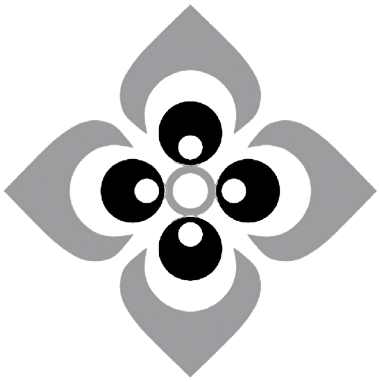

Consortium for Educational Communication

Module

on

Alkaloids

By

Dr Anu Appaiah K A
Principal Scientist

Microbiology and Fermentation Technology

CSIR-Central Food Technological Research Institute (CFTRI),

Mysuru 570020. India

Text

Introduction

The term alkaloids (or alkali-like) was first proposed by the pharmacist, W. Meissner, in 1819, for plant origin basic nitrogen-containing compounds. The first discovered alkaloid was narcotine, isolated from opium by Derosne in 1803. Ladenburg defined **alkaloids,—'as naturally occurring plant compounds having a basic character and containing at least one nitrogen in a heterocyclic ring.'** They are found in many plant families. Perhaps 20-30% of all plant species accumulate alkaloids. They are similar with families such as the *Solanaceae* and *Apocynaceae* where, as many as 60-70% of species accumulate alkaloids. Alkaloids are derived from a few common amino acids. Most of them have physiological activity. Majority of them are basic, but have non-basic forms also, such as quaternary compounds and *N*-oxides. Many alkaloids give simple color and precipitation reactions, swith Dragendorf's reagent, that make it relatively easy to determine their presence or absence in plant material.

More than 10,000 alkaloids are known, out of which about 16,000 are named in the NAPRALERT database. Many alkaloids are used in medicine. They sometimes are very expensive (e.g., vincristine, which sells for as much as Rs.1, 00,000 per gram). However, most alkaloids are toxic. They often are responsible for the properties of plants poisons.

Alkaloids are derived from a few common amino acids. All most all have physiological activity. Most are basic, but have non-basic forms, such as quaternary compounds and *N*-oxides. As a group alkaloids they can easily be isolated. They are extracted with lipophilic or non-polar solvents such as chloroform or petroleum ether, the solutions partitioned with dilute aqueous acid, washed with a non-polar solvent. The similarity of the structures of many alkaloids and their ability to attack the neurotransmitters makes them potent nervous system drugs. Among these neurotransmitters are acetylcholine, noradrenaline, dopamine, serotonin, and gaba are the common targets.

Alkaloid are compound with following characteristics:

(*a*) Complex molecular structure, and (*b*) Significant pharmacological activity.

They are unique molecules of the plant kingdom which has action on the animals.

Therefore, alkaloids are generally defined as 'physiologically active basic compounds of plant origin, in which at least one nitrogen atom forms part of a cyclic system.'

In 2008, the Botanic Gardens Conservation International (representing botanic gardens in 120 countries) stated that "400 medicinal plants are at risk of extinction, from over-collection and deforestation, threatening the discovery of future cures for disease." These included Yew trees (the bark is used for the cancer drug taxol (paclitaxel)); Hoodia (from Namibia, source of weight loss drugs); half of Magnolias (used as Chinese medicine for 5,000 years to fight cancer, dementia and heart disease); and Autumn crocus (for gout). The group also found that 5 billion people benefit from traditional plant-based medicine for health care.

Let us learn about the characteristics of Alkaloids

General Characteristics of Alkaloids:

The general characteristics of alkaloids may be grouped together in *two* categories, namely:(*a*) Physical characteristics, and (*b*) Chemical characteristics.

Physical Characteristics Alkaloids and their respective salts exhibit considerable variation in their solubility both in water and organic solvents. This can be attributed from their extremely complex and varied chemical structures. Free alkaloid bases are found to be fairly soluble in organic solvents, such as: ether, chloroform, hexane, benzene, petroleum, immiscible solvent, lower alcohols (methanol, ethanol); but they are either insoluble or very sparingly soluble in water.

The alkaloid salts are almost freely soluble in water, relatively less soluble in alcohol and mostly insoluble or sparingly soluble in organic solvents. Eg. Atropine sulphate and morphine hydrochloride are much more soluble in water than their corresponding bases *i.e.*, atropine and morphine.

Chemical Characteristics: The chemical characteristics of the alkaloids vary with individual compounds. They are classified based on their chemical nature as follows:

N-in the Molecule: The number of N-atoms vary from one in a molecule *e.g.*, cocaine, to even five in a molecule *e.g.*, ergotamine. It has been observed that these N-atoms are normally present as a part of the heterocyclic ring in the alkaloid molecule *e.g.*, quinine, whereas there are certain alkaloids that contain the N-atom in the aliphatic side chain. *Eg.* ephedrine, mescaline.

