *Aconitum* species growing wildly in Turkey.

The genus *Consolida* is represented with 27 species in Turkey; 13 of them are endemic plants.

There are 31 *Delphinium* species growing wildly in Turkey ; 19 of them are endemic plants.

# *Aconitum orientale*

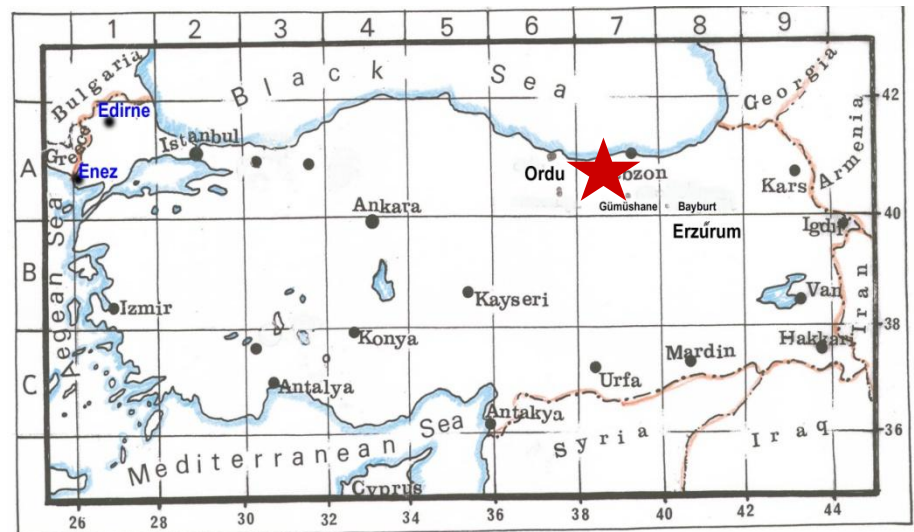
Grows in Black Sea Region of Turkey



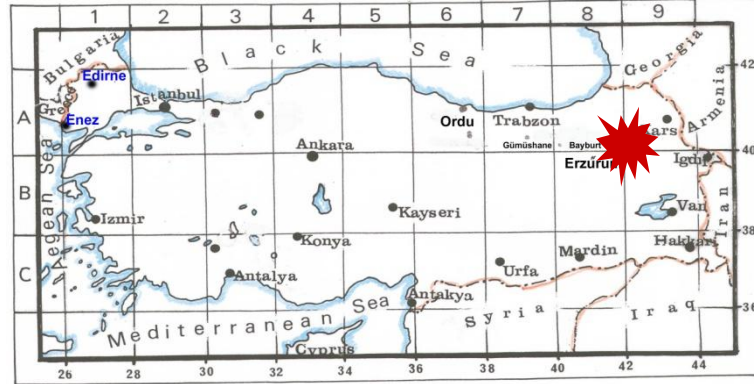


# *Aconitum nasutum*

Grows also in the Black Sea Region of Turkey

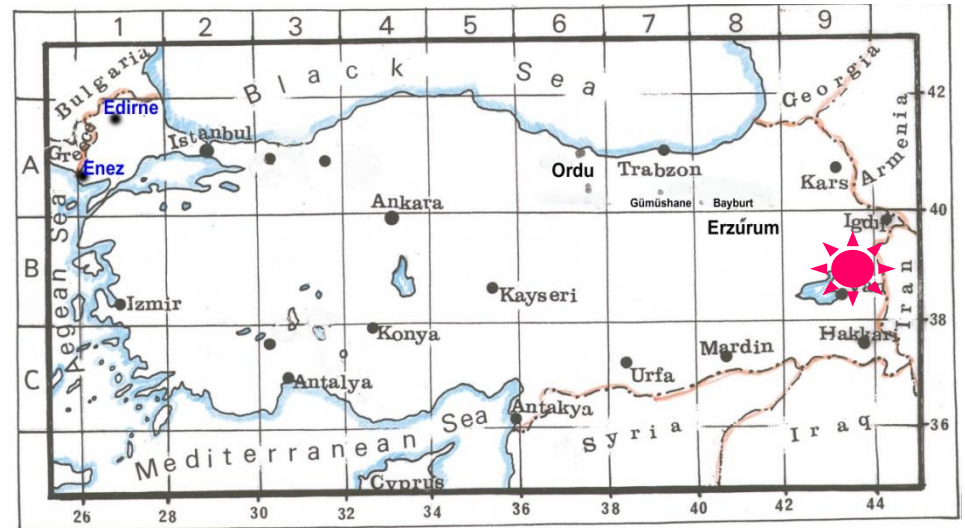


# *Aconitum anthora* : Grows in the North-eastern part of Turkey



# *Aconitum cochleare*

Grows in the Eastern part of Turkey around  
Van



