(Non-Medicinal Toxic Plants: Hallucinogenic, Allergenic, Teratogenic Agents, and Other Toxic Plants)

These plants are toxic species of a little use in modern medicine, but are of considerable interest to pharmacognosists, because of the pharmacological effects which they produce.

1- Hallucinogens:

These hallucinogens, often derived from plants, have frequently been used within a religious context.
With the exception of cannabis, the principal known hallucinogenic plants contain alkaloids related to the neurophysiological transmitters noradrenaline and 5-hydroxytryptamine (serotonin).

A- Fungi:

Some of the poisonous fungi when taken orally produce hallucinations; these include toadstools of the genera *Amanita, Psilocybe* and *Conocybe*.

The Amanitas. A number of *Amanita* species, in addition to promoting hallucinogenic effects, are extremely toxic.
The appearance of the serious symptoms is considerably delayed (particularly with amatoxins).
After ingestion, by which time effective treatment becomes difficult. Three classes of toxins are recognized in the genus—tryptamines (e.g. bufotenine), cyclic peptides (phallotoxins and amatoxins) and isoxazole alkaloids (e.g. ibotenic acid, formula). The three classes of compound appear to be restricted to certain specific sections of the genus.

Figure- 1: *Amanita muscaria* mushrooms

The fly agaric. The fly agaric (*Amanita muscaria*) is readily distinguished by its red or orange cap, often covered with white flecks.

It contains a mixture of isoxazole alkaloids ibotenic acid and muscimol. Polysaccharides and a carboxymethylated derivative of the fungus have been shown to possess antitumour activity.

The pigments (betalains) of the fungus, also found in the Caryophyllales, are formed from tyrosine.

The pharmacological effects appear within an hour or so of ingestion, with an initial period of excitation followed by muscular twitches, a slowed pulse rate, impaired breathing, delirium and coma; however, ingestion of the fungus is rarely fatal.

Hallucinogenic Mexican mushrooms. A number of small toad- stools particularly species of *Psilocybe* (*P. mexicana*), *Conocybe*(*C. cyanopus*) and *Stropharia*—constitute the Mexican hallucinogenic mushrooms (*teonanacatl*, 'flesh of the gods', much revered by the Aztecs).

The onset of symptoms after ingestion of the fungi is rapid, and includes inability to concentrate and the occurrence of hallucinations. The active constituents are the tryptamine derivatives psilocybin and psilocin, compounds related to serotonin.

What is claimed to be the highest proportion of psilocin contained in any mushroom (3.3%, dry weight) was reported in *Psilocybe cubensi.*

Puffballs. Species of *Lycoperda* contain constituents which produce auditory hallucinations and a state of half-sleep about half an hour after consumption. The effects are distinct from those caused by the mushrooms.

Figure- 2: Puffballs

B- Lysergic Acid Derivatives:

The hallucinogenic properties of lysergic acid, and, in particular, the diethylamide derivative (LSD), are well-known. This acid forms the non-peptide portion of a number of ergot alkaloids and can also be produced by suitable cultivation of the fungus in liquid culture.

Morning Glory seeds (ololiuqui) The climbing plant from which they were obtained was subsequently identified as *Rivea corymbosa*.

The seeds of *Ipomoea tricolor* (*I. violacea*) and those of various species of *Argyreia* are closely related in constituents and action.

The trade names of species of *Ipomoea* are endlessly mixed. The seeds of the above-mentioned *Ipomoea hederacea* have long been used in the East as a purgative and were formerly official in the *British Pharmacopoeia* under the name 'kaladana' or 'pharbitis seeds'.

Figure- 3: Morning Glory seeds (ololiuqui)

Peyote Certain cacti are of pharmaceutical and pharmacological interest, as they contain protoalkaloids, some of which have marked hallucinogenic properties. One of these is the cactus *Lophophora williamsii* which has long been used by Mexican Indians.

