Plant toxicity

- Many different plants contain pharmacologically active substances that cross the blood-brain barrier or could effect different organs

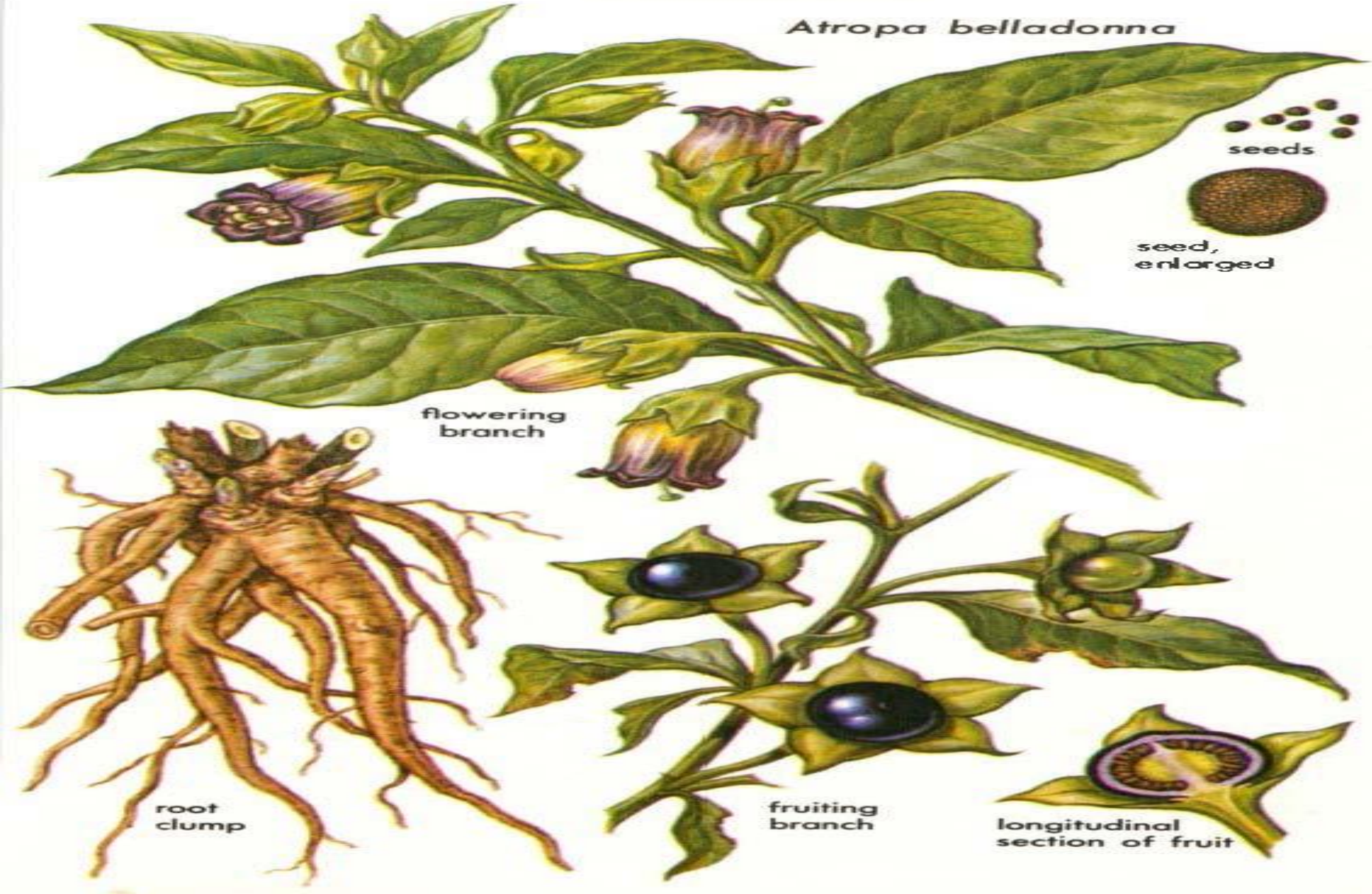
- Resultant central nervous system (CNS) effects include delirium, seizures, sedation, and hallucinations.