***Delphinium formosum***

***D. munzianum***

***Delphinium peregrinum***  
**(Cyprus)**

***D. staphisagria***  
**(Cyprus)**

***Delphinium caseyi* : Endemic, North Cyprus,  
above St. Hilarion**

***Consolida orientalis***

***C. raveyi***

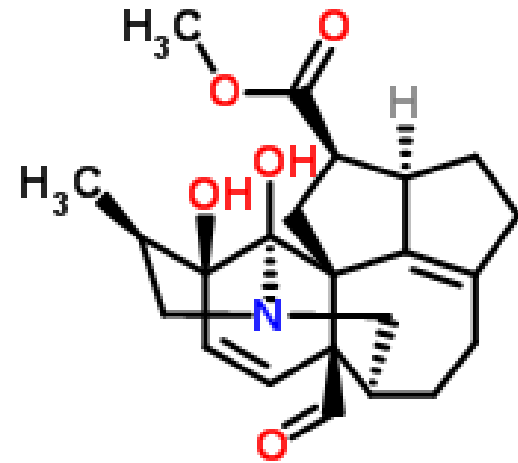
***Consolida regalis***

***C. oliveriana***



# TRITERPENOID ALKALOIDS

They are very seldom found in nature. They have been isolated from the Asian species of the genus *Daphniphyllum* (daphniphylline, yuzurimine)



**yuzurimine**

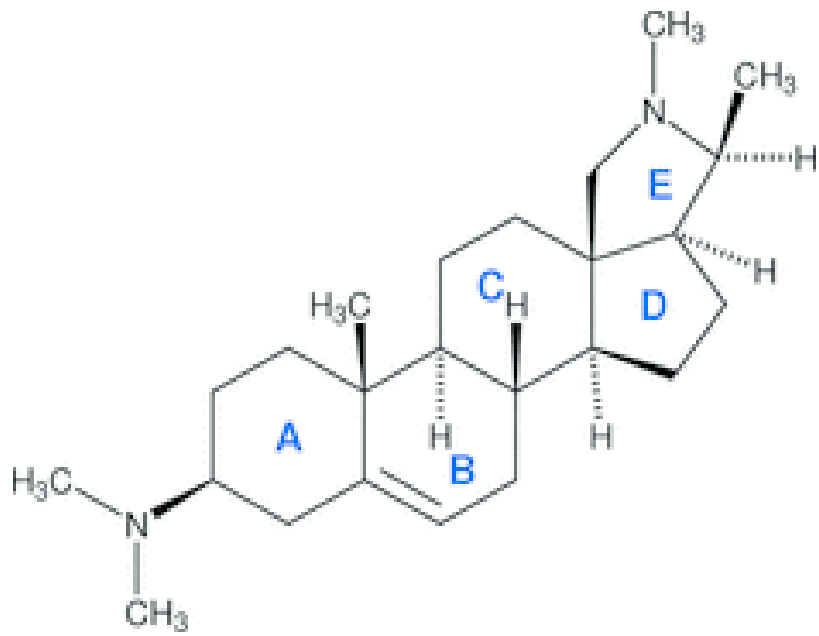
*Daphniphyllum macropodum*

# STEROIDAL ALKALOIDS

Steroidal alkaloids can be classified simply in three groups based on whether their skeleton contains 21, 24, or 27 carbon atoms.

