

PYRROLIZIDINE ALKALOIDS

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INTRODUCTION

Pyrrolizidine alkaloids have essentially been isolated only from the **Asteraceae and Boraginaceae**. In both families they were found in many genera Asteraceae : *Doronicum, Eupatorium, Petasites, Senecio, Tussilago* and Boraginaceae : *Alkanna, Anchusa, Cynoglossum, Echium, Heliotropium, Symphytum*.

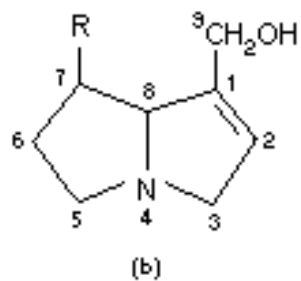
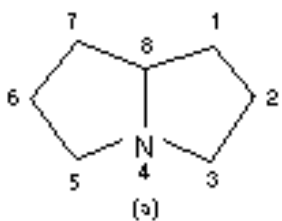
Therapeutic interest in these alkaloids is almost nil, despite the fact that some are cytostatic *in vitro*. In fact, it is their toxicity which the focus of attention. Indeed, they are responsible for serious toxic symptoms observed sporadically in humans and more often in animals.

Most of the alkaloids in this group are also mutagens and induce hepatic tumors. Such hepatotoxic and carcinogenic compounds occur in plants that are recommended in traditional medicines, but have no demonstrated therapeutic benefits, therefore using these plants seems unwise.

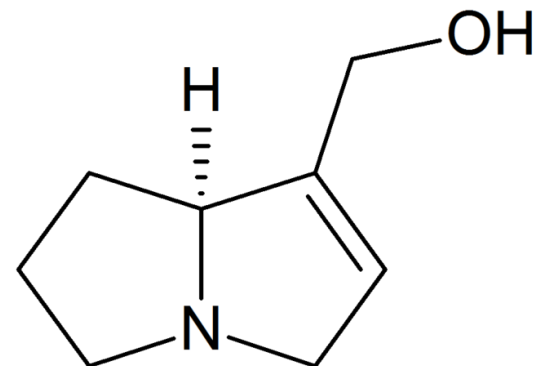
GENERAL STRUCTURE OF THE ALKALOIDS

The vast majority of these alkaloids are esters of amino alcohols and of one or two aliphatic carboxylic acids.

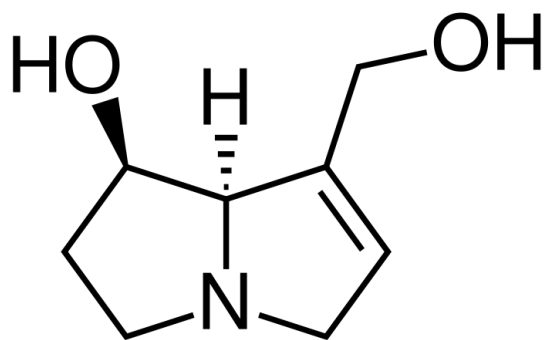
The amino alcohols, also known as **necines**, are derivatives of pyrrolizidine, in other words azabicyclo[3,3,0]octane. The configuration at C-8 varies, and is most often H-8 α . The ring is not always unsaturated at C-1, but it is always substituted by a hydroxymethyl group at this position.



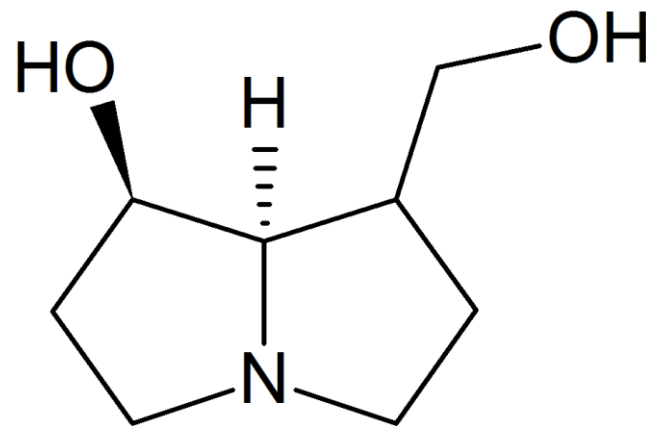
. Molecular structure of pyrrolizidine molecule.



supinidine



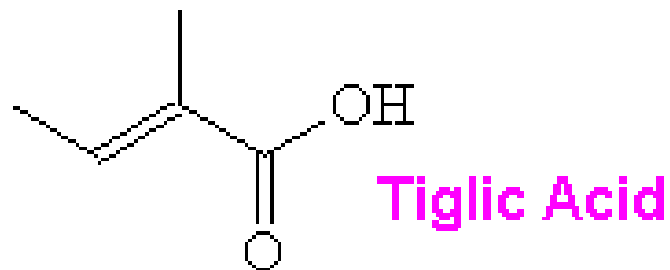
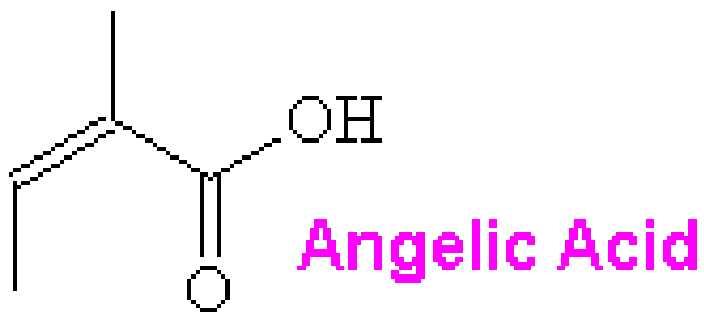
retronecine



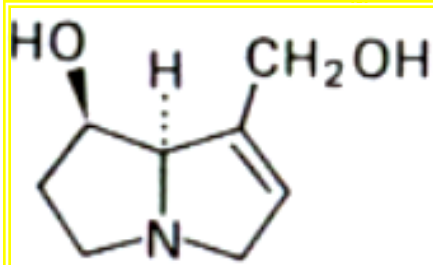
platynecine

General structure and some necines

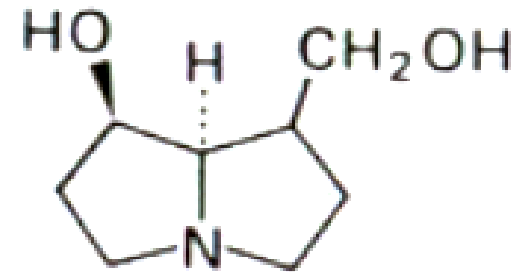
The acids (necic acids in the broad sense of the term) are C₅, C₇, C₈ or C₁₀ aliphatic acids. They are sometimes simple (angelic or tiglic acids with five carbons) but they are most often specific (senecic, jacobinecic acids)



