

Piperidine Alkaloids:

■ 2. اللوبيليا **Lobelia:**

- The herb *Lobelia inflata* (**Indian tobacco**). Family **Campanulaceae** {bellflower family} contains many alkaloids.
- The most important is **lobeline** which is optically active.
- By **reduction** it yields **lobelaniidine**, while **oxidation** will yield **lobelanine**.
- Lobeline HCl is exceptionally soluble in **chloroform**.

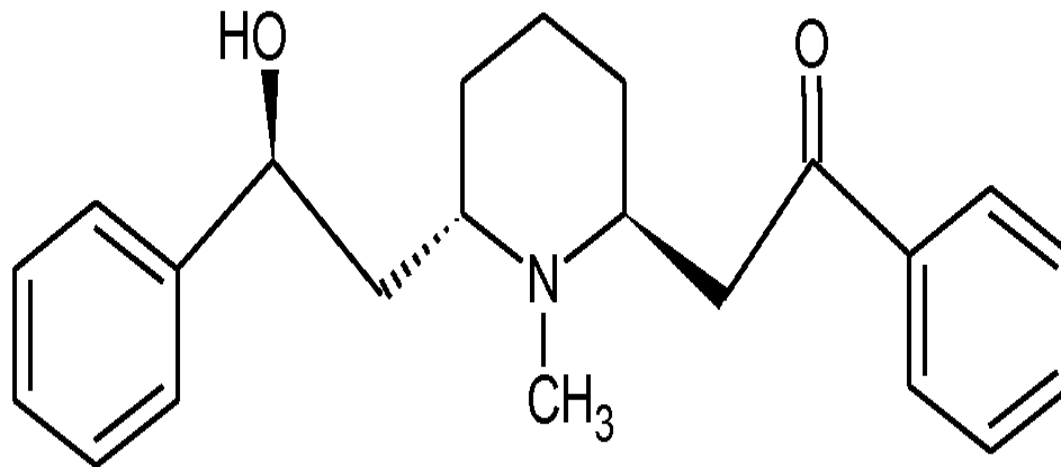
Biosynthetic origin:

Botanical source: form *Lobelia inflata* – *Campanulaceae*

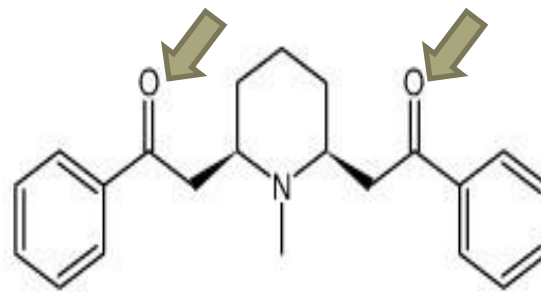
جرسية



Lobeline



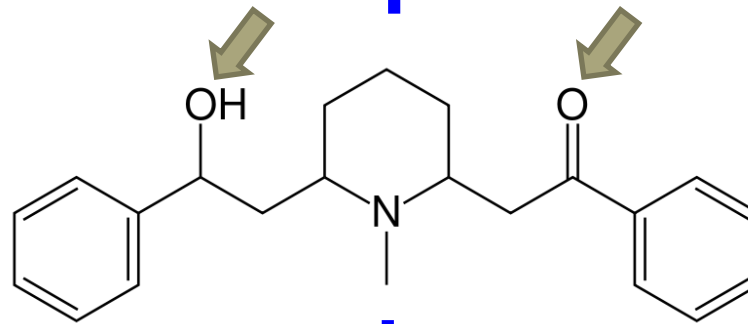
Lobelanine



Oxidation



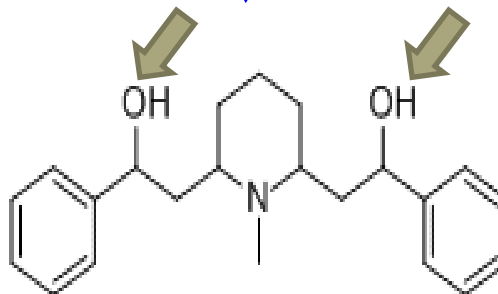
Lobeline



Reduction



Lobelanidine



Pharmacological effect:

1. Lobeline is quite similar in action to **nicotine**, but less active.
2. It is **stimulant** to the respiratory center, although of short duration and somewhat unreliable.
3. The extract has been incorporated in *Galanical preparations* as **expectorant**. This activity cannot be attributed to lobeline as it is unstable.
4. Used as tablets for **smoking cessation process**.

3. Arecoline Alkaloids:

فوقل كاتشوا والتبول Botanical sources: found in the betel **nuts** (seeds) of *Areca catechu* - , a type of palms that grows in India and Malaysia.

الفصيلة النخلية *Areaceae*.

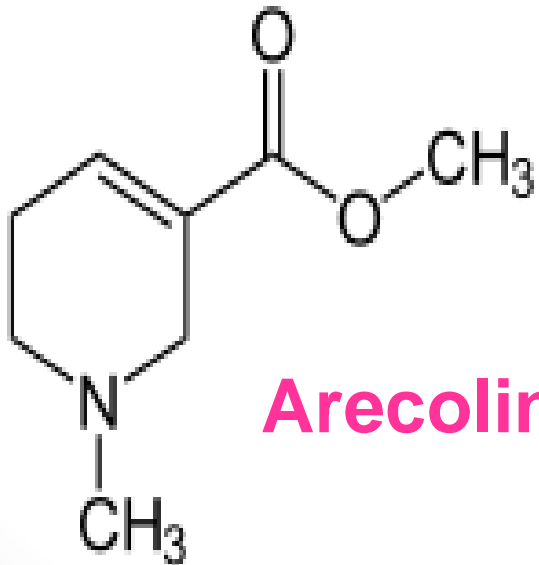
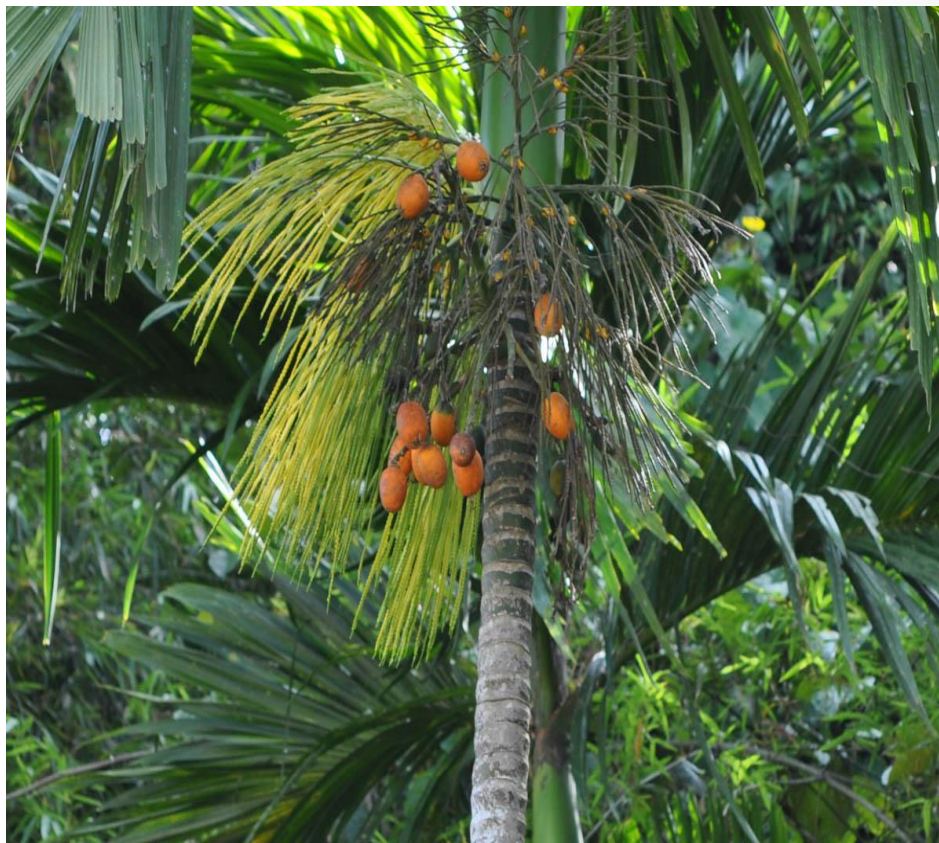
** Chewed in India for the **stimulant** effect of **Arecoline**.