C<sub>21</sub> alkaloids are derivatives of pregnane with a nitrogen-containing substituent at C-3, or C-20 or in both positions. The nitrogen atom may be a part of a side chain as an amine substituent at C-3, C-20 or both.

These alkaloids are especially characteristic of the Apocynaceae (*Holarrhena*, *Funtumia*).



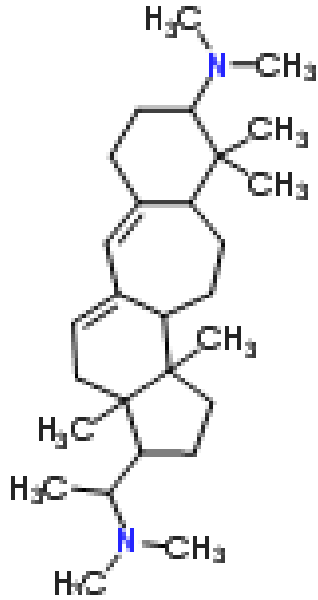
**Conessine**

*Holarrhena pubescens*

These alkaloids are devoid of interest. For a while, conessine hydrobromide was used for its toxicity in protozoans. Conessine is one of the principal alkaloids of the barks of an Asian species *Holarrhena pubescens*.

$C_{24}$  alkaloids are derived directly from cycloartenol, and are specific to the family Buxaceae. They have amine functions at C-3 and C-20, and have either retained the original skeleton (cycloartane), or have lost one of the methyl groups at C-4, or else they include a seven-membered ring arising from the 9,10-cleavage of the cyclopropane ring.

