ALKALOIDS
Learning Objectives

- Definition of alkaloid drugs
- Classification of alkaloid drugs
- Distribution, localization and function of alkaloids drugs.
- Physicochemical properties of alkaloids drugs.
- Extraction, detection, identification and characterization of alkaloids drugs.
- Biosynthetic origin of alkaloids drugs
- Pharmacological activity and uses of alkaloids drugs.
- Official names, synonyms biological sources, chemical constituents, uses, precautions, adverse reactions, contraindications and toxicity of some selected drug contain alkaloids.
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- Physicochemical properties of alkaloids drugs.
- Extraction, detection, identification and characterization of alkaloids drugs.
- Biosynthetic origin of alkaloids drugs. Pharmacological activity and uses of alkaloids drugs.
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References

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ALKALOIDS
The concept of alkaloid is relatively recent, the knowledge of the toxicity and properties of the plants containing them dates back to ancient times: opium, colchicum, belladonna, cinchona, ipecac and others have been used for centuries.

From 1803 till the second half of 20th century, many alkaloids have been isolated. Chemists attempted to elucidate the structure of these molecules very early on and they succeeded in some cases.

Today, advanced NMR-techniques and X-ray diffraction spectrometry allow the elucidation of most of complex structures.

Now, many alkaloids can even be synthesized and studies on their SAR, structural, biosynthetic, synthetic or pharmacological data are available.
Definition: The term “alkaloid” (alkali-like) is commonly used to designate basic heterocyclic nitrogenous compounds of plant origin that are physiologically active.
Deviation from Definition

- **Basicity:** Some alkaloids are not basic e.g. Colchicine, Piperine, Quaternary alkaloids.

- **Nitrogen:** The nitrogen in some alkaloids is not in a heterocyclic ring e.g. Ephedrine, Colchicine, Mescaline.

- **Plant Origin:** Some alkaloids are derived from Bacteria, Fungi, Insects, Frogs, Animals.
New Definition

Alkaloids are cyclic organic compounds containing nitrogen in a negative state of oxidation with limited distribution among living organisms.
Classification of Alkaloids

- **True (Typical) alkaloids** that are derived from amino acids and have nitrogen in a heterocyclic ring. *e.g.:* Atropine

- **Proto alkaloids** that are derived from amino acids and do not have nitrogen in a heterocyclic ring. *e.g.:* Ephedrine

- **Pseudo alkaloids** that are not derived from amino acids but have nitrogen in a heterocyclic ring. *e.g.:* Caffeine

- **False alkaloids** are non alkaloids give false positive reaction with alkaloidal reagents.
Trivial names should end by "ine". These names may refer to:

- The genus of the plant, such as Atropine from Atropa belladona.
- The plant species, such as Cocaine from Erythroxylon coca.
- The common name of the drug, such as Ergotamine from ergot.
- The name of the discoverer, such as Pelletierine that was discovered by Pelletier.
Pharmacological Action & Uses

**CNS (Central nervous system) Action:** stimulants (caffeine) or depressants (Depressants are commonly used to reduce anxiety) (morphine)

**ANS (Autonomic Nervous system; Heart rate, respiratory rate etc):** Sympathomimetics (ephedrine) or sympatholytics (yohimbine, ergot alkaloids), parasympathomimetics (pilocarpine), antichol Anergics (choline), ganglioplegics (nicotine).

**Also:** Local anaesthetics (cocaine), defibrillation (quinidine), anti-tumour agents (ellipticine), anti-malarial (quinine), anti-bacterials (berberine), and amoebicides (emetine).
Alkaloids are produced in plants by basic substances and reactions well-known in organic chemistry.

Biosynthetic origin cannot be discussed in general terms for all alkaloids, instead it has to be covered separately for each of the major groups of alkaloids.
The physiological action, such as Emetine that acts as emetic, Morphine acts as narcotic.