** It is an odorless oily liquid.

** Research results indicate that arecoline could induce neuronal apoptotic death by [1] **attenuating** antioxidant defense and [2] enhancing oxidative stress.

** It has been **used** as **vermicide** to eradicate worms in veterinary practice. YouTube:-

https://www.youtube.com/watch?v=9OgCjhAFCC0&ab_channel=KatieRose

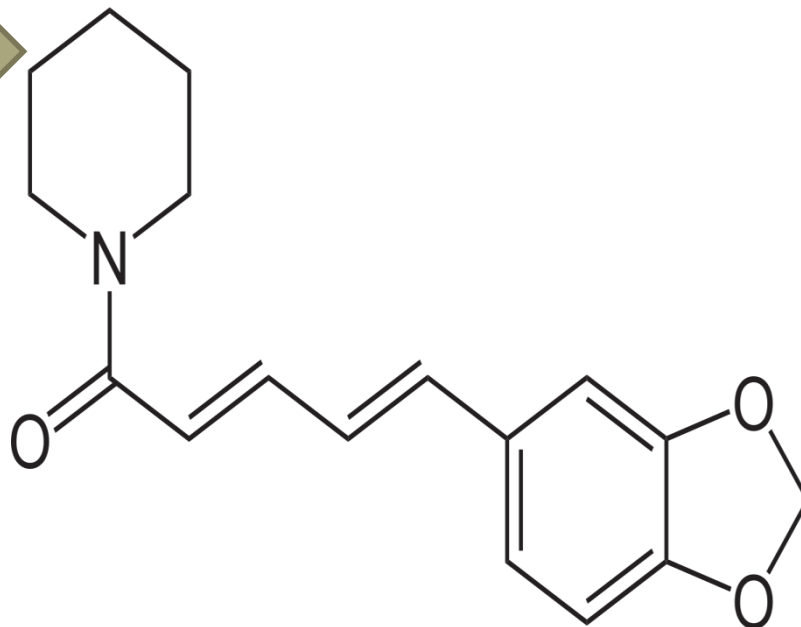


Arecoline

4. Pepper Alkaloids

- The pungent taste and irritant properties of pepper (*Pepper nigrum*) are due to the alkaloid piperine.

Piperidine

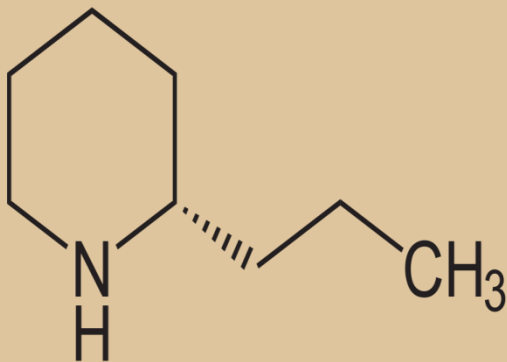


Piperine

- Piperine is involved to **increase the absorption of other nutrients** in the body and has other novel applications as well - such as helping **to fight colon cancer** and having **an anti-depressant effect** while **enhancing the cognitive functions of the brain.**
- Piperine and its synthetic derivatives **can stimulate pigmentation in the skin** especially when combined with **UV-R** treatment.” The researchers compared the effects. (e.g. vitiligo).
- The research, published in the *Journal of Agricultural and Food Chemistry*, found that piperine **blocks the formation of new fat cells.**
- Using laboratory studies and computer models, the researchers found piperine **interferes with the activity of genes that control the generation of fat cells.**

5. Conium Alkaloids

- The unripe fruit of *Conium maculatum* (Hemlock)
الشوكران الأبقع
- It contains 0.9% of alkaloids.
- The most important is **coniine**.
- It is an oil.
- These alkaloids are very toxic.