# Buxamine A

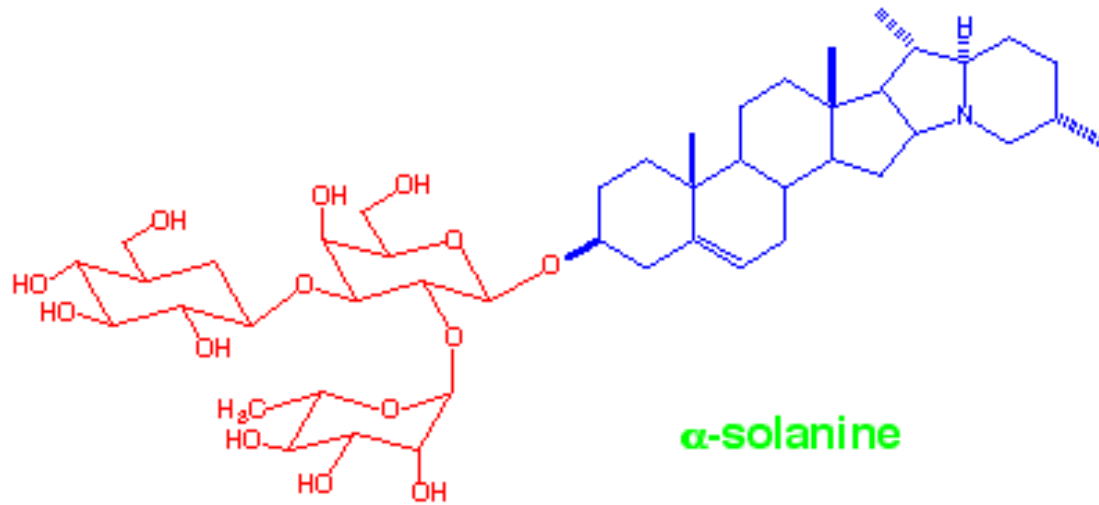


*Buxus sempervirens*

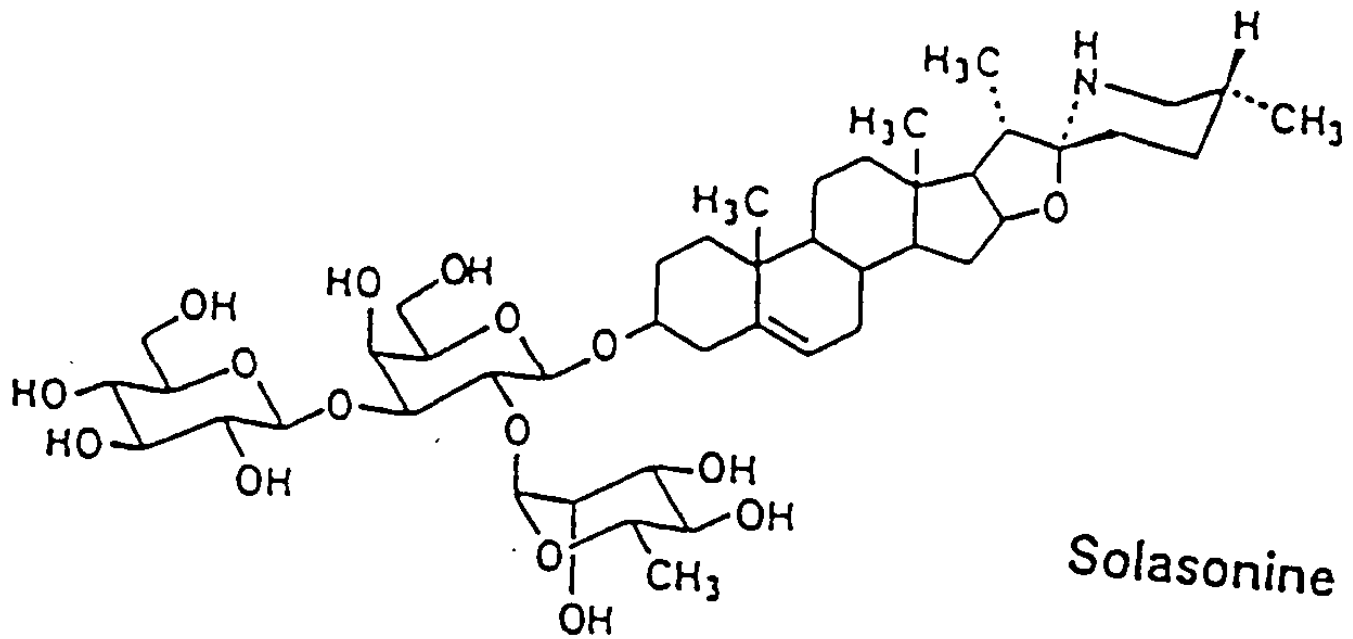
şimşir

$C_{27}$  alkaloids are found in the Solanaceae and Liliaceae. In the case of the family Solanaceae, they are true steroids, which are nitrogen-containing derivatives such as solanine, solasonine or tomatine. These alkaloids occur in the plants, as glycosides, and are closely related, structurally and biogenetically, to steroidal saponins with which they share many physico-chemical and biological properties.