- Many of these substances have medical uses, and some have been used for recreation or for religious ceremonies.

PLANTS CONTAINING ATROPINE AND RELATED ALKALOIDS

- Many members of the Solanaceae family contain the anticholinergic alkaloids
- Atropine is the primary alkaloid in *Atropa belladonna* . It acquired the name belladonna during the Italian Renaissance when women used it to beautify their eyes by enlarging their pupils.

- The foliage and berries are extremely toxic, containing tropane alkaloids. These toxins include atropine, scopolamine and hyoscyamine,
- These alkaloids are present in all parts of the plant in varying amounts.
- The seeds and unripe fruits contain hyoscyamine.
-


Atropa belladonna
seeds
seed, enlarged
flowering branch
root clump
fruiting branch
longitudinal section of fruit

- Ingestion of ripe berries from *Cestrum diurnum* and *Cestrum nocturnum* has resulted in poisonings.

- Solanine, an alkaloid with gastrointestinal (GI) toxicity, is the predominant alkaloid in unripe berries, while atropine predominates in ripe berries.

- The major alkaloid in *Hyoscyamus niger* is l-hyoscyamine. Scopolamine is the predominant alkaloid in *Mandragora officinarum*

- Chinese herbal medicines have been implicated in anticholinergic poisonings, either related to use of
- yangjinhua (dried flower of *Datura metel* containing 85 per cent scopolamine and 15 per cent hyoscyamine and atropine) for the treatment of asthma and bronchitis,
- or medicines contaminated with atropine-like substances. Anticholinergic poisoning associated with ginseng use is most likely related to adulteration

- Atropine and its related alkaloids are muscarinic receptor antagonists that block the binding of acetylcholine to muscarinic cholinergic receptors in smooth muscle, cardiac tissue, gland cells, autonomic ganglia, and the CNS.

- At low doses patients present with slight dryness of the mouth, decreased sweating, and bradycardia.

- At higher doses they develop tachycardia; mydriasis; dry, hot, flushed skin; hallucinations, delirium, and coma.

- There are quantitative differences between the pharmacologic actions of atropine and scopolamine.

- Scopolamine penetrates more readily into the CNS, resulting in drowsiness, euphoria, disorientation, hallucinations, delirium, and amnesia at lower doses.
- Atropine is less likely to produce CNS effects with therapeutic doses; however, it does cause CNS excitation following toxic doses.
- Paradoxically, low doses of both atropine and scopolamine will slow the heart rate. This transient slowing of the heart rate by atropine may be related to its blockade of central muscarinic receptor.

- Although higher doses of atropine cause persistent tachycardia, scopolamine more often produces transient tachycardia.

