INDOLE ALKALOIDS

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Dried root, rhizome and areal stem of *Rauwolfia serpentina*, *R. vomitoria* (African) (Apocynaceae)

Contains not less than 0.15% of the active alkaloid (Reserpine)
Rauvolfia = Dr. *Leonhard Rauwolf* (German botanist)

Serpentina = tapering, snakelike roots of the plant.
It was used in herbal medicine for treatment of a variety of diseases
The plant is a shrub reaches to 1m height. It is indigenous to India and South West Asia.
The principal alkaloids isolated are:-

1- Reserpine.

2- Rescinnamine.

3- Deserpidine.
Rauwolfia compositum

Homeopathic Medication

For the treatment of high blood pressure and accompanying symptoms:
- Vertigo
- Myocardial weakness
- Arteriosclerosis

-Heel Biotherapeutics

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The plant is available for commercial production of reserpine, no synthetic production is needed.
These alkaloids are antihypertensive agents used in essential hypertension.
The mechanism of their action: -
Depletion of catecholamine and serotonine stores in brain and adrenal medulla.
Metabolism of catecholamines

- Monoamine oxidase (MAO)
- Aldehyde dehydrogenase
- Aldehyde reductase
- COMT

Catechol-O-methyl transferase (COMT)

- Normetanephrine
- Norepinephrine

Metabolism of catecholamines: Vanillylmandelic acid, 3,4-dihydroxymandelic acid, 3-methoxy-4-hydroxyphenylglycol (MHPG), 3,4-dihydroxyphenylglycol
Reserpine effect on VMAT has long-lasting effect and may cause drug-induced parkinsonism.
Also reduces the re-uptake of catecholamines by the adrenergic neurons.

The above mechanism is also responsible for the tranquilizing and sedative actions.
After administration for treatment of hypertension, a reflex bradycardia followed by euphoria is experienced.
CLINICAL USES

1- Mild to essential hypertension.

2- As adjunct therapy with other antihypertensive agents for other types of hypertension.
CLINICAL USES

These alkaloids are co-administered with thiazide diuretics as well.
3- Antipsychotic agents (relief symptoms of agitated psychotic states (Schizophrenia)), especially in patients who cannot tolerate other antipsychotic agents.
Toxicities...

- Nasal congestion.
- Depression.
- Suicide attempt.
- Nausea.
- Vomiting.
Toxicities

- Weight gain.
- Gastric irritation.
- Erectile dysfunction.
- Hyperprolactinemia.
- Increase the risk of breast cancer.
- Not to be given during pregnancy.
Relevant researches...

Cytotoxicity of the indole alkaloid reserpine from *Rauwolfia serpentina* against drug-resistant tumor cells

(Sara A.A. Abdelfatah and Thomas Efferth, 2015)
2-YOHIMBINE

Is an indole alkaloid obtained from the bark of *Pausinystalia yohimbe* (Fam: Rubiaceae)
Yohimbine
The plant part which is used to obtain the active ingredient is the Bark which contain about 6% of the total alkaloids.

It is a mild MAO-I Indicated for the treatment of impotence secondary to diabetes.
Also in male sexual performance and erection linked to increased cholinergic activity.

This will result in increased penile blood flow, causing erectile stimulation.
Also used in dry mouth.

A side effect of Yohimbine is increasing salivation which may lead to interfere with digestion.
3-NUX VOMICA

Is the dried ripe seed of

*Strychnos nux-vomica*

Fam: Loganinaceae

*Strychnos* = Poison plant

(nut that cause vomiting)
Is a small tree (12m), native to east Indies and Seri Lanka. Also in Australia (North coast).
The total alkaloidal content is 1.5-5% mainly (Strychnine and Brucine)
Is a valuable Pharmacologic tool in physiologic and neuroanatomic research.

Act as central stimulant causing excitation of all parts of the central nervous system and blocks the inhibitory spinal impulses at the postsynaptic level.
This action result in exaggeration in reflexes, with resulting tonic convulsions.

Toxic doses (60-90mg)

Brucine is used as alcohol dentaurant.
The alkaloid show suppression action on allergen-specific Immunoglobulin E (IgE) antibody response in mice, which raise possibilities for future application in allergic conditions.

*In vitro* cell-line tests, inhibit the growth of AGS human gastric carcinoma cells.
Calabar bean

Is the dried ripe seed of *Physostigma venenosum* (Fam: Fabaceae)

Total alkaloid content 0.15%
The Calabar River is found on the West coast of Africa.
Physostigmine
Physostigmine should be preserved in tight containers in shadow to avoid degradation of the product to toxic metabolites.
It is a reversible inhibitor of the Cholinesterase enzyme leading to increase of Acetylcholine concentration in myoneural junctions.
On the eye.

Causes miosis, contraction of the ciliary muscles and decrease in intraocular pressure caused by increase out-flow of aqueous humor.

Used to treat glaucoma
The dried leaflets of *Pilocarpus jaborandi* (Fam: Rutaceae) is a shrub indigenous to Brazil.