O-in the Molecule: In addition to the common elements C, H and N, a

variety of alkaloids normally contains O-atom. Eg. pilocarpine.

Basicity (Alkalinity): In general, the alkaloids are basic (alkaline) in reaction, by virtue of the presence of N-atom present in the molecule (fig 1). Hence, they easily get converted to their respective salts with various acids.

Amphoteric alkaloids: There are some alkaloids which are amphoteric in nature *i.e.*, they are neither acidic nor basic in character; this is due to the presence of phenolic (–OH) moiety in morphine or the presence of carboxylic (–COOH) function in Narceine, as shown in (fig 2)

*Unstable alkaloidal salts***:** There exists some specific alkaloids that inherently possess weak basic properties and their salts are not so stable, eg. Piperine, papaverine, narceine, narcotine, and caffeine (fig 3).

Neutral or slightly acidic alkaloids: There are a few typical naturally occurring alkaloids that almost behave as either neutral or slightly acidic character, namely: ricinine and theophylline, as depicted in (fig 4)

The complete decomposition of alkaloids by strong acids results in the change of colour. The chemical changes caused by the mineral acids on them may be categorized into *three* different types, namely:

(*a*) Dehydration: Dehydration of alkaloids give rise to either *anhydro-* or *apo-* alkaloids, such as: Apomorphine obtained from Morphine, Apoatropine obtained from Atropine.

(*b*) Demethoxylation**:** The removal or elimination of the methoxyl groups from the alkaloids by treatment with either concentrated hydrochloride (HCl) to produce methyl chloride (CH3Cl) or methyl iodide (CH_3I) while giving rise to the corresponding hydroxy base. Eg. Codeine , quinine, narcotine and papaverine.

(*c*) Hydrolysis: A good number of naturally occurring alkaloids are obtained as esters. They easily undergo hydrolysis on being heated with either alkalis or mineral acids thereby resulting into the formation of the corresponding acids along with respective alcohols or phenols of the alkaloids.

Action of Alkalies: The action of alkalies like NaOH and KOH on the **a**lkaloids are found to be varying in nature as enumerated below:

(*a*) Dilute alkaline solutions of KOH or NaOH normally decompose most alkaloidal salts and finally liberate the free alkaloids.

(*b*) Certain alkaloids containing phenolic hydroxyl groups *e.g.*, morphine, on being treated with alkaline solutions yield, their corresponding soluble sodium or potassium salts.

(*c*) The ester alkaloids usually undergo hydrolysis on being treated with dilute alkalies, such as: atropine, cocaine.

(*d*) Racemic Isomeride: The action of alkali hydroxides on hyoscyamine in alcohol gives rise to the racemic isomeride atropine.

(*e*) Fusion of alkaloids with dry KOH or NaOH by the application of heat ultimately leads to drastic decomposition of the former thereby yielding ultimately the simple heterocyclic bases, for instance: pyridine, quinoline, pyrrolidine etc.

(*f)* Simple fusion of alkaloids with alkali hydroxides may give rise to distinct and visible colour changes.

Classification based on origins of alkaloids

Most alkaloids in plants are metabolised from amino acid like ornithine, lysine, nicotinic acid, anthranilic acid, phenylalanine, tyrosine, and tryptophan. The most common reactions during the biosynthesis are Schiff base formation, Mannich condensations, decarboxylation of amino acids, transamination, and conversion of amines to aldehydes by amine oxidases, which leads to the synthesis of some of the following alkaloids.

Ornithine and lysine derivative. They are non-protein amino acid, L-ornithine, usually constitutes an integral part of the 'urea-cycle' in animals, wherein it is eventually produced from L-arginine in a reaction sequence catalyzed by the enzyme arginase. The various alkaloids derived from ornithine may be categorized into three heads, namely:

(*i*) Pyrrolidine Alkaloids, eg. Hygrine, cuscohygrine and stachydrine

(*ii*) Tropane Alkaloids, eg. Atropine, cocaine, cinnamoyl cocaine, ecgonine and hyoscyamine

(*iii*) Pyrrolizidine Alkaloids eg. Retronecine and Senecionine

Phenylalanine/Tyrosine. These are alkaloid molecules derived from phenylalanine and tyrosine. They are classified based on the genus of the plants where they are present.