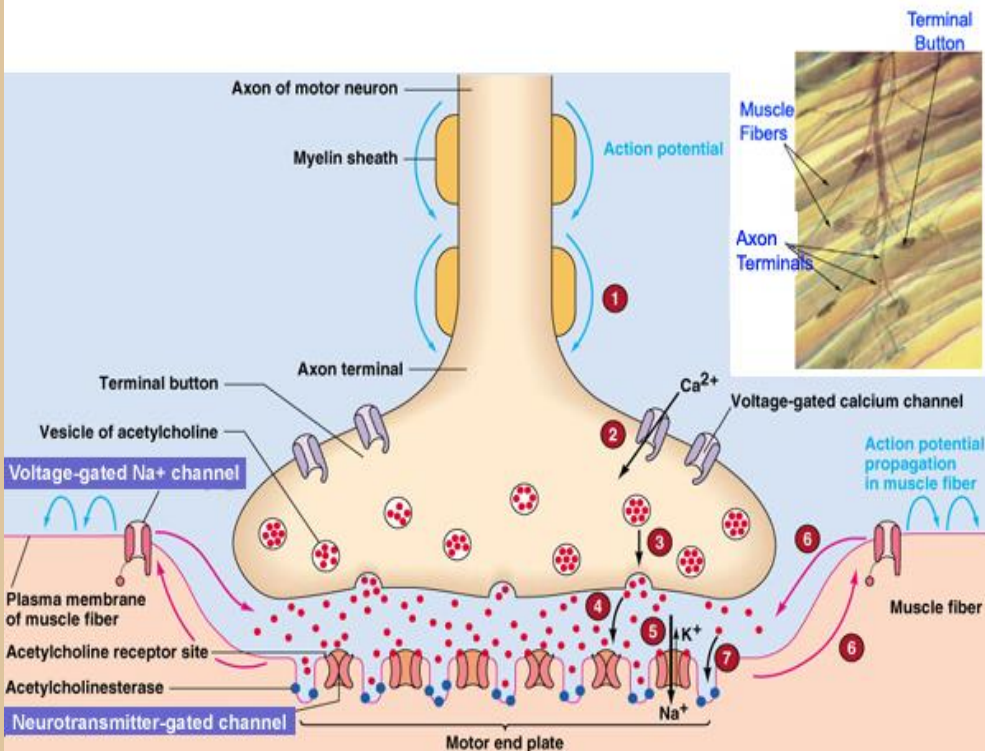
Coniine



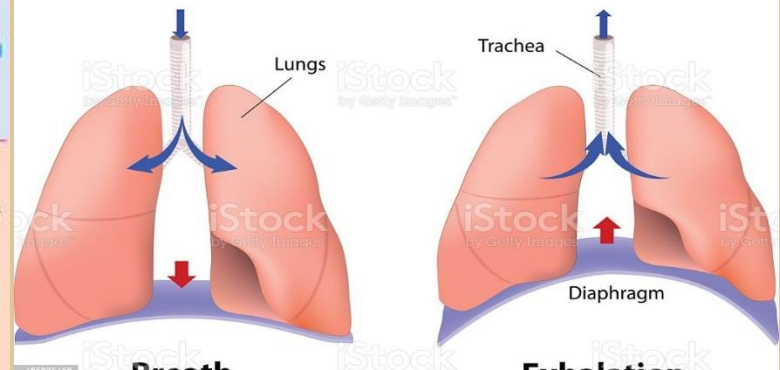
Its fruits are similar to anise seeds

- It is toxic to humans and all classes of livestock **مواشي**; less than 0.2g is fatal [6-8 leaves can kill a human being].
- It is **teratogenic**, and it produces crooked calf disease.
- **Coniine** paralyzes muscles by **blocking the nicotinic receptor** on the post-synaptic membrane of the neuromuscular junction causing a **flaccid paralysis** **مترهل**. This action is similar to that of **curare**.

The Neuromuscular Junction



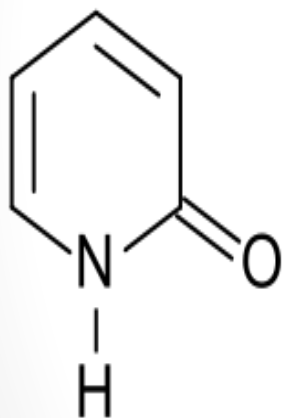
The diaphragm functions in breathing



- Symptoms of paralysis occur within a half hour, and death may take several hours.
- As the central nervous system is not affected, the person remains conscious and aware until **respiratory paralysis** results in **cessation of breathing**.
- The muscular paralysis is an **ascending** flaccid paralysis as the lower limbs are affected first.
- The person may have a **hypoxic convulsion** just prior to death, but this is greatly disguised (hidden) by the muscular paralysis and the person may just weakly shudder (shiver, shake).
- **The cause of death is lack of oxygen to the brain and heart as a consequence of respiratory paralysis.**
- A poisoned person will recover if artificial ventilation (breathing) is maintained until the toxin is removed from the receptor.
- Historically, this is the poison that killed Socrates.

Pyridone alkaloids

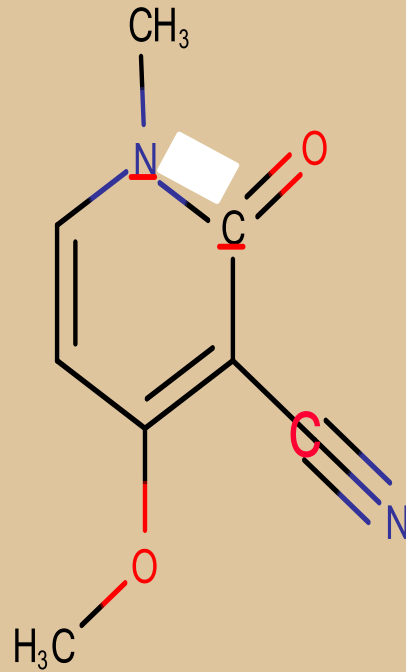
- **Ricinine:** isolated from the seeds of *Ricinus communis*
الخرع
(Family: **Euphorbiaceae**) الفربيونية أو الفصيطة اللبئية أو الحلابية.



Pyridone



Ricinine



1. Studies show that **ricinine** can **elicit seizures**.
2. It has an **anti-bacterial** effect.
3. The **extract** of the pericarp **غلاف الثمرة** of castor bean (*Ricinus communis*) showed some typical central nervous system **stimulant** effects when administered to **mice**.

- The animals became **exophthalmic**, presented tremors and **clonic seizures** and **died** a few minutes after receiving **larger** doses of the **extract**.
- At **lower** doses the extract **improved memory consolidation** (reinforcement) and **showed some neuroleptic-like properties (tranquilizing effect)**, such as a decrease in **exploratory behavior** and **catalepsy** **الانغماء التخشبي**.

NEUROLEPTICS = ANTIPSYCHOTICS:

- Medications primarily used to manage **psychosis** (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia but also in a range of other psychotic disorders. They are also the mainstay together with mood stabilizers in the treatment of bipolar disorder.
- **Mechanism:** blockage of dopamine receptors in the brain.

The **[1] memory-improving** effect and the **[2] seizure-eliciting** properties of the extract were also observed with the administration of **ricinine**, a neutral alkaloid isolated from the extract.

- However, the **neuroleptic-like properties** of the extract were not observed with ricinine.
- As the therapeutic index of **ricinine** is of the order of 200 (SAFE), the compound may be considered as **a promising cognition-enhancing drug** that may be used for the treatment of human amnesias.

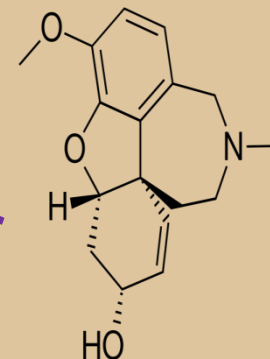
AMARYLLIDACEAE ALKALOIDS

- As the name implies, these alkaloids occur in plants of the family *Amaryllidaceae* **نرجسية**, many of which are ornamental plants like *Narcissus* spp. (**daffodils** نرجس او العبهر) and *Galanthus* spp. (**snowdrops** زهرة اللين).