A prominent physical character, such as Hygrine that is hygroscopic.
Occurrence

- Rare in small plants.
- Dicots are more rich in alkaloids than Monocots.
- Families rich in Alkaloids: Apocynaceae, Rubiaceae, Solanaceae and Papaveracea.
- Families free from Alkaloids: Rosaceae, Labiatae
Distribution in Plant

- All Parts e.g. Datura
- Barks e.g. Cinchona
- Seeds e.g. Nux vomica
- Roots e.g. Aconite
- Fruits e.g. Black pepper
- Leaves e.g. Tobacco
- Latex e.g. Opium
Forms of Alkaloids

- Salts with Organic acids e.g. Oxalic, Acetic acids
- Salts with inorganic acids e.g. HCl, H₂SO₄.
- Salts with special acids: e.g. Meconic acid in Opium, Quinic acid in Cinchona
Alkaloids Function in Plants

- They may act as protective against insects and herbivores due to their bitterness and toxicity.
- They are in certain cases, the final products of detoxification (waste products).
- Source of nitrogen in case of nitrogen deficiency.
- They, sometimes, act as growth regulators in certain metabolic systems.
Physical Properties

Condition

- Most alkaloids are crystalline solids.
- Few alkaloids are amorphous solids e.g. emetine.
- Some are liquids that are either:
  - Volatile e.g. nicotine and coniine
  - Non-volatile e.g. pilocarpine and hyoscine.
- MW: 200–900 amu
Physical Properties

Color

The majority of alkaloids are colorless but some are colored e.g.:
- Colchicine and berberine are yellow.
- Canadine is orange.
- The salts of sanguinarine are copper-red.

Solubility

Both alkaloidal bases and their salts are soluble in alcohol. Generally, the bases are soluble in organic solvents and insoluble in water.
Physical Properties

Exceptions

- Bases soluble in water: caffeine, ephedrine, codeine, colchicine, pilocarpine and quaternary ammonium bases.
- Bases insoluble or sparingly soluble in certain organic solvents: morphine in ether, theobromine and theophylline in benzene.
- Salts are usually soluble in water and, insoluble or sparingly soluble in organic solvents.
Oxygen

Most alkaloids contain Oxygen and are solid in nature e.g. Atropine.

Some alkaloids are free from Oxygen and are mostly liquids e.g. Nicotine, Coniine.

Stability

Effect of heat

Alkaloids are decomposed by heat, except caffeine (sublimiable).
According to basicity Alkaloids are classified into:

- **Weak bases** e.g. Caffeine
- **Strong bases** e.g. Atropine
- **Amphoteric (Acid and base)** e.g. Morphine
- **Neutral alkaloids** e.g. Colchicine
Chemical test for Alkaloids

Precipitation Reagents:

Mayer’s Reagent : Potassium Mercuric Iodide.
Dragendorff’s Reagents: Potassium Iodobismethate.

They are used to:

- Indicate the absence or presence of Alkaloids
- Test for complete of extraction

Disadvantages

Some non alkaloids interfere such as Proteins, lactones, coumarins
Medical Uses of Alkaloids

Many alkaloids are still used in medicine, usually in the form of salts, including the following:

- Atropine - Antitumor
- Cocaine - Anesthetic
- Codeine - Cough medicine
- Morphine - Analgesic
- Tubocurarine - Muscle relaxant
- Quinine - Antimalarial
Extraction of Alkaloids

- Extraction is based on the basicity of alkaloids and on the fact that they normally occur in plants as salts (i.e.: on the solubility of bases and salts in water and organic solvents).

- Herbs often contain other materials which can interfere with extraction such as large amounts of fat, waxes, terpenes, pigments and other lipophilic substances (e.g by forming emulsions)-avoided by defatting the crushed herb (using petroleum ether and hexane).
Extraction method normally depends on the raw material, the purpose of extraction & the scale on which is to be performed.

For research purposes: chromatography allows for quick and reliable results.

If larger amounts of alkaloids need to be extracted, one of the following methods can be used.

TLC profile

Spray reagent: 37% formaldehyde in conc. sulfuric acid (1:10)
Extraction of Alkaloids from plant powder

**Method I**

The powder is treated with alkalis to liberates the free bases that can then be extracted with water immiscible organic solvents.

**Method II**

The powdered material is extracted with water or aqueous alcohol containing dilute acid. Alkaloids are extracted as their salts together with accompanying soluble impurities.

