College of pharmacy /Al-Nahrain University

3rd stage/ 2nd coarse

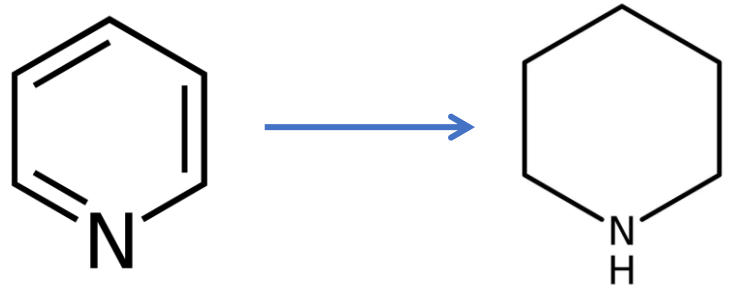
Pyridine-piperidine-pyrrolidine alkaloids

Pharmacognosy-Lecture 2

Lecturer Ayah Al-Qrimli

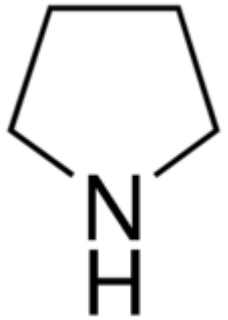
MSc pharmacognosy

Pyridine-piperidine-pyrrolidine alkaloids

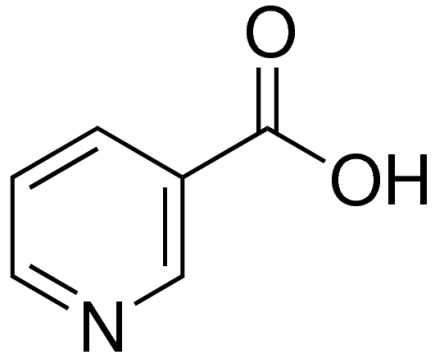


Pyridine
Tertiary base

Piperidine
secondary base



Pyrrolidine

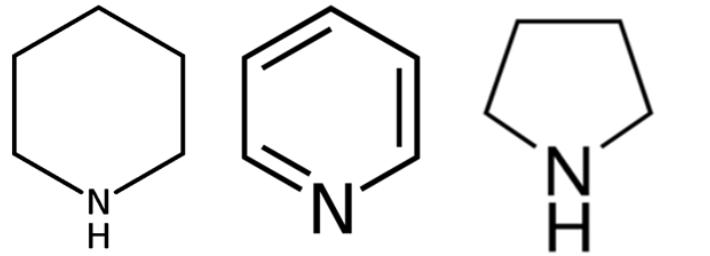


Nicotinic acid

- Upon **reduction** , the **tertiary** base pyridine is converted to the **secondary** base piperidine.
- These two nuclei form the basis for this group which can be divided into :

1- Derivatives of **piperidine** ex: **Lobeline** from lobelia.
2- Derivatives of **nicotinic acid** ex: **Arecoline** from areca.
3- Derivatives of **both pyridine and pyrrolidine** ex: **Nicotine** from tobacco.

Alkaloids are Basic



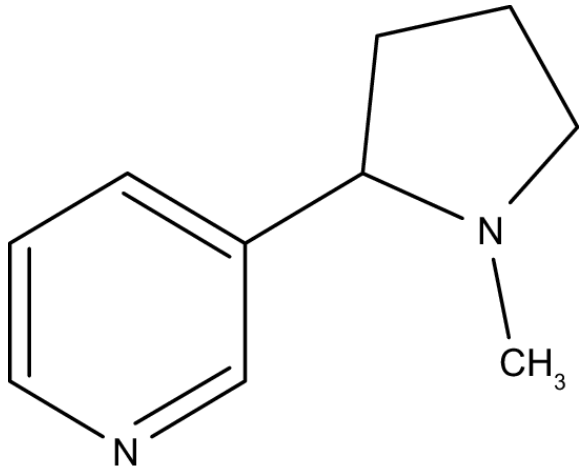
Piperidine Pyridine Pyrrolidine

- **Presence of tertiary or secondary nitrogen**
- **Ability to form salts with acids**
- **Pyridine (weak base, aromatic)**
- **Lone pair participates in aromatic stabilization (resonance)**
- **Aromaticity reduces basicity.**
- **Less available for protonation**
- **Piperidine (strongest base, saturated)**
- **Piperidine Lone pair is *freely available* = Not involved in aromaticity**
- **Piperidine alkaloids are strongly basic and easily form stable salts.**
- **Pyrrolidine**
- **Strong base, slightly less than piperidine**
- **Smaller ring → slightly more steric strain**

Drugs containing pyridine-piperidine alkaloids :
1. Tobacco

- It is the **dried leaves** of ***Nicotiana tobacco*** F: Solanaceae.
- It is cultivated for smoking, it contains alkaloids from **0.6-0.9%**, the main one is **nicotine** which is an **oily liquid alkaloid**,
- It is **colorless liquid** but when oxidized convert to yellow color.