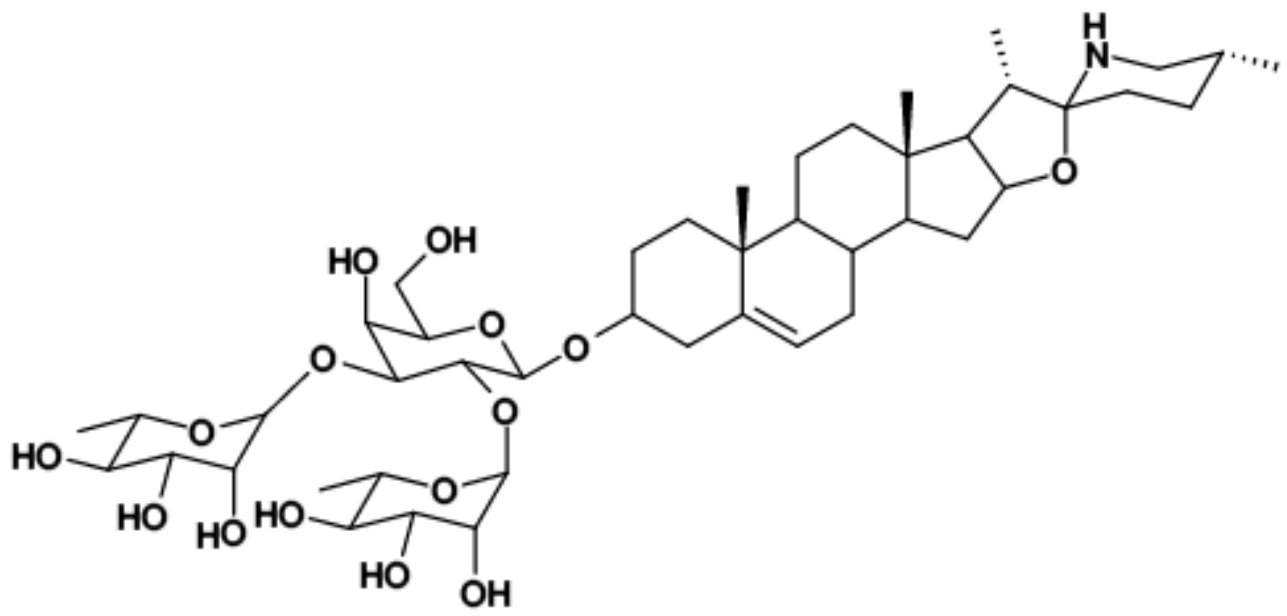




$\alpha$ -solanine

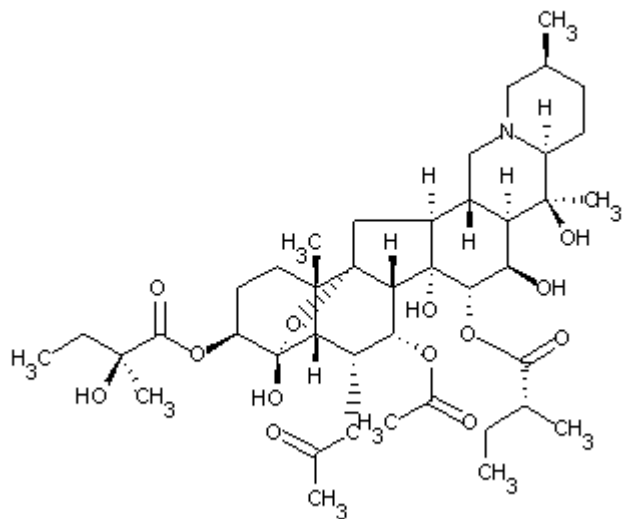


Solasonine

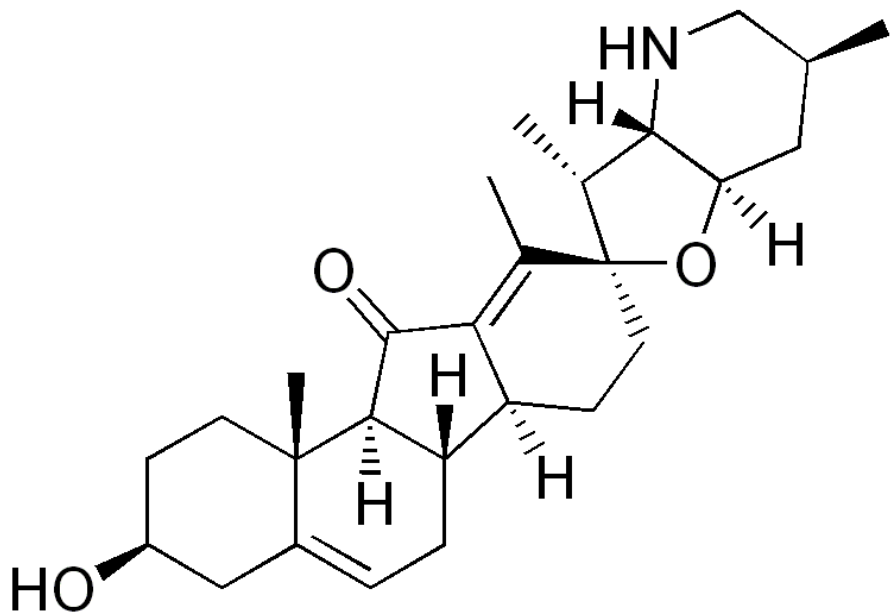


Tomatine

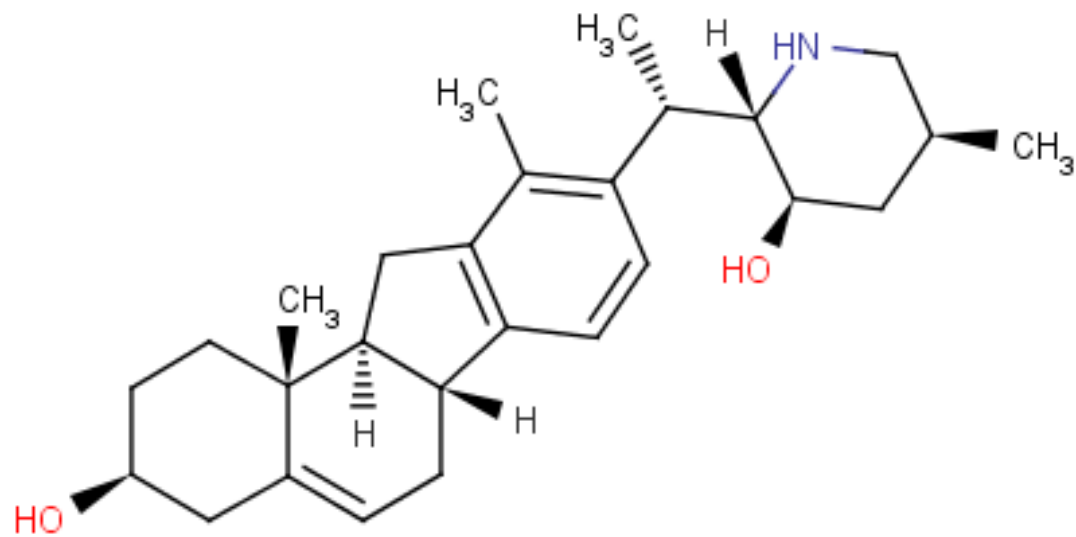
In the case of the Family Liliaceae, the C<sub>27</sub> skeleton undergoes, beyond the addition of an amine function and the cyclization of the side chain, a rearrangement of its rings a C-nor-D-homo-steroid, in other words the C ring loses a carbon atom, which gained by the D ring.



**Protoveratrine A**



**Jervine**



**Veratramine**

# Liliaceae Containing Steroidal Alkaloids

**White Hellebore**

***Veratrum album* (Veratri albi rhizoma)**

Beyaz çöpleme

**The Plant, The Drug :** A perennial plant, which grows from a rhizome; it grows on the mountains of Europe and northern Asia also on Northeast Anatolia.

