Alkaloids Derived from Tryptophan

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Calabar Bean, Physostigmas semen, *Physostigma venenosum* Balf., Fabaceae

This **climbing vine** whose trifoliate leaves are reminiscent of a creeping bean **grows wild** along the rivers of **the Gulf of Guinea** (Nigeria, Cameroon, Gabon).

**The seed** is 2-3 cm long and 12-15 mm wide, and has a **shiny brown** tegument. It is odorless, tasteless.

**Constituents.** Alkaloids (0.2-0.3%): (-) physostigmine (=eserine, 0.15%), norphysostigmine, eseramine, physovenine, geneserine.

**Properties and uses**

- **Physostigmine:** a **reversible cholinesterase inhibitor.** It behaves as a **parasympathomimetic causing myosis,** ..., 
- It is **used** only in ophtalmology in **case of glaucoma.**
- In therapy, it is **replaced by synthetic aceticholinesterases,** neostigmine and pyridostigmine.
- Their indications are myasthenia, post-operative intestinal or bladder atony, stubborn constipation, **decurarization.**
ERGOLINE ALKALOIDS
Classification of alkaloids derived from ergoline

They are commonly classified as clavines, simple lysergic acid derivatives, and ergopeptines. It is also possible to classify them as a function of their basic nucleus: ergolines, 8-ergolenes, 9-ergolenes, secoergolines, proergolines (= related structures).

![Chemical structures of ergoline alkaloids](image-url)
ERGOLINE ALKALOIDS, BIOSYNTHETIC ORIGIN (I)

Precursors of the ergoline nucleus

- **Tryptophan** provides the indole nucleus, C-4, C-5, and N-6;
- **mevalonic acid**, via dimethylallyl pyrophosphate, is the origin of C-7, -8, -9, -10, and of the C-8 substituent;
- **methionine** (as S-adenosyl-methionine) methylates N-6.
Biosynthesis of the alkaloids of the ergot of rye: key steps

DMAT formation
Alkylation of tryptophan by dimethylallyl pyrophosphate at C4.

Steps leading to Chanoclavine
DMAT N-methylated and decarboxylated, the -CH$_3$ group (Z) oxidized to a -CH$_2$OH group, the double bond isomerized.

Formation of Agroclavin
The double bond isomerized second time: the Z -CH$_3$ group becomes E, and the -CH$_2$OH group is oxidized to an aldehyde, which reacts with the secondary amine → closure of the D ring.
Elaboration of the Characteristic Tripeptide of the Ergot Alkaloids

The isolation of the ergopeptam (with no cyclol) proves that the hydroxylation at the 2’ position occurs late in the sequence.
Ergot of Rye, 
*Claviceps purpurea* (Fries) Tulasne, Clavicipitaceae

**Secale cornutum**: The resting form of the fungus.

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**Ergotism**

Occurred in Europe for several centuries (X-XIX).

The consequence of the ingestion by humans of the cereals contaminated by the fungus. The disease began with painful inflammation and resulted in numb, blackened, and dry extremities, and sometimes ended with loss at the joint.
Secale cornutum, Constituents

- Biogen amins: tiramine, histamine
- Lipids (40 %)
- Sterols (20-30 %): ergosterol and related compounds
- Pigments: minor and anthraquinone-like constituents (endocrocin, clavorubin); dominant constituents (xanthone dimers or ergochromes).

- **Indole alkaloids** (0.05-1 %)
  - Lyzergic acid derivatives
    - **Simple amides** (20 %, soluble in water): ergometrine, ergine, ...
    - **Ergopeptines** (80 %, insoluble in water): ergotamine, ergocristine, ...
  - Clavin alkaloids: agroclavine, elimoclavine, ...

![Ergonovine](image1.png)  
**Ergonovine** (= ergometrine, ergobasine)  

![Ergine](image2.png)  
**Ergine**
Ergopeptines of Rye

<table>
<thead>
<tr>
<th>R</th>
<th>A: Ergotamines</th>
<th>B: Ergoxines</th>
<th>C: Ergotoxines</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂ Ph</td>
<td>* Ergotamine</td>
<td>Ergostine</td>
<td>Ergocristine</td>
</tr>
<tr>
<td>CH₂ CH(CH₃)₂</td>
<td>α-Ergosine</td>
<td>α-Ergoptine</td>
<td>α-Ergocryptine</td>
</tr>
<tr>
<td>CH(CH₃)CH₂CH₃</td>
<td>β-Ergosine</td>
<td>*</td>
<td>β-Ergocryptine</td>
</tr>
<tr>
<td>CH(CH₃)₂</td>
<td>Ergovaline</td>
<td>Ergonine</td>
<td>Ergocornine</td>
</tr>
<tr>
<td>CH₂CH₃</td>
<td>Ergobine</td>
<td>Ergobutine</td>
<td>Ergobutyryine</td>
</tr>
</tbody>
</table>

* not known
Secale cornutum, Pharmacological Activity

The pharmacological activity of the ergot of rye alkaloids is particularly complex and is due to their analogy with endogenous amines.
Ergometrine (=ergonovine).