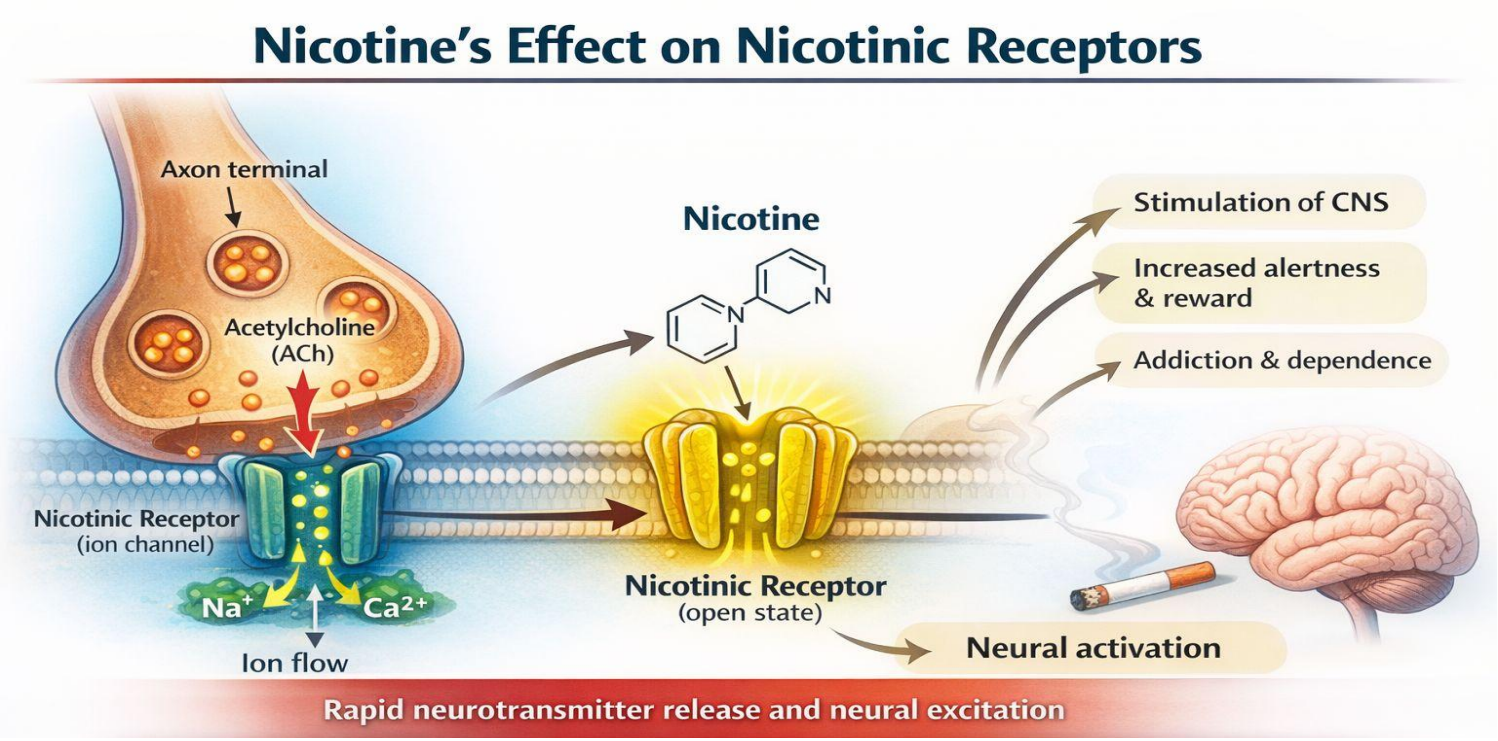


Nicotine



Nicotine effects

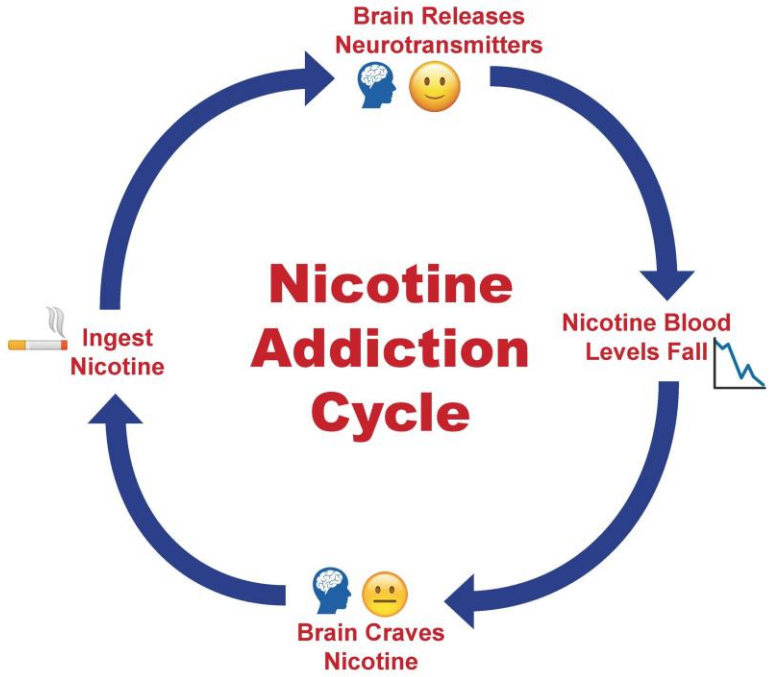
- Nicotine is a **nicotinic cholinergic receptor agonist (mainly in skeletal muscles).**
- Nicotine in **small doses**, can act as **respiratory stimulant** but in **large doses** it causes **respiratory depression** due to **receptor block.**
- **Initial depolarization → persistent depolarization → receptor blockade**





