Pharmacognosy and Phytochemistry

Alkaloids-Part 2

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

- **Amino alkaloids/proto alkaloids and biosynthesis**

  Ephedrine and pseudoephedrine, Cathinone, Mescaline, Capsaicin, Colchicine.

- **Aziridine Alkaloids: Mitomycin C**

Objective

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

Amino alkaloids/proto alkaloids and biosynthesis

- Amino alkaloids are also known as proto alkaloids.
- The nitrogen atom of an amino alkaloid is located in an amino group and is not a member of a heterocycle.

Example are:

1. **Ephedrine and pseudoephedrine**
2. **Cathinone (khat)**
3. **Mescaline**
4. **Capsaicin**
5. **Colchicine**

1. Ephedrine and pseudoephedrine

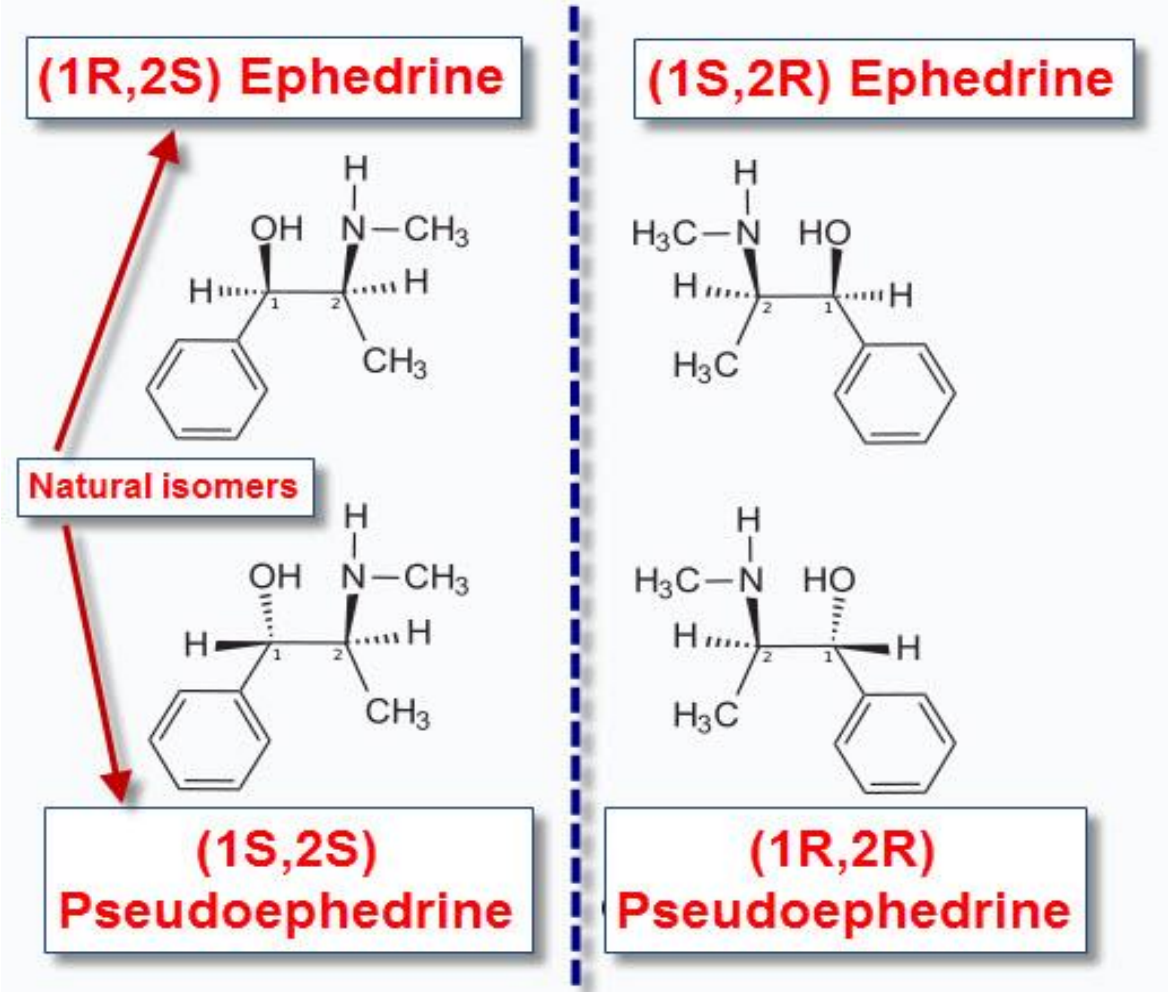
- Ephedrine and pseudoephedrine are obtained from the botanical source ***Ephedra sinica*** and related species.