Colchicine and related alkaloids: Colchicine is found in the leaves and seeds of at least 19 species of *Colchicum* and 10 other related genera

Amaryllidaceae alkaloids: Amaryllidaceae alkaloids includes compounds such as lycorine, norpluviine, lycorenine, and homllycorine

Mesembryanthemum alkaloids: Alkaloids found in the genera *Mesembryanthemum* and *Scletium*. About 25 alkaloids of this type are

known. Some of which are hallucinogenic.

Cephalotaxus and homoerythrina alkaloids: *Cephalotaxus* (Cephalotaxaceae) alkaloids have antitumor activity. Harringtonine, homoharringtonine, isoharringtonine, and deoxyharringtonine have significant antitumor activity. They inhibit DNA synthesis and protein synthesis.

Alkaloids Derived from L-Tryptophan are neutral heterocyclic amino acid containing essentially an indole ring system. This serves as a precursor for a wide spectrum of indole alkaloids. They are classified as

(i) Simple Indole Alkaloids; serotonin, psilocin and psilocybin

(ii) Simple b-Carboline Alkaloids; harman, harmaline, harmine and elaeagnine

(iii) Terpenoid Indole Alkaloids; ajmalicine, akuammicine, tabersonine, catharanthine

(iv) Quinoline Alkaloids; *Cinchona,* Cinchonine

(v) Pyrroloindole Alkaloids; Physostigmine

(vi) Ergot Alkaloids. ergotamine, ergosine, ergocristine, ergocryptine,

Alkaloids derived from a Xanthine Nucleus: - caffeine, theobromine, and theophylline.

Steroid Alkaloid : Solanine and chaconine

Classification based on pharmacological characters

Many alkaloids have documented multiple effects on different parts of body.They are as follows

- neurotransmitter receptors (nicotine, cocaine, morphine)
- neurotransmitter transport/degradation (cocaine)
- interfere with cytoskeleton (tubulin - taxol)
- ion channels (caffeine)
- enzyme inhibitors (caffeine, theobromine)

Biological activity

Medical use of alkaloid-containing plants has a long history. The first alkaloids were isolated in the 19th century, and applied in clinical practice immediately. The alkaloids exhibit a wide-spectrum and complete diversity of complex structures which ultimately is responsible for their extra ordinary broad-range of pharmacological activities covering both the cardio-vascular and central nervous system. Most alkaloids usually exert certain specific and definite pharmacological action. A small quantity of an alkaloid (0.1–1.0 mg) may bring about a marked and pronounced pharmacological action on various organs and tissues both of animal and human origin. Few of the alkaloids with their therapeutic action are listed in Table 1.

Pharmacological Activity

A typical pharmacological actions of some alkaloids are shown in table 2 indicating their broad spectrum of activities. The action of these compounds on various organs helps them to be used in treatment of various disorders. This also leads to the misuse of these molecules as drugs. The illegal market of these molecules is considered to be 3-5 times bigger than the legal markets. All the countries in the world are waging their war against the illegal markets. It is considered that this parallel economy helps in various terrorist activities.

Toxicity of alkaloids

The poisonous and therapeutic e□ects of plants have been known since time immemorial, but the active constituents have been studied for only about 200 years. Toxic effects, in general, depend on specific dosage, exposure time, and individual characteristics, such as sensitivity, site of action, and developmental stage. At times, toxicity effects can be both harmful and beneficial depending on the ecological or pharmacological context. Alkaloids in general have profound toxic effects on the nervous systems of mammals due to interaction with neuronal tissue. Mammalian nervous systems are served by two general types of neurohormonal

agents (neuro-transmitters):

(a) A transmitter that possesses an ammonium ion and facilitates cholingeric transmission. Eg. Acetylcholine

(b) Those transmitters that possess an aryl-ethyl-amino moiety (i.e, 13-phenethyl amino moiety) and facilitate andrenergic transmission. E.g: dopamine, norepinephrine; seratonin.

These neurotransmitters are believed to serve both the central and peripheral nervous systems. Alkaloids possessing either or both the quaternary ammonium ion or a physiologically induced equivalent (i.e. a protonated secondary or tertiary amine). The action of one or more of these neurotransmitters directly or indirectly exerting a neurological effect and thus toxicity.

At a lethal dose, the alkaloids from *Gelsemium elegans* produced violent chronic convulsions that leads to respiratory failure.

Taxines are the active, poisonous constituents in few plants (*Taxus spp*). It is suggested that their main action is on cardiac myocytes resulting in heart failure and death immediately in animal and humans.

Eight piperidinic alkaloids have been identified in *Conium maculatum*. Two of them, γ-coniceine and coniine are generally the most abundant and they account for most of the plant acute and chronic toxicity. These alkaloids produce a neuromuscular blockage leading to death due to its paralytic effect on the respiratory muscles. The chronic toxicity affects only pregnant animals. The alkaloid effects the development of foetus and the offspring is born with malformations, hence classified as a teratogen.