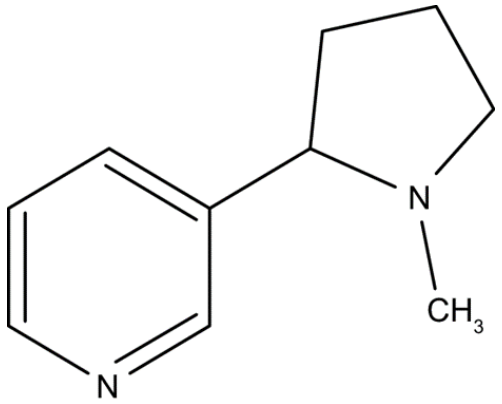
Nicotine effects

- Nicotine is a toxic alkaloid & a dose of **40mg** is said to be **fatal to humans**. **Death results from respiratory paralysis.**
- In lesser doses (an **average cigarette** yields about **1 mg of absorbed nicotine**), the substance acts as a **stimulant** in mammals, while high amounts (50-100 mg) can be fatal.
- This **transients CNS** and **respiratory stimulant effects** is likely to be a **major contributing factor** to the **dependence-forming properties of tobacco smoking.**

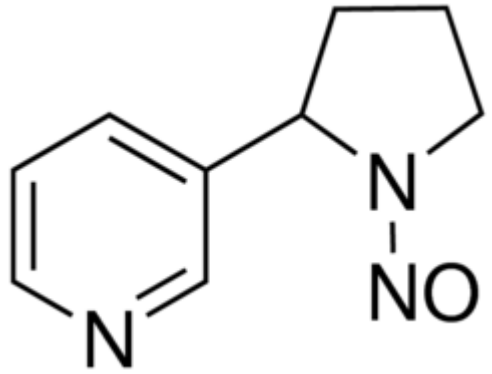




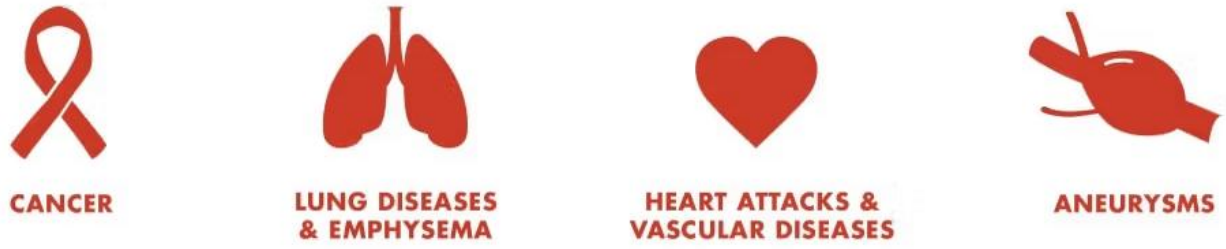
Nicotine effects



- Also, nicotine has pronounced effects on the **cardiovascular system**, where peripheral **vasoconstriction**, atrial **tachycardia** & an **increase in blood pressure** are observed.
- (**Nn receptors in autonomic ganglia and adrenal medulla**)
- It is worth noting that **50% of all smokers' die of heart disease** and **20% of lung cancer.**
- The **carcinogenicity** of tobacco is probably **not due to nicotine** but rather to a far more **potent carcinogen** (**N-nitroso nor nicotine**).
- It is found in cigarettes, cigars and chewing tobacco at levels in range of **2-90pp** parts per billion concentration of N-nitrosamines a