Ephedra:

- The dried aerial parts of *Ephedra sinica* (Gnetaceae) العلندة ، العليق,ذنب الخيل
- Comes from china where it has been used for treatment of common cold.
- Main sources nowadays are India and Pakistan.
- Collected in autumn season.
- Pseudoephedrine is a sterioisomer of ephedrine.

1. Ephedrine and pseudoephedrine: Structures

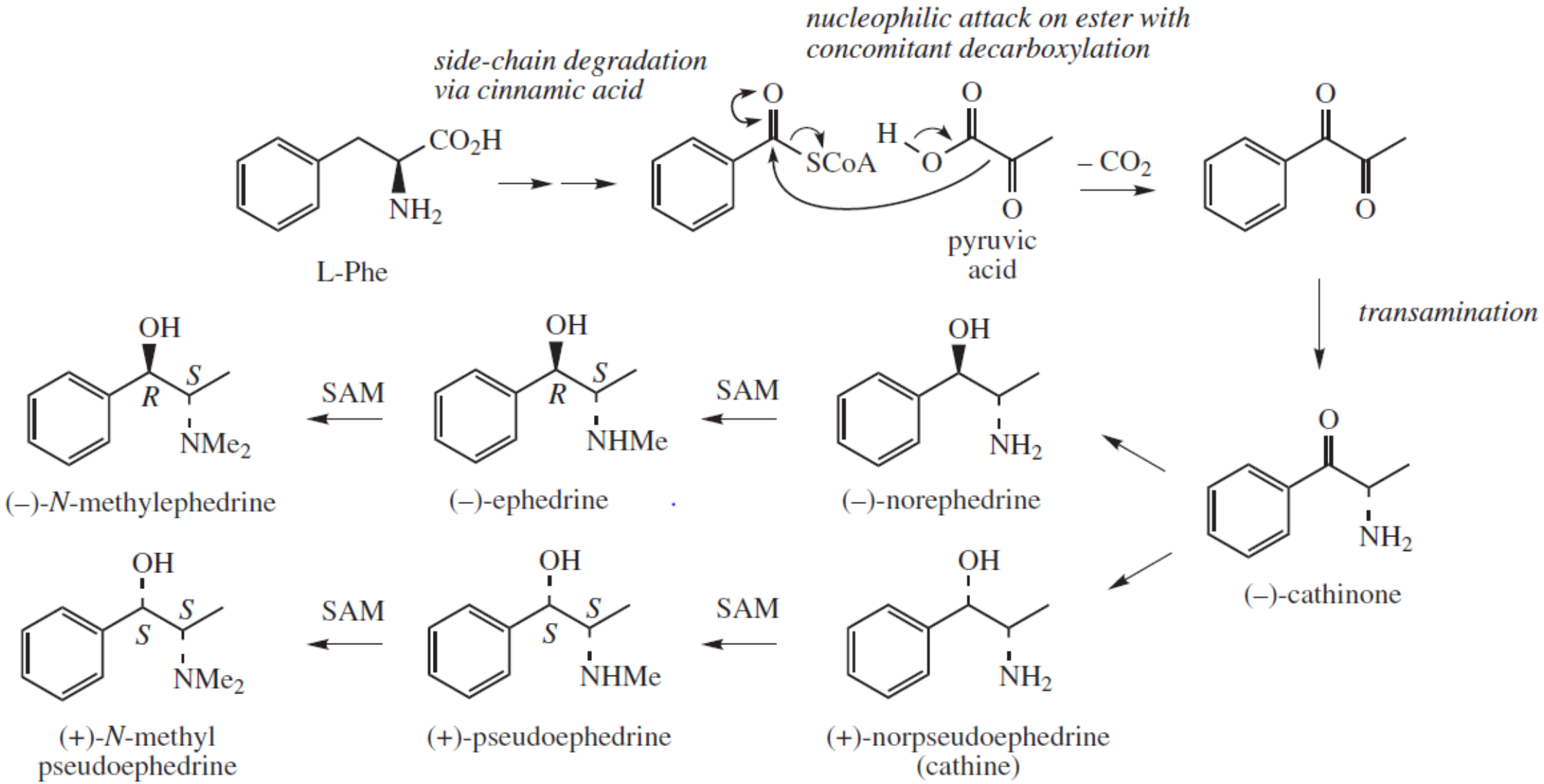
- Ephedrine, as a molecule, having **two chiral** centers. Due to this flexibility in its structure, it can exist in four states (or stereoisomers). They are:
- 1R,2S (-)- Ephedrine
- 1S,2S (+)- Pseudoephedrine
- 1S,2R (+)- Ephedrine
- 1R,2R (-)- Pseudoephedrine