**Method III**

The powder is extracted with water soluble organic solvents such as MeOH or EtOH which are good solvents for both salts and free bases.
Normally, Soxhlet apparatus is used for the extraction of alkaloids.
Separation of Alkaloids from plant powder

- Plant material and solvent
- Extract
- Concentration
- Acidification
- Acidified Extract (Alk. as salts)
- Alkalization
- Alkaline aqueous layer
- Organic solvent dissolve Impurities
- Organic solvent dissolve Alkaloids

8-Feb-20
Extraction of alkaloids

CHCl₃

Strong solvent can extract most of the alkaloids.

- Extracts contain more impurities.
- Carcinogenic

Ether

Gives cleaner Extract but have some disadvantages:

- High volatility
- Peroxide formation
Some Important Alkaloids and their medical uses

- **D-tubocurarine**: Muscle relaxant for surgery
- **Caffeine**: Insomnia
- **Vinblastine**: Chemotherapy medicine
- **Nicotine**: Insecticide
- **Quinine**: Cinchona tree, antimalarial
- **Reserpine**: Hypertension
- **Saxitoxin**: Suicide pill
Main Pre-cursors for Alkaloids

- **Group 1:** Aliphatic Amino Acids—ornithine & lysine
  Pre-cursors to pyrrolidien, piperridine & tropane alkaloids

- **Group 2:** Aromatic Amino Acids—Phenylalanine, tyrosine, tryptophane
  Pre-cursors to Hyoscyamine and Hyoscine
Tropane Alkaloids

- Some alkaloids are very closely related to each other
- All have pronounced physiological actions.

Natural alkaloids include:

- Hyoscyamine
- Hyoscine
- Atropine
- Cocaine

The above mentioned alkaloids occur within the Solanaceae family (except cocaine—from Erythroxylaceae family)
Isomeric alkaloids

- **Cocaine**
- **Hyoscyamine**

Chemical structures of cocaine and hyoscyamine are shown.
Atropine & Hyoscine

Have the same structure—differ only in their optical activity.

Also have different physiological actions

Atropine—Atropa belladonna: to dilates eye pupils, decreases sweating and saliva, produces stomach acid & relaxes smooth muscle (asthma and colic)

Hyoscine—black henbane, Hyoscyamus niger:
Limited influence on the CNS. Sedative

Cocaine: Narcotic properties & local anaesthetic action (e.g. used in eye drops).
Atropine & Hyoscine

Atropine

Hyoscine
**Datura stramonium** Family: Solanaceae

**Definition:** Stramonium Leaf consists of the dried leaves or dried leaves and flowering tops of *Datura stramonium*. The drug should contain at least 0.25% alkaloids calculated as hyoscyamine.

**Common names:** Stramonium leaf, Thorn apple, Jimson or Jamestown weed

Traditionally it is used for motion sickness
Main (Tropane) Alkaloids
- Hyoscyamine
- Hyoscine (2:1)

Younger plants: Hyoscine is predominant alkaloid

Also contains Atropine

Larger stems contain little alkaloid, and drug should contain no more than 3% of stems with a diameter >5mm
Uses of *Datura stramonium*

Atropine: Stimulant on CNS: Depresses nerve endings on the secretory glands and smooth muscle

Hyoscine: Lacks CNS stimulant action of atropine Sedative - motion sickness

Atropine & Hyoscine: Used in ophthalmic practice to dilate the pupil of the eye.
**Datura stramonium - Allied Drugs & Adulterants**

**ALLIED DRUGS**
- *Datura innoxia*
- *Datura metel* (dried leaves are also curled and twisted-like *D. stramonium*), but are browner in colour.
- *Datura sanguinea*

**ADULTERANTS**
- Xanthium
- *Carthamus* and
- *Chenopodium leaves* (easily distinguished from original herb)
**Hyoscyamus niger: Family: Solanaceae**

- **Definition:** Hyoscyamus leaf consists of the dried leaves or dried leaves and flowering tops of *Hyoscyamus niger*. It should contain at least 0.05% alkaloids – hyoscyamine.