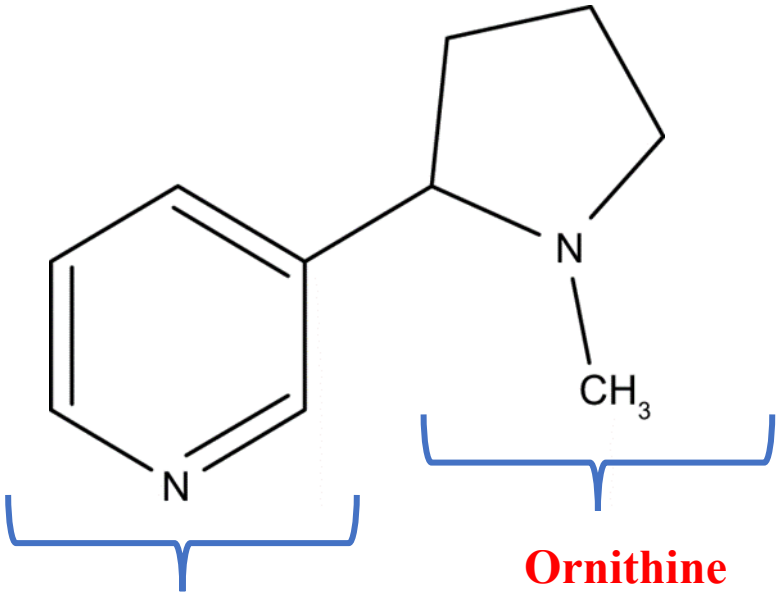


N-nitroso nor nicotine



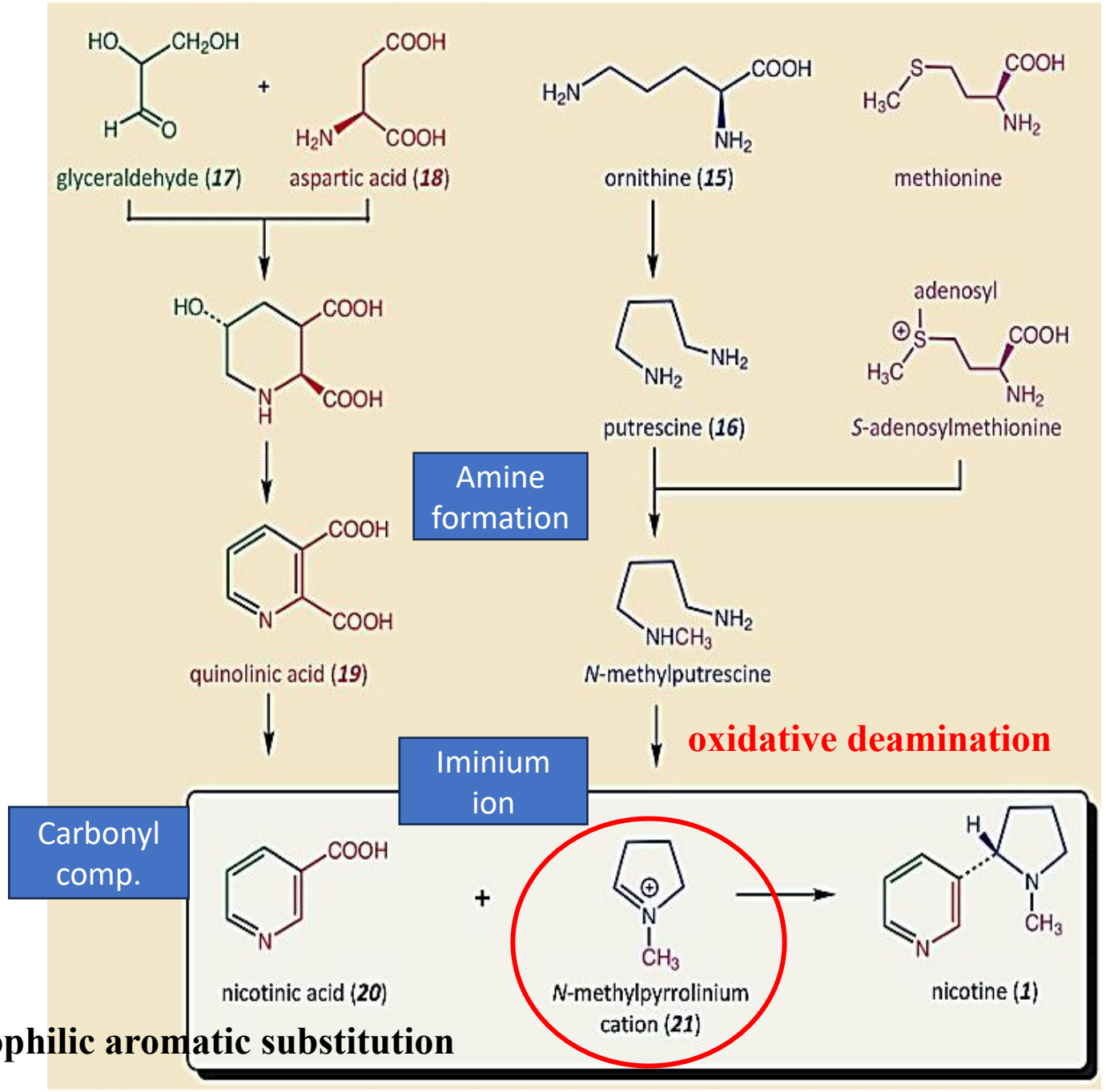
Biosynthetic pathway of Nicotine

- Nicotine is biosynthesized from **Ornithine, aspartic acid** and **glyceraldehyde.**



Ornithine

Aspartic acid & **Glyceraldehyde**



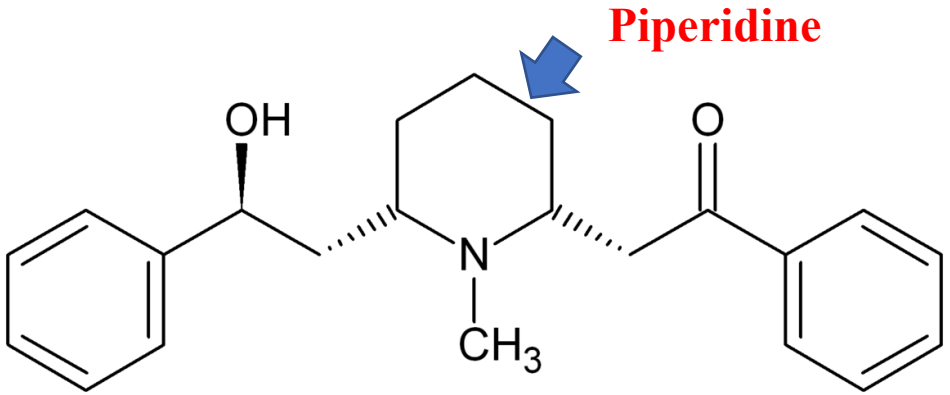
Biosynthesis of Nicotine (pyridine- piperidine alkaloid):