- A potent oxytocic: it increases the *basal tone*, and the *frequency* and the *strength* of uterine contractions.

- This activity is thought to be linked to the **stimulation of the α-adrenergic receptors in the myometrium**.

- Uterine hypotonicity is the origin of the **antihemorrhagic effects** of ergonovine. (In practice, *methylergonovine* is the preferred medication. It is more active in the uterus).
Secale cornutum, Pharmacological Activity and Uses II.

Ergotamine.

- At low doses is a potent vasoconstrictor acting by stimulation of the $\alpha$-adrenergic receptors (the serotonergic receptors in case of brain blood vessels).
- The *change in vascular tone* is particularly marked peripherially and in the branches of the external carotid.
- At high doses, an adrenergic antagonist activity appears, which is weak and illustrates the duality in the activities of this compound.
- It is an oxytocic.
Hydrogenated Derivatives of Naturally–Occurring Alkaloids

9-10 hydrogenation greatly decreases the agonist activity at the α-adrenergic receptors and reinforce the potency of adrenergic and serotonergic antagonist activity.

- **9-10-Dihydroergotamine.** It is a vasoregulator „stabilizes the vascular tone”

- **Dihydroergotoxin** (9,10-dihydroergocornine, -cristine, -crintine).
  - It has complex pharmacology (stimulation of central receptors, peripheral vasodilation, regulating activity on the neuronal metabolism).
  - It is *a treatment in case of* behavioral problems due to *senile cerebral insufficiency*. 
Secale cornutum, Pharmacological Activity and Uses IV.

Other Semisynthetic or Synthetic Derivatives

- **Methysergide.** A potent serotonergic antagonist. A basic treatment in migraine headaches.

- **2-Bromo-α-ergocryptine** — postsynaptic dopaminergic agonist → A treatment in case of prolactin-secreting adenomas and in Parkinsonism.

- **LSD** (=Lysergic acid diethylamide): It is a semisynthetic derivative. It is an exceptionally potent psychotomimetic (hallucinogenic) drug. An effective oral dose is from 30 to 50 μg. It acts by interfering with normal serotonergic transmission.
Monoterpenoid Indole Alkaloids
Biosynthetic origin of strictosidine
Biosynthetic origin
Biogenetic homogeneity of indole alkaloids

The part of the polycyclic structure that arises from secologanin is drawn in boldface. For the sake of simplification, only the skeleta of compounds currently used are shown.
Nux Vomica, *Strychnos nux-vomica* L., Loganiaceae

- The nux vomica tree is a species from the south of Asia, with
- indeciduous leaves, whose
- fruit, a corticose berry with an orangy epicarp, contains
- two to five seeds swimming in a white pulp.
Strychni semen

The seed is disc-shaped, and has a rounded edge, somewhat like a button.

With a diameter of 20-25 mm and an average thickness of 5 mm, it is generally light gray and has a silky aspect due to a downy cover of tightly pressed, fine hairs radiating from a central point on each side of the seed.

One side is marked by a radial ridge: the raphe.
**Strichni semen**

**Constituents**

- **1-3 % alkaloids:** *strychnine* (45%) and its dimethoxylated derivative, *brucine* (53%).
- Minor alkaloids with similar structure: colubrines, ijacine, vomicine, novacine, pseudo- and isostrychnine.

![Chemical structure](image)

\[ R_1 = R_2 = H : \text{Strychnine} \]
\[ R_1 = R_2 = \text{OCH}_3 : \text{Brucine} \]
Strichni semen

Effects

• Strychnine produces excitation of all portion of the CNS.

Strychnine intoxication

• It is reminiscent of tetanus.
• Symptoms include anxiety, increased sensitivity to noise, and light resulting in periodic convulsive attacks.
• Death occurs by asphyxia following the contraction of the diaphragm.

Uses

• Strychnine was formerly used mainly to poison rodents.
• It is a barbiturate antagonist which no longer used in therapy.
• The galenicals obtained from the drug were ingredients of replenishing and invigorating „tonic” preparations.
• A few rare proprietary products based on nux vomica tincture are still available.
• S. ignatii Berg. is still used in homeotherapy.
Curares, *Strychnos species*, Loganiaceae

**Calabash-curares**

Extracts of trunk barks of various shrub or vine species of the genus *Strychnos* including *S. toxifera*, *S. castelnaeana*, *S. letalis* and *S. rondetelioides*.