**The rhizome is short, dark brown and completely surrounded by tortuous roots ranging in color from chestnut brown to brownish-black.**

**Chemical Composition :** The total alkaloids of the rhizome (1.5%) are a complex mixture of steroidal alkaloids, which are almost all C-nor-D-homo steroids, and which fall into two groups

**- The alkaloids of the jerveratrum group, which contain one to four oxygen atoms, and which also occur as free alkylamines or monoglycosides: jervine, rubijervine, veratramine and the corresponding glycosides.**



-The bases of the cerveratrum group. They contain many more oxygen atoms and occur in the plant as esters : protoveratrines A, B.

**Pharmacological Activity** : The alkaloids of the drug are highly toxic for coldblooded animals. The powder of the drug was formerly used as an external parasiticide. They increase the permeability of fast sodium channels in the membranes of excitable cells, which causes iterative impulses after a unique stimulation.

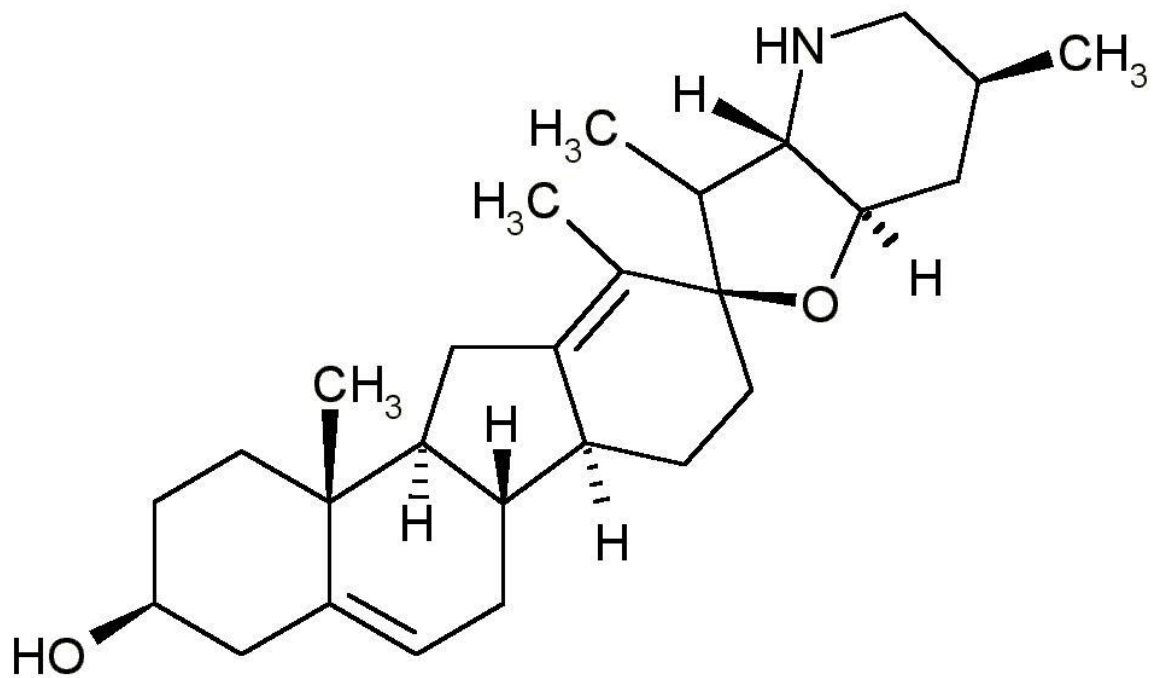
The results are bradycardia and severe hypotension. These alkaloids are also emetic and at high doses, they have a direct toxic action on the myocardium.

**Toxicity** : Formerly used to treat arterial hypotension, the toxemia of pregnancy, and cardiac insufficiency, the drug has been completely abandoned.

The intoxication rapidly manifests itself by numb extremities, malaise, and digestive symptoms (nausea, vomiting, abdominal pain). Next to appear are cardiac symptoms : bradycardia, severe hypotension. The administration of atropine makes the symptoms subside.