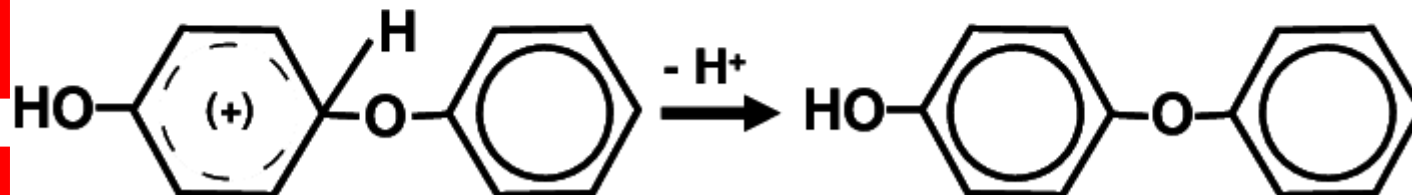
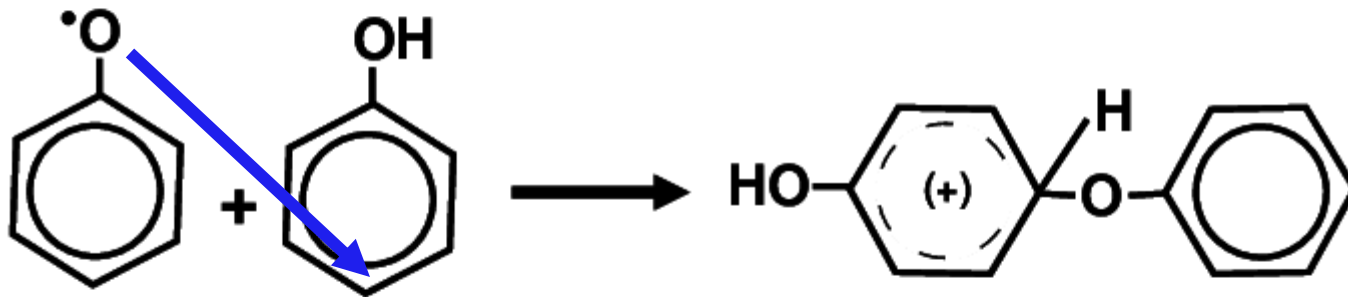
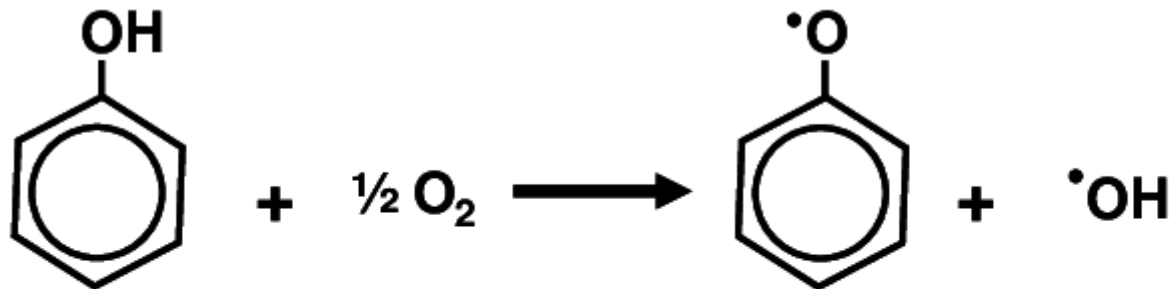


الترجسية **Amaryllidaceae** alkaloids

- Over 100 alkaloids have been isolated from plants of this family.
- These alkaloids are toxic and only one – **galanthamine** (galantamine)– has found use in medicine.
- Galanthamine has been originally isolated from bulbs of snowdrops, and has also been found in other genera of the *Amaryllidaceae* family.
- It is extracted from bulbs of *Leucojum aestivum* (snowflake) **ندفة الثلج**.
- *Narcissus* spp are used as a commercial source of galanthamine.
- The structure of the alkaloid indicates that the molecule is the product of **an intramolecular oxidative coupling** within a precursor of

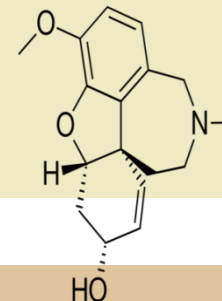


OXIDATIVE COUPLING



Amaryllidaceae alkaloids

Galanthamine



..... Of the C₆C₂ –N-C₁C₆ type.

- C₆C₁- unit comes from **phenylalanine**, while **tyrosine** delivers the –N-C₂C₆ unit.
- Galanthamine is an **acetylcholinesterase inhibitor** which is used for the treatment of Alzheimer's disease; an age-dependent neurodegenerative disorder characterized by multiple cognitive deficits, including worsening of memory, judgment and comprehension.
- The cognitive deficits are thought to be related to the degeneration of cholinergic neurons in the cortex and hippocampus, resulting in deficits of cholinergic transmission and reduced levels of acetylcholine in these patients.

Amaryllidaceae alkaloids

Galanthamine

- Patients may, however, also have a loss of other neurotransmitters.
- There is no cure for patients suffering from Alzheimer's disease, and symptomatic treatment focuses on the restoration of cholinergic function.
- Inhibition of acetylcholinesterase has been shown to significantly improve cognition in Alzheimer's disease patients.
- Galanthamine is a reversible, competitive inhibitor of acetylcholinesterase that potentially enhances cholinergic function in the brain through two mechanisms of action:
 1. **The inhibition of the enzyme.**
 2. **The potentiation of the effects of acetylcholine at nicotinic acetylcholine receptors.**

الانرجسية Amaryllidaceae alkaloids

- In Eastern Europe, galanthamine is used a reversal agent in anesthetic practice, because it neutralizes the neuromuscular blockade induced by tubocurarine.
- Besides, it acts as a mild analeptic and shows analgesic power as strong as that of morphine (structure similarity).

NOTE: The term **analeptic** typically refers to respiratory **analeptics**.

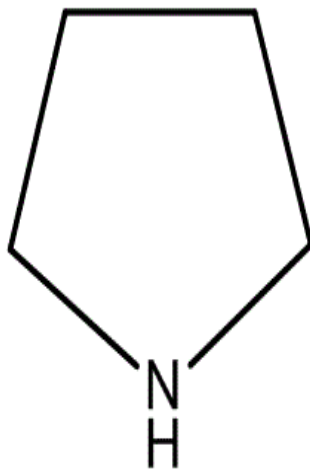
Analeptics are central nervous system **stimulants** that include a wide variety of medications used to treat depression, attention deficit hyperactivity disorder (ADHD), and respiratory depression.

- When applied in eye drops, it reduces the intraocular pressure.

الانرجسية **Amaryllidaceae alkaloids**

- As galanthamine can be used in the treatment of depression, this highlights its putative effect on the other neurotransmitters, in addition to its effect on acetylcholine level and mode of binding.

Pyrrolidine Alkaloids



Hygrine:

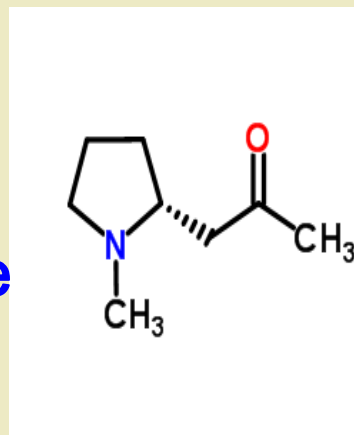
** It is a liquid alkaloid found with cocaine in Peruvian coca leaves.

** This group also includes cuscohygrine and stachydrine.

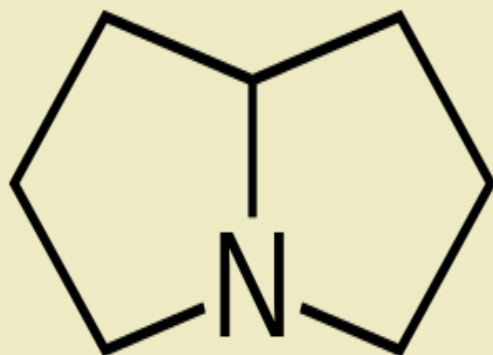
Stachydrine is found in *Stachys tubrifera*.