The chief active constituent is the alkaloid mescaline. By 1973 some 56 alkaloids had been characterized from the cactus and these could be classified as:

(1) Mono-, di- and trioxygenated phenethylamines and their amides.
(2) Tetrahydroisoquinoline alkaloids and their amides.
(3) Phenethylamine conjugates with Kreb's cycle acids.
(4) Pyrrole derivates.

The alkaloids can arise in the plant from dopamine.

Indian Hemp

The Indian hemp plant was originally considered as a distinct species but came to be regarded as a variety of *Cannabis sativa.*

Three distinct species. *C. sativa, C. indica* and *C. ruderalis* was presented by American taxonomists.

The plant is found wild in India, Bangladesh and Pakistan. The drug consists of the dried flowering and fruiting tops of the pistillate plants (female flower) from which no resin has been removed.

In temperate climates large quantities of hemp are grown for the stem fibre and for the seeds, which yield 30–35% of a drying oil.

Figure- 4: Indian hemp

Hemp products:

Three main type of narcotic product are produced.

1. The Indian hemp or *ganja:* This is the *flat-* or *Bombay-ganja*, which was formerly official in many pharmacopoeias. Round- or *Bengal-ganja* is prepared by rolling the wilted tops between the hands.

2. *Bhang* (Hindustani) or *Hashish* (Arabic): consists of the larger leaves and twigs of both male and female plants. It is used in India for smoking, either with or without tobacco and drugs such as opium or datura, or is taken in the form of an electuary made by digestion with melted butter.

3. *Charas* or *churrus* is the crude resin. This is obtained by rubbing the tops between the hands, beating them on cloths or carpets, or by natives who wear leather aprons walking among the growing plants.

The resin is scraped off and forms an ingredient of numerous smoking mixtures. Like *bhang*, it is also used with butter.

In America and Europe the product used by addicts is known as *marihuana*, in north Africa as *kief*, in South Africa as *dagga*, and in Arabia and Egypt as *hashish*.

Constituents. The narcotic resin is a brown, amorphous semisolid; soluble in alcohol, ether and carbon disulphide. It contains over 60 compounds (cannabinoids).

Some principal components are cannabinol, tetrahydrocannabinol (THC), cannabidiol (CBD), cannabidiol- carboxylic acid, cannabigerol and cannabichromene.

Cannabinodiol is the aromatic analogue of cannabidiol. Cannabigerol precedes Δ9-THC in the biosynthetic pathway and is incorporated, by the plant, into the latter and other neutral cannabinoids.

Δ9-THC is the principal psychoactive constituent; Δ8-THC is almost as active but is only present in the plant in small amounts; cannabinol is less potent; although lacking psychotropic properties cannabidiol has anticonvulsant and possible analgesic effects.

Cannabichromene may enhance THC activity and has antifungal, antimicrobial and anti-inflammatory activity.

Resin production. In practice, two varieties of *Cannabis sativa* are recognized: one produces fibre and the other resin.

The chemical capacity to become either fibrous or resinous, depending on the climate.

Cannabis evaluation. The many factors above which determine the cannabinoid composition mean that care must be taken in ascertaining the chemical phenotype of a plant.

The general view that cannabis preparations can be evaluated on their Δ9-THC content neglects other active components, and in attempts to classify cannabis on the basis of its narcotic/fibre content, a relatively simple relationship introduced by Waller is based on the combined Δ9-THC and cannabinol (CBN) in relation to cannabidiol (CBD).

The phenotype is expressed as:

$$= \frac{\Delta^9\text{-}THC + CBN}{CBD}$$

A sample with a value greater than 1 = a drug type of cannabis; a sample with a value less than 1 = a fiber type.

Uses.

1- In the mid-nineteenth century it was used in Europe as a hypnotic, anticonvulsant, analgesic, antianxiety and antitussive agent.
2- Promising results on the use of Δ9-THC (dronabinol) for the relief of nausea and vomiting caused by cancer chemotherapy led to its use in the USA as an antiemetic.
3- It is also employed to stimulate the appetite of AIDS patients.
4- Nabilone, a synthetic cannabinoid antiemetic, it is recommended to be administered in a hospital setting under close observation.
5- Cannabis also appears to have value in the relief of the symptoms of multiple sclerosis and other neurological disorders.

