Pharmacognosy and Phytochemistry

Alkaloids-Part 4

B. Pharm. Semester-1

Course Code: 0510221; Session: 2022-2023

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Learning Outcomes

At the end of this lesson, students will be able to explain

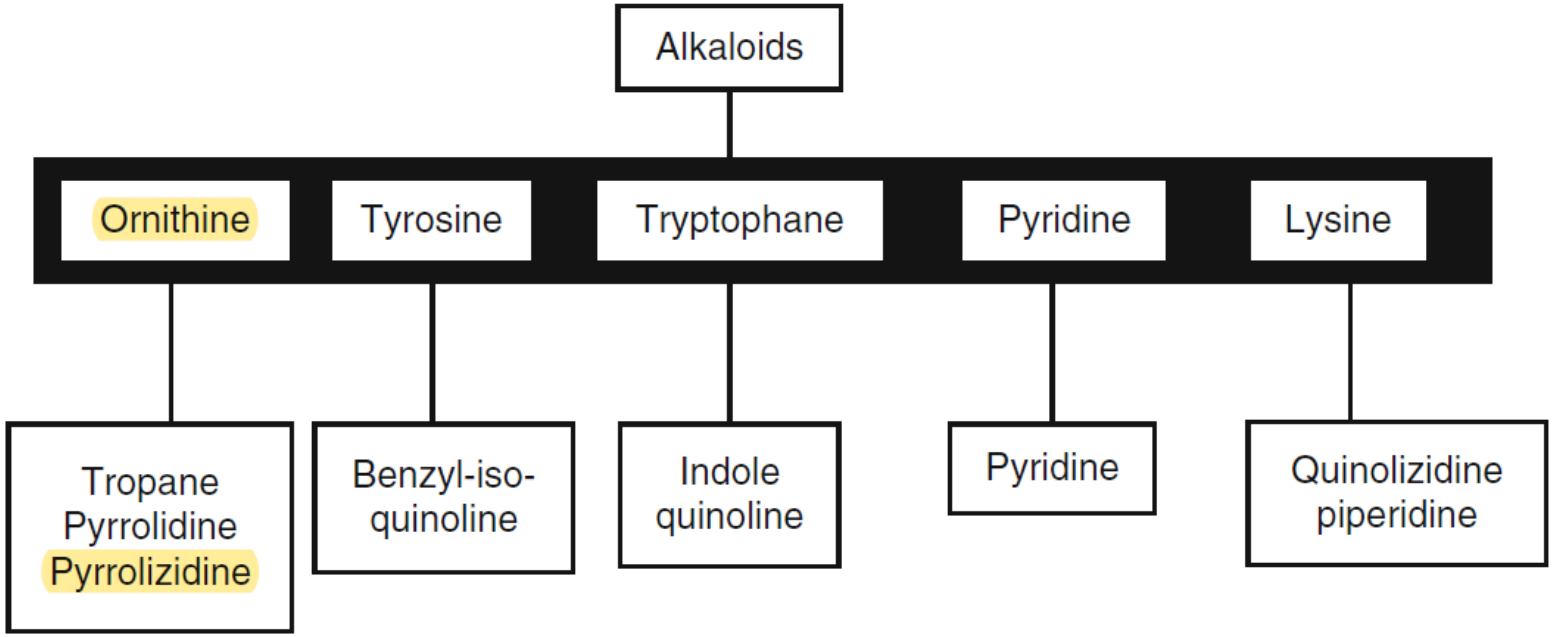
Pyrrolizidine alkaloids: Retronecine, Echinatine, Dicotaline and Indicine-*N*-oxide

Tropane alkaloids: Hyoscyamine, atropine, scopolamine, and cocaine.
Traditional Herb: Mandrake

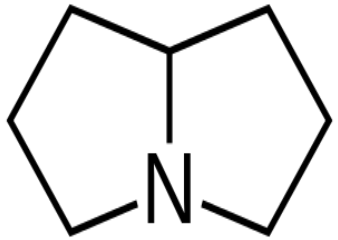
Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the alkaloids as major phytoconstituents.