** The uses of these alkaloids: like for cocaine, that leaves are chewed to overcome fatigue, thirst and hunger.

Hygrine



Pyrrolizidine Alkaloids:



PYRROLIZIDINE ALKALOIDS:

- These alkaloids constitute a large group which is found in different families like:

1. Compositae (**Asteraceae**; **النجمية** **largest family in terms of number of species**). In *Senecio* (a genus) that includes about 1000 species.

2. Boraginaceae (**الحممية**).

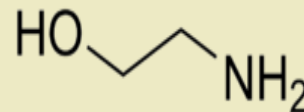
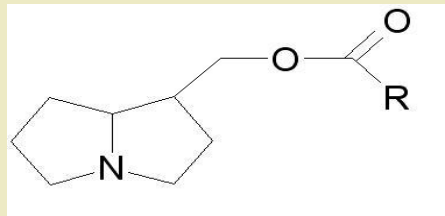
3. Leguminosae. (**البقوليات**).

➤ They cause **cattle disease** (horse staggers **ترنج في المشي** or walking disease).

➤ Also, they cause hepatotoxicity and liver cirrhosis leading to liver tumors.

➤ On hydrolysis, they produce aminoalcohol (**the Necine moiety**), (**containing both an amine and an alcohol group**) and necic acid.

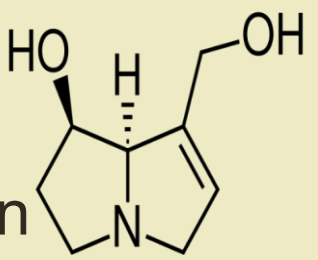
Necic acid



Aminoalcohol

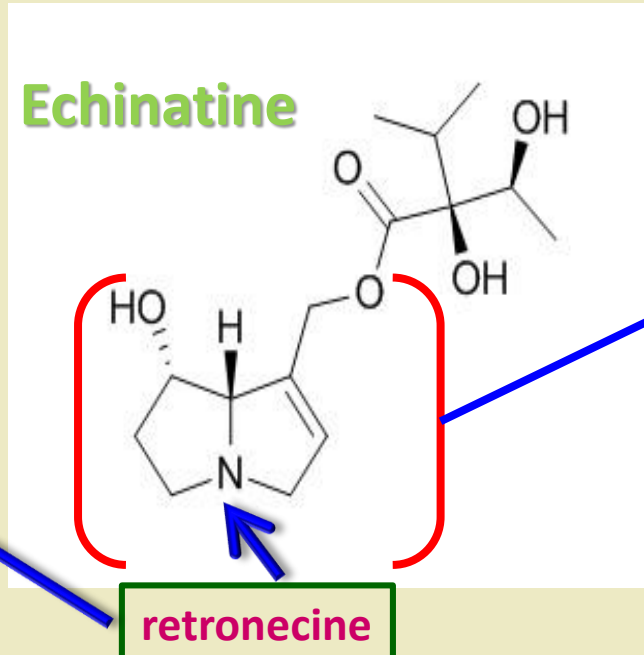
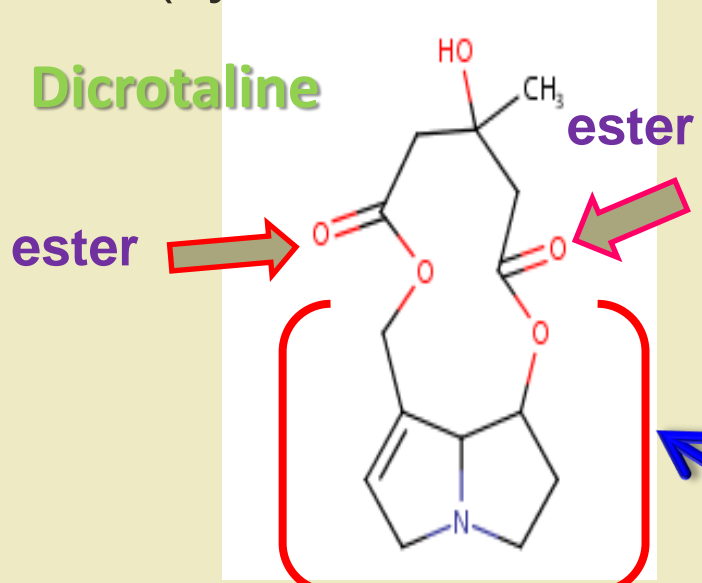
1. Retronecine: is a pyrrolizidine alkaloid found in a variety of plants in the genera *Senecio* and *Crotalaria*, and the family *Boraginaceae*. It is the most common central core for other pyrrolizidine alkaloids.

➤ The necic acids are mono- or di-carboxylic acids in the range of C3-C7 which may contain additional double bonds and hydroxyl groups. Some are mono esters or di-esters and other cyclic di-ester.



2. Echinatine (contains a monoester).

3. Dicrotaline (cyclic di-ester).

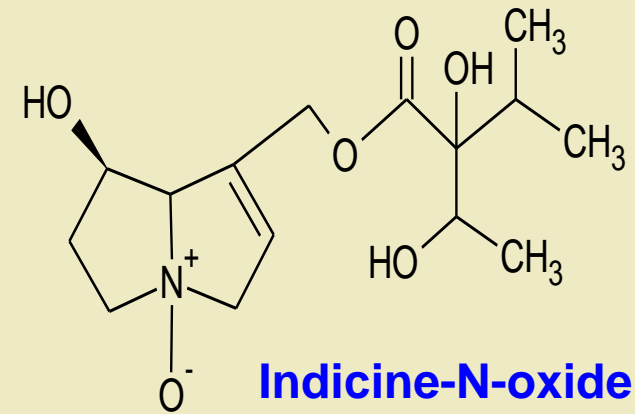


- The toxicity increases with the increase of the number of ester groups and cyclic ester.

Some of these alkaloids produce bronchopneumonia.

4. Indicine-N-oxide: is a natural pyrrolizidine alkaloid with **antineoplastic** properties (active against a number of tumors in mice).

From *Holiotropium indicum*, that is native to Asia.