The natives of South America formerly used these preparations, as hunting poisons in forest areas, to coat the tip of blow darts.
Loganiaceae curares – Chalabash-curares

- They owe their activity to **extracts of trunk barks of** various shrub or vine species of the genus *Strychnos* including *S. toxifera*, *S. castelnaeana*, *S. letalis* and *S. rondetelioides*.

- The **active constituents** are symmetrical **bisindoline, bis quaternary ammonium alkaloids** (8-10%), arising from the **doubling of a strychnane-type unit**:

- **C-toxiferine**, C-curarine, C-calebassine.

- They occur alongside „monomeric alkaloids of the strychnane type, or of related types.
Pharmacological activity

- Naturally-occurring curares are *non-depolarizing* (competitive) *neuromuscular blocking agents*.
- They compete with acetylcholine for the cholinergic receptors at the motor end-plate.

Uses

- **Alcuronium chloride** INN (*N,N*-diallylnortoxiferinium chloride), a *semisynthetic derivative of C-toxiferine*:
  - It is used as an adjunct in anesthesia, particularly **to achieve muscle relaxation during surgical procedures**.
  - It is also used in preparations for **tracheal intubations**.
- (Tubocurarine: pharmacological reference product for this class.)
Madagascan Periwinkle, *Catharanthus roseus* (L.) G. Don, Apocynaceae

- *C. roseus* is a **perennial subshrub** with stems (60-80 cm) that are lignified at the base, and with
- **opposite leaves with an oval and entire blade** generally rounded at the apex.
- The **flowers** are showy and reminiscent of those of the periwinkle: **constructed as a type 5**, they are **pink, purple, white**, sometimes ocellate.

- It is **indigenous to Madagascar**, and is widespread in all of the tropical regions of the globe.
- It is planted in western Europe and the U.S.A. and is cultivated as an annual plant because of the rigorous climate.
Catharanthi herba, Constituents

Alkaloids: 0.2-1 %, about 95 constituents.

Indole- or dihydroindole structures:
- **vindoline** (the principal constituent), **catharanthine**, **ajmalicine**, akuammine, locherine, tetrahydroalstonine

Binary alkaloids (~20):
- They are formed by coupling of two “monomeric” alkaloids, an indole, and a dihydroindole.
- **Vincristine** 0.0003 %, > **vinblastine**: they differ by the nature of the subtituent on the $N_a$ of the dihydroindole moiety, which is either formyl group (vincristine), or a methyl group (vinblastine),

![Catharanthine](image1)  
**Catharanthine**

![Vindoline](image2)  
**Vindoline**

![Vinblastine](image3)  
$R = CH_3$: Vinblastine  
$R = CHO$: Vincristine
Pharmacological activity (vincristine és vinblastine)

- They are **antimitotics**.
  - They **bind to** tubulin.
  - They **prevent the formation of the microtubules** required for the formation of the mitotic spindle.
  - Thus these compounds **block the mitosis** and cause an accumulation of cells in the metaphase.
- They are **neurotoxic** (prevent the formation of axon microtubules).
- They are generally **in vitro** inhibitors of the biosynthesis of proteins and nucleic acids.
- They application on cell population leads to an accumulation of the cells in the M and G2 phase, and the effect is lethal in the S phase.
Catharanthi herba

Uses

- Catharanthi herba is only used to extract the binary alkaloids.

- Vincristine sulfate is indicated in combination chemotherapy, especially in the treatment of Hodgkin’s disease, of non-Hodgkin’s lymphoma, of breast cancer, of uterine cancer, of small cell bronchial cancer, and of various sarcomas.

- Vinblastine sulfate is indicated in the treatment of Hodgkin’s disease, of non-Hodgkin’s lymphoma, of advanced testicular cancer, of breast and ovary epithelioma, of Kaposi’s sarcoma, of choriocarcinomas, and in some cases of histiocytosis.

- The treatment is the responsibility of competent and specialized services. In most cases, vincristine and vinblastine are included in complex combination chemotherapy protocols.
Toxicity

**Vinblastine**
- Highly leukopenic,
- It induces gastrointestinal distress (nausea, vomiting, constipation with apparent occlusion),
- Neurological symptoms (headaches, neuritis, loss of the tendon reflexes, depression),
- Respiratory difficulties and alopecia.

**Vincristine**
- Central neurotoxic effects (possible convulsive episodes).
- Peripheral neurotoxic effects (paresthesia, neuralgia, myalgia).
- Digestive effects: (constipation up to paralytic ileus)
- Multiple side effects: alopecia (frequent), and less frequently, dyspnea, brochospasm, headaches, transient blindness, buccal ulcerations, amenorrhea, and azoospermia.

Contraindications
Pregnancy and breast feeding. Both compounds are very irritating.
Common periwinkle, Vincae minoris herba, Vinca minor L., Apocynaceae

The common periwinkle is a perennial, herbaceous plant with trailing stems that occasionally root into the ground, bearing persistent, opposite, and tough leaves with shiny blades.