- The biosynthetic pathway leading to this compound is summarized as follows:
- **Ornithine** is incorporated into nicotine by tobacco plants.
- This incorporation result in a symmetric labeling pattern of nicotine.
- **Putrescine** and **N- methylputrescine**, are all incorporated.
- By **oxidative deamination** the amine is oxidized (Ammonia (NH_3) is removed), the **aldehyde is formed** and **Intramolecular Schiff base formation** (key step) takes place
- The **N-methyl-pyrrolinium** ion is the **key intermediate** which, through **electrophilic aromatic substitution (Mannich reaction)** attached to C-3 of the **pyridine ring of nicotinic acid** (**aspartic acid + glyceraldehyde**)

2. Lobelia or (Indian tobacco)

- It is the dried **leaves & tops** of ***Lobelia inflata*** F:Lobeliaceae.
- The drug contains up to 14 alkaloids, of which **lobeline** is the major & most important.
- Lobeline occurs in **colorless crystals** very slightly soluble in water, but readily soluble in hot alcohol.





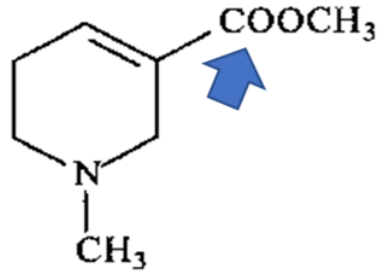
Q/Compare the basicity of lobeline to that of nicotine??

Uses and Dose of Lobeline:

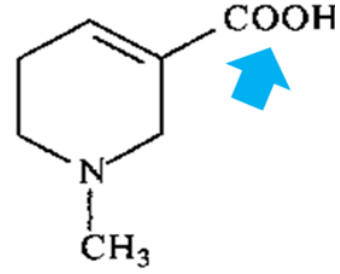
- Preparations of Lobelia were formerly used for **expectorant purposes.**
- Lobeline is a **respiratory stimulant**, but its action is somewhat unreliable and of **short duration of action.**
- **Lobeline effects resemble those of nicotine**.
- For this reason, **0.5 to 1.5 mg** doses of lobeline sulfate are incorporated in **tablets or lozenges** which are intended to aid in **breaking the tobacco habit.**
- Lobeline tab has been used as a **smoking cessation** aid and may have application in the treatment of other drug addictions such as **addiction to amphetamines, cocaine or alcohol**.
- It is also used as **anti-asthmatic.**

3. Areca , areca nut, or betel nut.

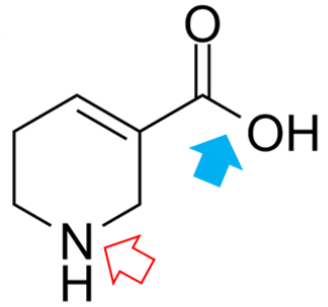
- It is the **dried, ripe seeds or nuts** of ***Areca catechu*** F:Palmae.
- The content of total alkaloids ranges up to 0.45%.
- It is rich in group of alkaloids mainly **nicotinic acid derivatives**:
- **Arecoline** (arecaidine methyl ester),
- **Arecaidine** (N- methyl guvacine),
- **Guvacine** (tetrahydronicotinic acid),
- **Guvacoline** (guvacine methyl ester).
- **Carboxylic acid groups reduce the basicity** of alkaloids by internal salt formation.**(zwitterions).**
- **Ester forms behave as true alkaloid base,** this is why arecoline **is the most active alkaloid in areca nut**



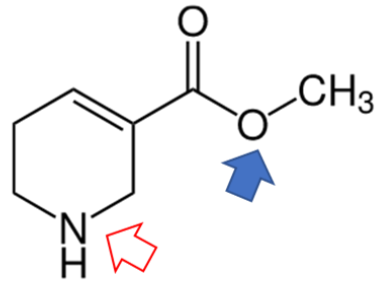
Arecoline



Arecaidine



Guvacine



Guvacoline



Uses:

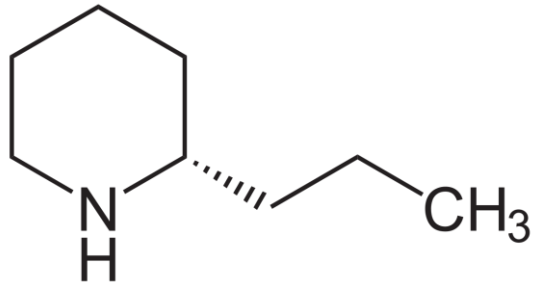
- **Owing to its muscarinic and nicotinic agonist properties (cholinergic)**,
- Arecoline has shown improvement in the learning ability of healthy volunteers. **Since one of the hallmarks of Alzheimer's disease is a cognitive decline, arecoline was suggested a treatment to slow down this process.**
- Arecoline administered intravenously did show modest memory improvement in Alzheimer patients, though due to arecoline's possible **carcinogenic properties**, **it is not the first drug of choice for this degenerative disease.**
- **Despite cholinergic activity, chronic use is associated with carcinogenesis.**
- **Topically:** Arecoline has also been used medicinally as an **anthelmintic** drug against **parasitic worms** especially **Tinea** (used in veterinary medicine).
- Its is biosynthesized from **Aspartic acid** (True alkaloid).



