



Pharmacognesy III

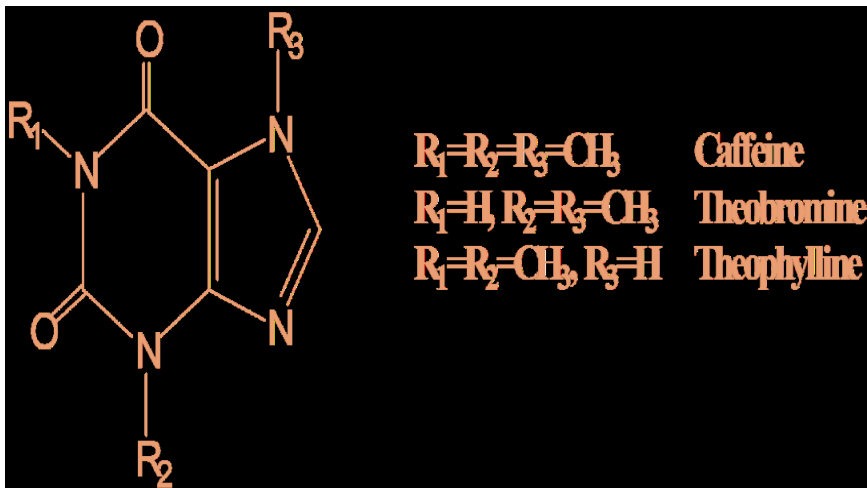
From textbooks: (*Pharmacognesy and Pharmacobiotechnology, 9th ed, Robbers JE, Speedie MK, Tyler VE.*)

Purine (Xanthine) Alkaloids

- The purines are consisting of a six-membered pyrimidine ring fused to a five-membered imidazole ring.
- The pharmaceutically important bases of this group are all methylated derivatives of 2,6 dioxypurine (Xanthine).
- This group includes mainly Caffeine, theobromine and theophylline alkaloids.
- These alkaloids are weak bases, they give no precipitate with Mayer's reagent.



Caffeine, Theobromine and Theophylline



1- Caffeine:

• Occurrence:

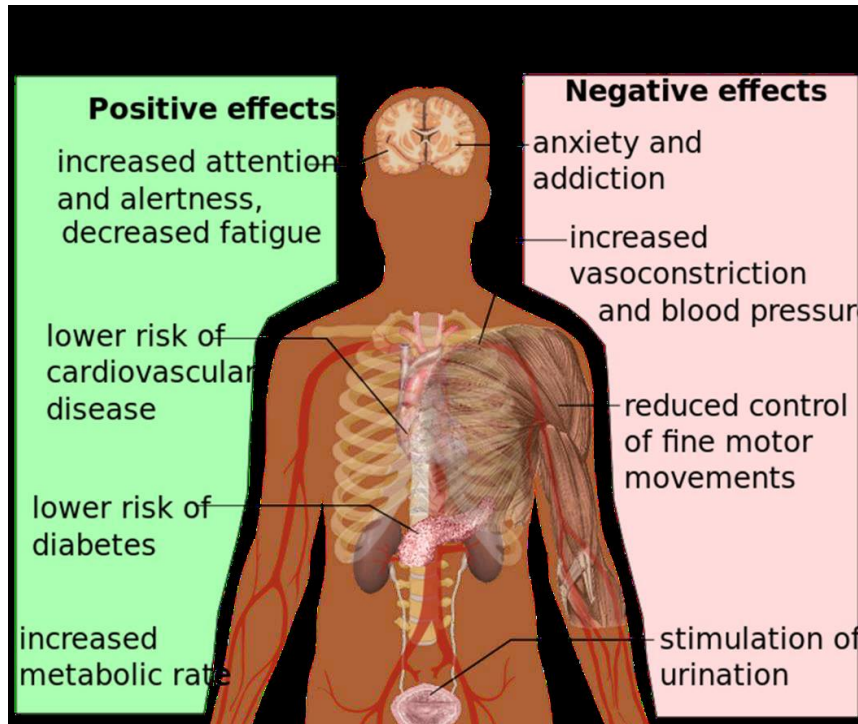
- Tea leaves (2- 5%), Coffee seeds (1-2 %), Cola leaves (2- 3%), Gurana seeds (2.5- 5 %) and Cacao seeds, (0.2- 0.5 %).

- **Properties:** 1- Water soluble. 2- Sublimable.