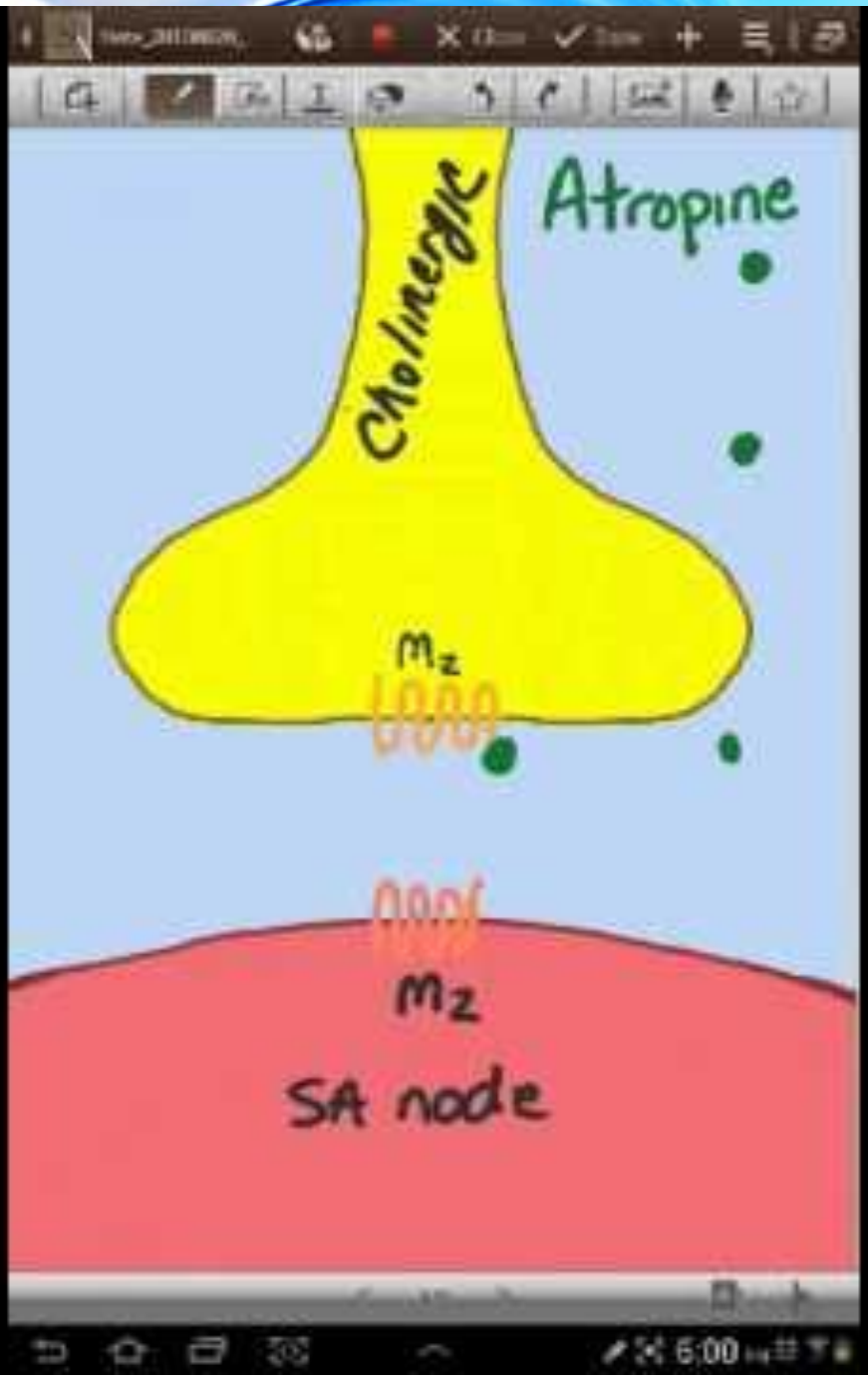

Cholinergic
Atropine
M2
M2
SA node

Table 116-1 -- Clinical Signs and Symptoms of Atropine and Related Alkaloid Poisoning

	Signs and Symptoms	Comments
Central nervous system	Restlessness, agitation, aggressiveness, irritability, confusion, disorientation, bizarre behavior, myoclonus, hallucinations, delirium, coma, seizures, amnesia	Hallucinations are of simple objects, not brilliant colors, and occur in 50–100% of patients in published cases; [15] [23] [42] patients may pick at imaginary objects
HEENT	Mydriasis, nonreactive pupils, blurred vision	Mydriasis may persist up to 2 weeks
Dermatologic	Dry, hot, flushed skin and mucous membranes	
Cardiovascular	Sinus tachycardia	
Gastrointestinal	Dry mouth, difficulty swallowing, thirst, diminished bowel motility	Seeds may remain in stomach up to 36 hours
Genitourinary	Urinary retention	
Other	Fever	

Treatment

- Treatment consists of supportive care, GI decontamination with activated charcoal, benzodiazepines,
- therapy with physostigmine (Physostigmine, an acetylcholinesterase inhibitor, causes acetylcholine to accumulate at the cholinergic receptor.
- Physostigmine reverses both peripheral and central anticholinergic effects Short duration of action;
- may cause seizures; contraindicated if ECG conduction disturbances

STIMULANT PLANTS

- Plants with stimulant properties cause symptoms ranging from anxiety and insomnia to seizures followed by CNS depression.

- The *Cicuta* species Common names include water hemlock. As members of the carrot or parsnip family (Umbelliferae), they closely resemble edible plants in this family.