Pyrrolizidine alkaloids



Structure of Pyrrolizidine



Pyrrolizidine alkaloids

- Pyrrolizidine alkaloids (PAs), sometimes referred to as necine bases, are based on the structure of pyrrolizidine.
- Pyrrolizidine alkaloids are produced by plants as a defense mechanism against insect herbivores.
- More than 660 PAs and PA N-oxides have been identified in over 6,000 plants, and about half of them exhibit hepatotoxicity.
- They are found frequently in plants in the Boraginaceae, Asteraceae, Orchidaceae and Fabaceae families; less frequently in the Convolvulaceae and Poaceae, and in at least one species in the Lamiaceae.

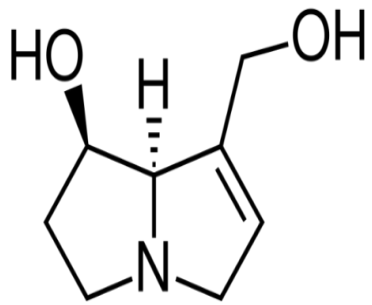
Pyrrolizidine alkaloids

Retronecine: It is a pyrrolizidine alkaloid found in the family Boraginaceae.

It is the most common central core for other pyrrolizidine alkaloids.

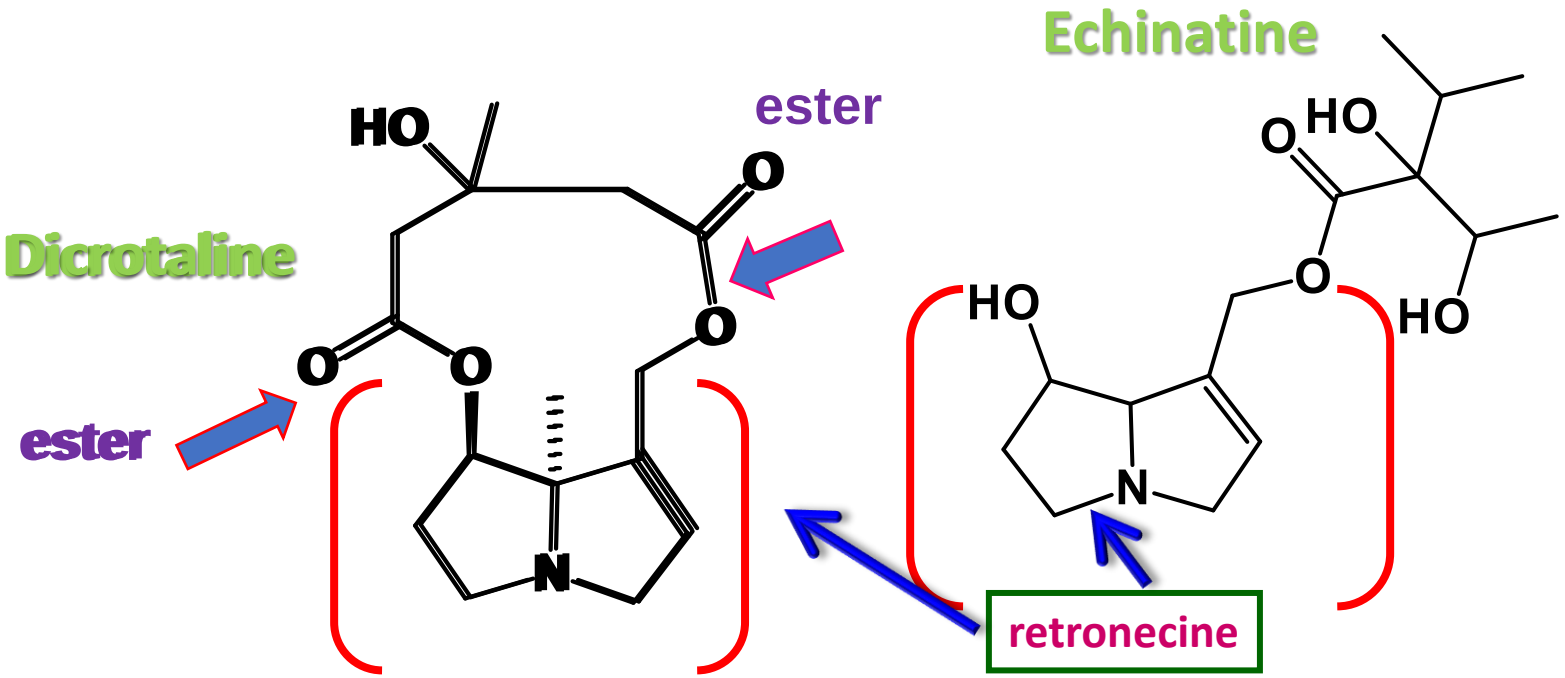
The necic acids are mono- or di-carboxylic acids in the range of C3-C7 which may contain additional double bonds and hydroxyl groups. Some are mono esters or di-esters.