1. Ephedrine and pseudoephedrine: Pharmacological Activity

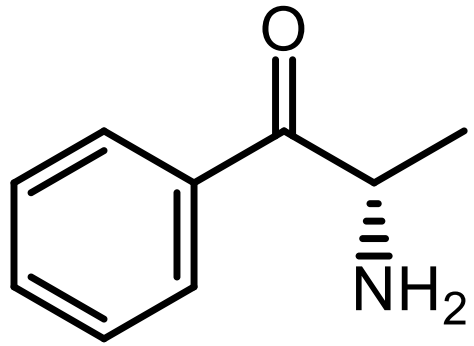
- ✓Ephedrine is a **sympathomimetic**, which means that its effects are similar to those which arise on the **stimulation of sympathomimetic nerves**.
- ✓Ephedrine causes **increased blood pressure** and pulse, contraction of blood vessels, and **dilation of the bronchi**.
- ✓It **stimulates the central nervous** system like amphetamine, but less strongly.
- ✓Ephedrine sulphate and chloride are used as **bronchodilators** in the treatment of asthma and colds.
- ✓Pseudoephedrine has **α-adrenergic activity** and used in treatment of **rhinitis** because of its ability to decrease swelling of the mucous membranes.

1. Ephedrine and pseudoephedrine: Biosynthesis



2. Cathionine (Khat)

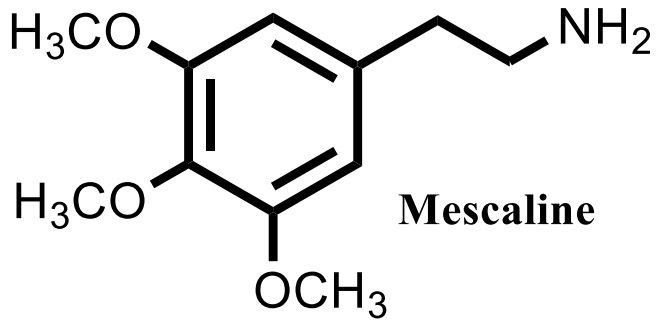
- ✓ It is the **leaf** of *Catha edulis* (*Celastraceae*) الفصيلة الحرابية
- ✓ A shrub or a small tree native to East Africa. It is cultivated in lands of Yemen, Ethiopia and Kenya.
- ✓ Leaves are chewed or used for preparation tea, as a stimulant. **Fresh leaves** are preferred.
- ✓ Khat counteracts **fatigue**, facilitates strenuous muscular work and causes a light elation (pleasure) with talkativeness and sociability.
- ✓ Effect after chewing appears after about half an hour.
- ✓ The effects described above are due to **cathinone**. Its effect is similar to that of amphetamine (Structural similarity).



Cathinone

3. Mescaline

Mescaline or mescalin (3,4,5-trimethoxyphenethylamine) is a naturally occurring **psychedelic protoalkaloid** of the substituted phenethylamine class, known for its hallucinogenic effects comparable to those of LSD and psilocybin.