- The toxic alkaloid cicutoxin is present in all parts of the plant but is concentrated in the roots.
- Death has occurred following ingestion of a small piece of the root. The overall mortality rate in the reported cases of water hemlock poisoning is close to 30 per cent.

- *Strychnos nux vomica* contains strychnine and brucine, which cause tetanic muscle contractions, which may be mistaken for seizures.
- Plants used as stimulants in herbal medicine often contain either ephedrine, caffeine, or similar ingredients.

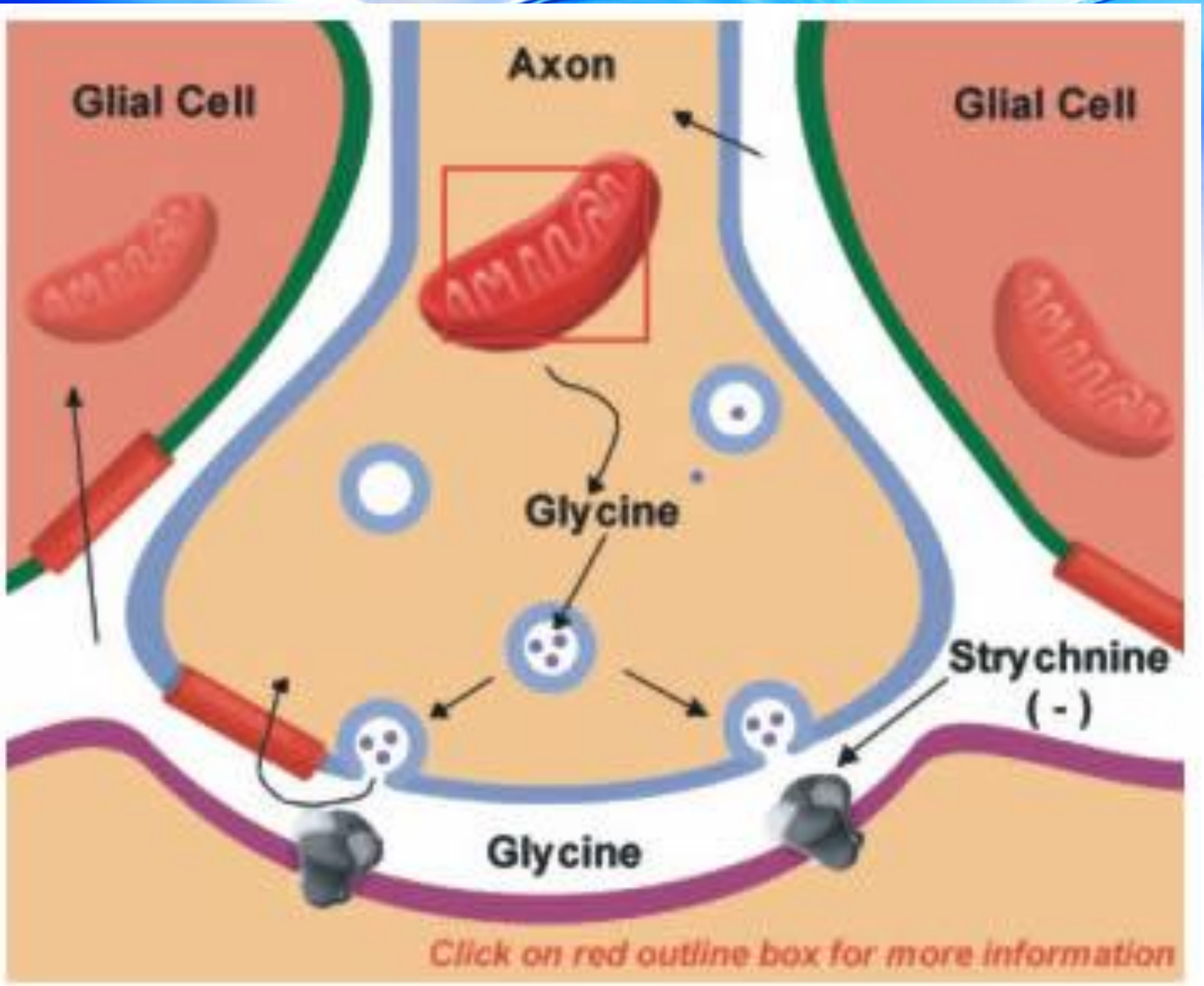
- Catha edulis (khat), which
- contains norpseudoephedrine

- and Ephedra nevadensis (Mormon tea), which contains ephedrine, can cause euphoria, insomnia, anorexia, tachycardia, hypertension, and mydriasis.