Structure of Retronecine



Pyrrolizidine alkaloids

Echinatine (contains a monoester) and Dicrotaline (contains cyclic di-ester)

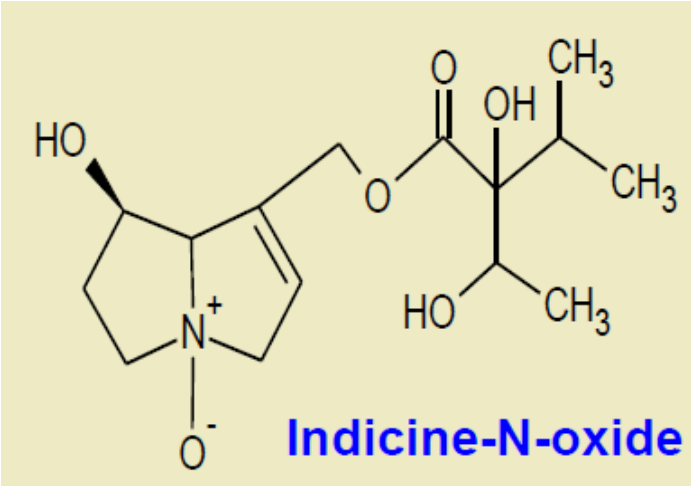


Pyrrolizidine alkaloids

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

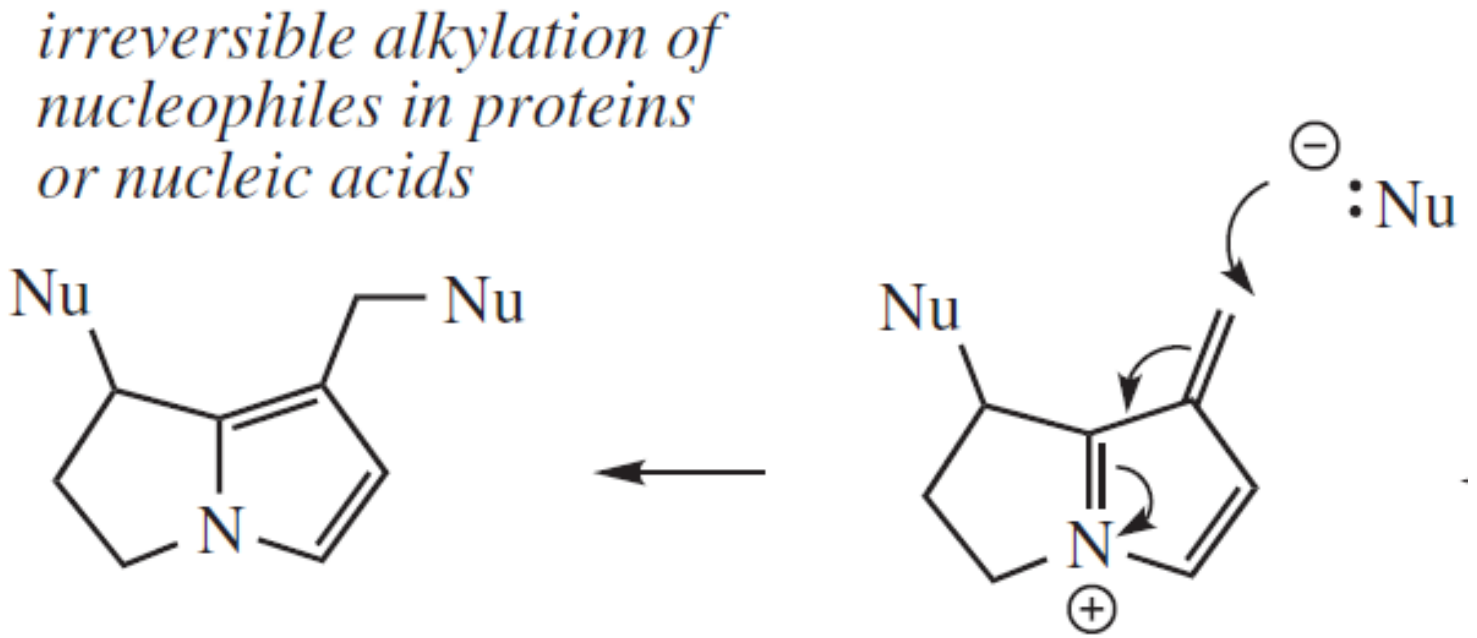
It is present in the plant *Heliotropium indicum* showed promising cytotoxic activity in various tumor models.