The flowers have a corolla that is tubular at the base, with five deep blue, spread out, truncated lobes.

The fruit consists of two follicles.

Common in all of Europe. It grows preferentially in cool woods and on shady rocks.
Vincae minoris herba

Constituents
0.3-1.0 % alkaloid (about 40 components)
- eburnan types: vincamine (10 %), vincine, epivincamine, eburnamonine,
- aspidospermane types: vincadifformine, minovincine, vincadine, quedrachamine,
- corynanthean type
Vincae minoris herba

Vincamine

- It increases the cerebral blood flow.
- This circulatory activity could be the result of a metabolic activity: increase in oxygen and glucose consumption.
- This increase in glycolysis, by causing an increase in pCO₂, is thought to be the origin of the vasodilation.

Uses

*Vincae minoris herba*: to extract vincamine

*Devincan (=vincamine)*

- as a geriatrics,
- to treat the physiological and behavioral problems of cerebral senility (attention deficit, memory loss, dizziness)
- to treat the sequelae of cerebrovascular accidents, and of cranial trauma,
- cochlear and vestibular problems,
- retinal symptoms of ischemic origin

Contraindications: cerebral tumors with intracranial hypertension, pregnancy
Rauwolfia = Snakewood, *Rauwolfia serpentina* (L.) Benth. et Kurz, Apocinaceae

Rauwolfia is an evergreen shrub with a big root system and slender stems (0.5-1 m).

The leaves are verticillate, in groups of three to five and have a membraneous blade.

The flowers are small, white or pinkish, pentamerous, and grouped into cymes.

The fruit is a black drupe normally 1-seeded.

Growing wild in India, Pakistan, Burma, Thailand, Malaysia, and all the way to Indonesia, *R. serpentina* is a forest species, which can be cultivated.

**Other Rauwolfias.** The extraction industry also uses various species:

- *R. vomitoria* Afz., an African species with 7-10% of total alkaloids;
- *R. tetraphylla*, a collective species of northern South America and of Central America.
Rauwolfiae radix, Constituents

**Alkaloids** (0.8-3 %; 30 component)

- **Yohimbane-type Derivatives:**
  - six asymmetrical centers, C16,-17,-18 substitutions
  - reserpine: trimethoxybenzoate of methyl reserpate,
  - rescinnamine: trimethoxycinnamate of methyl reserpate
  - deserpidine: trimethoxybenzoate of reserpate,
  - yohimbine, corynanhteine

- **Hetroyohimbane Derivatives** (heterocyclic E ring):
  - ajmalicine; quaternary bases: serpentine and alstonine

- **Dihydroindole Derivatives**: ajmaline
Rauwolfiae radix, Pharmacological Activity

Reserpine ((rescinnamine, deserpidine)):
- antihypertensive activity (peripheral cathecolamine depletion),
- sedative and neuroleptic activity (central neurotransmitter depletion),

Serpentine: antihypertensive activity,

Ajmalicine (=raubasine):
It is an α-blocking spasmolytic, which at high doses inverts the effects of adrenaline, and moderates the activity of the vasomotor centers, especially in the brain stem.
It causes a transient increase of the blood flow to the brain and is slightly anxiolytic.

Ajmaline
(It is toxic and no longer used in France.)
As an antiarrhythmic, it decreases the rate of depolarization of atrial and ventricular cells substantially (decrease in excitability and conduction velocity, increase in refractory period).
**Rauwolfiae radix**

**Uses**
- *Rauwolfias* are used for extraction of alkaloids.
- *Reserpine*
  - in the treatment of arterial hypertension (0,1-1 mg/day, *per os*),
  - earlier it was used as a tranquilizing agent (antipsychotic, 3-10 mg/day),

**Side effects**
Accumulation, parasympathomimetic dominance, drowsiness, nasal congestion, salivary and gastric hypersecretion, paradoxical anxiety, depression, Parkinson-syndrome.

**Contraindications**
Depression, combination with MAO inhibitors or levodopa, peptic ulcer, hypersensitivity to the rauwolfia alkaloids.
IBOGA, *Tabernanthe iboga* H. Bn., Apocynaceae

- Iboga is a shrub indigenous to equatorial Africa, particularly the clearings of the rain forest of Congo and Gabon (delta and banks of the Ogooué river).

- The bark of its big roots contains 5 to 6% indole alkaloids: ibogaine (principal constituent), tabernanthine, ibogaline, and ibogamine.

- In Gabon, the root is used for
  - its antisoporific properties and
  - its ability to increase resistance to fatigue.
  - With a reputation as an aphrodisiac, it has been used during initiation ceremonies.

- Ibogaine is a CNS stimulant, either amphetamine-like or hallucinogenic depending on the dose; it is presented by some as useable in the treatment of opiate and cocaine dependence.