## OTHER *VERATRUM*

*Veratrum californicum* contains teratogenic alkaloids like cyclopamine. It does not grow in Europe.



**Cyclopamine**

## **Solanaceae Containing Steroidal Alkaloids**

The steroidal alkaloids of the Solanaceae fall into two groups. The solanidane type characterized by an indolizidine moiety, and the spirosolane type which the nitrogen atom is part of an oxoazaspirodecane structure : this explains why some workers consider them “nitrogen-containing saponins”. In addition they occur as glycosides in which the sugar is generally an oligosaccharide.

Biosynthetically, these alkaloids arise from the metabolism of cholesterol.

The steroidal glycoalkaloids are soluble in water and, like saponins, they are surface active. They are less sensitive than true alkaloids to the precipitating action of the general reagents (Dragendorff, Mayer).

Biologically, the steroidal glycoalkaloids cause cell membrane alterations like saponins.

The glycoalkaloids of the Solanaceae are potential insecticides, some are cytotoxic, and they are not used in pharmaceuticals. It is useful to know about them because of their potential toxicity.



Woody Nightshade

Black Nightshade

*Solanum dulcamara*

*Solanum nigrum*

Solani dulcamarae herba

Solani nigri herba

Both species are wide spread in Europe and in Turkey, only *Solanum nigrum* grows in Cyprus. They contain steroidal glycoalkaloids (solamargine, solasonine). They are not used in pharmaceuticals today. They can cause serious intoxications.

***Solanum dulcamara***

Tilki üzümü

***Solanum nigrum***

# **POTATO** (patates)

*Solanum tuberosum*

The glycoalkaloids occur in the leaves (30-90 mg/100 g), fruits (40-100 mg/100 g), flowers (200-500 mg/100 g) and especially in the sprouts (500 mg/100 g and more). These alkaloids are not destroyed by cooking and are toxic. They cause necrosis of the gastric and intestinal mucosa. But poisoning is particularly rare.

# ALKALOIDS WITH MISCELLANEOUS STRUCTURES

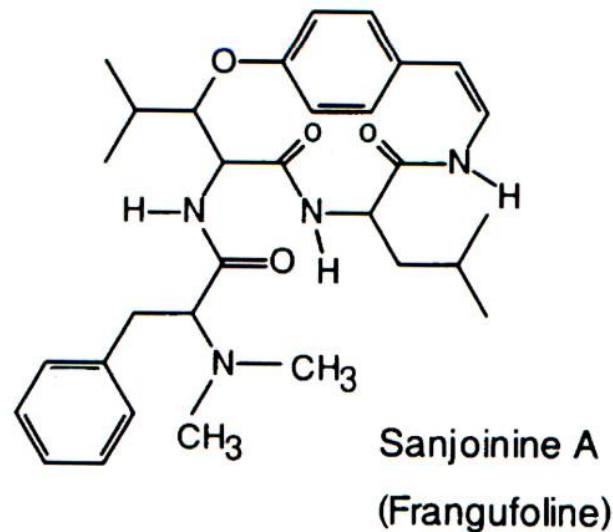
## Macrocyclic Peptides, Peptide Alkaloids

These compounds behave themselves more like peptides than alkaloids. They occur mostly in Rhamnaceae (*Rhamnus*, *Ziziphus*). None compound is currently use, even though some of them have some activity (some sedative properties)

# JUJUBE TREE

*Ziziphus jujuba* (Jujubae fructus) Rhamnaceae

Native to China, the jujube tree is acclimatized in southern Europe and in the southern United States. The fruits contain alkaloids like sanjoinine.



*Ziziphus zizyphus* hünnap

*Ziziphus lotus*

# Maytansinoids

Isolated from various African Celastraceae in the genera *Maytenus*, these alkaloids have a complex structure. These compound (maytansine, maytanbutine) are of interest because their antitumor activity.





## **Reference Books :**

### **Main Book**

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### **Other Books**

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