5-IMIDAZOLE ALKALOIDS (PILOCARPINE)

Total Alkaloid Yield = 0.5-1%
Pilocarpine
The alkaloids are:-

1-Pilocarpine
2-Isopilocarpine
3-Pilocarpidine
4-Pilosine
Is a muscarinic stimulant.

In the eye:-

Causes constriction of the pupil and contraction of the ciliary muscles.
Used in narrow-angle glaucoma, since miosis open the anterior chamber angle to improve the outflow.
Available as:

Ophthalmic drops (0.25 to 10%) as nitrate salt.

Warning:

Patient should be advised to wash hands immediately after application of the drops.
See the references...

Quinoline Alkaloids
Quinines and chemical modulation...

Resistance to anticancers...
Introduction

Quinoline Alkaloids

These alkaloids contain Quinoline nucleus, a major alkaloids belong to this class are cinchona alkaloids, which has therapeutic activity.
The plant is indigenous in the Western Andes of South America and were first described and introduced by Jesuit priests who did missionary work in Peru.
Cinchona alk. obtained from the dried barks of the stem and the root of

*Cinchona succirubra*,
*Cinchona officinalis*,
*Cinchona calysaya* and
*Cinchona ledgeriana*

(F: Rubiaceae)
Cinchona is a genus of 23 species, all trees, growing on the eastern slopes of the Andes, mainly in Bolivia, Ecuador and Peru.
The discovery of cinchona 1630-1650...
The Condesa de Chinchón was cured by cinchona bark is now known to be untrue, but led Linnaeus to name the genus after her.
It is, however, certain that by 1650 regular shipments of cinchona bark were reaching Spain. By the 1670s the bark was a well-established remedy in Britain.
The bark was often adulterated with useless bark from other trees.

In 1751 the Spanish Crown declared a monopoly on imports.
By the beginning of the 19th century, as Spain’s American colonies gained independence, there was serious concern in Europe over the quality, quantity and price of exports of bark.
Cracking the cinchona code: botany and pharmacy 1850-1930

Until the 1820s pharmacists had to judge the quality of cinchona bark, as it arrived at London Docks, by colour and taste. There was no assay to measure the active components.
In 1820 the first quinine alkaloids were extracted and described by Pierre Pelletier and Joseph Caventou. Within five years, the extracted alkaloids had become standard treatment for malaria.
Transplantation 1860-1880
The decline of quinine \( (20^{\text{th}} \text{ Century}) \)
The chemistry and biosynthesis of cinchona alkaloids

L-Tryptophane → Secologanin → Strictosidine → Corynantheal → Quinine
Methods of extraction follows the general method for the extraction of alkaloids.
Filodipine was developed from quinines for anticancer activities, but later researches showed that filodipine devoid such activity. It is used as antihypertensive drug.
Quinidine is free alkaloid within plant and is prepared as quinidine sulfate.

Quinidine is white odorless crystals, when exposed to light, become dark. It is soluble in organic solvents and sparingly soluble in water.

Quinidine sulfate is freely soluble in water and ether.
Quinidine is an antiarrhythmic drug act as membrane stabilizer...

Dosage (8 mcg/ml).
Cinchonism

- Blurred vision
- Skin rash
- Flushing
- Fever
- Lost of hearing
- Ringing in the ears
Indications

✓ Atrial fibrillation
✓ Atrial flutter
✓ Ventricular and atrial tachycardia
- Quinididine gluconate (as injection)
- Quinididine galactoronate (as oral tablets)

Advantages: It releases its content slowly and constantly, enabling steady distribution of the drug and half life. Also, it has less stomach irritability when compared to the other products.
Quinine
In 2013, malaria caused an estimated 584,000 deaths (with an uncertainty range of 367,000 to 755,000), mostly among African children (WHO 2014).
Quinine physicochemical properties...
Quinine sulfate is readily soluble in water while insoluble in organic solvents.
These agents are rigid planner polycyclic molecules...
It is Antimalarial drug, acting by intercalation of the quinine moiety into the DNA strands...
When parasite develops resistance to the drug...
Derivatives of the quinines

-Chloroquine

- More water solubility
- Better absorption form the GIT
- Less side effects
- Longer half life
- Less frequency in dosing
- Less resistance.
*Plasmodium falciparum* ring-forms and gametocytes in human blood.

A plasmodium sporozoite travels the cytoplasm of a mosquito.
Anopheles albimanus mosquito feeding on a human arm. This mosquito is a vector of malaria and mosquito control is a very effective way of reducing the incidence of malaria.
Countries which have regions where malaria is endemic as of 2003 (coloured yellow). Countries in green are free of indigenous cases of malaria in all areas.
Antimalarial drugs

Quinine and related agents
Chloroquine
Amodiaquine
Pyrimethamine
Proguanil
Sulfonamides
Mefloquine
Atovaquone
Primaquine
Artemisinin and derivatives
Halofantrine
Doxycycline
Clindamycin
Thanks for listening...
Any questions?