2- Natural Allergens:

A large number of plant and animal materials give rise to allergic reactions in certain individuals.
The allergenic material is transmitted by direct skin contact, by airborne pollens, smoke and dried plant particles, and on the coats of domestic animals.
Once a person has been sensitized to a particular allergen, subsequent exposure to the materials produces an antigen–antibody reaction which results in the liberation of histamine or histamine-like compounds which in turn cause the allergic symptoms.
Allergies are commonly manifested as hay fever, asthma and dermatitis. Desensitization is often possible once the specific cause has been established.
Pollens. Responsible for seasonal hay fever, which may progress to chronic asthma.
Common grasses involved include timothy (*Phleum pratensis*), cocksfoot (*Dactylis glomerata*) and perennial rye (*Lolium perenne*). The pollen of nettle (*Urtica dioica*) is second in importance to the grasses in this connection in the UK.
Tree pollens are contained in the atmosphere in the spring; they are not as common as allergens as those of grasses.
Spores. A number of common moulds produce spores which cause rhinitis and asthma in sensitive individuals.
They are often responsible for those conditions which extend beyond the normal pollen season and up to the beginning of frosts.
In the UK the spores of *Cladosporium herbarum* and *Sporobolomyces roseus* cause the most trouble. Exposure to lycopodium spores has caused allergic reactions varying from dermatitis to severe asthma attacks.
There are also reports of spores causing adhesions on serous surfaces and foreign-body granulomas in soft tissues.
***A- Rhus* (Toxicodendron) spp.** *Rhus radicans* (poison ivy), *R. toxicodendron*

(poison oak), *R. diversiloba* (Pacific poison oak) and *R. vernix* (poison sumach, poison elder) (Anacardiaceae) contain contactant allergens which produce severe dermatitis associated with watery blisters which burst and quickly spread across the skin.

Allergens are contained in the plant sap and are easily transmitted (on clothing, hands, animal fur and even as the result of bush fires).

B- Sesquiterpene lactones. These compounds obtained from members of the Compositae, Lauraceae and Magnoliaceae andfrom the liverwort *Frullania* (Jubulaceae), are a major class of substances causing allergic contact dermatitis in man.

The presence of an **α**-methylene group, exocyclic to the γ-lactone, appears to be the principal immunochemical requisite for activity.

Two other plant species which can give rise to allergic reactions are the common rue (*Ruta graveolens*) and the indoor ornamental 'dumb cane' (*Dieffenbachia seguine*, Araceae).

In the latter instance it would appear that the irritant substances are introduced into the body tissues by abrasion, through punctures caused by acicular crystals of calcium oxalate contained in idioblasts.

C- Miscellaneous. Hair, feathers and house dust can all act as allergenic material; house dust often includes mites. Numerous other materials, not of natural origin (e.g. detergents, dyes, cosmetics), may also act as contact allergens.

3- Teratogens of Higher Plants

Teratogenic substances, when ingested by the mother, can cause abnormalities in the developing fetus; thalidomide represents the tragic example of a synthetic drug having such undetected properties at the time of its use.

Teratogens usually, but not invariably, act during a short, relatively early period of the gestation cycle.

The range of plant constituents known to have teratogenic effects, includes 14 different groups of alkaloids, coumarins, lignans, macrolides, nitriles, terpenoids, toxic amino acids and unidentifiedcompounds of many plants. As with the hallucinogens, the majority of teratogens contain nitrogen.