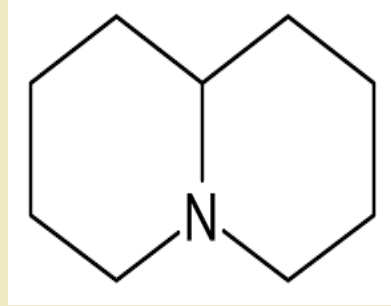


Indicine-N-oxide

رقيب الشمس الهندي



Quinolizidine Alkaloids:

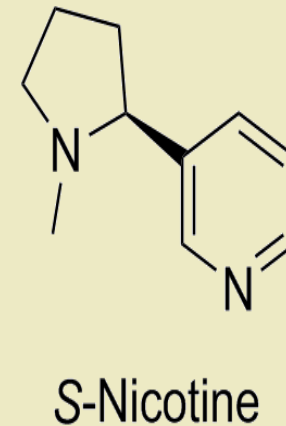
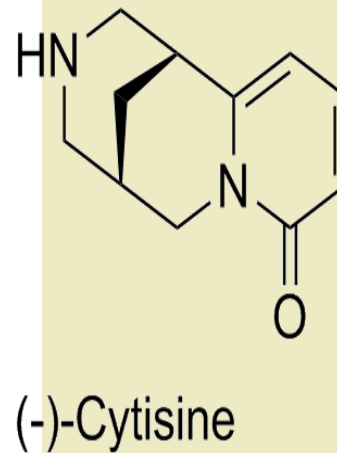
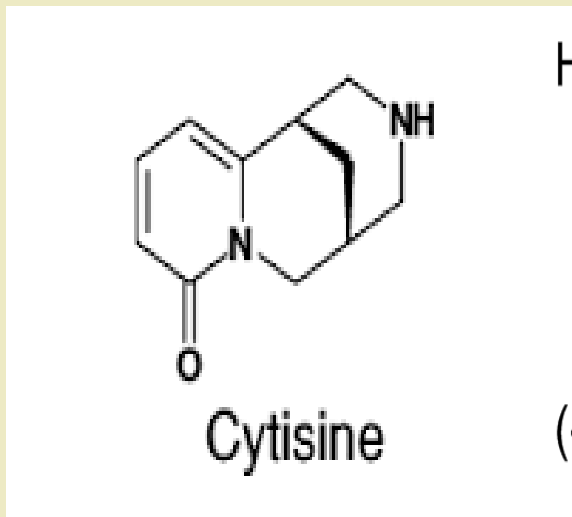
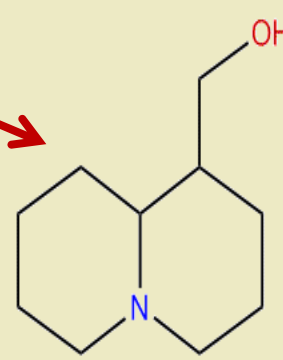


- ❖ These alkaloids are toxic and repel animals from feeding on the plants containing them, but there are certain strains with acceptable low alkaloid content and with a high protein content like *Lupinus luteus* (Fabiaceae).

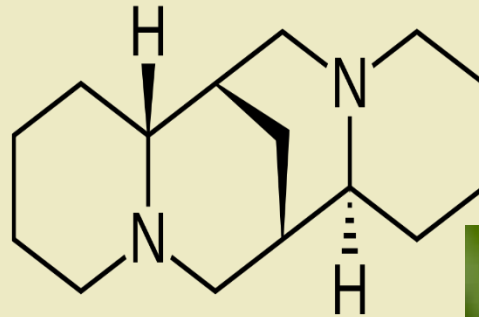
الأصفر



1. **Lupinine (Bicyclic lupin alkaloid):**
 2. **Cytisine (Tricyclic lupin alkaloid):**
- ❖ It has been used medically to help with **smoking cessation** in Eastern Europe.
 - ❖ Its molecular structure has some **similarity** to that of nicotine and it has similar pharmacological effects.
 - ❖ Cytisine (**broom family, Fabaceae**) is a partial agonist of nicotinic acetylcholine receptors.



3. **Sparteine** (tetracyclic lupin alkaloid): from *Cytisus scoparius* Scotch broom (*Leguminosae*).



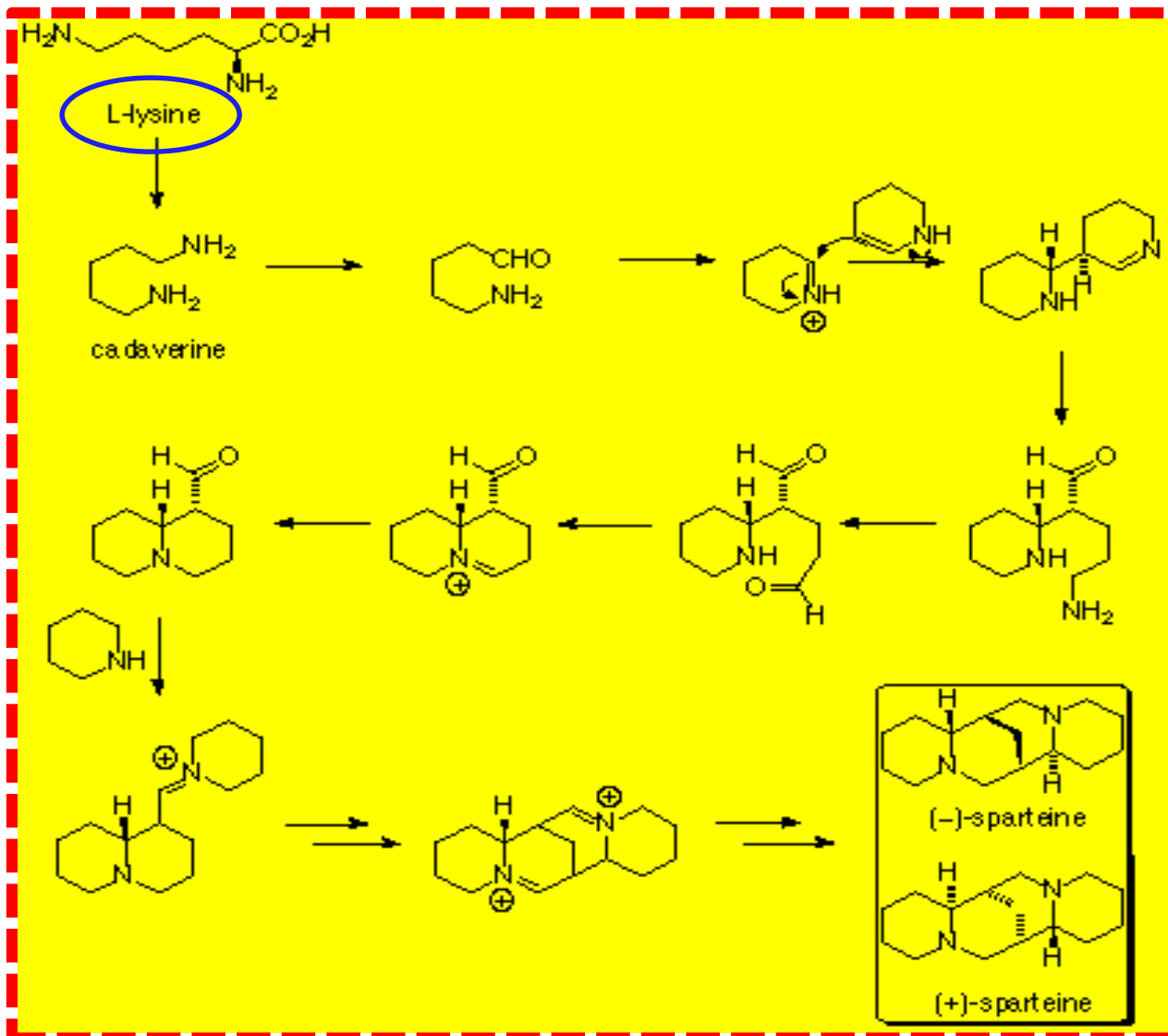
Uses:

1. Sparteine sulphate is used in Europe in the **treatment of cardiac insufficiency** .
2. It is used as an **oxytocic**, and it acts by stimulation of uterus contraction.