Necins

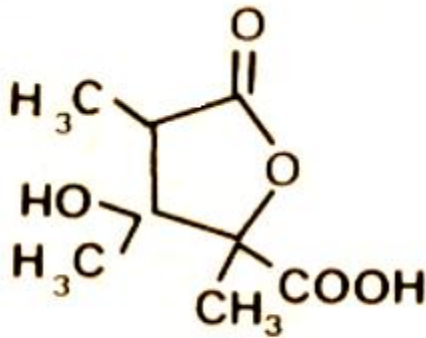


retronecin

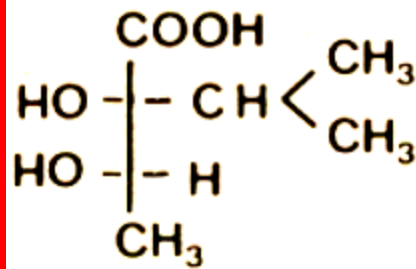


platinecin

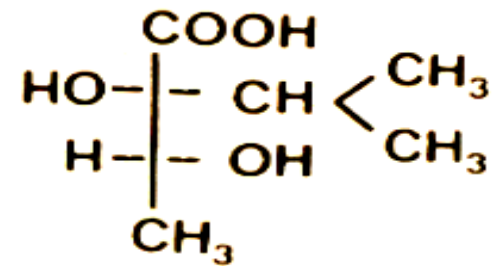
Necic acids



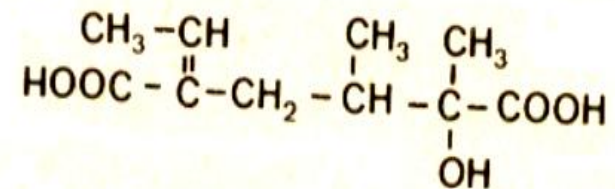
Monocrotalic acid



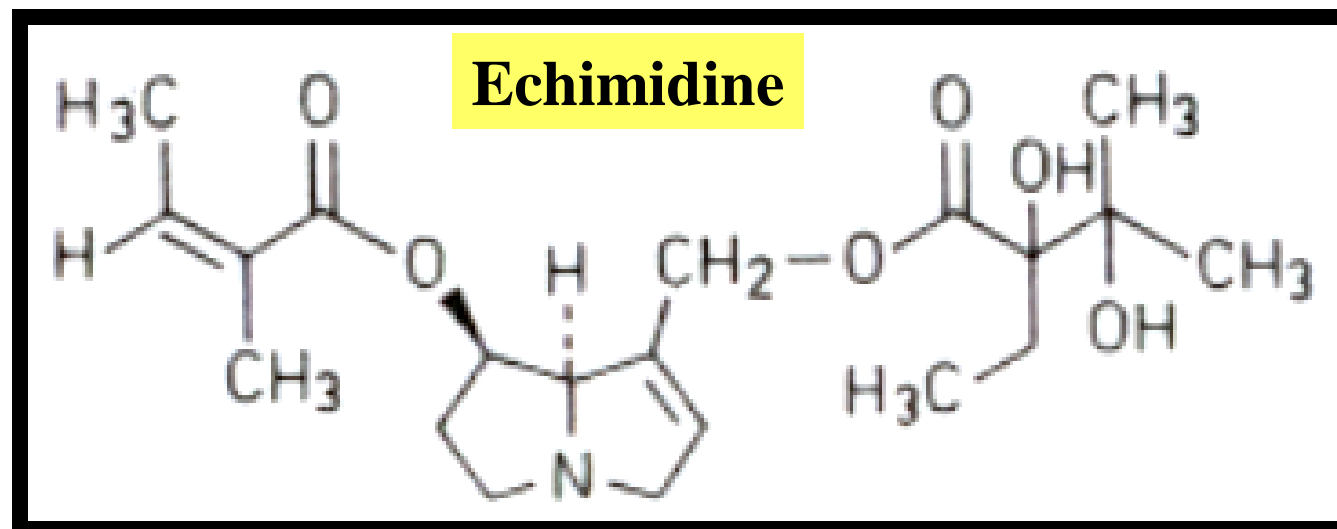
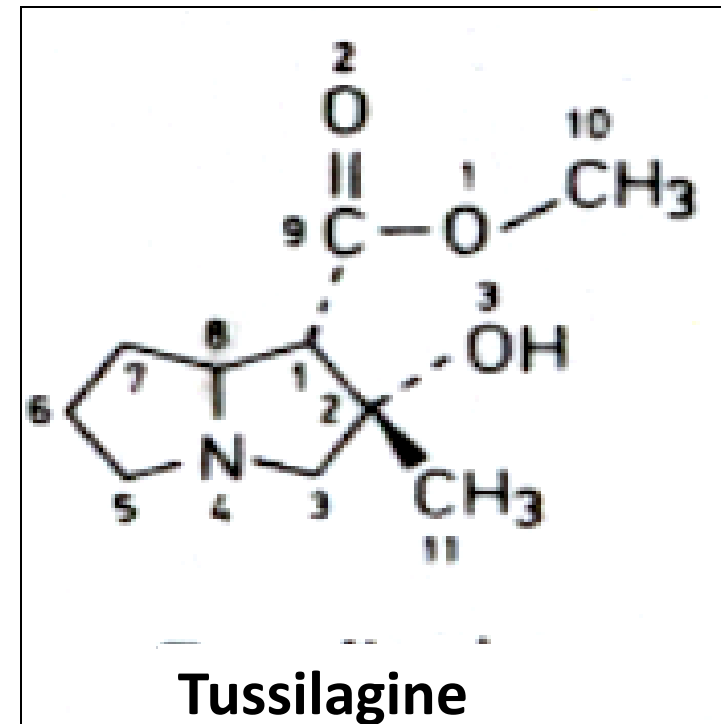
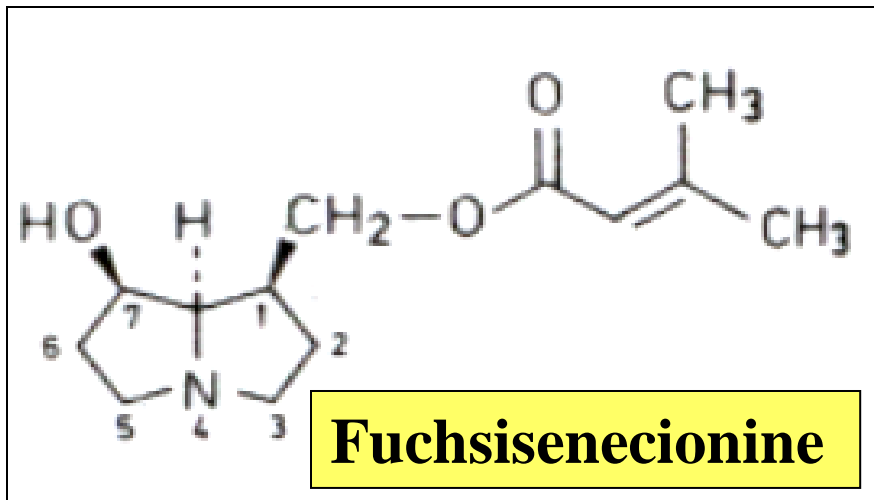
Trakelantic acid