- **Uses:** Caffeine has a CNS stimulant effect, it is used mainly to relieve headache.

- Inside the body caffeine acts through several mechanisms, but its most important effect is to counteract a substance called adenosine that naturally circulates at high levels throughout the body, and especially in the nervous system.

- In the brain, adenosine plays a generally protective role, part of which is to reduce neural activity levels.
- Adenosine acts as an inhibitor neurotransmitter that suppresses activity in the central nervous system.
- Consumption of caffeine antagonizes adenosine and increases activity in neurotransmission including acetylcholine, epinephrine, dopamine, serotonin, glutamate, norepinephrine, cortisol, and in higher doses, endorphins which explains the analgesic effect to some users.
- At very high doses (exceeding 500 milligrams) caffeine inhibits GABA neurotransmission. This evidence explains why caffeine causes anxiety, insomnia, rapid heart and respiration rate.



2- Theobromine:

- **Occurrence:** Cacao seeds.
- **Properties:** 1- Sparingly soluble in water. 2- Sublimable. 3- Amphoteric.
- In modern medicine, theobromine is used as a vasodilator (a blood vessel widener), a diuretic (urination aid), and heart stimulant.
- Theobromine increases urine production. Because of this diuretic effect, and its ability to dilate blood vessels, theobromine has been used to treat high blood pressure and other circulatory problems including arteriosclerosis, certain vascular diseases, angina pectoris, and hypertension.

- **2- Theophylline**

- **Occurrence:**

Traces in Tea leaves, mostly synthetic.

- **Properties:** Sparingly soluble in water.

- **Uses:**

Theophylline and derivatives are smooth muscle relaxant especially in the upper respiratory tract.

They used as bronchodilator. Theophylline also act as diuretic.

- **Color tests:**

- **Murexide test:** (caffeine, theobromine and theophylline).

- Crystals of caffeine + drops of concentrated HCl and traces of $KClO_3$ → evaporated on water bath → red color is produced which turns to violet on exposure to ammonia vapor.

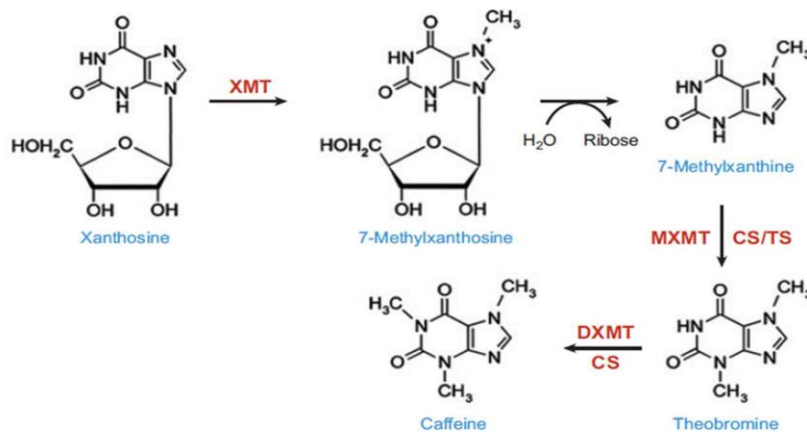
- **Tannic acid test:** (caffeine and theophylline):

- A concentrated solution of the alkaloid + tannic acid → white precipitate is obtained that dissolves in excess of the reagent.

- **Ferrous sulfate test: (theobromine)**
- To a solution of the alkaloid + drops of concentrated HCl + few drops of Br₂ water + a drop of FeSO₄ + few drops of ammonia → Blue color.

Alkaloid biosynthesis in plant

- purine alkaloids



Amino alkaloids or alkaloidal amines

- **General characteristic features:**

1- Proto-alkaloids:

- Have no nitrogen as the part of the heterocyclic ring (nitrogen atom found in side chain), so it is called atypical alkaloids.

2- Derived from amino acid like phenyl alanine or tyrosine.