The compound exhibited severe toxicity to hepatocytes and bone marrow cells.



Pyrrolizidine alkaloids: Mechanism of toxicity

They are potent alkylating agents and react with suitable cell nucleophiles, e.g. nucleic acids and proteins.



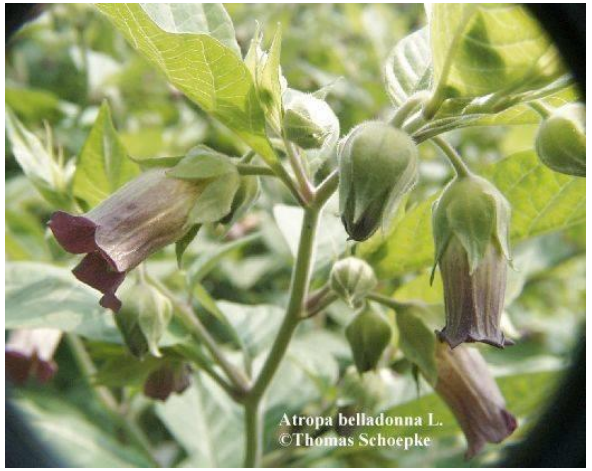
Tropane alkaloids

S. No.	Name of the Tropane Alkaloid	Botanical Source	Family
1	Hyoscyamine	*Datura stramonium*	Solanaceae
2	Atropine	*Atropa belladonna*	Solanaceae
3	Hyoscine or Scopolamine	*Hyoscyamus niger*	Solanaceae
4	Cocaine	*Erythroxylum coca*	Erythroxylaceae

Tropane alkaloids: Solanaceae

Thorn Apple, Stramonium, Jimson Weed *(Datura stramonium)*

Deadly nightshade *(Atropa belladonna)*



Henbane *(Hyoscamus niger)*

All these three plant species have parasympatholytic activity.
They may be considered as **anticholinergics**, acting upon the muscarine receptor. All of them contain (-)-hyoscamine and (-) hyoscine.

Tropane alkaloids: Pharmacological Uses

All these three plant species have parasympatholytic activity, considered as **anticholinergics**.

1-Decreases saliva secretion and GIT secretions so used in pre-operative.

2-Decrease motility of smooth muscles so used as antispasmodics.

3-Stimulate respiratory system.

4- Have a mydriatic effect (cause dilatation of the eye pupil).

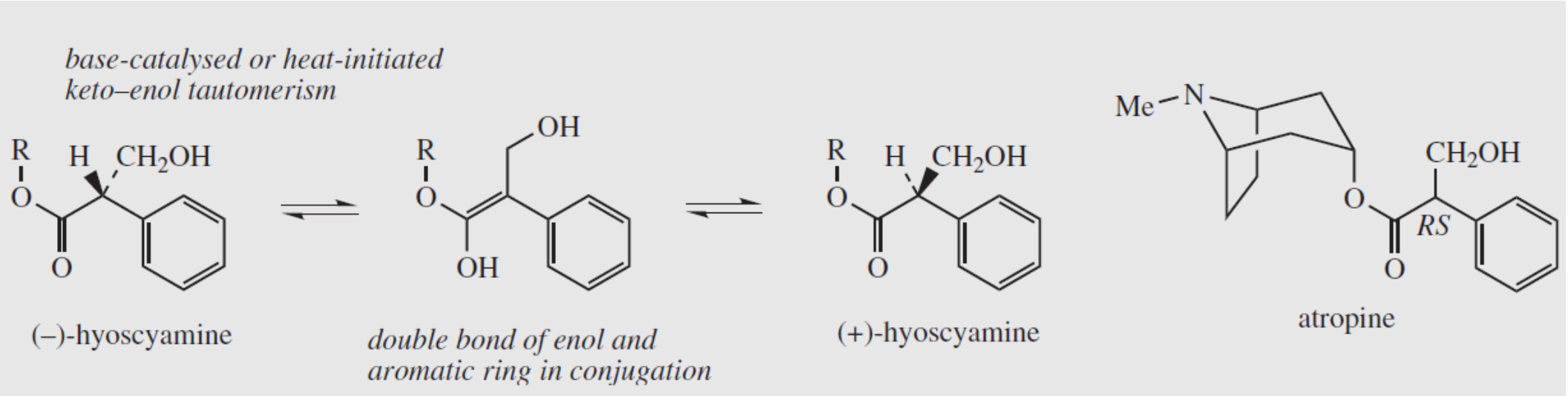
5-An antidote to organophosphorus poisoning.