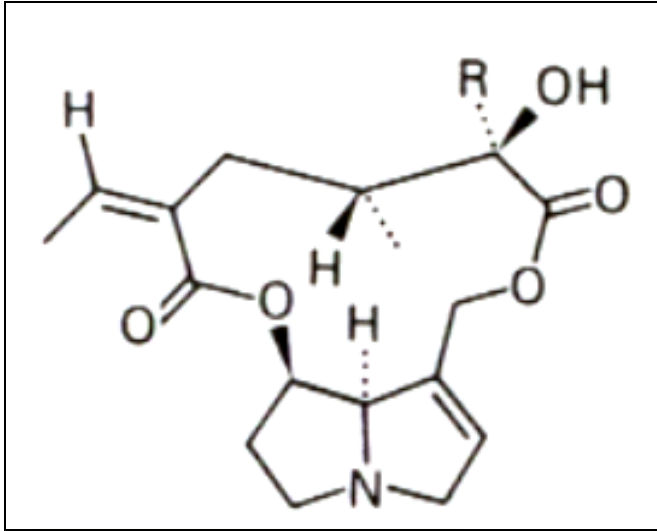


Viridifloric acid

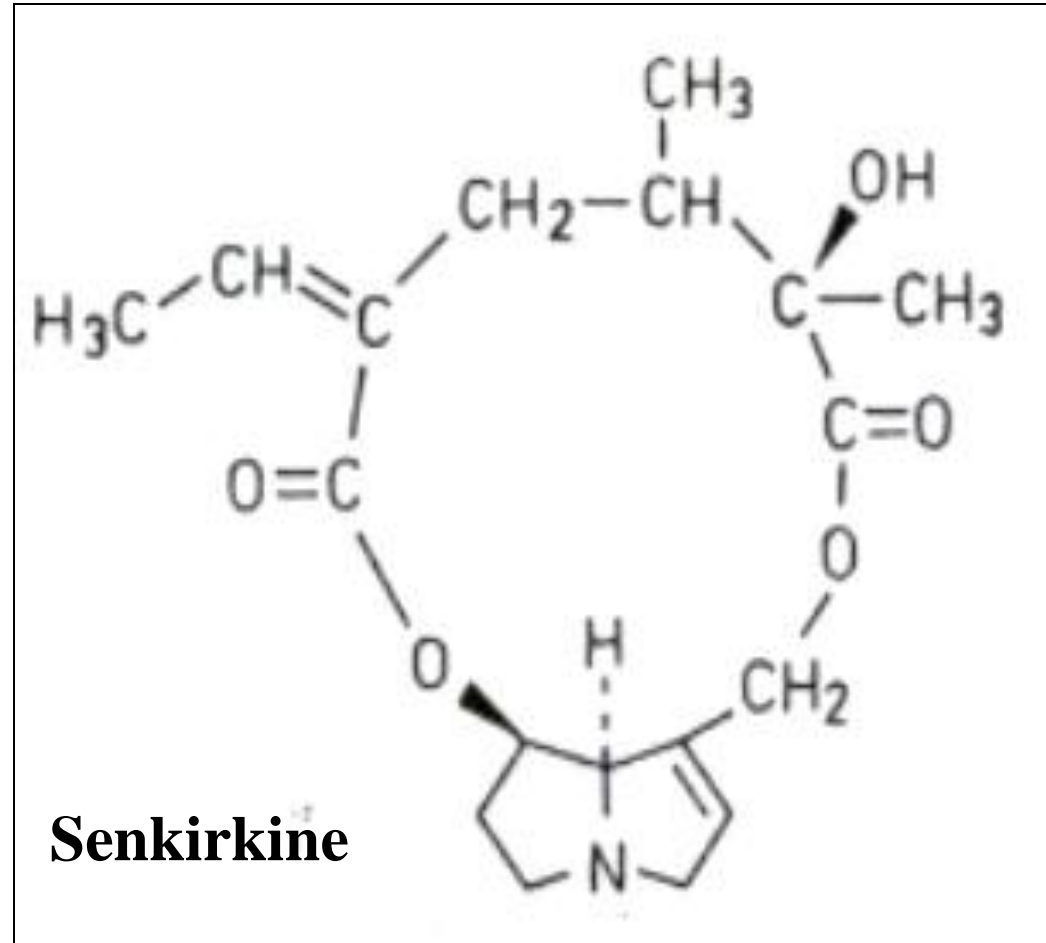


Senecic acid



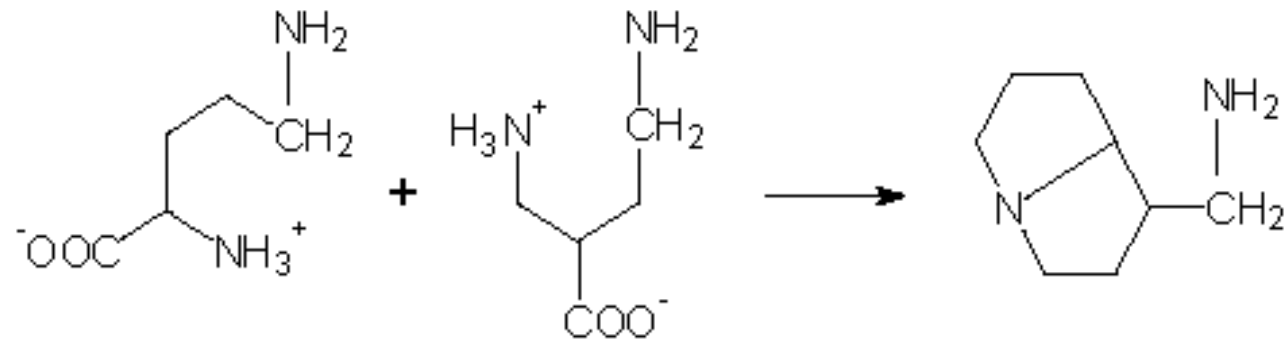


Senecionine



Senkirkine

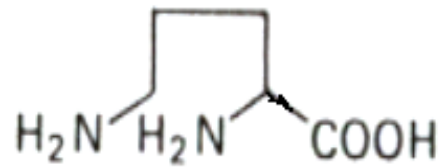
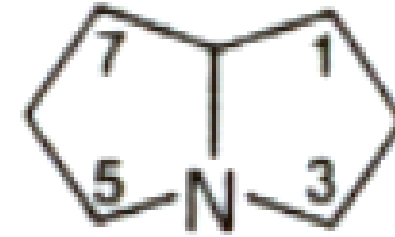
BIOSYNTHESIS



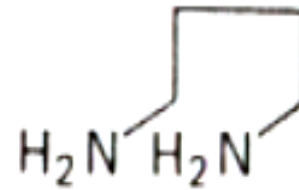
2 x ornithine

pyrrolizidine alkaloid

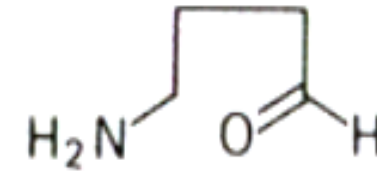
(*Senecio* Alkaloids)



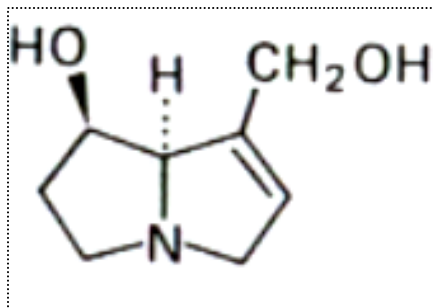
2 Ornithine



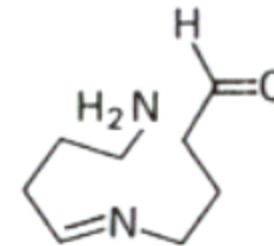
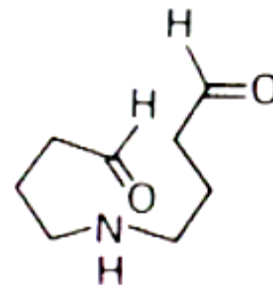
2 Putrescine

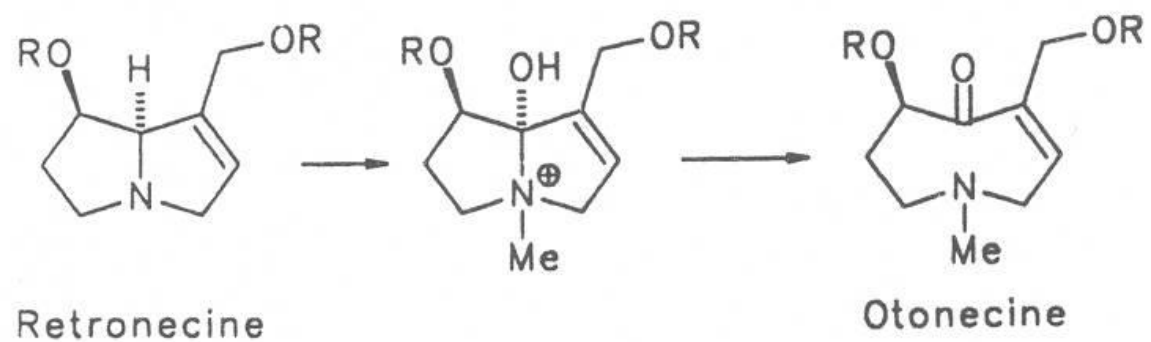
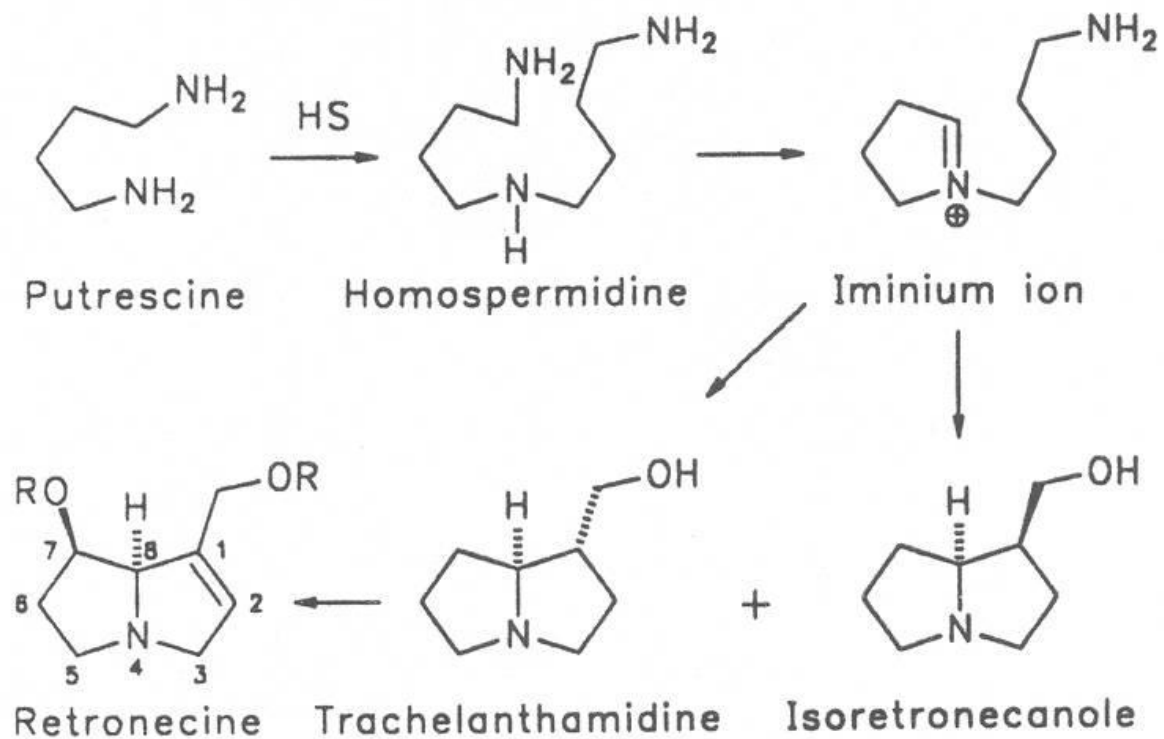


2 [4-aminobutanal]



Retronecine





TOXICITY

For animals : Although the Boraginaceae and Asteraceae species containing pyrrolizidine alkaloids are not normally grazed by the animals, the absence of other food, and especially contamination of fodder and silage can lead to accidental consumption, and therefore to chronic or acute intoxications, for which no truly efficacious treatment is possible. The toxicity is chiefly hepatic.

For humans : The various plants in this group have apparently never caused any acute intoxication in humans. They are, however, responsible for chronic intoxications marked by loss of appetite, abdominal pains and swelling, ascites and hepatomegaly.

All the pyrrolizidine alkaloids do not have the same toxicity. As a general rule, the monoesters are less toxic than the acyclic diesters, which are themselves less toxic than the macrocyclic diesters.