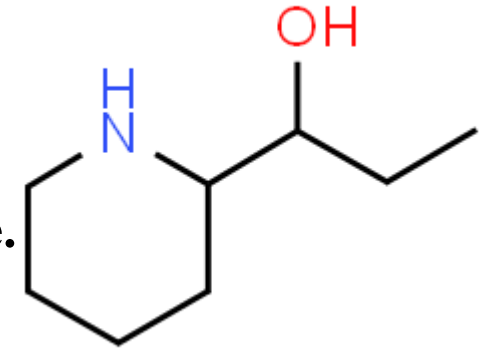
4. Conium (poison hemlock):

- It is the **full-grown unripe fruit** of ***Conium maculatum*** F. Umbellifarea
- It contains number of alkaloids the important of which is **Coniine & Conhydrine.**
- It is used as **anti spasmodic.** However, it's a **very toxic** compound.
- **Like nicotine it has a strong effect on CNS.**
- Mechanism of poisoning involves disruption of the central nervous system, with **death caused by Respiratory paralysis.**
- Socrate the Greek philosopher , Sentenced to death by Athenian court, Execution method: poisoned hemlock
- **Biosynthetic precursor is lysine**
- **differentiate?**

coniine



conhydrine.



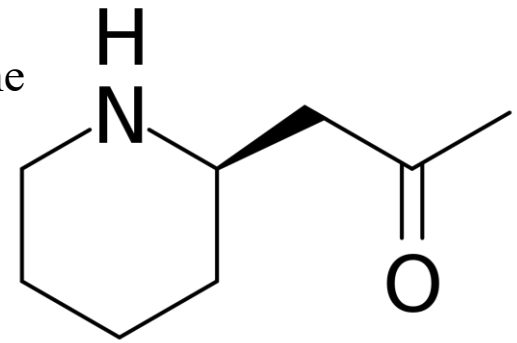


5.Pomegranate



- It is the fruit **root and bark of stem** of ***punica granatum*** F:Punicaceae.
- It contains many alkaloids namely **Pelletierine and pseudopelletierine, together with about 22% of tannin.**
- **Despite containing oxygen, pelletierine remains liquid because** it **lacks strong intermolecular hydrogen bonding** and has a **flexible molecular structure,** It is used as **anthelmintic.**
- Palletrine (piperdine alkaloid) can cause **with NMJ blockade, CNS depression and respiratory paralysis (nicotinic receptor)**
- **Pelletierine tannate (alkaloid base + tannins), a mixture of the tannates of the alkaloids, was included in the BP 1948 and was used as an oral anthelminthic on tapeworms. (intestinal parasites locally in the gut)**
- Tannins **reduce the absorption** of the alkaloid thus **reduces systemic toxicity** and add **synergistic effect** by **precipitation pf parasite protein**
- Is biosynthesized **from lysine**. (**TRUE**)

Piperidine



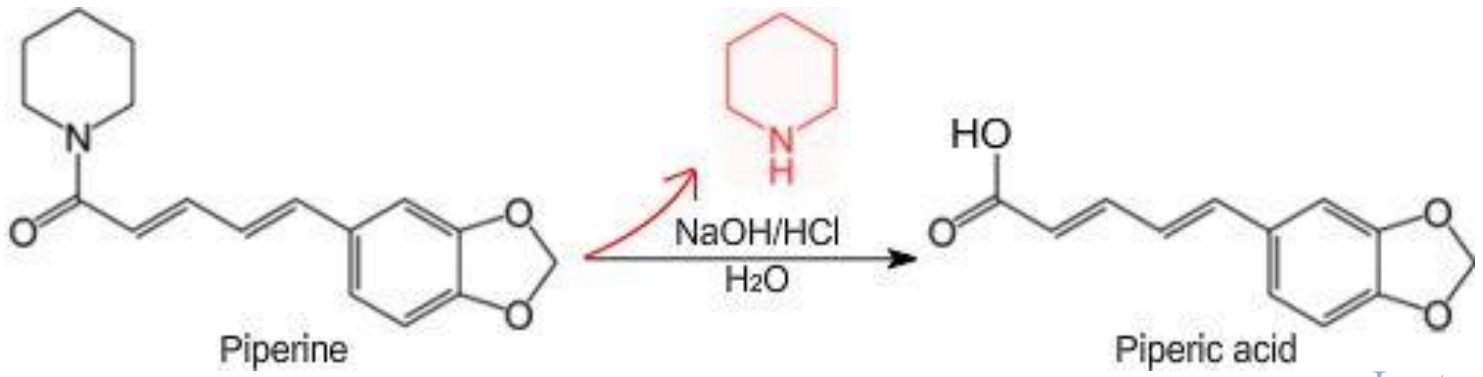
Pelletierine

Strong piperidine base despite the carbonyl No conjugation

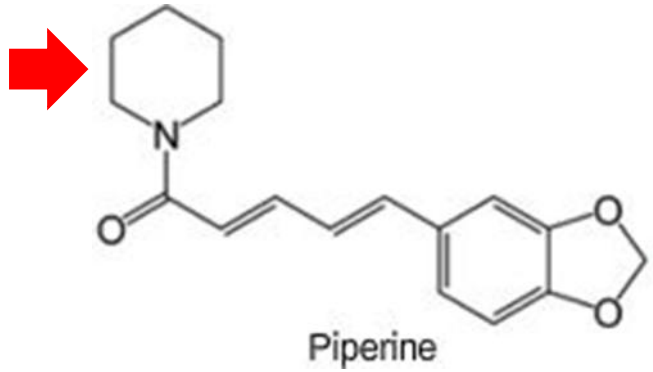
6. Pepper:



- It is the dried **full-grown unripe fruit** of *Piper nigrum* F: Piperaceae.
- It contains up to 4.5-8% of **Piperine.**
- **Piperine, along with its isomer chavicine, is the alkaloid responsible for the pungency of black pepper** and long pepper.
- It has been used as a **condiment** and in some forms of tradition medicine as **anticonvulsant, hepatoprotective** and as an **insecticide**.
- Used as **bioavailability enhancer of drugs** (curcumin, rifampicin, etc.) Curcumin formulations and Modern herbal supplements
- On hydrolysis of Piperine, we get **piperidine** and piperic acid.

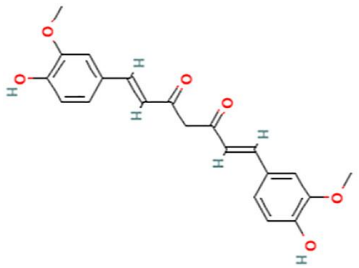


Piperine



- Although **piperine contains a piperidine moiety**, its nitrogen exists in an **amide form**, **making it weakly basic**; therefore, **unlike other piperidine alkaloids, piperine behaves almost as a neutral compound.”**
- **Piperine → does not form stable salts easily**.
- Because piperine is:
- Mostly **unionized** it is **Lipophilic (Crosses membranes easily)**
- **Inhibits CYP450 enzymes**
- **Inhibits P-glycoprotein**
- The **low basicity** of piperine contributes to its high **lipophilicity** and **bioavailability-enhancing effect**





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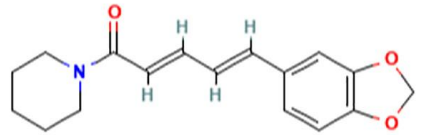

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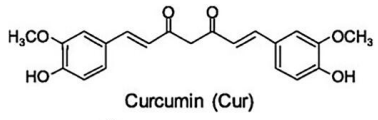
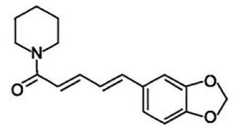


Curcumin (Cur)



Piperine (Pip)



+



=



Curcumin + Piperine

Curcumin

+

Piperine

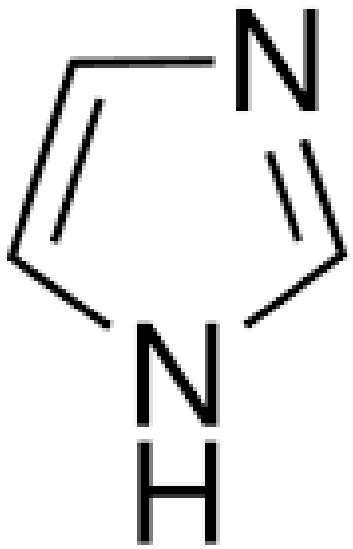
=

Curcumin + Piperine (bioavailability in-creases by 2000%)

X

Glucuronidase in intestine and liver

Curcumin metabolism and its urine excretion

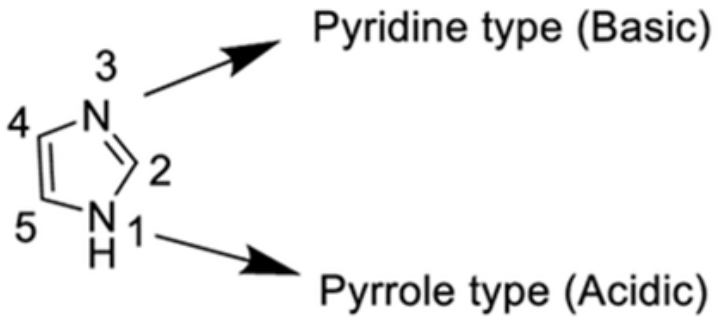


Imidazole alkaloids

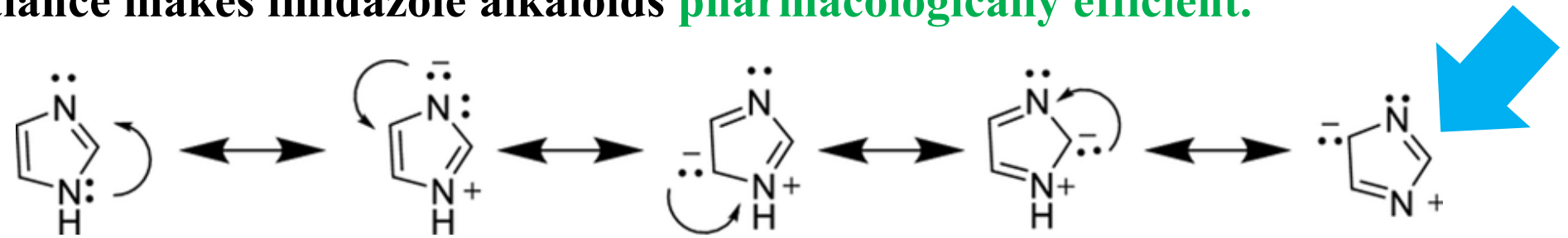
- The imidazole ring is the principal nucleus in this group. The most important drug of this group is **pilocarpine.**