- High doses in humans can cause paralysis and even respiratory arrest. Its neurotoxicity is also well known (high doses induce Purkinje cell degeneracy).

- Ibogaine is prohibited in several countries.
**Voacanga africana** Stapf, *V. thouarsii* Roem. and Schuldt., Apocyanaceae

- The main interest of these African plants (*Voacanga* spp.) is that they produce seeds rich in **tabersonine**.
- Tabersonine is an aspidosperman-type alkaloid and is *used for the semisynthesis of vincamine*.

![Chemical structures and reaction pathways](image-url)
*Ochrosia elliptica* Labill., *O. borbonica* Gmelin, *O. balansae* Bail, Apocynaceae

**Ochrosia species** are shrubs or trees of the islands of the Indian Ocean and Pacific Ocean, and of the Australian continent.

- Their **trunk bark** contains specific **alkaloids**: ellipticine, 10-methoxyellipticine, and heteroyohimbane-type alkaloids (reserpineline, isoreserpineline).

**Ellipticine and 10-methoxyellipticine.**

- They have an **antitumor activity**, but also possess **side effects** that preclude their use in therapy.

![Chemical structure of ellipticine and methoxyellipticine](image)
N-Methyl-10-hydroxyellipticinium acetate

- It is a more active and less toxic compound synthesized.
- It is an anticancer agent which acts by DNA intercalation and resulting stabilization of the complexes formed by topoisomerase II.

**Therapeutic indication**

Metastasized breast cancer.

**Contraindications**

Preexisting renal disease, pregnancy and breast-feeding.

**Side effects**

The risk of hemolysis, which leads to a strict requirement for close medical supervision.

Most frequently: Digestive, neurovascular, and local venous reaction problems.
Cinchona, *Cinchona pubescens* Vahl., Rubiaceae

The genus *Cinchona* comprises about forty species, which are trees reaching, in their natural habitat, 15 to 20 meters in height.

All cinchonas are indigenous to the eastern slopes of the Amazonian Andes (Colombia, Equator, Peru, Bolivia), where they are grow between 1,500 and 3,000 m in areas with substantial rainfall and humidity, and constant temperature.

The leaves, opposite and decussate, have pinnate veins, often reddish, and a petiole, also reddish.

The flowers are regular, white or pinkish, pentamericous, and have a corolla with lobes covered with white hairs; they are grouped in racemes of apical cymes.
Cinchonae cortex Ph. Eur., Ph. Hg. VIII.
Cinchonae cortex, Constituents (I)

- Alkaloids (2-9%)

<table>
<thead>
<tr>
<th>Species</th>
<th>Total alkaloids (%)</th>
<th>Quinine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. calisaya</em></td>
<td>3-7</td>
<td>0-4</td>
</tr>
<tr>
<td><em>C. pubescens</em></td>
<td>4.5-8.5</td>
<td>1-3</td>
</tr>
<tr>
<td><em>C. officinalis</em></td>
<td>5-8</td>
<td>2-7.5</td>
</tr>
<tr>
<td><em>C. ledgeriana</em></td>
<td>5-14</td>
<td>3-13</td>
</tr>
</tbody>
</table>

R = OCH₃ : (-)-Quinine (8S, 9R)
R = H : (-)-Cinchonidine (8S, 9R)

R = OCH₃ : (+)-Quinidine (8R, 9S)
R = H : (+)-Cinchonine (8R, 9S)
Cinchonae cortex, Constituents (II)

- Organic acids (quinic acid).
- Phenolics
  - cinchonaines Ia-d (flavan-3-ols substituted by a caffeic acid), cinchonaines IIa and IIb (cinchonaines Ia [or Ib]–(4→8)epicatechin)
  - proanthocyanidin dimers (B-2, B-5, A-2) and trimers (C-1)
- Dicarboxylic triterpenoid saponins
- Essential oil (0.005%)
Cinchonae cortex, Pharmacological Activity

Quinine

- An antimalarial
  - It is active on the asexual forms: the erythrocytic forms, up to the young trophozoite stage.
  - It is active on *Plasmodium vivax, - falciparum, -malariae*.
  - It is inactive on the sporozoites and tissue stages, and virtually inactive on the gametocytes.
- It is only *modestly* antipyretic and analgesic.
- Its action on the myocardium, as well as of quinidine, but a lesser extent, is a decrease in excitability, conductibility and contractility.
- An uterine contraction stimulant.

Quinidine

- An atiarrhythmic
Cinchonae cortex

**Quinine.** Indications:

1. Malaria
   - the treatment of malaria attacks (particularly in case of resistance to other antimalarials).
   - for prophylactic treatment in case of resistance to other antimalarials.
2. The symptomatic treatment of fevers and aches as well as flu-like states.
3. Older medications with miscellaneous indications: cardiac rhythm abnormalities, palpitations, anguish, precordial pain;

Quinine is **contraindicated** in case of A-V conduction abnormalities.