Experiments in rats have shown that several alkaloids (retrorsine, senkirkine, lasiocarpine) and a number of plants (*Tussilago farfara*, *Symphytum officinale*, *Petasites japonicus*) induce hepatic tumors when they administered orally on a regular basis experimentally. The mutagenic and teratogenic properties of several alkaloids in this group have also been shown experimentally.

Borage

Borago officinalis

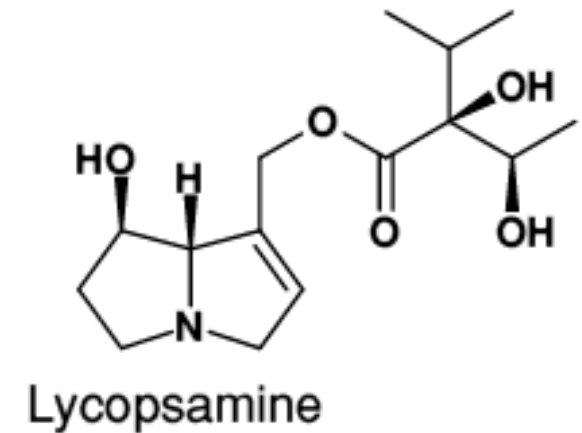
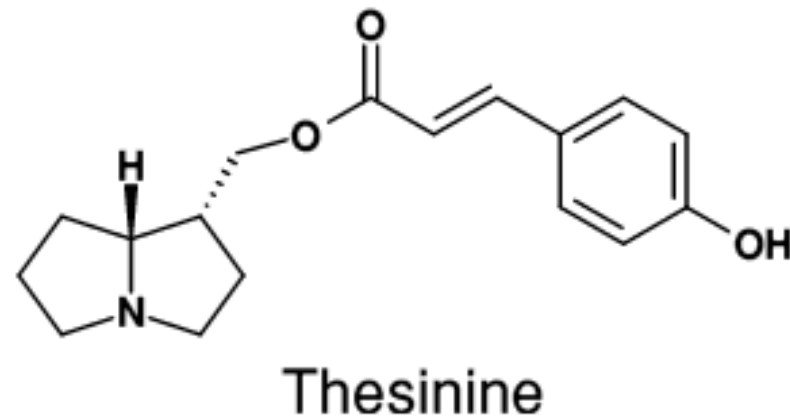
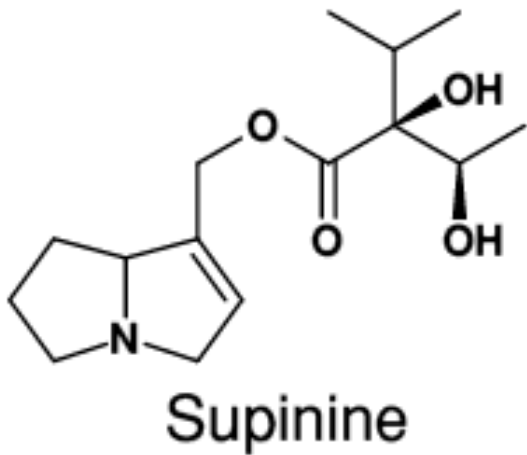
Borago herba

Boraginaceae

borago, hodan

The plant also grows in Cyprus

The stems and leaves contain mucilage (11%) and 2-8 mg/kg pyrrolizidine alkaloids, lycospamine, amabiline, supinine. Thesinine is the principal alkaloid in borago seeds.



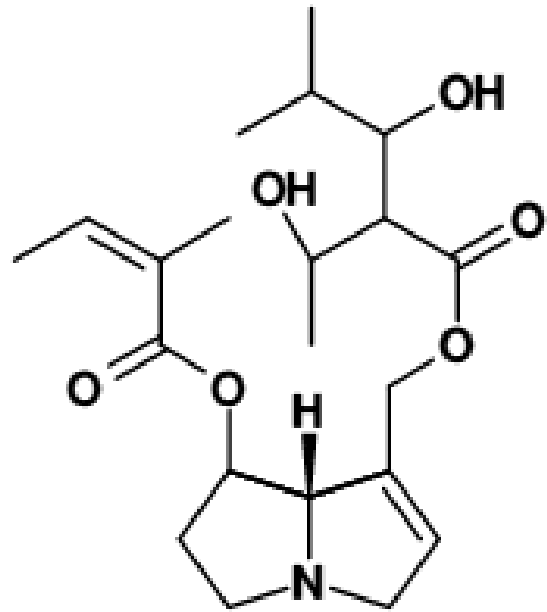
Common comfrey

Symphytum officinale

Symphythi radix

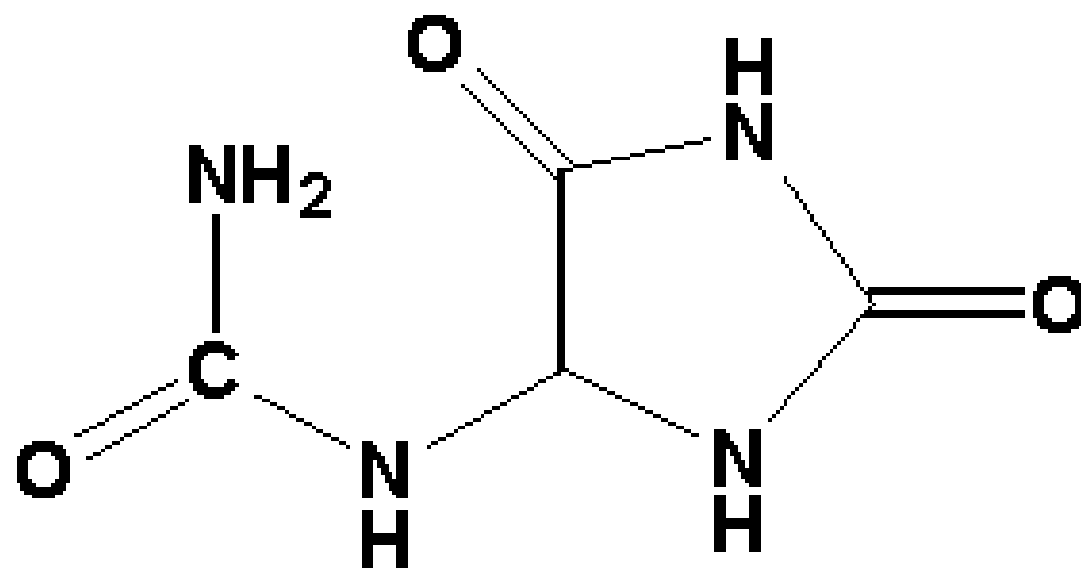
Boraginaceae karakafes otu

Symphythi radix is thought to contain allantoin. It also contains fructanes, triterpenoid mono- and bidesmosides, and also 0.2-0.4% pyrrolizidine alkaloids lycopsamine and symphytine.



Symphytine

Symphythi radix is said to have healing properties attributed allantoin and polysaccharides. The root is traditionally believed to have the power to relieve pain in the joints of gastritis. When administered orally to rats for a long period of time, the roots and leaves induce hepatic tumors. **The German Comission E monograph describes the anti-inflammatory and healing effects of Symphyti radix, which is to be used only for external application.**



Allantoin

Coltsfoot

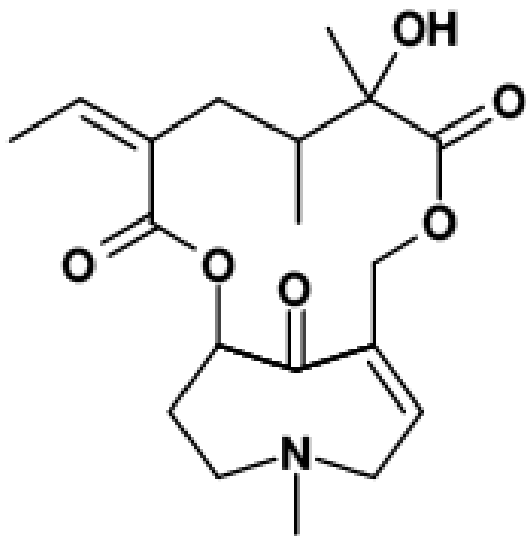
Farfarae folium/flos

Tussilago farfara

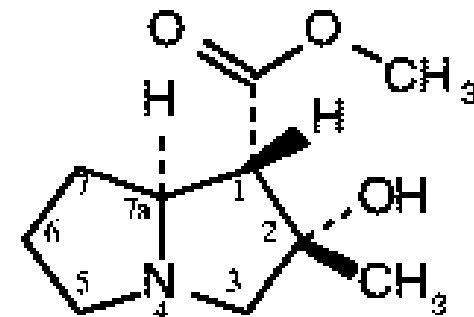
Asteraceae

öksürük otu

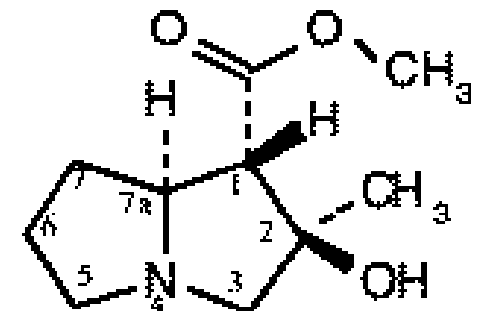
Tussilago farfara is a small perennial plant very common in Europe and northern Asia, also in Turkey. Farfarae flos contains an acidic mucilage, flavonoids, carotenoids, triterpenes, a sesquiterpenoid ester tussilagone and pyrrolizidine alkaloids : unsaturated at C-1, C-2, senkirkine (major) and senecionine, and saturated tussilagine and isotussilagine.