Mescaline

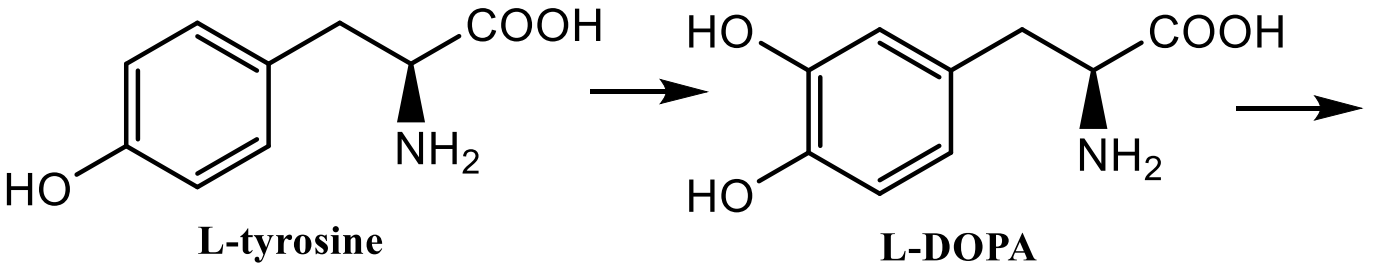
Mescaline is obtained from species of cacti, belongs to the family Fabaceae. Amongst, Peyote cactus (*Lophophora williamsii*) having higher percentage of Mescaline.

Peyote cactus is also known as peyoti, or mescal buttons.

3. Mescaline

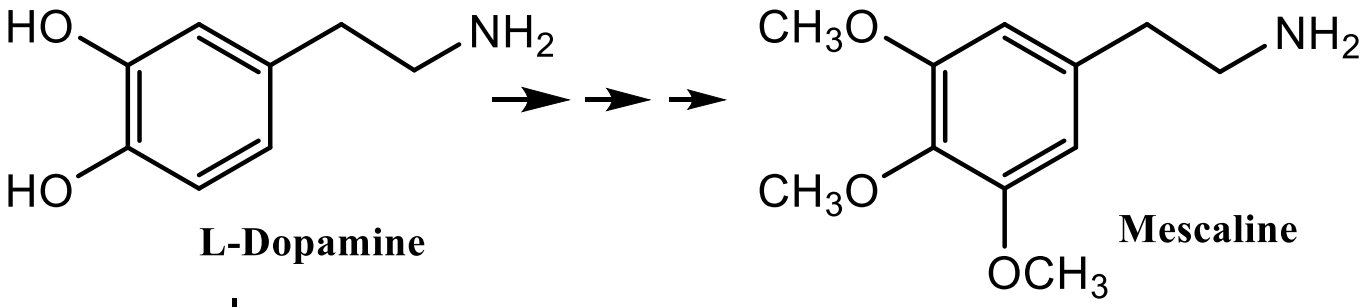
- Mescaline Spineless cactus growing wildly in Northern Mexico, Arizona and Texas, Used by Aztecs and Native American Indians.
- The use by Indians prohibited by anti-drug law.
- Psychic effects - distortion of the perception of shapes and time, auditory hallucinations, and intensification of colors.
- Intensity and the nature of the effects are highly dependent on the environment and the intellect of the subject.
- The doses required to observe hallucinogenic symptoms are 300-500 mg.
- At higher doses - memory loss, hypertensive encephalopathy, and intracranial hemorrhage may be observed.
- Structural similarity to dopamine explains its CNS activity.
- Mescaline stimulates $5HT_{2A}$ serotonin receptor.