- Similar clinical effects are produced by the caffeine and theobromine in Cola nitida (kola nut, botu cola),

- The toxic constituent of water hemlock, cicutoxin, is an unsaturated aliphatic alcohol that produces toxicity by central cholinergic stimulation.
- Seizures are the most serious manifestation.
- Initial hypotension and bradycardia mediated by muscarinic receptors is followed by hypertension and tachycardia due to nicotinic receptor stimulation.

- Strychnine interferes with the postsynaptic binding of glycine, an inhibitory neurotransmitter. The result is a loss of motor inhibition in parts of the brainstem and spinal cord.
- The tetanic spasms that occur with strychnine are the result of continuous discharging of the disinhibited motor neurons and are not actually seizures.
- Hypoxia results from diaphragmatic or respiratory muscle paralysis.


Glial Cell
Axon
Glial Cell
Glycine
Strychnine
(-)
Glycine
Click on red outline box for more information

Treatment

- Treatment consists of supportive care, seizure control, and GI decontamination.
- Patients with serious intoxications should be on continuous cardiac monitoring.

- In patients with strychnine poisoning, it is critical that stimulation be avoided. The patient should be placed in a quiet dark environment with minimal tactile stimulation.

- Mechanical ventilation may be required for respiratory failure, especially with strychnine poisoning.

CNS DEPRESSANT PLANTS

- Plants such as Chamaemelum nobil, Humulus lupulus , Lactuca sativa are used in herbal medications for their sedative-hypnotic properties or to induce a state of relaxation.
- Rhododendron spp. (rhododendron, azalea)contain Andromedotoxin.

- MISCELLANEOUS PLANTS
- **Aconitine**
- The herb aconite is used by herbalists as an analgesic and anti-inflammatory.
- Aconite has predominantly cardiovascular (bradycardia, ventricular tachycardia) and gastrointestinal (nausea, vomiting, diarrhea, hypersalivation) toxicity
- Aconite is commonly derived from the plant *Aconitum nepellas*

- Four terpene alkaloids (aconitine, mesaconitine, hypaconitine, jesaconitine) have been isolated, the roots and flowers contain the highest concentration of alkaloid and are the most poisonous

- **MISCELLANEOUS PLANTS**
- **Aconitine**
- Ingestion and dermal absorption can cause toxicity.
- Even picking the flowers of this plant has been reported to cause paresthesias of the fingers.
- The mechanism of toxicity may be related to blockade of the voltage-sensitive sodium channel.
- The peripheral neurologic manifestations of poisoning by *Aconitum* include sensory and motor abnormalities.
- Paresthesias of the extremities can progress, in severe cases, to numbness of the oral cavity and generalized weakness can progress to paralysis.

- Treatment is largely supportive. Therapy with atropine may be indicated if hypersalivation and bradycardia are prominent.

Plants: Cardiovascular Toxicity

- The five most common classes of plants causing cardiovascular toxicity contain

(1) cardiac glycosides
(2) cardioactive steroids or alkaloids
(3) cholinergic toxins
(4) anticholinergic toxins, and
(5) adrenergic substances.

Plants with pharmaceutical derivatives have well-characterized pharmacologic effects

- *Coca* (cocaine) and *Ephedra* (ephedrine) exert their actions through α- and β-adrenergic receptors,
- *Digitalis* (digoxin) affects the myocardial sodium-potassium ATPase pump,
- plants with anticholinergic alkaloids produce vagolytic tachycardia and hypertension, as well as the familiar anticholinergic syndrome.
- Plants with cardioactive steroids or alkaloids represent a diverse group of plants from various families that share toxic effects on cardiac conduction.