Senkirkine



tussilagine



isotussilagine

1,2-saturated

The leaves contain 6-10% mucilage and the same alkaloids as the capitulum.

Pharmacological Activity : As its name indicates (*tussis*, is coughing fit, *ago, agere*, to chase, to push) the drug is reputed as an antitussive. In oriental medicines attribute to it the same virtues and use to treat asthma, bronchitis, and other respiratory ailments. For some, the action that is observed is merely the consequence of the soothing effect of mucilage on the irritated mucosa of the larynx.

Uses : Infusions of the drug continue to be used in phytotherapy (tracheitis, chronic bronchopneumopathy). It is also widely self-administered (cough teas).

Is the consumption of preparations dangerous? Opinions differ. For some authors, since a cup of infusion contains on average 1 ppm of alkaloids, there is no reason to condemn this drug. For other authors, the presence of hepatotoxic alkaloids, even in trace amounts, must lead to prohibiting the regular use of this drug.

The German Commission E monograph only authorizes the use of the *Farfarae folium* (acute catarrh of the respiratory tract with cough and hoarseness, moderate inflammation of the throat mucosa). It specifies that the daily intake of alkaloids must be less than 10 µg (in infusion) or less than 1 µg (extract or plant juice), and that the duration of use must be limited (no more than 4 to 6 weeks per year).

European ragwort

Senecio jacobea

Senecio jacobaeae herba

Asteraceae

Common groundsel

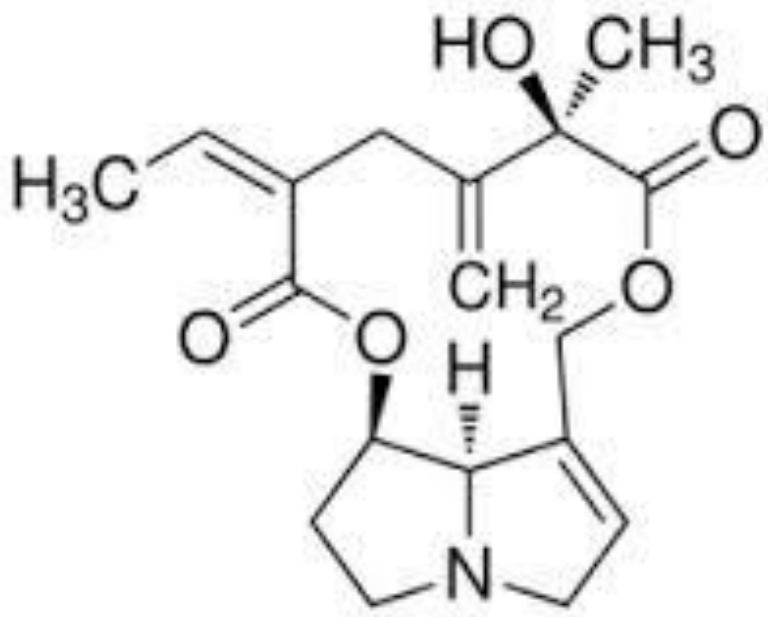
Senecio vulgaris herba

Senecio vulgaris

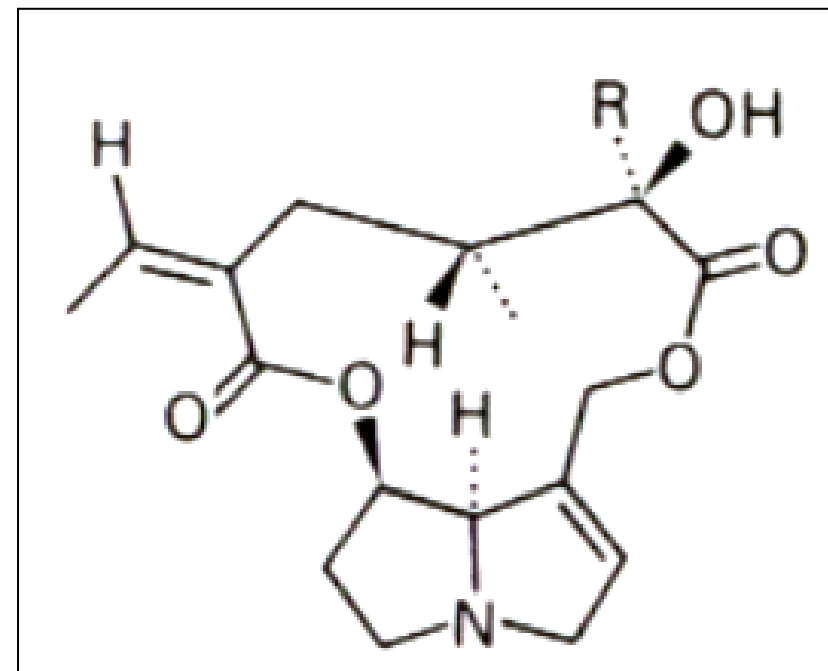
Asteraceae

kanarya otu

All of the parts of both plants contain pyrrolizidine alkaloids such as seneciphylline and senecionine. The amount of total alkaloids ranges between 0.005 – 0.1%.



seneciphylline



senecionine

The species is infamous because of the intoxications that they cause in horses and bovines. Horses lose their appetite and develop jaundice, edema, ascites, and finally as encephalopathy which induces gait anomalies.

The hepatic toxicity of *Senecio* has long been known. Several manufacturers have removed from their products recently with good reason.

QUINOLIZIDINE ALKALOIDS

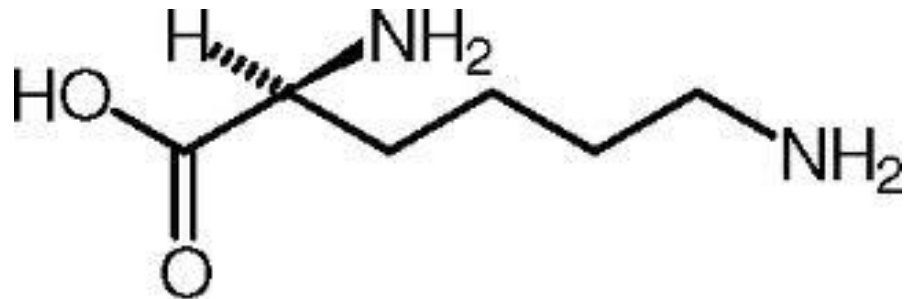
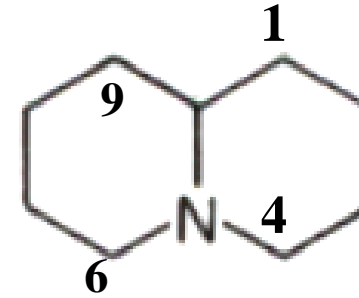
Quinolizidine is a bicyclic nitrogen-containing heterocycle which is particularly common in alkaloid structures.

The quinolizidines to be mentioned here are the bi-, tri-, or tetracyclic derivatives which characterize the Family **Fabaceae**, and in which in a certain number of cases, are responsible for their toxicity. Nearly 200 quinolizidines are known.