Metabolic formation of dopamine, mescaline, noradrenaline, and adrenaline



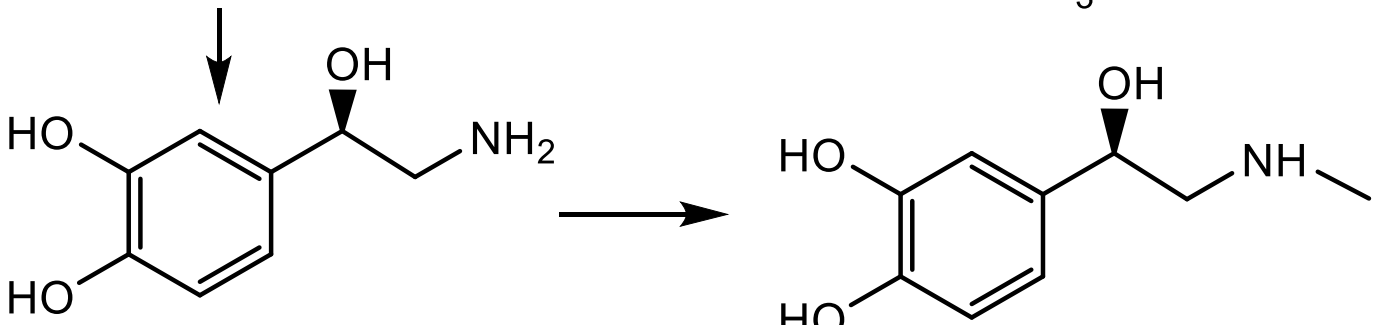
L-tyrosine

L-DOPA



L-Dopamine

Mescaline

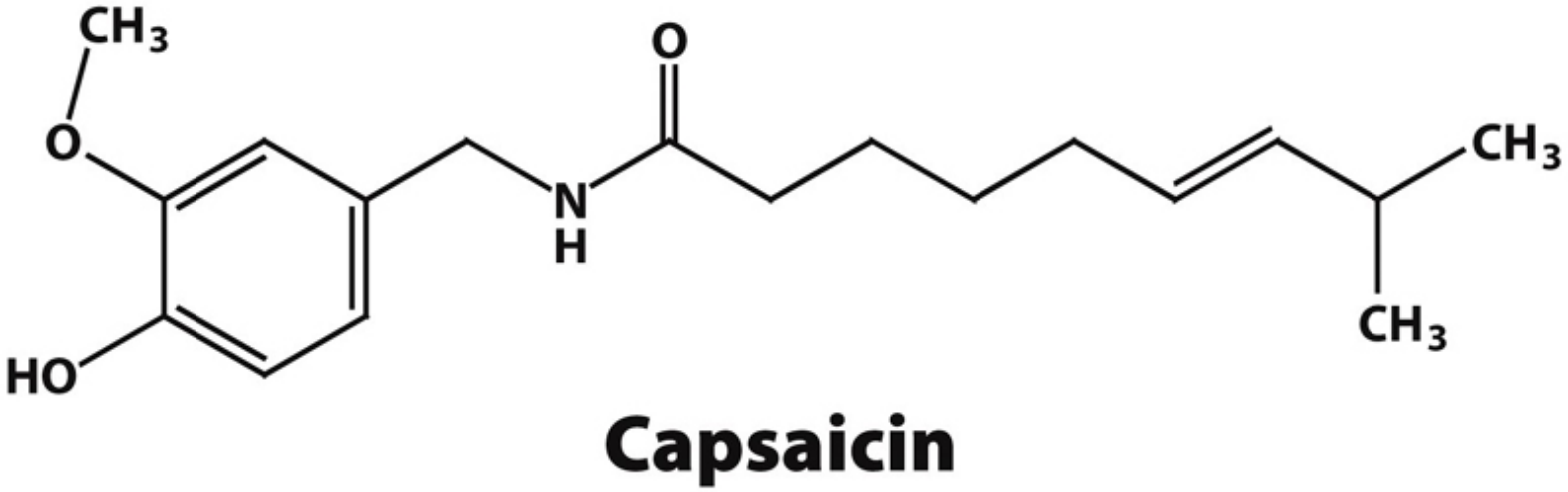


Noradrenaline (norepinephrine)

Adrenaline (epinehrine)