Pharmacology:

- **SODIUM-CHANNEL BLOCKER** → → **ANTIARRHYTHMIC** (yet, it is not approved for human use). It reduced ventricular tachycardia and fibrillation.
- In the pancreas, it **INDUCES INSULIN SECRETION** → hypoglycemic effect.
- It has been used to **INDUCE UTERINE CONTRACTIONS** and has been demonstrated to exhibit **DIURETIC** and **ANTI-INFLAMMATORY** activities.
- Can **CHELATE DIVALENT CATIONS**, such as calcium and magnesium.
- Sparteine has been found to exhibit **BACTERICIDE-LIKE** activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Bacillus thuringiensis*.
- **ANTICONVULSANT** effect: due to the cholinergic effect and the subsequent release of GABA.

BIOSYNTHETIC PATHWAY



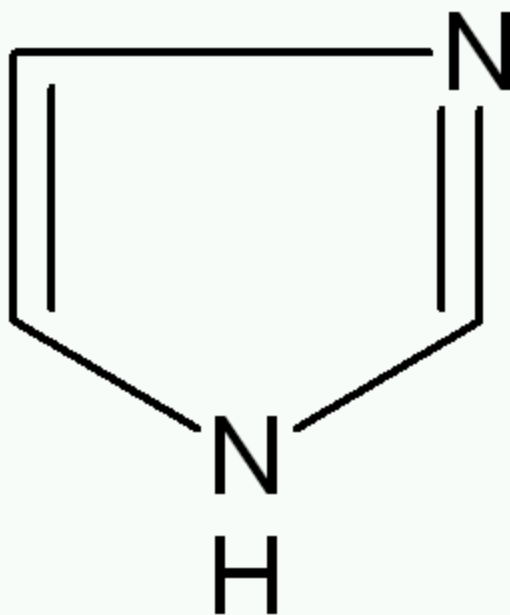
4- Anagyrine:

- An alkaloid in Western American lupines.
- It causes **crooked** (curved, bent) **calf disease** as it is teratogenic to cow fetus (causes paralysis of the fetus).



Lupine-caused crooked calf disease

IMIDAZOLE ALKALOIDS



IMIDAZOLE ALKALOIDS

Example: Pilocarpine

Botanical sources: *Pilocarpus jaborandi* -
Rutaceae.

الفصيلة السذابية هي فصيلة نباتية تشمل مجموعة الحمضيات.

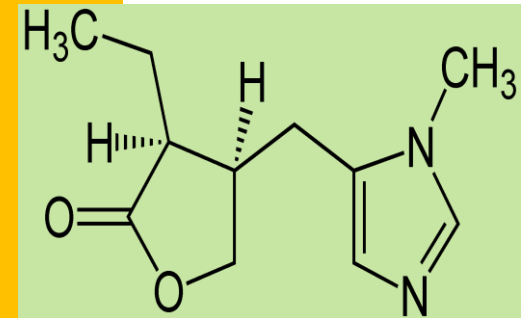
Pharmacological effect:

parasympathomimetic.

Uses: in glaucoma (wide and narrow angle
Glaucoma).

Keep away from light.

Side effect: bronchoconstriction (bronchial
contraction), bradycardia, **It is not the first
choice for glaucoma** because of headache
and increase in lacrimation.

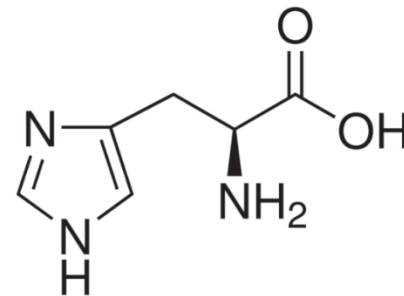


Pilocarpine

IMIDAZOLE

- Biosynthetic pathway: from **HISTIDINE**.

PILOCARPINE: acts on the ciliary muscle and causes it to contract. When the ciliary muscle contracts, it opens the trabecular meshwork through increased tension on the scleral spur. This **action** facilitates the rate that aqueous humor leaves the eye to decrease intraocular pressure.