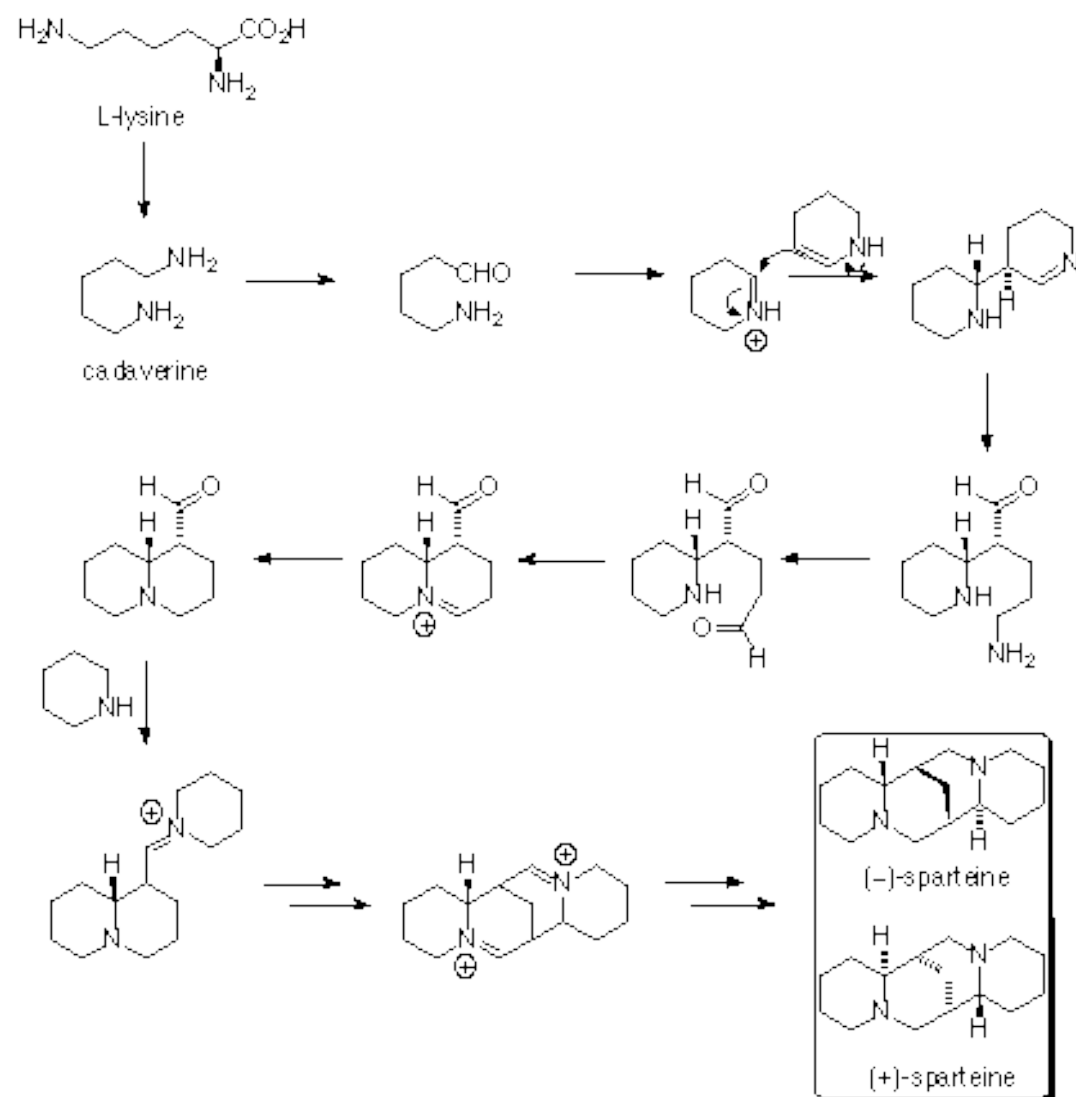
(*Lupinus* Alkaloids)

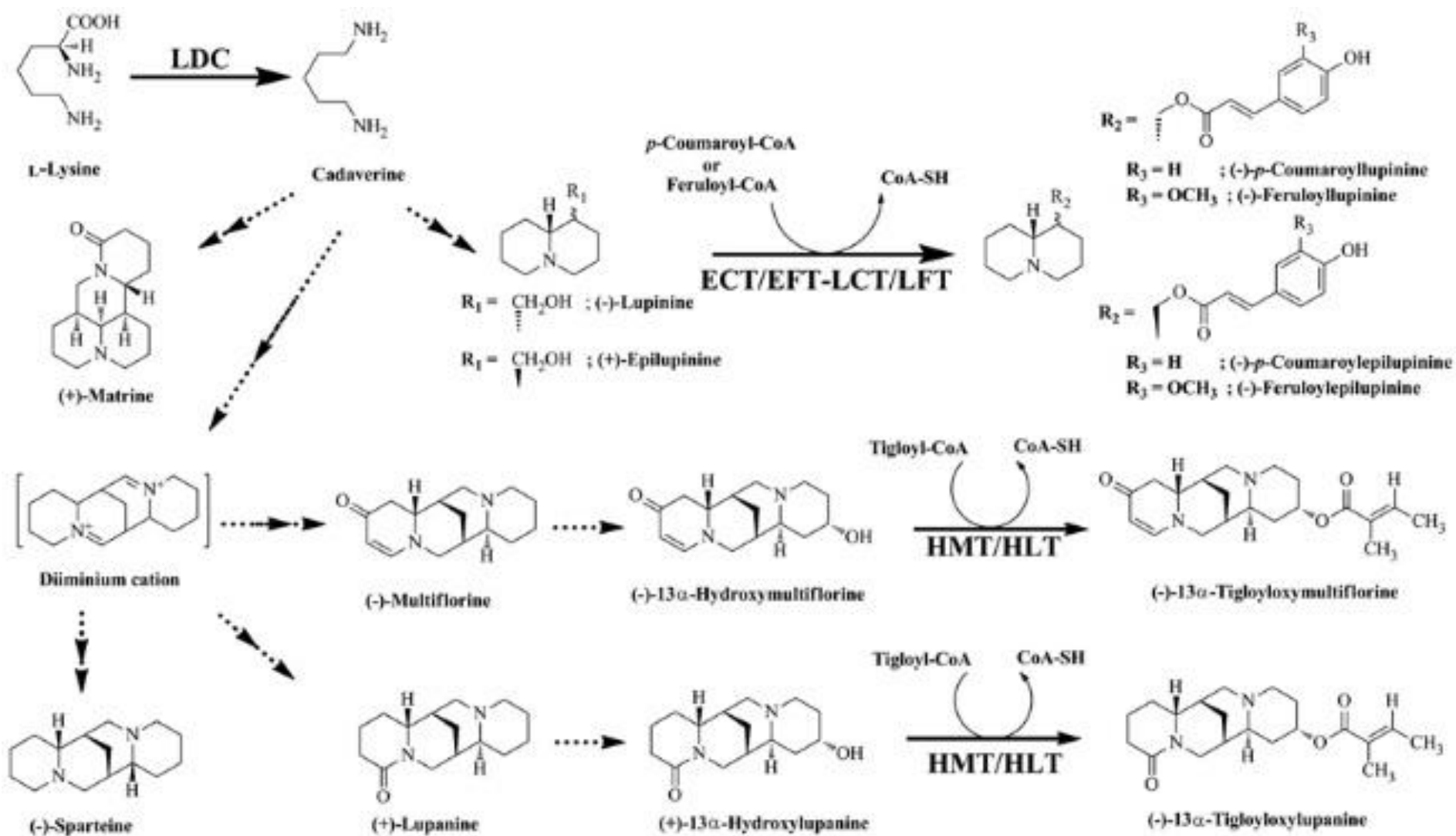
Biosynthesis begins from lysine.

Biogenetically, cadaverine plays a role of precursor.



L-lysine





Scotch broom

**Sarothamni scoparii herba (stems),
Sarothamni scoparii flos**

Cytisus scoparius* = *Sarothamnus scoparius

Katır tırnağı

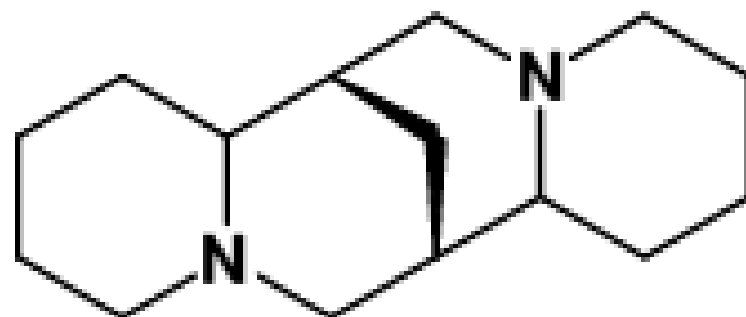
The plant has been used Antiquity to prepare diuretic infusions. Its branches are a source of sparteine, a quinolizidine alkaloid which is a ganglioplegic and a cardiac analeptic. Sparteine sulfate is listed in the pharmacopoeias, as is the dried flower.

***Sarothamnus scoparius* : The plant is very common
in Europe and Turkey**

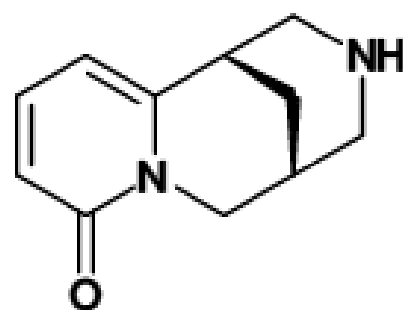
Chemical Composition : The plant is rich in active substances belonging to different chemical classes.

Amines (tyramine, dopamine); Flavonoids (as isoflavones and flavone C-glycosides; scoparoside)

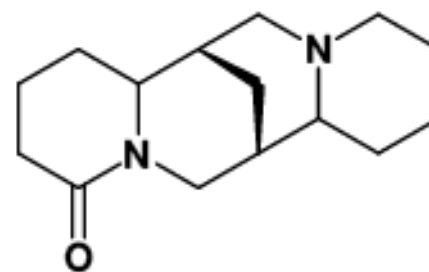
Alkaloids are represent by a major constituent (0.5-1%), by far the chief constituent in the brances (60%), namely (-)-sparteine, a tetracyclic alkaloid without oxygen atoms (alkaloids without oxygen atoms are volatile compounds) and with two *trans*-fused *cis*-quinolizidine nuclei(6R, 7S, 9S, 11S isomer). The other alkaloids are cytisine and lupanine.