4. Capsaicin

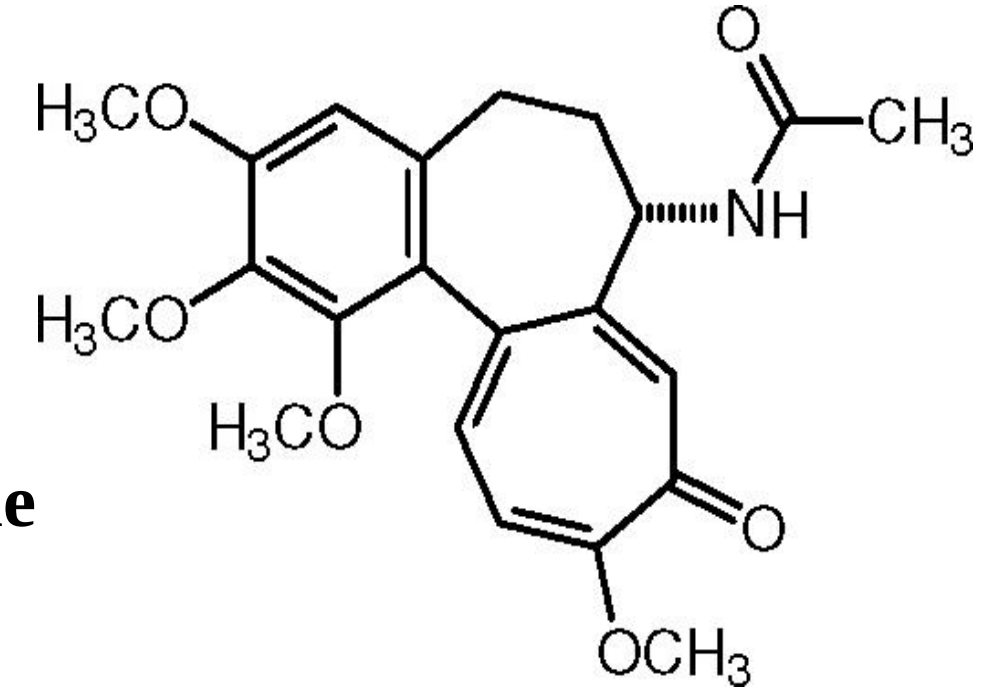
- It is a pungent substance occurring in the fruits of certain Capsicum species (Solanaceae) which causes irritation of the skin (Rubefacient)
- Biosynthetically, it originates from phenylalanine.
- It is used as topical analgesic, anti-inflammatory agent.



Capsaicin

5. Colchicine

- Colchicum seed and corm are derived from the Autumn crocus حلاحor meadow saffron, *Colchicum autumnale*.
- Amorphous, yellow-white alkaloid (darkens on exposure to light), dissolves readily in water, alcohol and chloroform, but only slightly in ether or petroleum spirit.



Colchicine

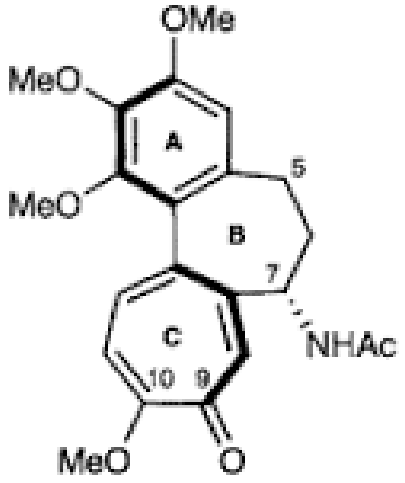
5. Colchicine: Chemistry and uses

- **Colchicine** consists of an aromatic group (A) with three methoxyl groups, 7-membered ring (B) carrying an acetylated amino group, and a tropolone ring (C) whose hydroxyl group is methylated. As the nitrogen atom is part of an amide function, colchicine is less-basic.
- In medicine, colchicine is used as a remedy **against gout**, a disease caused by the disposition of uric acid in the joints.
- It is highly poisonous, and the treatment must be carefully supervised.
- It inhibits division of animal cell, but it is too poisonous to be used to arrest tumor growth.