- **Common names:** Henbane

- **Traditionally** this plant used as a urinary tract infections
Hyoscyamus niger - Constituents

Tropane Alkaloids

Mainly

- Hyoscyamine
- Hyoscine (main constituent)
Hyoscyamus niger—Allied Drugs

- *Hyoscyamus albus* (petiolate stem—leaves and pale yellow, non-veined petals—bottom left).
- *Hyosycamus muticus* (top right)
- *Hyoscyamus pusillus*
- *Hyoscyamus aureus*
- *Hyoscyamus reticulatus* (Indian henbane—bottom right)
Resembles belladonna and stramonium in action—only weaker.

Higher hyoscine content—less likely to cause cerebral stimulation.

Used to relieve spasm of the urinary tract.
**Atropa belladonna** - Family: Solanaceae

- **Definition:** Belladonna herb consists of the dried leaves and flowering tops of *Atropa belladonna*, containing at least 0.3% alkaloids (hyoscyamine).
- **Should not contain** >3% stem >5mm in diameter.
- **Traditionally it is used as** to stop saliva.
Atropa belladonna - Constituents

Main (Tropane) alkaloid
- Hyoscyamine

Also contains
- Scopoletin
- Calcium oxalate
**Atropa belladonna**

**ALLIED DRUGS**

- Indian belladonna (*Atropa acuminata*) - yellow-brown flowers & brown-green leaves.

- *Atropa baetica* (yellow flowers and black berries) - endangered species

**ADULTERANTS**

- *Phytolacca decandra*
- *Ailanthus glandulosa*
Atropa belladonna - Uses

- Used as a sedative
- To stop bodily secretions (e.g. saliva)
- Root preparations are used externally
Pyridine Alkaloids

- Also referred to as Pyrrolizidine alkaloids. Include
- **Lobeline** (Lobelia herb) – respiratory stimulant → Used in asthma preparations.
- **Nicotine** (*Nicotiana tabacum* and other *Nicotina* spp) – toxic → Used as an insecticide
**Lobelia inflata**- Family: Capmanulaceae

**Definition:** Lobelia herb consists of the dried aerial parts of *Lobelia inflata*.

**Common Names:** Lobelia, Indian Tobacco

**Traditionally used by the Native Americans for asthma.**
Lobelia inflata – Constituents

Contains Pyrrolizidine Alkaloids

Most important

- Lobeline

Also

- Lobelidine
- Lobelanine
- Isolobelanine
Lobelia inflata - Uses

- Asthma
- Chronic bronchitis
- Anti-smoking preparations
- Injection of lobeline hydrochloride is used in the resuscitation of newborn infants.
- Caution: Toxic doses the herb has a paralytic effect.
Quinoline Alkaloids

Consist of alkaloids and alkaloid salts obtained from the bark of certain Cinchona species (Quinine, Quinidine, Cinchonine, Cinchonidine).

The amount of alkaloids present depend on the species, environment of the tree, age, and method of bark collection.

Quinine: Anti-malarial

Synthetic alkaloids are now used as substitutes for quinine for malaria.
Cinchona Bark - Family: Rubiaceae

Definition: Cinchona bark consists of various species races and hybrids of Cinchona, large trees indigenous to Colombia, Ecuador, Peru & Bolivia.
Historically Cinchona is played an important role in the treatment of malaria. This has now lessened with the introduction of synthetic drugs.

Traditionally not used by the native South American Indians (bitter taste inspired them with fear). First used as a medicine in Peru in 1630 –used to cure fevers.
Cinchona - Constituents

Quinoline Alkaloids

Mainly
- Quinine
- Quinidine

Also
- Quinicine
- Cinchonicine
- Cinchotannic acid
- Anthraquinones

- Leaves contain Indole alkaloids
Chemical tests

- Colour reaction for quinine and quinidine alkaloids
- Use bromine and ammonia (the thalleioquin test)
- Powdered cinchona is slightly moistened with glacial acetic acid & heated in an ignition tube
- Red drops condense on the sides of the tube.
- Cinchona bark therefore gives reactions for phlobatannins.
Barks of certain species of Remijia

- R. pedunculata
- R. purdiena
Cinchona Bark - Uses

- Bitter tonics
- Stomachics
- Used as gargles (tannins in bark - astringent)
- Malaria
- Prophylaxis of cardiac arrhythmias
- Treatment of atrial fibrillation
Thank you!