Sparteine



Cytisine



Lupanine

Pharmacological Activity : Sparteine is a mild ganglioplegic, with blocks conduction and prevents the depolarization of the post-synaptic membrane. In the heart, after a transient phase of ganglionic excitation, it shields the myocardium from central neurovegetative regulation, and decreases excitability, conductivity, and the frequency and amplitude of the contractions. This alkaloid is also cytotoxic. It causes a moderate increase in the tone and strength of the contractions of the uterus.

Uses : The potency of sparteine (particularly on the heart) is the reason why broom stems are **not used to prepare infusions**, but only to extract sparteine : after extracting with acidified water, the aqueous phase is alkalized and undergoes steam distillation; sparteine separates within the condensate, based on the difference in density. The crude product is purified and converted to the sulfate.

Uses of the drugs : In France, phytomedicines based on broom flowers may be (traditionally) used to enhance urinary and digestive elimination functions and to enhance the renal excretion of water (because of the flavonoid compounds).

The German Commission E monograph states that hydroalcoholic extracts of broom stems are used for cardiac and circulatory functional disorders (because of sparteine). Package inserts must bear a warning not to use broom preparations during pregnancy and in case of hypertension. The occurrence of tyramine in broom creates a risk of drug interaction with MAO inhibitors.

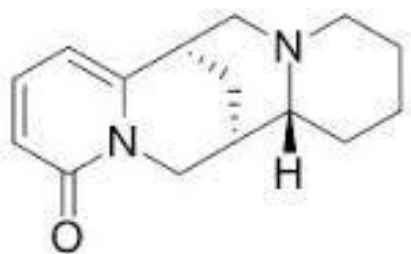
Lupines

Lupini semen

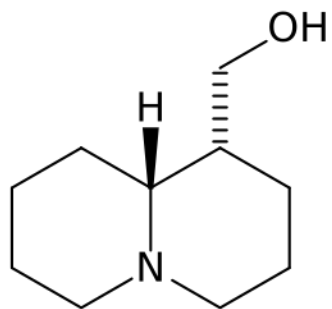
***Lupinus* ssp. (*Lupinus albus*, *L. angustifolius*) acı bakla**

Lupinus ssp. are toxic plants growing in Europe, Asia and America

The drugs contain quinazolidine alkaloids like anagryne and lupinine. There are only anecdotal intoxications in humans : the contamination of milk is possible, if the cows eat the plants, but it is normally limited by the industrial practice of mixing the milk from the several cows, and the reported cases of poisoning are limited to families their own dairy products or to insufficient debittering of alkaloid-containing lupines.



anagryne



lupinine

Lupinus micranthus grows in Cyprus

Special case : Alkaloids of the Lycopodiaceae

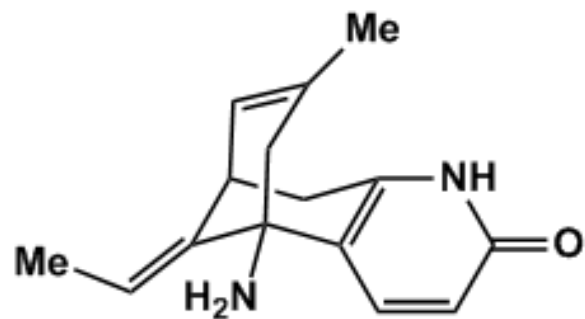
Huperzia serrata = Lycopodium serratum

Huperziae herba

Traditionally the spores of the *Lycopodium* are used as an absorbent powder. *Huperzinia serrata* is a traditional Chinese remedy (Qian Ceng Ta) said to have been used to treat fever and inflammation. It contains alkaloids huperzines A and B, lycodine, lycodoline and serratidine.

Pharmacologically huperzine A is a reversible inhibitor of acetylcholinesterase, like physostigmine. Animal experiments show that huperzine A has an interesting potential for the treatment of poisoning by soman and other chemical weapons and that it counteracts the memory loss caused by scopolamine.

According to clinical trials conducted in China, huperzine A is not very toxic and is thought to have some potential for the treatment of memory loss. It has also been tested in the treatment of myasthenia and in the context of Alzheimer's disease.



(-)-Huperzine A

Piperidine Alkaloids

Here we have only two interesting drugs
namely, Lobeliae herba and Granati radice
cortex

Indian tobacco

Lobeliae herba

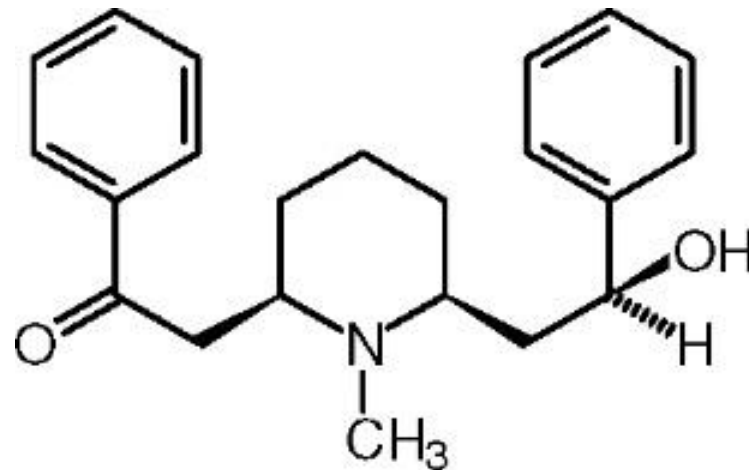
Lobelia inflata

Lobeliaceae

lobelya

Initially used by the native peoples in North America as a substitute for tobacco this plant appeared in Europe in the beginning of the 19th century, where it was recommended for the treatment of asthma.

Chemical composition : The drug contains from 0.2 to 0.5% total alkaloids including piperidines [(-)-lobeline, *meso*-lobelanine and *meso*-lobelanidine)]. The chief constituent is (2R, 6S, 8S-(-)-lobeline.



(-)-lobeline

Pharmacological Activity : Pharmacologically, lobeline is a respiratory stimulant, which enhances and accelerates the respiratory movements by improving the reactivity of the brain stem centers to carbon dioxide and also acting by a reflex mechanism involving the carotid chemoreceptors. Secondly, it is a gangliotic stimulant and a β -adrenergic bronchodilator.

Uses : Formerly used (IM or SC) for resuscitation after asphyxia, particularly to treat apnea in newborns, lobeline is no longer used because of its substantial side effects and poor therapeutic index. Lobeline sulfate is still commercialized as an adjuvant in smoking cessation programs (*per os*).

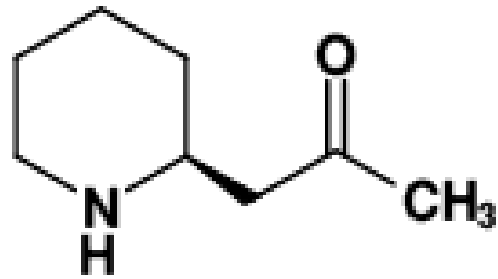
Pomegranate

Granati radicis cortex (nar ağacı kök kabuğu)

Punica granatum

Punicaceae

The root bark, recommended in 1550 B. C. In the Ebers Papyrus to treat worm infestations, was used as an **anthelmintic**, primarily a taenicide, until the first half on the 20th century. It contains 0.5-0.7% total alkaloids : (-)-pelletierine, isopelletierine and N-methylated analogs.



Pelletierine

Piperidine Amides : Piperaceae

Black pepper

Piperis nigri fructus

kara biber

Piper nigrum

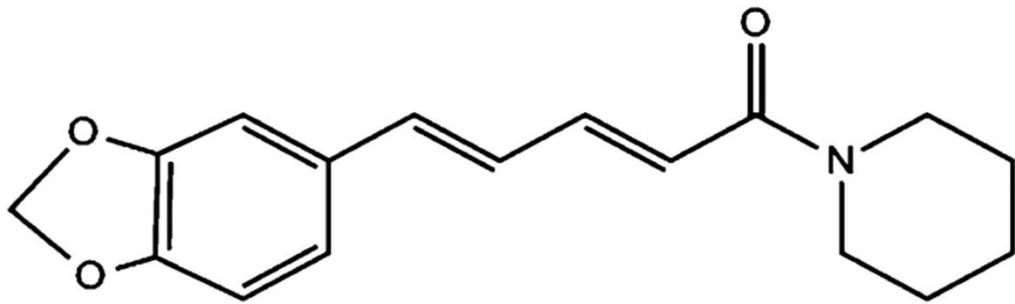
Pepper is one of the most ancient spices. Used since time immemorial in India, it was known in the Greece and Rome antiquity. It is the fruit of *Piper nigrum*, a perennial plant originally from the south-west of India, and now cultivated in India, Indonesia, Malaysia, Sri Lanka and also South America (Brasil).