**Side effects**, at high doses,

- nervous and sensory side effects (partial loss of hearing, ringing in the ears, visual problems),
- abnormalities of intraventricular and A-V conduction, and
- gastrointestinal distress.
Cinchonae cortex

Uses
Quinidine (different quinidine salts)
• to treat cardiac arrhythmias,
• to maintain the sinus rhythm after normalization of atrial fibrillation, flutter, or tachycardia;
• in the case of atrial and ventricular extrasystoles,
• in the preventive treatment of paroxysmal supraventricular tachycardia.

The physician must take into account the contraindications (wave burst arrhythmia, A-V blocks, uncompensated cardiac insufficiency, hypersensitivity to quinidine) and

the drug interactions
  – which constitute further contraindications (ritonavir, antiarrhythmic or other drugs that cause wave burst arrhythmia: bepridil, amiodarone, sotalol, bretylium, disopyramide, vincamime, sultopride), or
  – which are subject to precautions (urinary alkalinizing agents, digoxin, beta-blockers, drugs that lower the blood potassium level, enzyme inducers).

Principal side effects: minor gastrointestinal symptoms, abnormalities in cardiac rhythm or conduction (extrasystoles, wave burst arrhythmia), and hematologic effects.
**CAMPTOTHECA ACUMINATA** Decsne., Nyssacea

- The genus Camptotheca is a monotypic genus of the family Nyssaceae, a small family of the order Cornales (Rosidae).
- The trunk bark, root bark, and the fruits of this large tree indigenous to southeastern China contain 0.01, 0.02, and 0.03% camptothecine, respectively.
- Camptothecine is characterized by a pyrrole[3,4b]quinoline sequence.
- It is biogenetically related to the indole group: strictosidine and strictosamidine (the corresponding lactam) are its precursors;
- The neutral lactam (it does not react with the general reagents for alkaloids and does not form stable salts) is particularly insoluble in conventional solvents.
- Camptotecine have **cytostatic** and **antitumor activity** and substantial toxicity.

![Camptothecine molecule](image)
Synthetic camptothecine analogs

Several compounds with reduced toxicity have undergone preclinical or clinical investigations, or both. Two of them were marketed.

Irinotecan has the following indication: second-line treatment of metastatic colorectal cancer after failure of a previous valid treatment including 5-fluorouracil.

• Irinotecan is metabolized to an active metabolite.
• During human trials, it had a response rate of nearly 25% with a mean survival time of 12 months for metastatic colon cancer refractory to 5-fluorouracil.
• Irinotecan is particularly toxic: neutropenia, acute cholinergic syndrome, nausea, vomiting, and delayed diarrhea.
• The delayed diarrhea and neutropenia can be life-threatening and can make hospitalization in an intensive care unit necessary.

Topotecan is indicated for metastatic ovarian cancer after failure of one or more lines of chemotherapy.

• Because of its toxicity (severe neutropenia and thrombopenia), it is necessary to monitor hematological parameters regularly.
• The clinical trials have shown the best response rates for small cell bronchial cancer (39% for first-line treatment); response rates for other types of tumors are more modest (e.g., 14% for ovarian cancer).
Alkaloids Derived from Phenylalanine and Tyrosine

- Phenylethylamines and simple tetrahydroisoquinoline alkaloids
- Benzyltetrahydroisoquinoline alkaloids
- Phenethylisoquinoline alkaloids
- Terpenoid tetrahydroisoquinoline alkaloids
- Amaryllidaceae alkaloids

- Decarboxylation of l-tyrosine gives the simple phenylethylamine derivative tyramine, which on di-N-methylation yields hordenine, a germination inhibitory alkaloid from barley (Hordeum vulgare; Graminae/Poaceae). More commonly, phenylethylamine derivatives possess 3,4-di- or 3,4,5-trihydroxylation patterns and are derived via dopamine, the decarboxylation product from l-DOPA.
For the shake of clarity, the substituents have been omitted purposely (H or CH$_3$ on the nitrogen atom; OH, OCH$_3$, O-CH$_2$-O, or H on the aromatic carbon atom).
Phenethylamines
Ephedras, Ephedra spp. Ephedraceae

- Ephedras are **dioecious subshrubs**
  - with slender, angular, and striated branches, and
  - with leaves *reduced to membranous scales*.
  - The **female flowers** are *reduced to the ovule* and *surrounded by bracts* that are red and fleshy at maturity.
  - The **male flowers** are grouped in yellowish catkins.