3- Physiologically active compounds:

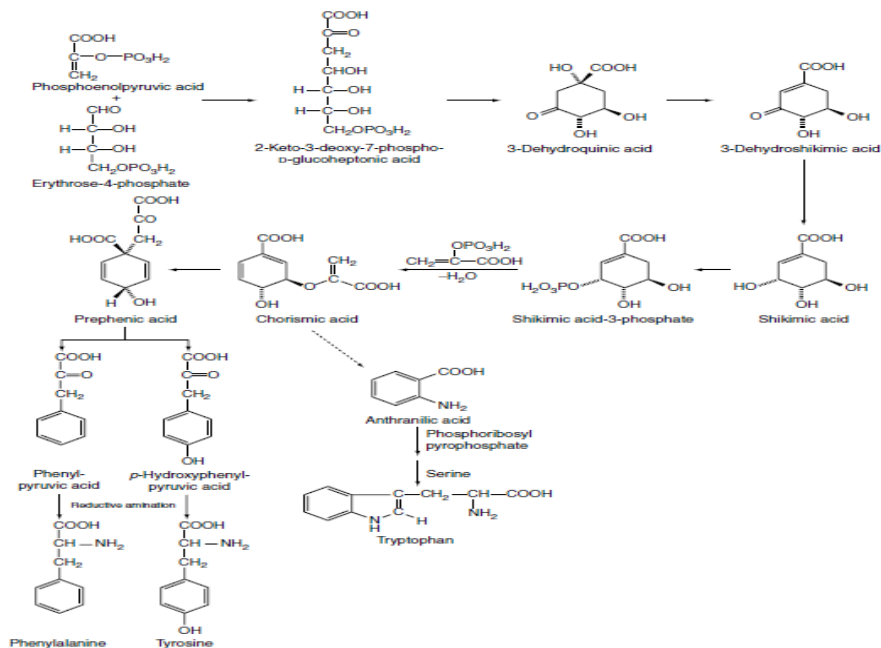
- Ephedrine (*Ephedra* species)
- Colchicine (*Colchicum autumnale*)
- Cathinone (*Catha edulis*).
- Mescaline (*Lophophora williamsii*).

BIOSYNTHESIS OF AMINO ALKALOIDS

- Amino alkaloids are derived from amino acid through shikimic acid pathway.
- The pathway finds its route from carbohydrates for the biosynthesis of C₆-C₃ units (i.e., phenylpropane derivatives) like phenyl alanine and tyrosine.
- Shikimic acid through a series of phosphorylated intermediates yield chorismic acid which is an important branch-point intermediate.
- One branch leads to anthranilic acid then to tryptophan. The other leads to prephenic acid which is the last non aromatic compound in the sequence.

BIOSYNTHESIS OF AMINO ALKALOIDS

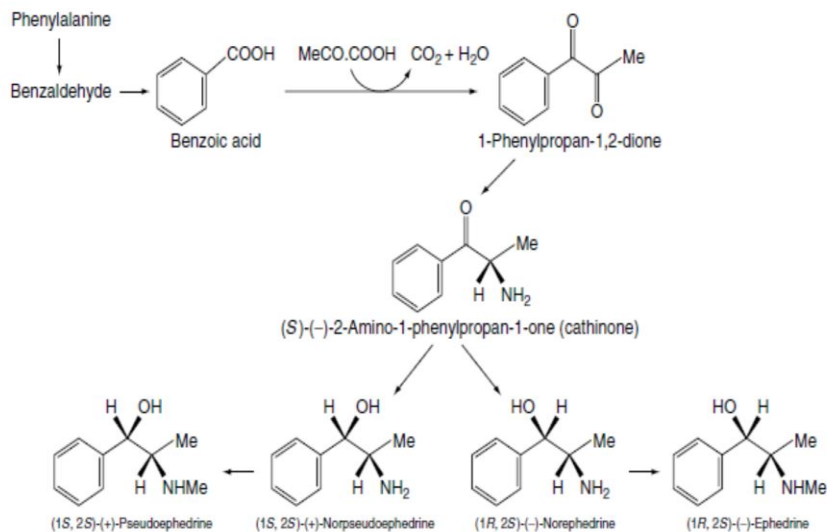
- Prephenic acid can be aromatized in 2 ways.
- The first proceeds by dehydration and simultaneous decarboxylation to yield phenyl pyruvic acid, the direct precursor of phenylalanine.
- The second occurs by dehydrogenation & decarboxylation to give p-hydroxy phenyl pyruvic acid, the precursor of tyrosine.