6-Hyoscine has a more central effect, so it is used as a sedative and hypnotic.

7-Hyoscine is also used as antiemetic.

Tropane alkaloids: Hyoscyamine

- Hyoscyamine is the major natural alkaloid with negative optical rotation
- (l- form) [(-)-hyoscyamine that is racemized to atropine].
- Because the α-carbon is asymmetric, so two stereoisomers are possible.
- During the extraction, hyoscyamine racemizes to the optically inactive dl Atropine.
- Both hyoscyamine and atropine are composed of tropine base and tropic acid.



Tropane alkaloids: Atropine

- *Atropa belladonna* is toxic, belladonna berries (2 to 5 berries can kill a child, 10-20 to kill adults).

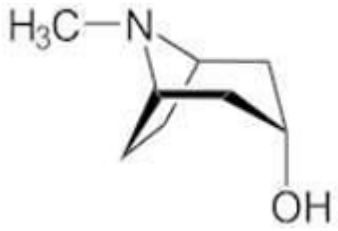
- Toxic symptoms after ingestion of Belladonna are:
  - red face, dry mouth, intense thirst
  - substantial increase of heart rate, dilation of pupils (mydriasis)
  - nausea, hallucinations, delirium, fatigue, hyperthermia,
  - agitation and loss of motor coordination, coma
  - death by respiratory failure

- Atropine is a mixture of (+) and (-)-hyscyamaine.

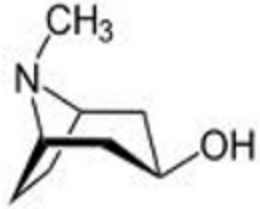
Tropane alkaloids: Atropine

α-tropanol (tropane-3 α-ol) gives **atropine**, while β-tropanol gives **pseudoatropine**.

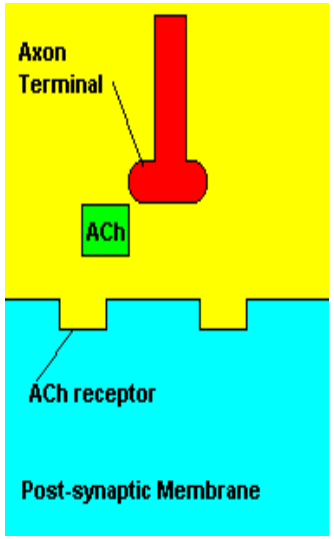
α-tropanol →



β-tropanol →



***Atropa belladonna* (*Solanaceae*)**



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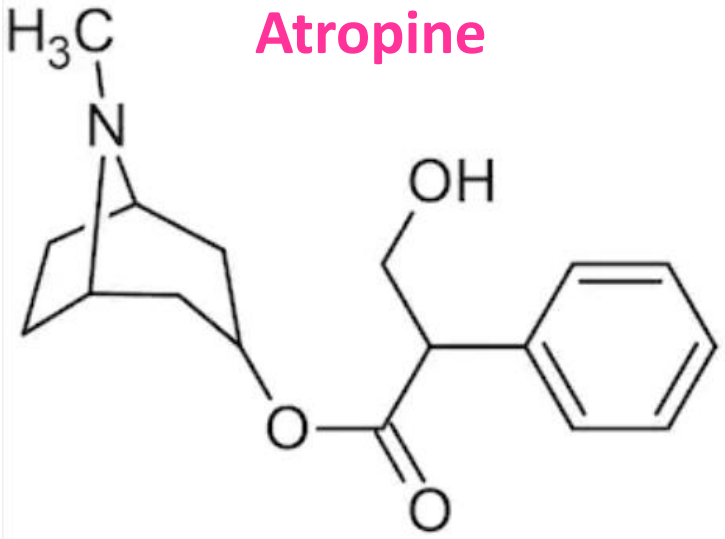
Atropine



Pharmacological actions of Atropine

Atropine is a **cholinergic-blocking agent**, it occupies the postsynaptic receptor-site, and prevents the normal neurotransmitters (acetylcholine) from acting, so atropine has the following pharmacological actions:

a- **Antispasmodic**: It relaxes the smooth muscles of intestine.

b- **Mydriatic**: It is used in ophthalmology during examinations of eyes.

c- In small doses, atropine is a smooth stimulant to respiration and myocardium.

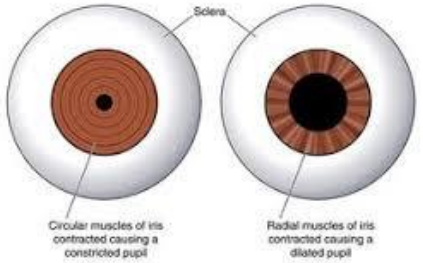
d- Locally, atropine ceases pain (slight paralysis of nerve endings)

e- It is used pre-operative to decrease the salivation, secretions of GIT

f- It is an **antidote** against the poisoning with the following agents: Physostigmine, neostigmine, pilocarpine, organophosphorus insecticides and muscarine.

Pharmaceutical Products of Atropine

Atropine eyedrops : To induce mydriasis during examinations of eye.

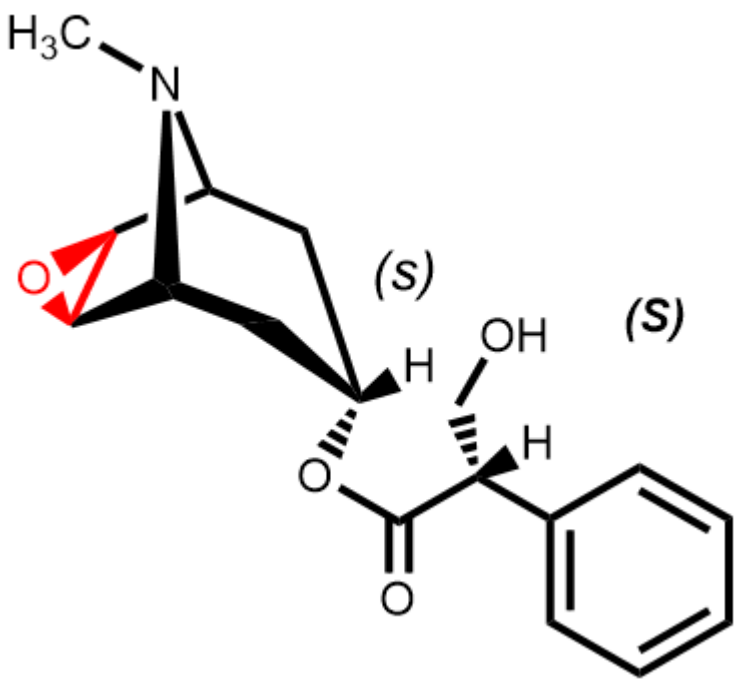


Ipratropium bromide
Atrovent inhaler
Anticholinergic bronchodilator

Atropine Injection (preoperative or as antidote)

Tropane alkaloids: Hyoscine or Scopolamine

(-)-Hyoscine or Scopolamine



Hyoscyamus niger (البنج الأسود, **henbane**, **black henbane** or **stinking nightshade**) and *Hyoscyamus muticus* (البنج المصري) which is indigenous to Egypt (Solanaceae).

They are esters of tropic acid and alcoholic base tropanol which have either α- or β- configuration

Tropane alkaloids: Hyoscine or Scopolamine

It is selectively sedative to the CNS, and it quiets excitability especially in the insane patients.

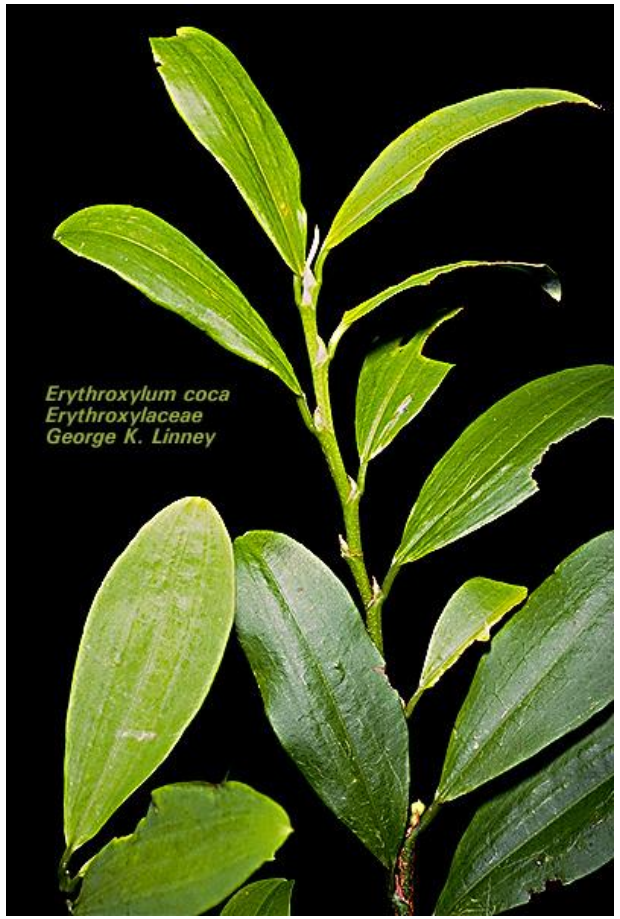
It is used in motion sickness (nausea caused by motion, especially during travelling).

Tropane alkaloids: Cocaine

- Cocaine is obtained from the leaves of the shrub *Erythroxylum coca* (Bolivian coca, 1%), or *E*, *truxillens* (Peruvian coca, 2%); Family: Erythroxylaceae.
- Cocaine is quickly absorbed from the mucous membranes and is used only **topically as anesthetic** in ophthalmology (salt 1%).
- 50 mg of cocaine lead to euphoria and hallucinations.
- Larger doses lead to cerebral cramps, hyperirritability and paralysis and makes drug-addiction.

Tropane alkaloids: Cocaine

Erythroxylum coca
(Bolivian or Huanuco Coca)



Erythroxylum novogranatense var. truxillense
(Peruvian or Truxillo Coca)

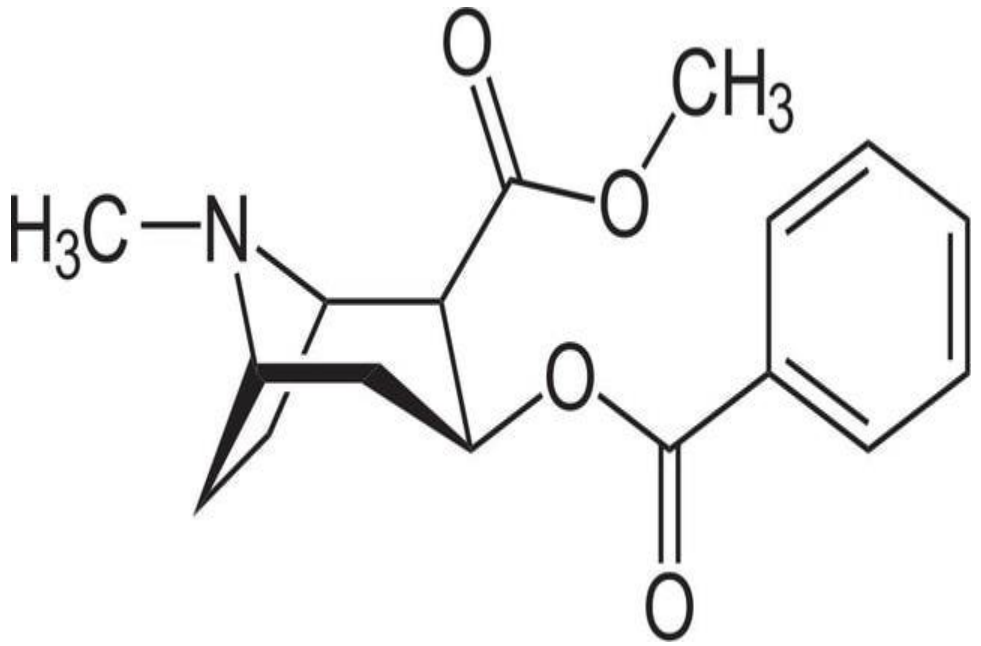
Erythroxylum novogranatense var. novogranatense

Tropane alkaloids: Cocaine

- Cocaine is the major alkaloid in Coca leaves, Cocaine is diester alkaloid.
- Heating at 160 °C in conc. HCl leads to hydrolyses of cacaine to MeOH, benzoic acid and ecogonine base.
- Main Alkaloids are:
  1- Cocaine.
  2- Cinnamylcocaine.
  3. Truxilline.
- The base for Coca Alkaloids is called “Ecogonine”

Tropane alkaloids: Cocaine: Structure and Uses

- Cocaine is used as local anesthetic.
- Cocaine has a CNS stimulant activity.
- It is one of the widely abused drugs.



Cocaine: benzoylmetheylecogonine

Pharmacological actions of Cocaine

1. **Local anesthetic -** blocks ion channels in neuron membranes.
2. **Sympathomimetic -** acts as an adrenergic stimulant by noradrenaline reuptake blockade. It doesn’t act directly on adrenergic receptors, but indirectly by inhibition of Adrenaline reuptake in the synaptic cleft.
3. Peripherally causes hyperthermia, mydriasis, and vasoconstriction, which contributes to increasing blood pressure.
4. At low doses, it increases the heart rate, at high doses, it causes cardiac arrest.
5. In CNS, it produces a sensation of euphoria with intellectual stimulation and other effects.

Symptoms of higher Use of Cocaine

1. Cocaine hydrochloride is generally taken by the intranasal route, less often by iv injection.
2. Cocaine intake causes euphoria, intellectual stimulation, hyperactivity, a feeling of hyperlucidity, and an acceleration in the elaboration of ideas.
3. Its over use produces the decrease in fatigue, insomnia, anorexia, and increased talkativeness. With chronic use, mental confusion and depression.
4. Prolonged use leads to delusions (compulsive scratching) parasitosis and hallucinations.
5. The most serious complications are cardiovascular such as induction of coronary insufficiency.
6. Massive overdose may lead to coma, convulsions and cardiac alterations.

Synthetic preparations related to Cocaine

Safer and less toxic anesthetics, related to Cocaine are:-

1. **Benzocaine -** a topical anesthetic with short duration of action.
2. **Levobupivacaine** (S-enantiomer) and bupivacaine (racemic form) are most widely used local anesthetics in surgery due to their long duration of action.
3. **Tetracaine -** local anesthetics used in ophthalmology.
4. **Lidocaine -** the most widely used local anesthetic.

Oragel
Benzocaine

Lidocaine injection

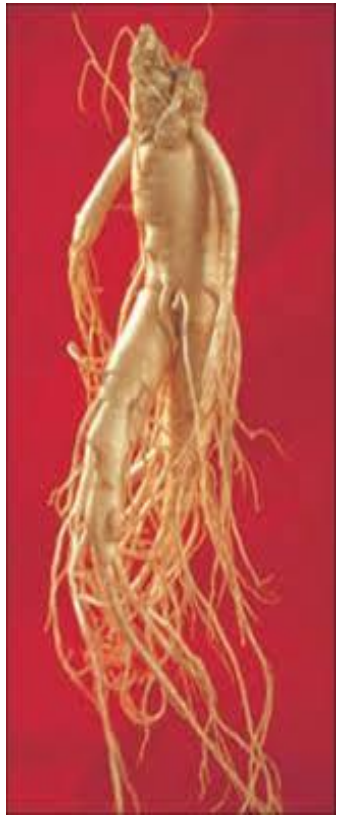
Traditional Herb: Mandrake

Mandragora officinarum & Mandragora autumnalis

M. officinarum (Solanaceae) is limited to small areas of northern Italy and the coast of former Yugoslavia.

M. autumnalis, the autumn mandrake is native to the Medditerranean countries, like Palestine, Jordan, Tunisia, Turkey, Lebanon, Syria, Morocco, … etc.

Traditional Herb: Mandrake



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3. **Medicinal Natural Products: A Biosynthetic Approach, 2nd Edition, 2002, Author: Paul M Dewick, Publisher: John Wiley and Sons Ltd, ISBN: 0471496405.**

Supplementary book:

Fundamentals of Pharmacognosy and Phytotherapy. A Guide for Health Care Professionals by Carol A. Newal, Linda A. Anderson and J. David Phillipson. (2010). the Pharmaceutical Press, London, UK; ISBN: 0 85369-474-5.