- The **species** that contain substantial quantities of alkaloids are mostly Asian
  - *E. equisetina* Bunge and *E. sinica* Stapf from China,
  - *E. intermedia* Schrenk and C A Meyer, and *E. gerardiana* Wall ex Stapf from India and Pakistan

- The genus is represented in Europe by species with very few alkaloids, for example *E. distachya* L. of the Atlantic coast (shrubby horsetail).
Ephedras

Chemical Composition

- Flavonoids and proanthocyanidins.
- **Protoalkaloids.** These are phenethylamine-type derivatives and their concentration can exceed 2%.
  - The chief constituent is almost always (−)-ephrine [=(1R,2S)-1-phenyl-2-methylaminopropan-1-ol], which represents from 40 to 90% of the total alkaloids.
  - It occurs alongside (+)-pseudoephrine (1S,2S configuration) and the corresponding *nor* and *N,N*-dimethyl derivatives.
- Traces of cyclic compounds: **5-phenyloxazolidines** and ephedroxane (a 3,4-dimethyl-5-phenyloxazolidone).
Ephedras, Pharmacological Activity

**Ephedrine** is an indirect sympathomimetic, a *CNS stimulant similar to amphetamine*.

- Structurally very close to adrenaline, it **triggers the release of endogenous catecholamines from the post-ganglionic sympathetic fibers**.
- It stimulates cardiac automaticity and has a positive inotropic activity;
- it accelerates respiration and increases its intensity; it is a **bronchodilator**;
- it decreases the contractility of the bladder.
- **CNS.** Releasing mediators centrally, has a **stimulating psychic effect**: stimulation of the attention and of the ability to concentrate, decrease in the sensation of fatigue and the need for sleep, and so forth (qualitatively, amphetamine like activity);
- **Side effects** include anguish, tremors, and insomnia.

**Ephedroxane** and **(+)pseudoephedrine** are experimental **anti-inflammatory agents**.
Uses of Ephedrine

Ephedrine hydrochloride

• to treat the acute attack of asthma (as a bronchodilator and analeptic).
  – Its multiple activities,
  – numerous contraindications (coronary insufficiency, arterial hypertension, closed angle glaucoma, hyperthyroidism),
  – drug interactions (MAO inhibitors, tricyclic antidepressants),
  – the required precautions (prostatic hypertrophy, cardiac insufficiency, diabetes),
  – potential adverse effects (tachycardia, headaches, sweating, agitation, insomnia, anxiety),
  – as well as the fact that the effects wear out if the doses are repeated in close time proximity (tachyphylaxis) have led to its infrequent use.

• for its vasoconstrictive properties,
  – in nasal sprays/drops (still available), for the antiseptic and vasoconstrictive treatment of the acute congestion of rhinitis, sinusitis, and rhinopharyngitis.
  – Contraindications: childrens under three years of age (risk of central excitation symptoms); closed angle glaucoma and treatment with MAO inhibitors.
  – Precautions. For hypertensive and coronary patients, Limiting the use of these solutions to a short time is crucial, because they can induce iatrogenic rhinitis.

• for the symptomatic treatment of non-productive coughs (in sirups and other formulations).

• for the topical treatment of ear inflammations.

Ephedrine is a banned stimulant in sports (positive doping control test).
Uses of Pseudoephedrine

Pseudoephedrine hydrochloride/sulphate

- Alone or in combination (with chiorphenamine, ibuprofen, paracetamol, or triprolidine), for the symptomatic treatment of nasal congestion and rhinorrhea (coryza).

- **Contraindicated** in children, in pregnant or breast-feeding women and in patients taking MAO inhibitors.

- They must be **used with caution** in case of hypertension or urination difficulties.

- Pseudoephedrine has a **low toxicity**, but it can cause dryness of the mouth, insomnia, sweating, and anxiety. The onset of tachycardia requires discontinuing the treatment.

- A **banned stimulant in sport** (a risk of positive doping control test).
KHAT, Catha edulis Forsk., Celastraceae

• A shrub of modest size in arid areas (1-2 m), but reaching 10 m in the tropics.
• Leaves: highly polymorphic, indeciduous.
• Also known as Abyssinian tea, it is native to the horn of Africa (but some think that it originated in Yemen).
• It is cultivated in the south-east of the Arabian peninsula (Ta’izz, Yemen), in Somalia, Sudan, Ethiopia (Harrar), and as far as Kenya (Meru district) and Madagascar.
• The leaves are harvested from the tip of the branches in the morning and carefully wrapped (banana leaves, damp paper, plastic) for protection against drying and wilting.
KHAT, Chemical Constituents of Leaves

- Flavonoids, some essential oil,

- **Cathedulines**: complex polyesters of polyhydroxylated dihydroagarofurans (sesquiterpenes). Mw: 600 -1200.