CLINICAL PRESENTATION

- Most nonedible plants, including those with later cardiovascular effects, produce early nausea and vomiting.
- Early vomiting may reduce the quantity of absorbed toxin.
- Bradycardias are the most common cardiac disturbance.
- Tachydysrhythmias are uncommon following plant ingestion, with the important exception of aconitine-containing plants.
- Plant toxins can lead to confusing gastrointestinal, neurologic, and cardiovascular syndromes.

Treatment Essentials for Cardiotoxic Plant Poisoning

- *Cardiac glycosides*

✓ Activated charcoal
✓ Fluid replacement Electrolyte correction
✓ Antiemetic (ondansetron)
✓ Atropine 0.5 mg IV (0.02 mg/kg for children)
✓ Digoxin-specific Fab fragments

- *Cardioactive steroids, alkaloids, terpenoids*

✓ Activated charcoal
✓ Consider whole bowel irrigation with polyethylene glycol solution
✓ Fluid replacement electrolyte
✓ Antiemetic
✓ Bradycardia: atropine 0.5 mg/kg (0.02 mg/kg for children)
✓ Tachycardia: lidocaine, amiodarone, procainamide

- *Cholinergic alkaloids* Activated

✓ charcoal
✓ Antiemetic
✓ Atropine 0.5 mg/kg (0.02 mg/kg for children);
✓ Bronchodilators

- *Anticholinergic alkaloids*

✓ Activated charcoal
✓ Benzodiazepines such as diazepam 5–10 mg IV, 0.25 mg/kg for children,
✓ Avoid phenothiazines
✓ Physostigmine only for severe intoxication,

- *Adrenergic* Activated

✓ charcoal
✓ Benzodiazepines such as diazepam 5–10 mg IV, 0.25 mg/kg for children, or lorazepam 1–2 mg IV, 0.05 mg/kg for children

Plants: Gastrointestinal Toxicity

- Over 80 % of reported plant exposures occur in children less than 6 years of age who are attracted to the colorful flowers, berries, and leaves.

- Much more serious exposures occur in plant gatherers who mistake a morphologically similar yet highly toxic plant for an edible variety.

- For example, a number of fatalities have resulted when the root of water hemlock was mistaken for wild carrot. Herbal remedies are becoming increasingly popularity and misidentification or overzealous use has also lead to significant toxicity.

- Accurate identification of the ingested plant may be difficult even when a common name is known.

- For example *Atropa belladonna* which can cause anticholinergic poisoning, is often confused with common nightshade, a member of the Solanaceae family that produces severe gastroenteritis.

- Often no remnant of the ingested plant is available for identification. Descriptions such as “a small houseplant with green leaves” or “a small, red berry” leave much to be desired.

- In addition, most physicians lack the botanical training to identify specimens or even to describe them accurately to a phone consultant.

- The actual toxicity of a plant depends upon several factors

1. Season,
2. the plant's age and sex,
3. and the plant structure(s) ingested.

- The common tomato plant, a member of the Solanaceae family, has obviously edible fruit but its leaves and stalks contain toxic solanaceous alkaloids.

- Foxglove *(Digitalis purpurea)* and oleander *(Nerium oleander)* have higher concentrations of cardiac glycosides (digoxin-like substances) within their flowers. Their toxicity also increases with age.

- Some exposures to highly toxic plants have limited clinical effects due to limited availability of the toxin. The hard seeds of the castor bean and rosary pea prevent release of the potent toxalbumins contained inside.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plant affecting gastrointestinal divided into three groups:

(1) those with isolated oral irritant effects;