IMIDAZOLE

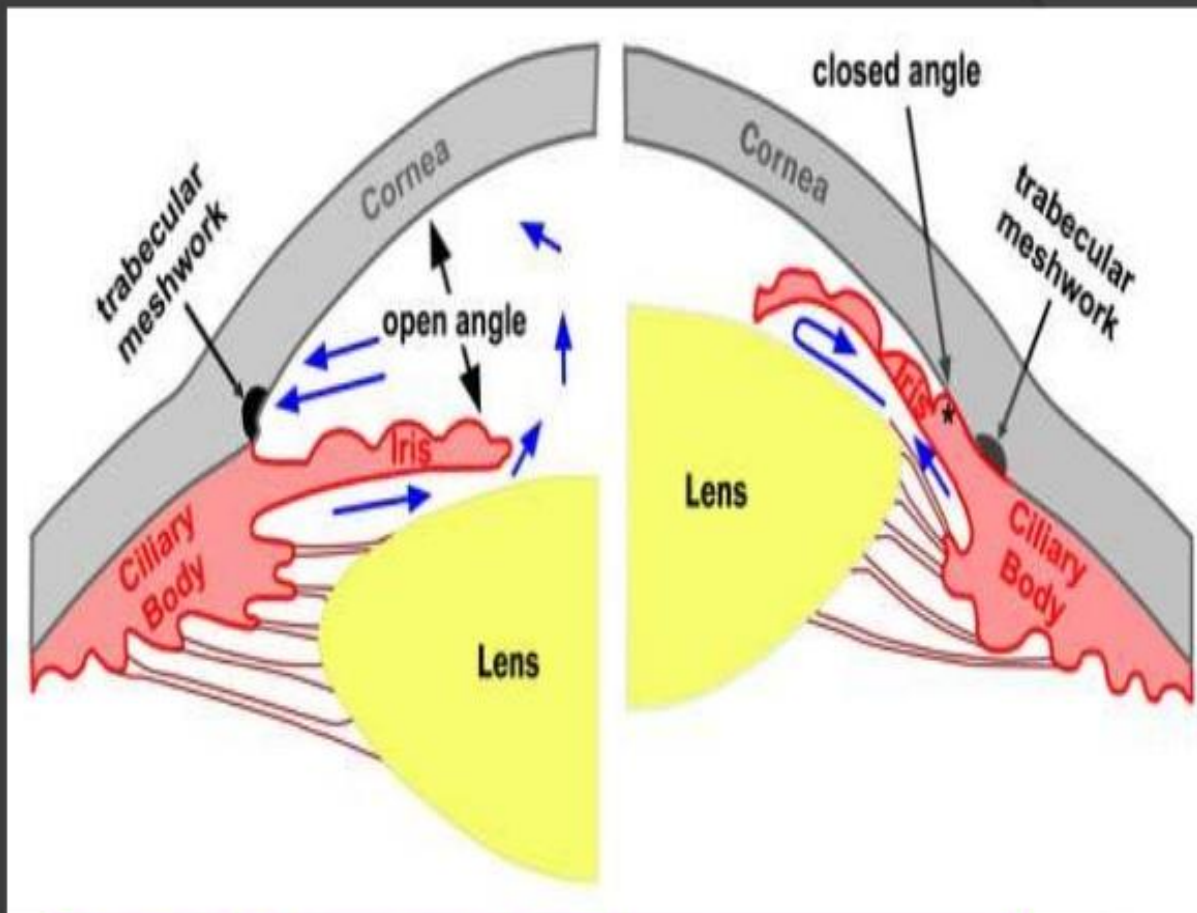


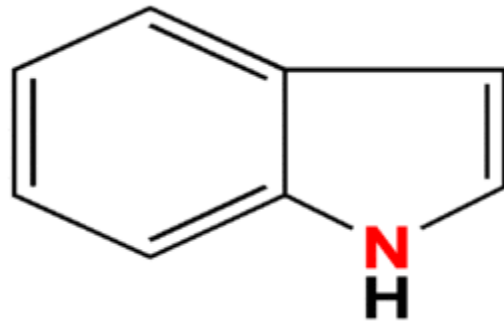
Fig:- open and closed angle glaucoma

IMIDAZOLE

USES:

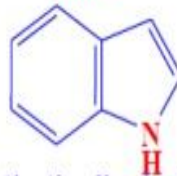
- ❖ To prevent and treat dry mouth (such as, in radiotherapy during the treatment of head and neck cancer).
- ❖ To treat dry eye.
- ❖ It is, sometimes, used immediately before certain types of corneal grafts and cataract surgery.
- ❖ To prevent intraocular pressure.
- ❖ To decrease light glare in patients who had been subjected to implantation of intraocular lenses (by miotic effect).
- ❖ In sweat test; to stimulate sweating to measure the concentration of sodium and chloride that are secreted in the sweat.

Indole Alkaloids



Alkaloids of the Indole Group

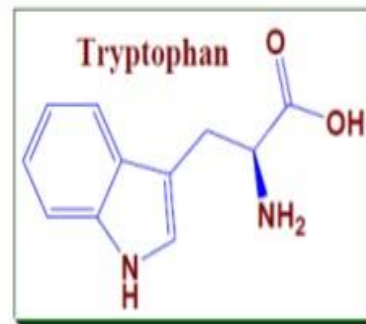
Indole



Indole alkaloids are biosynthetically derived from Tryptophan amino acid.

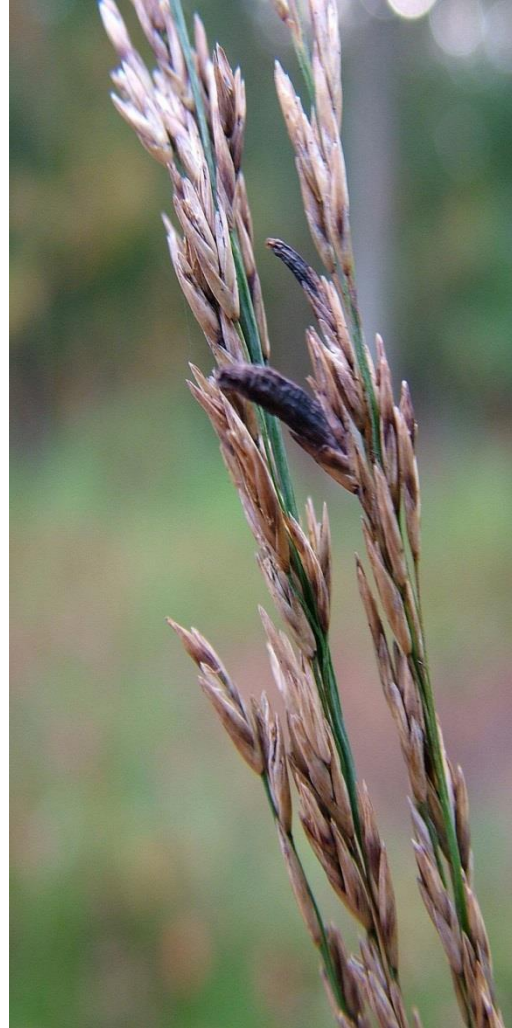
This group includes:

- * *Physostigma* alkaloids.
- * Ergot alkaloids.
- * *Nux vomica* alkaloids.
- * *Vinca* alkaloids.
- * *Rauwolfia* alkaloids.



ERGOT:

- Ergot is the product of filamentous fungus (dried sclerotium= **the hard dark resting body of certain fungi, consisting of a mass of hyphal threads, capable of remaining dormant for long periods**) of *Claviceps purpurea* {{family Hypocreaceae **المستحمية**}} that grows parasitically on rye and other graminaceous plants **النجليات**.
- In the past, ergot played a tragic role as cause of a devastating epidemic poisoning in Europe in the middle ages, called Saint Antony fire (Ergotism). The toxicity is manifested in two forms:
 1. **Ergotism:** gangrene of the extremities which resulted in bloodless, often dramatic , loss of blackened limbs (vasoconstriction).
 2. **Delirium and hallucination:** which could lead to convulsions.

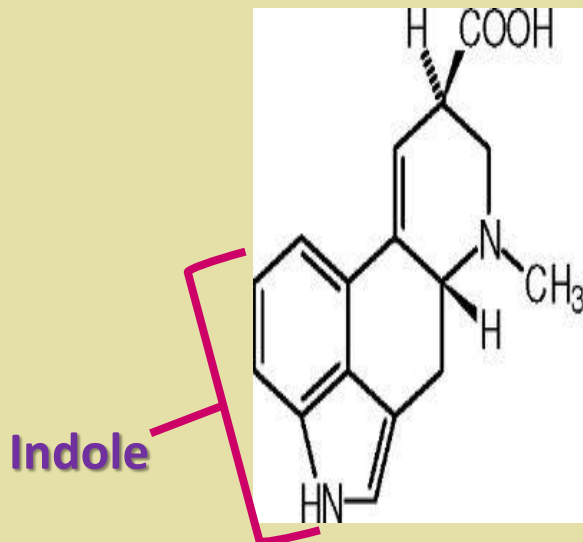


Ergot:

Chemical structure:

- Ergot alkaloids are composed of **lysergic acid** and its isomer **isolysergic acid**, combined through an **amide** linkage with a **peptide** {tripeptide of 3 amino acids} (**ergotamine group**) or with an **aminopropanol** (**ergometrine group**).

Structure of lysergic acid:



❖ Ergotamine is a cyclic peptide containing the following amino acids: α -hydroxyalanine, proline, phenylalanine.

❖ Other cyclic peptide ergot alkaloids (like ergotamine): ergocristine, α -ergocryptine, β -ergocryptine, ergocornine.

Ergot:

Lysergic acid and isolysergic acid structure:

