Conium maculatum
Pyridine-piperidine Alkaloids

Pyridine alkaloids and Nicotinic acid derivatives:

- **Biosynthetic origin:**
  - **Nicotine:** very toxic compound
  - **Botanical source:** leaves of *Nicotiana tobacum* - Solanaceae
  - **Pharmacological effect:**
    - It works on the nicotinic receptor (starts by stimulation then inhibition).
    - Highly hydrophobic, so can cross blood brain barrier.

- **In low doses,** such as those inhaled in smoking, nicotine causes hypertension, respiratory stimulation, stimulation of secretion from several glands and stimulation of CNS.
  
  The lethal dose (50-100 mg) corresponds to 5-cigarette content of nicotine, but it is destroyed by heat or distributed into the air.
  
  **Toxic doses** cause hypotension and death occurs as a result of respiratory arrest.
Uses:

- Nicotine in medical products is used to aid in smoking cessation (available in form of chewing gum, nasal spray and nicotine-impregnated patches).
- Enhances hippocampal transmission and improves long-term memory.
- Potential evidence: in ulcerative colitis.
- Vehicle on CNS (stimulant), dental carries, in Alzheimer and Parkinson [is still not clear].
- Insecticide especially in gardening (and is prepared by isolation from tobacco waste).

- It's an oily liquid compound, yellowish in color.
- Oxidized by light to form a brown color.
- **Toxicity:** Cancer and atherosclerosis, as it yields nitrous amine (very nucleophilic), leads to change in DNA structure, pulmonary and cardiac disease, effect on hepatic system, it leads to increase metabolism.
  - Smoking tree, *Nicotiana*, cuases deaths more than any other plant.
  - Smokings is responsible for causing one-third cancer cases.
  - It is estimated that more than 3 million deaths occur annually (2004).
  - The mortality is expected to jump to 10 million deaths by 2030.
  - The leaf contains more than 4,000 chemicals, with nicotine coming on the top of the list.
  - Nicotine is responsible for the addiction in smokers.
Biosynthesis of nicotine

Nicotine

It is a pyridine alkaloid yet it contains another heterocyclic ring, pyrrolidine.
1. Pelletierine:

- It is found in pomegranate tree bark, *Punica granatum*, (Punicaceae).
- The official drug is the tannate salt of this alkaloid.
- It is used as a vermicidal as it is toxic to tape worms and has been used as anthelmintic.
Piperidine Alkaloids:

2. 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 lobelanidine, while oxidation will yield lobelaine.
   - Lobeline HCl is exceptionally soluble in chloroform.

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

اللوبيليا. 2. *Lobelia*:
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Biosynthetic origin:
Botanical source: form *Lobelia inflata* – *Campanulaceae*
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. It is incorporated in Galanical preparations as expectorant. This activity cannot attributed to lobeline as it is unstable.

4. Used as tablets for smoking cessation process.
3. Arecoline Alkaloids:

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

**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 attenuating antioxidant defense and enhancing oxidative stress.**

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

![Image of Areca catechu nuts and palms](image-url)
4. Pepper Alkaloids

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

- 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) 千里光
- It contains 0.9% of alkaloids.
- The most important is *coniine*.
- It is an oil.
- These alkaloids are very toxic.

It is toxic to humans and all classes of livestock 毒性大; less than 0.2g is fatal [6-8 leaves can kill a human being].

- It is teratogenic, and it produces crooked calf disease.

- Used in homeopathy {is a system of alternative medicine created in 1796 by Samuel Hahnemann based on his doctrine of like cures like}, a claim that a substance that causes the symptoms of a disease in healthy people would cure similar symptoms in sick people}.

- Coniine paralyzes muscles by blocking the nicotinic receptor on the post-synaptic membrane of the neuromuscular junction causing a flaccid paralysis. This action is similar to that of curare.
- 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.

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**Pyridone alkaloids**

- **Ricinine**: isolated from the seeds of *Ricinus communis* (Family: **Euphorbiaceae**).
Ricinine

1. Studies show that ricinine can elicit seizures.
2. It has an anti-bacterial effect.
3. The extract of the pericarp 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.
- The memory-improving effect and the 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*, many of which are ornamental plants like *Narcissus* spp. (daffodil) and *Galanthus* spp. (snowdrops).

- Over 100 alkaloids have been isolated from plants of this family.
- These alkaloids are toxic and only one — *galanthamine* — 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).
- *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...
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.

• 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.

الترجمة Amaryllidaceae alkaloids

• 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.

• In Eastern Europe, galanthamine is used as 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.

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

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

Hygrine

![Hygrine structure]
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 (الحمصية).
  3. Leguminosae (البقوليات).

- They cause cattle disease (horse staggers 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.

\[
\text{Necic acid} \quad \text{Amino-alcohol}
\]
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.
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* (Fabaceae).

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.

![Cytisine and related compounds](image_url)
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.

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

Example: Pilocarpine
Botanical sources: *Pilocarpus jaborandi* - Rutaceae.

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.
Indole Alkaloids

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* {{family Hypocreaceae}}) that grows parasitically on rye and other graminaceous plants انجمادات النجلييات.

- 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:**

```
H       COOH

```

- 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:**

```
O
```

- Lyseric acid

```
O
```

- L-isolysergic acid

```
O
```

- Isolysergic acid
**Ergot:**

- **Ergometrine (ergonovine) structure:**

  ![Ergometrine Structure](image)

  - This alkaloid causes prompt and vigorous contraction of the uterus (**oxytocic action**),
  - As a result, it is used for **prevention of hemorrhage after childbirth**.

**Ergot:**

- **Ergotamine structure:**

  ![Ergotamine Structure](image)

  - Ergotamine is a cyclic peptide containing the following amino acids: α-hydroxyalanine, proline, phenylalanine.
  - The official salt is ergotamine **tartrate**.
  - It is unstable, specially in **aqueous solution** and on **exposure to light**.
  - On hydrogenation, **dihydroergotamine** is produced, which is used as **migraine analgesic (Cafergot® tablets with caffeine)**.
Ergot:

Lysergic acid ethylamide (LSD):
- LSD is a potent psychotic drug.
- It is thought to act by interfering with normal serotonergic transmission.
- The psychic effects are very marked (marks of psychosis):
  I. Perceptual changes (shapes, sounds, colors).
  II. Subjective time alteration {{Living in the past or future; refers to a person's subjective impression of the speed at which time passes}},
  III. A disintegration of the self {{Schizophrenia}}.
  IV. An increase in suggestibility, i.e. {{a person will accept the suggestions of another person and act accordingly}}.

Vinca rosea alkaloids

Vincristine and vinblastine:
- These are obtained from *Catharanthus roseus* (Vinca rosea) which is a Madagascar periwinkle. *Apocynaceae*.
- Now, it is widely cultivated.
- It was used in Europe in folklore medicine for diabetes for centuries and had a reputation as magic plant.
- The alkaloids in this plant are referred to as Vinca alkaloids.
A screening program at the Pharmaceutical company Eli Lilly revealed that this plant extracts inhibited growth of certain types of cancer cells.

Bioassay–guided isolation of extracts of the plant led to the finding of these 2 alkaloids.

The problem with this plant is that the content is too low (500 kg to produce 1 g of vincristine, and the extraction and purification are too complicated).

Content of vinblastine is higher, but it is vincristine that is demanded more.

The generic name {{The chemical name of a drug. A term referring to the chemical makeup of a drug rather than to the advertised brand name under which the drug is sold. A term referring to any drug marketed under its chemical name without advertising}} for it is Oncovine (vincristine, Eli Lily).

Used for acute leukemia, Hodgkin's disease and other lymphomas.

Vinblastine: the other drug which is used for Hodgkin's disease, lymphomas, advanced testicular and breast cancer.

The generic name is Velban

Mode of action: Inhibition of mitosis by binding to tubulin dimers preventing spindle formation by keeping the chromosomes aligned in the middle of the cell, thus preventing assembly of tubules (preventing polymerization).
Vinca Alkaloids

- Mechanism of action
  - Bind to tubulin
  - Prevent polymerization of tubulin thus preventing microtubule formation
  - Chromosomes remain lined up in middle
  - Apoptosis
- Small differences in structure changes toxicity and activity
  - vincristine active in leukemia and is neurotoxic
  - vinblastine active in lymphomas and testicular cancer and is myelosuppressive
  - vinorelbine active in lung cancer and is neurotoxic and myelosuppressive

Biosynthesis of strictosidine-derived terpenoid indole alkaloids

Fig. 222: Biosynthesis of 3αβ-strictosidine
Overview of the pathway to the bisindole alkaloids Vinblastine and Vincristine. Dotted lines: Two or more reactions.

© Joachim Schröder
**Strychnine and Brucine:**

Botanical source: *Nux-vomica*

Seed of *Strychnos nux-vomica* - Loganiaceae.

Very toxic compound which stimulates the CNS, greatly increasing the reflex excitability, presumably by preventing the effect of the chemical signals that control muscle contractions by normally exerting a “switch-off” on them, so it causes spasms.

**Used only for studying the sympathetic and parasympathetic action of drug.**

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**Physostigmine and Neostigmine Alkaloids:**

Biosynthetic origin: *Physostigma venenosum*

Botanical source: seed of *Physostigma venenosum* - Fabaceae.

Common name: Calabar bean.

- Pharmacological effect:

  A reversible cholinesterase inhibitor (parasympathomimetic i.e increases the effect of Acetylcholine).

  **Used in acute open-angle glaucoma (in combination with pilocarpine).**

  1. It increases the contraction of ciliary muscles and 2. increases excretion of aqueous humor 3. decreases intraocular pressure (IOP).

  - Given I.V or I.M for its toxicity, and because it is an unstable compound as it is an (ester and amide).

  - Antidote of choice against *Datura stramonium* poisoning.
Neostigmine:

- Not an indole alkaloid.
  **Action:** normalizes contraction of striated muscles by facilitating nerve impulse (muscles will work better).
  Has a positive charge (4° alkaloid), therefore it is soluble in water. Accordingly, it can be given S.C.

**Uses:**
1. For **diagnosis and treatment** of **myasthenia gravis** (a rare chronic autoimmune disease marked by muscular weakness without atrophy, and caused by a defect in the action of acetylcholine at neuromuscular junctions).
3. To reverse the effect of muscle relaxants e.g. tubocurarine.

**Side effect:** miosis, convulsions, respiratory arrest, bradycardia (all are due to the cholinergic effect).