Plants containing amino alkaloids

1- Ephedra:

- It consists of dried young stems of *Ephedra gerardiana* F. (Ephedraceae).
- Ephedrine is produced either by extraction of plant material or by chemical procedure or could be produced by fermentation of sugar in the presence of benzaldehyde & methyl amine.
- By using ¹³C- and ²H-labelled precursors in feeding experiments have shown that benzoic acid combines with the intact CH₃CO group of pyruvic acid to form ephedrine and related alkaloids with 1-phenylpropan-1,2-dione and (S)-(-)-2-amino-1-phenylpropan-1-one (cathinone) serving as intermediates.



(Biosynthetic pathway of ephedrine)

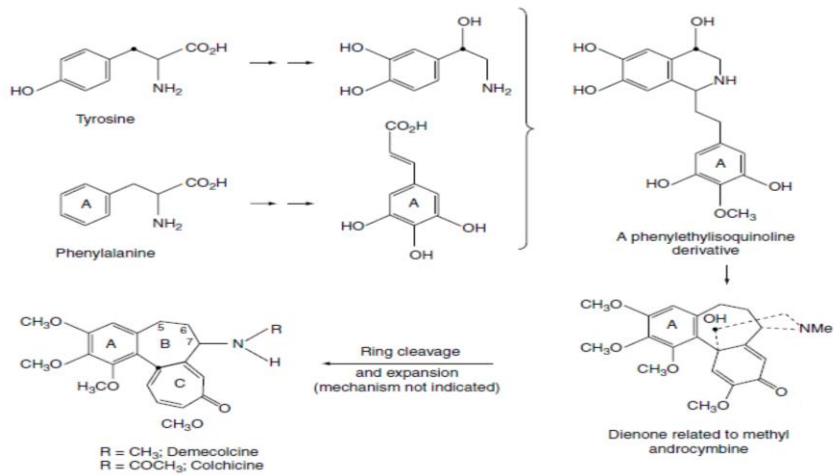
- Ephedrine is an adrenergic compound used as Bronchodilator in asthma, it is a potent Sympathomimetic.
- It excites the sympathetic nervous system cause vasoconstriction, cardiac stimulation & rise in blood pressure.
- It works mainly by increasing the activity of nor epinephrine (nor adrenaline) on adrenergic receptors.
- It is used as a stimulant, concentration aid, decongestant, appetite suppressant & to treat hypotension associated with anesthesia also in the treatment of allergic conditions like hay fever.

2- Colchicum:

- It consists of dried ripe seeds and fresh or dried corms of *Colchicum autumnale* (F. Liliaceae).
- The main alkaloids found in this plant Colchicine which is used in the treatment of gout.
- Colchicine lacks basicity & does not form a well-defined series of salts as do other alkaloids, it is used in gout to increase the secretion of uric acid.



(Colchicum)

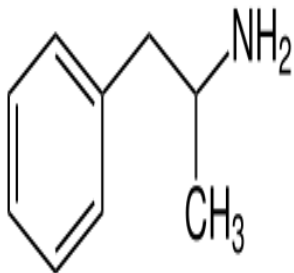


(Biosynthetic pathway of colchicine)

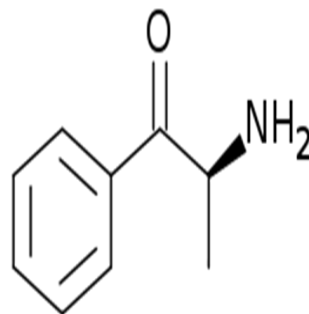
- Ring A and carbons 5, 6 and 7 are derived from phenylalanine; the tropolone moiety arises from tyrosine by ring cleavage followed by closure to give a seven-membered ring.
- In contrast to mold metabolism, acetate does not contribute directly to the tropolone ring but is merely effective in supplying the N-acetyl group.
- An intermediate formed early in the pathway as the result of union of the two amino acids is a 1-phenylethylisoquinoline derivative.

3- Khat or Abyssinian tea:

- This consists of the fresh leaves of *Catha edulis* (F. Celastraceae).
- Khat contains a potent phenylalkylamine alkaloid called (Cathinone).
- It has pharmacologic properties analogous to those of amphetamine and is of similar potency with a similar mechanism of action.
- The alkaloid cathinone, a stimulant, cause excitement, loss of appetite, and euphoria.
- The World Health Organization (WHO) classified it in 1980 as a drug of abuse that can produce psychological dependence, although the WHO does not consider khat addiction to be a serious problem.