(2) those with gastrointestinal irritative effects; and

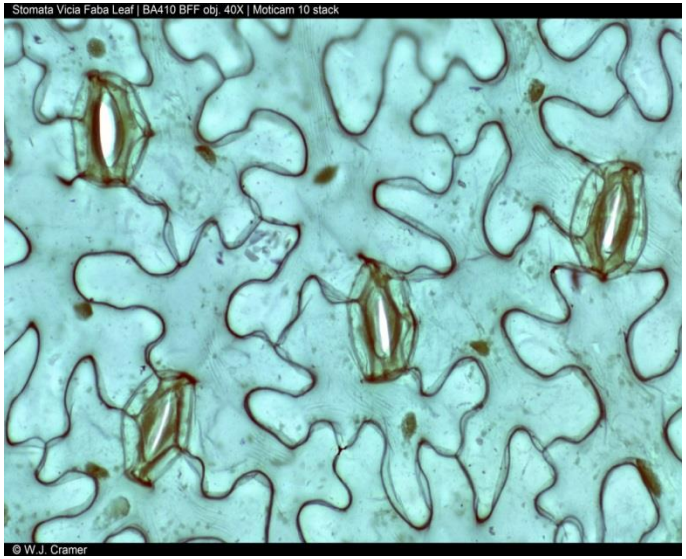
(3) those in which gastrointestinal manifestations predominate but systemic toxicity can occur.

Oral Irritants

- Calcium Oxalate Crystals
- Classic examples of plants that cause oral mucosal irritation are found in the Arum family.

- These are attractive indoor plants with smooth, broad green leaves that are often streaked or mottled with white.

- Plant members of this family contain insoluble calcium oxalate crystals that are arranged in bundles within pressure-sensitive, cigar-shaped structures called idioblasts.



Oral Irritants

- When mechanically deformed they fire calcium oxalate needles into the mucosa, producing immediate local pain.
- They also precipitate the release of bradykinin and histamine, which cause vasodilation and vascular permeability, resulting in edema.
- Patients describe a sensation akin to chewing on pins or glass.
- Symptoms are usually self-limited and resolve over a few hours.
- In severe exposures symptoms can last days and mucosal ulcerations or airway obstruction may occur.
- Arum family also includes well-known plants as jack-in-the-pulpit *(Arisaema triphyllum)* and elephant ear.

Oral Irritants

- Arum family also includes well-known plants as jack-in-the-pulpit *(Arisaema triphyllum)* and elephant ear.

Capsaicin Alkaloids

- Local irritation also occurs after exposures to members of the Capsicum, or hot pepper, family.
- The toxins involved are capsaicin and other related alkaloids that deplete substance P and serotonin from efferent and sensory nerve terminals.
- When ingested, these plants cause an immediate sensation of warmth and burning, which can progress to severe pain following large exposures.
- Simply handling the peppers causes adherence of capsaicin to the skin, which may then be transferred to the eyes and other sensitive mucous membranes.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Gastrointestinal Irritants

- Many plants produce isolated gastrointestinal symptoms which include nausea, vomiting, and diarrhea.
- Common examples include Pokeweed also known as ink berry.
- Young, tender leaves of poke are frequently eaten as cooked greens or in salad. Parboiling may render them harmless, but poisoning is still possible.
- Children who ingest only a few ripe berries are usually unaffected.

Gastrointestinal Irritants

- All parts of the pokeweed plant contain the toxins phytolaccine and pokeweed mitogen
- greatest concentrations in the roots and the least in the ripe berries.
- Phytolaccine is a potent gastrointestinal mucosal irritant.
- Pokeweed mitogen typically produces clinically insignificant lymphocytosis 2–3 days postingestion and resolves spontaneously within 10 days.
-
- Symptoms begin within 2–4 hours after ingestion. These include a burning or bitter sensation in the mouth followed shortly by nausea, vomiting, crampy abdominal pain, and foamy, sometimes bloody diarrhea.

Prominent Gastrointestinal Symptoms with Potential Systemic Toxicity

- This group includes plants that contain potent toxins that produce profound gastrointestinal symptoms.
- Systemic poisoning may also occur in large ingestions.
- Toxins include toxalbumins found in the castor bean and the rosary pea;
- Solanaceous alkaloids found in parts of the common potato , the tomato, and the jerusalem cherry *(Solanum pseudocapsicum)*
- mitotic inhibitors such as colchicine and podophyllotoxin found respectively in the *(Colchinum autumnale)* and the *(Podophyllum peltatum)*.