- **Khatamines**: arylalkylamines responsible for the activity of the drug.
  - *In the fresh and young leaves*, the chief constituent is *cathinone* = (S)-α-aminopropiophenone.
  - *In the dried drug and in older leaves*, this (−)-cathinone has been converted to an 80-20 mixture of (S,S)-(+)-*norpseudoephedrine* and (R,S)-(−)-*norephedrine*.
  - *Fresh drug from northern Kenya* also contains the **C6-C4 homologs of these phenyipropylamines**: (R,S)-(+)-*merucathine*, (S)-(+)-*merucathinone*, and (S,S)-(−)-*pseudomerucathine*.
  - The phenylpropylamine content is maximal in the young shoots and appears to depend on the geographical origin.
  - A wide range of variation has been observed for the level of cathinone (9-300 mg/100 g) and of norephedrine and norpseudoephedrine.
KHAT, Chemical Constituents II.

(-)-Cathinone
(+)-Norpseudoephedrine
(-)-Norephedrine

Merucathine
D-Amphetamine
Catheduline E2
KHAT, Pharmacological Activity - Toxicity

- The activity of (—)-cathinone is qualitatively quite comparable to that of D-amphetamine:
  - it causes anorexia, hyperthermia, respiratory stimulation, mydriasis, arrhythmia, and hypertension.
  - This amine *induces the release of catecholamines from storage.*
  - Its effects on the CNS depend in part on the subject’s environment; they are characterized by a subjective and euphoric *sensation of increased energy*, well-being, *self-confidence*, mental acuity, and *ease in thought formation*.
  - Objectively, *slight euphoria* can be observed in a *talkative* and sometimes *hyperactive* subject.
  - Later on, *undesired effects* can appear: *insomnia, nervousness,* and *nightmares*; toxic psychosis in rare cases. *Depression* is then observed, and even schizophreniform or paranoid symptoms.
  - *Psychic dependence:* *moderate,* but common—the use becomes compulsive; *no physical dependence or tolerance*; withdrawal syndrome in heavy abusers only.
  - The tannins in the drug can cause constipation in regular users.
Use of Khat

- The fresh leaves, sold within 24 hours of harvest, constitute a masticatory known for its stimulating properties.
  - In some countries (Yemen), khat use is an ancient custom and it is practiced at social events, thereby strengthening social bonds.
  - In other countries, khat is used mainly to seek the pharmacological effects of the alkaloids (to suppress the appetite and to combat fatigue).
  - Traditionally, the leaves (50-200 g) are chewed one by one, kept in the mouth for a while, then most often spit out.
- In the early 1990s, the number of daily users was estimated to be between two and eight million (northeast Africa, Yemen).
- Khat use is officially forbidden in some countries (Saudi Arabia, Sudan, Somalia) and more or less tolerated in other countries (Yemen, Ethiopia).
- The use of the drug is at the origin of serious socio-economic problems linked to the possible malnutrition, drug-seeking behaviors and its negative impact on agriculture.
- Cathinone is on the list of substances whose production, marketing and use are prohibited.
Peyote, *Lophophora williamsii*, Cactaceae

- **Peyote** is a *globular cactus, fleshy*, composed of rounded lobes and spineless, reaching a maximum of 20 cm in height and 5-10 cm in diameter.
- The fleshy stem is divided into 5-14 prominent ribs, themselves further divided into „tubercles”.
- The **solitary flower** is pink, white or yellow.
- **Peyote grows from the north of Mexico to Texas**, on high limestone plateous.
- Considered a divine plant by the Astecs, this cactus is a **particularly potent hallucinogen**.
Peyote

- The drug consists of the aerial part, sliced and dried in the sun.
- It causes visual hallucinations, due to the CNS activity of a phenethylamine alkaloid, mescaline.
- Constituents:
  - Phenethylamines: include mescaline, and its N-substituted and demethyl derivatives, hordenine, tyramine and its N-methylated derivatives and dopamine.
  - Tetrahydroisoquinolines: anhalamine, pellotine, lophophorine and others.
  - A large amount of mucilage.

Mescaline has clinical effects resembling those of LSD: psychic, cognitive, and physical.
- Main symptoms: A distortion of the perception of shapes, an intensification of colors, auditory hallucinations, a slowing in the perception of time.
- The nature of the effects are highly dependent on the environment and the intellect of the subject.
- Physical symptoms: mydriasis, tachycardia, bradypnea, a sensation of change in temperature, nausea, and possibly agitation and anxiety.
- At high doses: memory loss, hypertensive encephalopathy and intracranial hemorrhage may be observed.
- Th use of peyote and mescaline is disallowed by antidrug law in the USA.
Tyrosine → Tyramine → Hordenine

Dopamine

\[ R-CO_2H \]

\[ R = CH_3 : \text{Anhalonidine} \]
\[ R = H : \text{Anhalamine} \]

\[ R_1 = R_2 = CH_3 : \text{Mescaline} \]

Phenethylamines and alkaloids of peyote (E. williamsii, Cactaceae)
Thank you for your attention!