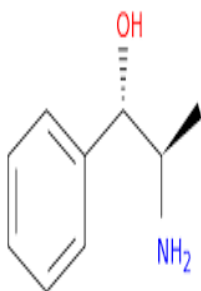


Amphetamine

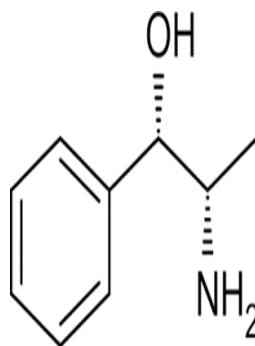


Cathinone

- Cathinone is not very stable and breaks down to produce cathine and norephedrine.
- These chemicals belong to the PPA (phenylpropanolamine) family, a subset of the phenethylamines related to amphetamines and the catecholamines epinephrine and norepinephrine.



Norephedrine

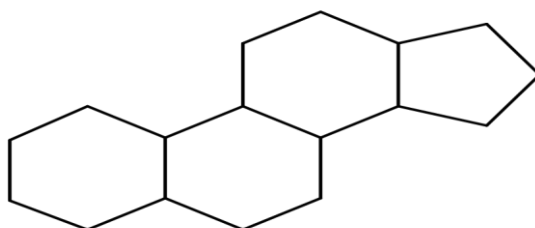


Cathine

Steroidal Alkaloids

- These contain the perhydrocyclopentano-phenanthrene skeleton characteristic of sterols.
- They usually occur in glycosidal combination with sugars and thus called glucoalkaloids e.g. *Solanum* and *Veratrum* alkaloids.

Cyclopentaphenanthrene



1- **Solanum** alkaloids:

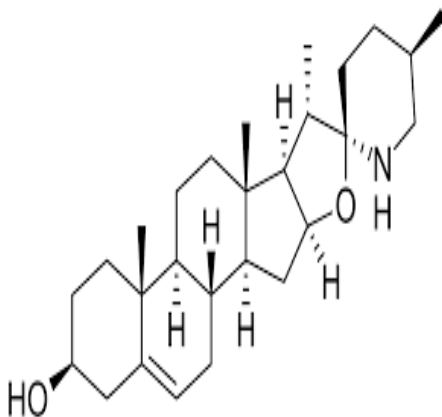
Many plants belonging to *Solanaceae* contains several steroidal alkaloids based on C27 cholestane skeleton such as solasodine , tomatidine, solanidine.

These alkaloids usually occur in genus *Solanum* (*exp. S. nigrum,* *S. oviculare*)

Solasodine is a poisonous alkaloid chemical compound that found in plants of Solanaceae family .

Solasodine and solamargine are glycoalkaloid derivatives of solasodine.

Solasodine is teratogenic used as precursor for the production of steroidal compounds like contraceptive pills.



(Solasodin)

2- *Veratrum* alkaloids (Hellebore):

Contain highly toxic steroidal alkaloids that activate sodium ions channels and cause rapid cardiac failure and death if ingested, all parts of plant are poisonous specially root & rhizomes.

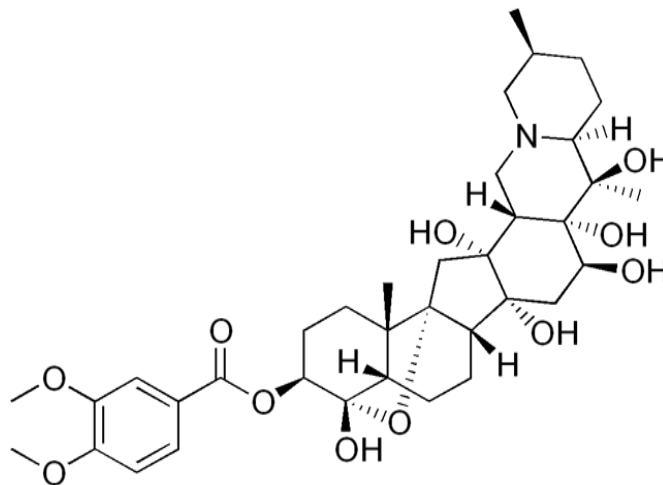
- They are of 3 types:

1. **Group 1** consists of esters of steroidal bases (alkamines) with organic acids like cevadine, germidine, veratridine.

2. **Group 2** consists of glucosides of the alkamine like pseudo jervin & veratrosine.

3. **Group 3** consists of the alkamines themselves like germine, jervine, veratramine

The 1st group only is pharmacologically active & used as hypotensive and cardiac depressant and sedative.



(*Veratridine*)

THANK YOU