Imidazole alkaloids

- Imidazole contains two nitrogen: a **pyridine-like basic nitrogen without hydrogen** and a **pyrrole-like non-basic** nitrogen **bearing hydrogen.**
- Protonation occurs at the pyridine-like nitrogen **(basic),** and the resulting cation is stabilized by resonance



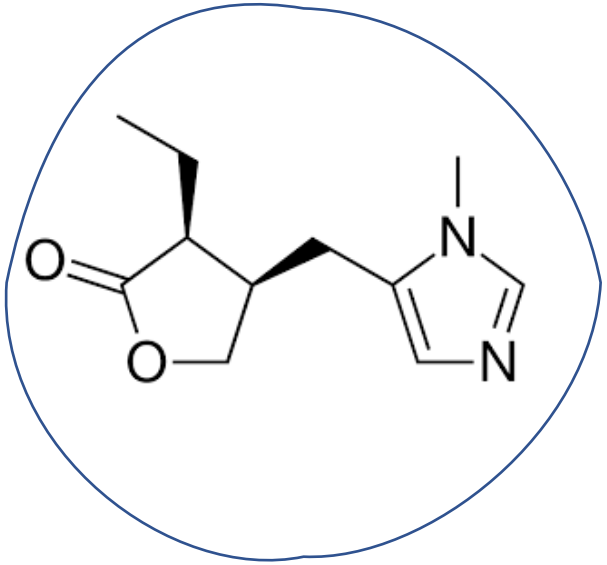
- **Pyridine-like N → basic**
- **Pyrrole-like N-H → non-basic (lone pair in aromaticity)**
- **Only one nitrogen can accept a proton.**
- Imidazole alkaloids show **moderate physiological basicity.**
- **At physiological pH, imidazole alkaloids exist partly ionized and partly unionized.**
- **Ionized form → receptor binding**
- **Unionized form → membrane penetration**
- **This balance makes imidazole alkaloids pharmacologically efficient.**



Pilocarpine

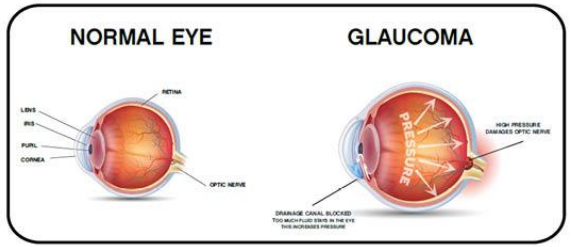


- Pilocarpine is an alkaloid obtained from **leaflets** of *Pilocarpus jaborandi* , P: Rutaceae.
- All the commercial kinds of Pilocarpus when **freshly dried** yield 0.5-1% of the alkaloid pilocarpine.
- Recommendation: **Even under ideal storage conditions**, the **leaves lose at least half of their alkaloidal contents in one year through deterioration. (must be used fresh in a year)**
- **Leaves that are two years old are practically worthless.**
- **The active parts in the structure of pilocarpine are the lactone ring** and **imidazole ring.**

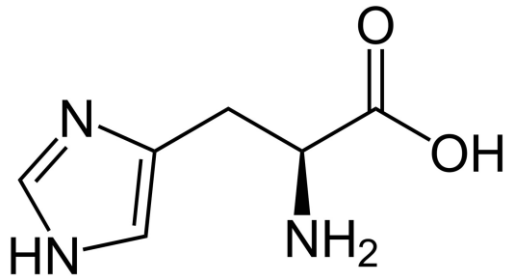


Pilocarpine

Uses of Pilocarpine



- Pilocarpine stimulates the **muscarinic receptors in the eye**, **causing constriction of the pupil (miosis).**
- It is a **non-selective muscarinic receptor agonist in the parasympathetic nervous system**, which acts therapeutically at the muscarinic acetylcholine receptor **M3** due to its topical application, e.g., **in glaucoma**.
- It is **a cholinergic drug**, found **as eye drop & ointment used in the treatment of glaucoma.**
- The most common concentration for this use is pilocarpine **1%.**
- It is on the World Health Organization's **List of Essential Medicines** a list of the most important medication needed in a basic health system.
- Structural studies suggest that pilocarpine is formed from **histidine.**





Uses of Pilocarpine

- Pilocarpine is used to **stimulate sweat glands in a sweat test to measure the concentration of chloride and sodium that is excreted in sweat. It is used to diagnose cystic fibrosis.**
- Pilocarpine **stimulates the secretion of saliva and sweat. It is used to treat dry mouth (xerostomia)** , which is also as a side effect of radiation therapy for head and neck cancer.



THANK YOU