Effects of Drug/Alcohol Abuse

The immediate adverse effects of drugs and alcohol abuse are manifested in the form of reckless behavior, vandalism and violence. Excessive doses of drugs may lead to coma and death due to respiratory failure, heart failure or cerebral hemorrhage. A combination of drugs or their intake along with alcohol generally results in overdosing and even deaths. The most common warning signs of drug and alcohol abuse among youth include drop in academic performance, unexplained absence from school/ college, lack of interest in personal hygiene, withdrawal, isolation, depression, fatigue, aggressive and rebellious behavior, deteriorating relationships with family and friends, loss of interest in hobbies, change in sleeping and eating habits, fluctuations in weight, appetite, etc.

There may be some far-reaching implications of drug/alcohol abuse. The

adverse effects are just not restricted to the person who is using drugs or alcohol. At times, a drug/alcohol addict becomes the cause of mental and financial distress to his/her entire family and friends. Those who take drugs intravenously (direct injection into the vein using a needle and syringe), are much more likely to acquire serious infections like AIDS and hepatitis B. The viruses, which are responsible for these diseases, are transferred from one person to another by sharing of infected needles and syringes. Both AIDS and Hepatitis B infections are chronic infections and ultimately fatal. AIDS can be transmitted to one's life partner through sexual contact while Hepatitis B is transmitted through infected blood.

The use of alcohol during adolescence may also have long-term effects. It could lead to heavy drinking in adulthood. The chronic use of drugs and alcohol damages nervous system and liver (cirrhosis). Another misuse of drugs is by certain sportspersons to enhance their performance. Narcotic analgesics, anabolic steroids, diuretics and certain hormones are abused in sports to increase muscle strength and bulk and to promote aggressiveness as a result increase athletic performance. The side-effects of the use of anabolic steroids in females include masculinization (features like males), increased aggressiveness, mood swings, depression, abnormal menstrual cycles, excessive hair growth on the face and body, enlargement of clitoris, deepening of voice. In males it includes acne, increased aggressiveness, mood swings, depression, reduction of size of the testicles, decreased sperm production, kidney and liver dysfunction, breast enlargement, premature baldness, enlargement of the prostate gland. These effects may be permanent with prolonged use. In the adolescent male or female, severe facial and body acne, and premature closure of the growth centers of the long bones may result in stunted growth. Induced vomiting and gastric lavage are protective measures to reduce absorption of the toxic compounds.

Production in Cell Culture

Many useful plants grow in inaccessible parts of the world or where access is limited by political uncertainties. Some are in short supply and do not lend themselves to farming, or are perhaps slow growing (e.g. the Pacific Yew, *Taxus brevifolia*). Sometimes the desired alkaloid is present only in trace quantities (e.g. vinblastine from *Catharanthus roseus*).For these reasons, there has been an enormous e□ort to grow medicinal plants in flasks (or fermenters) where alkaloid production may be optimized, carried out without seasonal variations and as required. Plants are di□erentiated into roots, shoots, etc. and within the tissues into xylem, phloem, etc. Under the influence of plant hormones IAA, (indole acetic acid) and 2,4-D, plants cells grow into identical single-cell clumps

(callus). Callus can be broken down into a suspension culture when the culture fluid is agitated. Unfortunately, despite much e□ort, cultures are unable to produce the quantity of alkaloid found in the parent plant. Hairy root cultures are used more in research for biosynthesis of alkaloids. They are produced by exposing sterilized plant parts to strains of the soil microorganism *Agrobacterium rhizogenes*, which is able to transfer part of its own DNA (T-DNA) from a plasmid (a circular loop of double-stranded DNA) to the plant's nuclear genome. By inserting desirable genes into their plasmids, Agrobacteria are used to transfer new genes to plants. The T-DNA carries genes encoding the biosynthesis of plant hormones. For the production unusual nutritional amino acids are required by the microorganism. When such cells are grown they continue to produce the alkaloid.

Conclusion

Alkaloids are one of the largest groups of plant secondary metabolites, being present in several economically relevant plant families. Alkaloids are neuroactive molecules, such as caffeine and nicotine, as well as life-saving medicines e.g emetine which is used to fight oral intoxication and the antitumorals vincristine and vinblastine. Detailed understanding of alkaloid biosynthesis and mechanisms of action is essential to improve production of alkaloids of interest. The discovery of new bioactive molecules, and its sustainably exploit them against targets of interest, such as herbivores, pathogens, cancer cells, or unwanted physiological conditions is being pursued throughout the world.