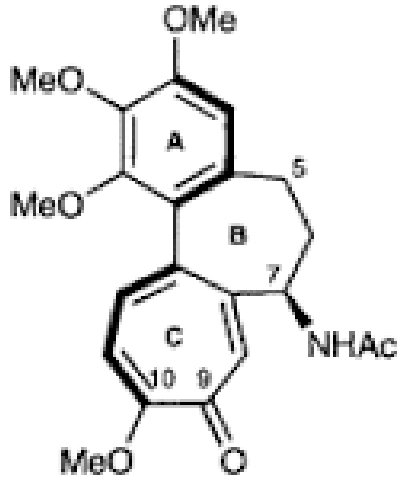
5. Colchicine: Biosynthesis and uses

- **Colchicine's** Ring A is derived from phenylalanine, which also contributes carbon atoms 5, 6 and 7 of ring B.
- The tropolone is derived from tyrosine by ring expansion involving β-carbon atom of tyrosine which becomes C-12 of the tropolone ring.
- The nitrogen atom in colchicine is also derived from tyrosine.
- The methoxyl substituents coming from methionine or methanol.

Atropisomers of Colchicine



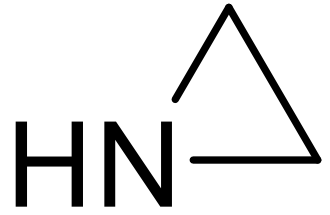
4: (–)-(a*R*,7*S*)-colchicine



5: (+)-(a*S*,7*R*)-colchicine

Aziridine alkaloids

- Aziridines are the nitrogenous analogues of epoxides. The aziridine group is 3-membered heterocyclic with one amine group and two methylene groups.
- The simplest compound is aziridine, which is present in many natural products with anticancer and antibacterial.



Mitomycin C

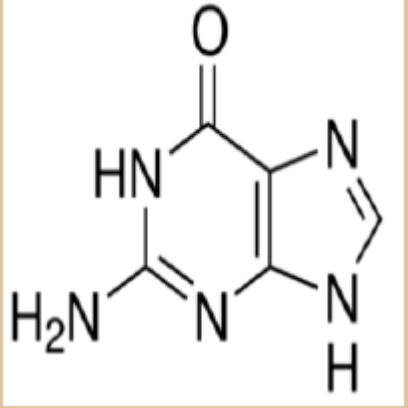
- Mitomycin C is produced by *Streptomyces lavendulae* {a species of bacteria from the genus Streptomyces. It is isolated from soils globally and is known for its production of medically useful biologically active metabolites}.

Mitomycin C

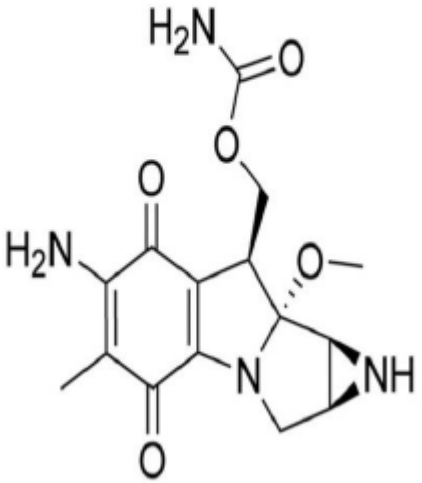
- It is a highly toxic antibiotic with antineoplastic properties which is used for treatment of solid tumors of the bladder, breast, cervix, eye, stomach, and prostate.
- It is a prodrug that requires activation by enzymes such as [1] DT-diaphorase which is an enzyme that targets novel anti-cancer drugs and reduces them for sake of activation, or by the enzyme [2] NADH cytochrome c reductase.
- The **mechanism of action** involves interaction of the aziridine ring with guanine in DNA causing intra-and inter-strand DNA cross-linking, leading to selective inhibition of DNA synthesis, mutagenesis, induction of DNA repair and induction of apoptosis {programmed cell death}.

Structures

Guanine



Mitomycin c



Aziridines having adverse effects:

1. Delayed cumulative bone marrow suppression, and doses have to be adjusted according to the effect on the bone marrow.
2. Renal damage.
3. Pulmonary toxicity.

REFERENCES

Textbooks:

1. **Trease And Evans Pharmacognosy, 16th Edition, 2019, Author: William C Evans, Publisher: Elsevier, ISBN: 978-8131261187.**
2. **Textbook of Pharmacognosy and Phytochemistry 2nd Edition, 2019, Authors: B. Shah, A. N. Kalia, Publisher: Elsevier, ISBN: 978-978-9386217738.**
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.