Solanaceous Alkaloids

- Many members of the Solanum family contain the toxic glycoalkaloid solanine.
- These include the common potato , the Jerusalem cherry
- Solanine concentrations vary greatly, depending on the growing conditions. Unripe fruit from stressed plants contains the highest concentrations, while ripe fruits, which are the most commonly ingested portion of the plant, have the lowest.
- The structure of solanaceous alkaloids consists of a central steroid-like structure, the aglycon
- The intact glycoalkaloid is severely irritating to the mucous membranes and gastrointestinal tract, and causes nausea, vomiting, and diarrhea within hours of ingestion.

Solanaceous Alkaloids

- Once in the stomach it is hydrolyzed and systemically absorbed.
- Absorbed toxin can produce neurologic symptoms including mydriasis, lethargy, delirium, hallucinations, central nervous system depression, and, rarely, death.
- Direct myocardial effects, similar to those of cardiac glycosides, and some anticholinergic effects have also been described.

Mitotic Inhibitors

- Mitotic inhibitors including colchicine and podophylline. The highest concentrations of these toxic alkaloids are found in the roots and tubers of these plants.
- These toxins bind to microtubular structures and inhibit normal cell division, leukocyte migration, and axonal transport.
- Within hours of ingesting these plants, patients complain of oral and pharyngeal burning
- followed by nausea, vomiting, colicky abdominal pain, and diarrhea.

Mitotic Inhibitors

- Tremendous fluid losses may result in tachycardia and hypotension.
- After 24–72 hours, sudden cardiovascular collapse may occur due to direct myocardial toxicity.
- Severe poisoning may also result in acute respiratory distress syndrome (ARDS) and oliguric renal failure as components of multiorgan system failure.
- Bone marrow suppression manifests within 4–7 days with leukopenia and thrombocytopenia, placing the patient at great risk of infection
-

Mushrooms

- Poisonous M. account for 50-100 of 5000 species in USA.
- Poisoning unpredictable
- some are poisonous only if eaten raw and other only if eaten at certain stage of growth.
- The problem is compounding further because poisonous M may grow next to non poisonous variety.
- In general most of cases in M poisoning due to Amanita genus especially A.muscaria and A. phalloides and this responsible for 90% of M. poisoning.
- Amanita M contain a mixture of thermostable cyclopeptides including phalloidin, phalloin and amanitin congeners.

- Muscarine is the toxin in clitocype and Inocybe, and provokes symptoms of toxicity within a few minutes to hours.
- Onset of symptoms in phalloidin, phalloin and amanitin delay up to 24 hours.
- They initiate cellular destruction by inhibiting nuclear RNA polymerase 2, which blocks protein synthesis leading to cell death.
- Primary action seen in GIT mucosa, hepatocyte, and renal tubular cells.
- There are rapid uptake of toxin in liver.

Characteristics of M poisoning

- Delayed onset of symptoms usually mean the ingestion of A.phalloides is likely.
- Most non lethal M produce symptoms early after ingestion.
- Because symptoms may delay up to 24 hr the victim or physician may not suspect that symptoms due to M poisoning.
- The characteristic in A.phalloides can be described in 3 stages:

1- Early stage (6-24) hr. there is generally abrupt onset of severe abdominal pain associated with profuse, cholera- like diarrhea and emesis.

Characteristics of M poisoning

2- The next (24-48) hr. is usually marked by a period of apparent recovery.

- During this time cellular destruction of kidney and liver is ongoing.

3- The third phase occur about (3-5) days post ingestions and is characterized by hepatocellular damage and renal insufficiency.

- Circulatory failure manifests later, with the victim showing signs of becoming jaundiced and hepatic coma within week.

- Death occur in 4-7 days of M consumption.

Management of M poisoning

- Supportive care including fluid replacement and correction of metabolic disturbances.
- For A.muscaria, if ingestion is suspected, administered ipecac and observe for signs and symptoms for at least 3 hours.
- For A.phalloides if the time since ingestion is less than 4hr. ipecac induced emesis may be beneficial.
- Since signs and symptoms delayed it is unlikely to detect poisoning before 4 hr.
- activated charcoal and cathartics have been recommended.