The different kinds of pepper are well recognized :

- Green pepper consists of whole fresh berries. Generally conserved in acidic aqueous solutions (or frozen, or pasteurized), it is highly aromatic.
- White pepper consists of the fruits collected at full maturity. After being soaked in water for several days, the fruit pericarp and the external layers of mesocarp are removed, and the fruits are dried.

- Black pepper is prepared from the spikes collected immediately after the first berries turn red. After drying, the fruits are separated from the stalks. The dried fruits are spherical (3-6 mm) and particularly hard. Their surface is brownish black and extremely wrinkled.

The pepper odor is due to 1 to 3.5% of an essential oil rich in terpenoid hydrocarbons, and the pungent taste to amides (5-10%). The chief constituent is piperine, an amide of piperidine and piperic acid.



piperine

Peppers (*P. longum*, *P. nigrum*) are frequently used in Ayurvedic medicine, in several cases, it appears that they increase the bioavailability of active ingredients with which they are mixed. Piperine is a CNS depressant and anticonvulsant in rats. Some of its synthetic derivatives have been used in China as anti-epileptics.

Piper spp. for other uses : 1. *Piper bettle* of India and Southwest Asia, whose leaves are masticated. 2. *Piper cubeba* of Indonesia, with a reputation as an antiseptic, used as such in aromatherapy. 3. Kava-kava, the dried root of *Piper methysticum*, used in the islands of Pasific Ocean to prepare an inebriating beverage.

PIPERIDINE ALKALOIDS

not from the Metabolism of Lysine

This is a limited group comprising piperidines substituted by a short aliphatic side chain (coniine, pinidine) or a long one (carpaine, cassine). Some are toxic, for example coniine and coniceine from poison hemlock (*Conium maculatum*).

Poison hemlock

Conii fructus

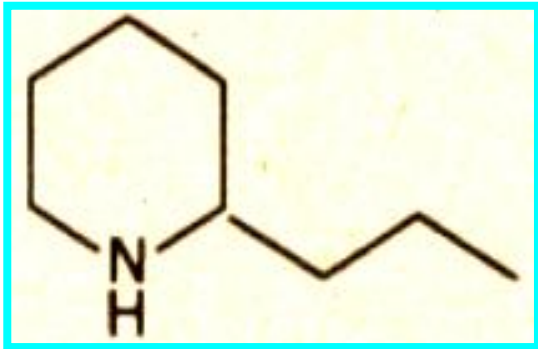
Conium maculatum

baldıran

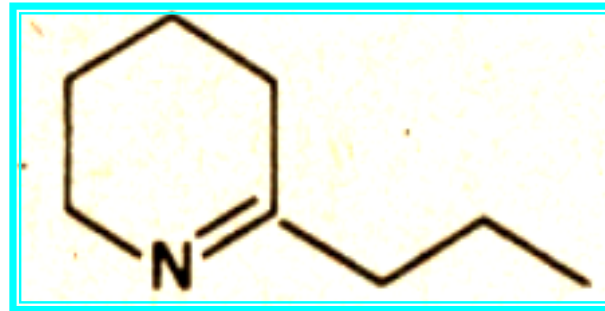
Apiaceae

Famous for having caused the death of Socrates, the fruit of the plant was used for its antineuralgic properties. Although the use of the plant has now been abandoned, it ought to be known because of its toxicity.

The chief alkaloids found in the plant coniine (a volatile alkaloid that can be steam distilled), γ -coniceine, conhydrine, and conhydrinone. The ripe fruit can contain more than 1.5% alkaloids, mostly represented by coniine. In the vegetative parts, γ -coniceine is the chief constituent, especially at the beginning of the growth phase (furthermore, it is six to eight times more toxic).



coniine



γ -coniceine,

Toxicity : Coniine blocks neurotransmission in ganglions and neuromuscular junctions. The classical example of its toxicity is the death of Socrates : «But he walked about, until he said that his legs were getting heavy; then he lay down upon his back, as he had been directed, and the man at intervals examined him, feeling of his feet and legs. Then, pressing hard against his foot, he asked him if he felt it. Socrates said 'No'; and after that he did it to his shins, and moving upwards, showed us that he was growing cold and stiff, and, touching Socrates, he said that when it reached the heart, he would be gone..., but in a little while there was a convulsive movement, after which the man uncovered him. His eyes were fixed.»

ALKALOIDS DERIVED from NICOTINIC ACID

Tobaccos

Nicotiana tabacum, N. rustica

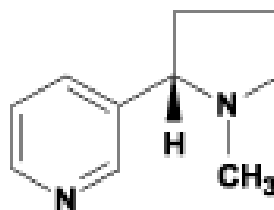
Solanaceae

Nicotianae folium

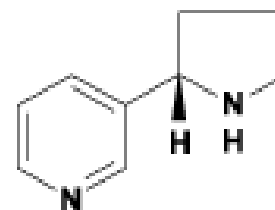
tütün, deli tütün

Nicotiana tabacum

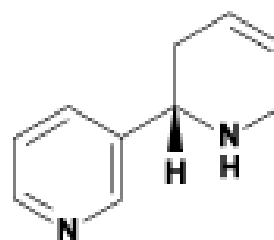
The tobaccos *Nicotiana tabacum* and *N. rustica* and their multiple cultivars, are grown for the production of leaves for smoking. They are toxic plants, which contain alkaloids chiefly represented by nicotine. The other alkaloids are very close structurally (anabesine, nornicotine).



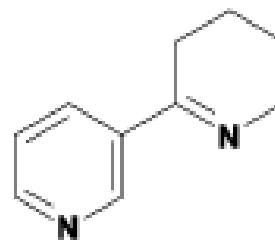
(S)-Nicotine



(S)-Nornicotine



(S)-Anatabine



Anabesine

Nicotiana rustica

Green tobacco leaves are rich in sugars, proteins and organic acids. The alkaloid concentration varies greatly depending on cultivation practices and the variety (2-10%, more than 15% in some cultivars of *N. rustica*). The chief alkaloid is (S)-(-)-nicotine.

Nicotine is a strong volatile base. Its structure comprises a pyrrolidine and a pyridine ring, biosynthesized from putrescine and nicotinic acid, respectively. The formation of anabasine and other piperidine analogs involves lysine.

Pharmacological activity : The immediate toxicity of tobacco is linked to the presence of nicotine : the responsibility for the genesis of cancer is that of the combustion products, especially the nitrosamines arising from nicotine. In the long run nicotine is responsible for the genesis of the cardiovascular and pulmonary diseases other than tumors. The lethal dose of nicotine is near 60 mg *per os* for an adult.

Nicotine is readily absorbed through the mucosas and through the lungs.

Betel (Nut) Palm

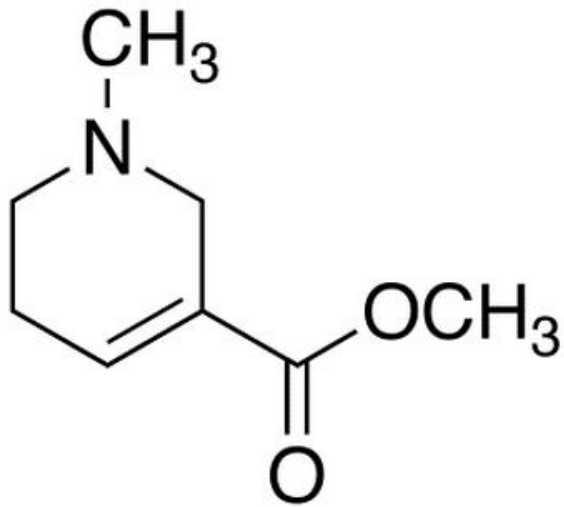
Areca catechu

Arecae semen

Palmae

The betel palm is a palm tree with a slender stipe ending with a bunch of feathered leaves. The tree is widely cultivated from India and Sri Lanka to the South of China and the Philipinnes.

Chemically, the drug contains 50-60% sugars, 15% lipids, flavan-3-ols, condansed tannins and 0.2-0.5% alkaloids : arecoline, arecaidine, guvacine and guvacoline.



arecoline

Arecoline is a parasymptomimetic which acts on muscarinic receptors, and at high doses, on niconitic receptors.

This results in multiple actions : vasodilation, hypotension, and reflex tachicardia at low doses, stimulation of intestinal tone and peristalsis, increase in secretions, (hypersalivation, sweating), myosis, and bladder contraction. Known and used as a taenicide in oriental medicine, the drug has been used as such, especially in veterinary medicine. Arecoline has been tested with more or less success in senile patients suffering Alzheimer-type dementia.

Traditional Use : Betel chewing probably originated in Malaysia. Betel has a reputation for being psychoactive. Chewing betel turns the mouth red and chewers spit frequently, their saliva also colored red. Betel chewing can induce oral submucosus fibrosis of the mouth and oropharinx which, in the late stages, causes swallowing and speech difficulties.

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