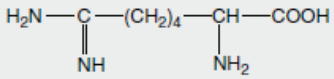
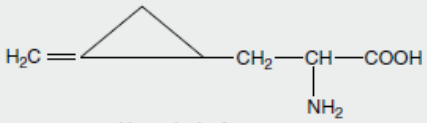
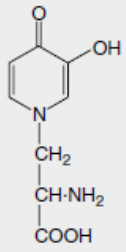
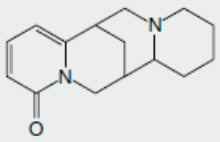
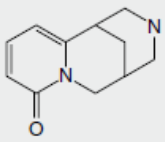
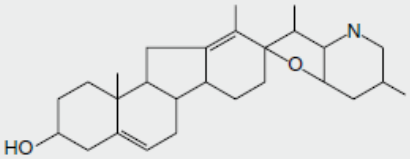
4- Other Toxic Plants

Cases of poisoning of humans by higher plants are most likely to occur with children and to involve those plants that produce attractive berries (e.g. belladonna,), seeds (e.g. laburnum) eaten for green peas, and those which may be introduced into the mouth for other reasons.

The poisoning of livestock by plants is relatively common, particularly in extensive grazing areas where there is no attempt to control weeds.

Poisonous plants may be consumed by animals because the plants happen to be growing among the fodder or were collected and dried with hay.
In the latter case some unstable poisonous constituents may disappear with drying and storage. In poor seasons animals may forage and consume plants which they would not normally eat.
Some widespread poisonous plants owe their properties to the presence of hepatotoxic pyrrolizidine alkaloids.
These include the *Senecio* spp. (ragworts) and members of the tribe Eupatorieae of the Compositae.
Another group of compounds which has been shown to promote liver cancer in rats is that containing safrole and other alkenylbenzene derivatives.
Fungi have a geographically universal potential as toxic agents, and the significance of their active constituents, mycotoxins, is only now coming to be fully appreciated.
The mycotoxins produced by various *Aspergillus* spp. (e.g. *A. flavus*, *A. parasiticus*) are termed aflatoxins, all having a coumarin nucleus fused to a bifuran unit and possessing in addition a pentenone ring (B series) or a six-membered lactone (G series).
Crude drugs, unless sterilized, are often grossly contaminated with mould spores, and if such drugs are to be consumed as such (as distinct from use for the isolation of active constituents), then it is important that they are free of dangerous mycotoxins.

Table 39.1 Teratogens of higher plants.

Plant source	Constituents	Notes
Senecio spp. (Compositae)	Pyrrolizidine alkaloids: lasiocarpine, retrorsine	Possible teratogenic effects in rats and *in utero* deaths of calves
Indigofera spicata (Leguminosae)	 Indospicine	Cleft palate and embryo lethality in rats. Possible malformations in domestic livestock. Indospicine teratogenesis
Nicotiana spp. (Solanaceae), *Lobelia* spp. (Campanulaceae)	Pyridine alkaloids	Probably responsible for some skeletal deformations in pigs but effect not positively attributable to alkaloids
Blighia sapida (Akee) fruits and seeds (Sapindaceae)	 Hypoglycin A	Hypoglycin A is known to be hypoglycaemic in humans and teratogenic in rats; it is twice as toxic as its peptide derivative hypoglycin B
Leucaena leucocephala; Mimosa spp. (Leguminosae)	 Mimosine	Large quantities toxic to livestock. Teratogenic effects demonstrated in pigs and rats
Locoplants e.g. *Astragalus lentiginosus* (Leguminosae)	Unknown	Contains osteolathyrogens (substances ingested by young through mother's milk), and teratogens characterized by causing excessive flexure of carpal joints or contracted tendons
Lupins e.g. *Lupinus sericeus* (Leguminosae)	Quinolizidine alkaloids, e.g. cytisine, anagyrine  Anagyrine  Cytisine	Teratogenic effect results in crooked calf disease
Conium maculatum (Umbelliferae)	Coniine	Alkaloid teratogenic, shown to produce crooked calf disease
Veratrum californicum (Liliaceae)	Many steroidal alkaloids  Cyclopamine	Teratogenic effect causes cyclopian and related cephalic malformations in lambs. The three active alkaloids have a fused furanopiperidine ring E/F arrangement as in cyclopamine