

Toxic Effects of Plants and Animals

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Introduction to Plant Toxicities

History is replete with stories of the earliest humans using plant extracts and animal venoms for hunting, war, assassination, and political intrigue for millennia.

The toxic properties of plants and animals often enhance their ability to survive.

Some toxic compounds are used primarily to aid an animal in obtaining food while plants have developed toxic properties to specially ward off being used as food.

One major complication to the study of plant and animal poisons arises from their complexity as mixtures.

Table 26-1

Poisoning Syndromes Caused by Plants

| SYNDROME | GENERA | MECHANISM(S) |
|----------------|---|--|
| Antimuscarinic | <i>Atropa, Datura, Hyoscyamus, Solanum</i> | Blockade of muscarinic cholinceptors |
| Cardiotoxic | <i>Adenium, Digitalis, Convallaria, Nerium</i> | Inhibition of cellular Na ⁺ ,K ⁺ -ATPase increases contractility, enhanced vagal effect |
| Convulsants | <i>Anemone, Conium, Labrunum, Nicotinia, Ranunculus</i> | Blockade of gamma-aminobutyric acid (GABA) receptor on the neuronal chloride channel, alteration of acetylcholine homeostasis, mimic excitatory amino acids, sodium channel alteration, hypoglycemia |
| Cyanogenic | <i>Eriobotrya, Hydrangea, Prunus</i> | Gastric acid hydrolysis of cyanogenic glycosides releases cyanide |
| Dysrhythmia | <i>Acotinum, Rhododendron, Veratrum</i> | Sodium channel activation |
| Nicotinic | <i>Conium, Laburnum, Lobelia, Nicotinia</i> | Stimulation of nicotinic cholinceptors |
| Pyrrolizidine | <i>Crotalaria, Heliotropium, Senecia</i> | Pyrroles injure endothelium of hepatic or pulmonary vasculature leading to veno-occlusive disease and hepatic necrosis |

Antimuscarinic

Blockade of muscarinic cholinergic receptors (Muscarinic acetylcholine receptors)

PLANTS:

Atropa (顛茄屬)

Datura (曼陀羅屬)

Hyoscyamus (天仙子屬)

Solanum (茄屬)



Muscarinic acetylcholine receptors(mAChRS)

G protein-receptor complexes in the cell membranes of certain neurons cells.

Acting as the main **end-receptor** stimulated by acetylcholine in the **parasympathetic nervous system**.

Muscarinic receptors were named as such because they are more sensitive to muscarine than to nicotine.

Cardiotoxic

- Inhibition of NA-K ATPase, increases contractility, enhances vagal effect

Plants:

Adenium (天寶花屬)

Digitailis (毛地黃屬)

Convallaria (鈴蘭屬)

Nerium (夾竹桃)



Convulsions

- Blockade of gamma-aminobutyric acid (GABA) receptor on the neuronal chloride channel.

- Plants:

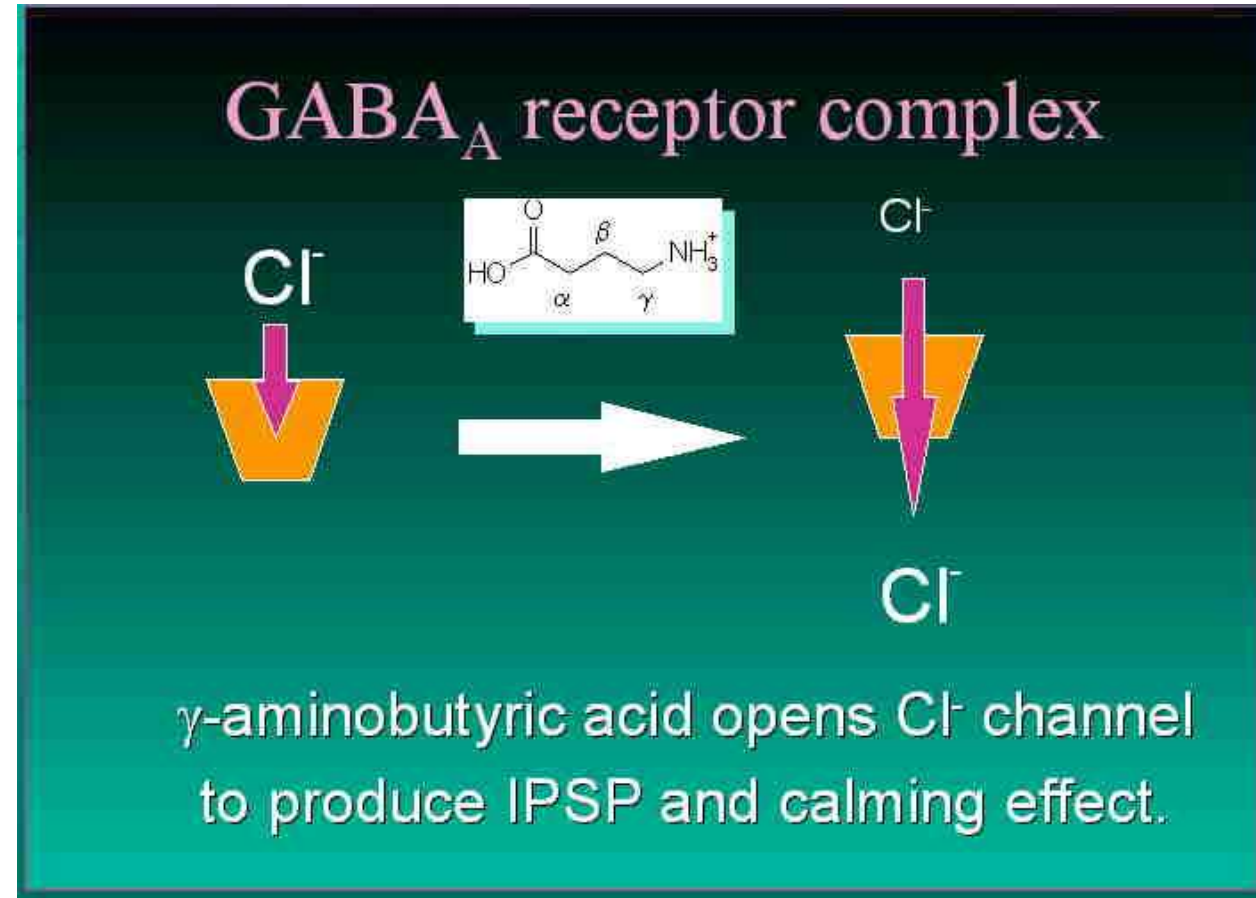
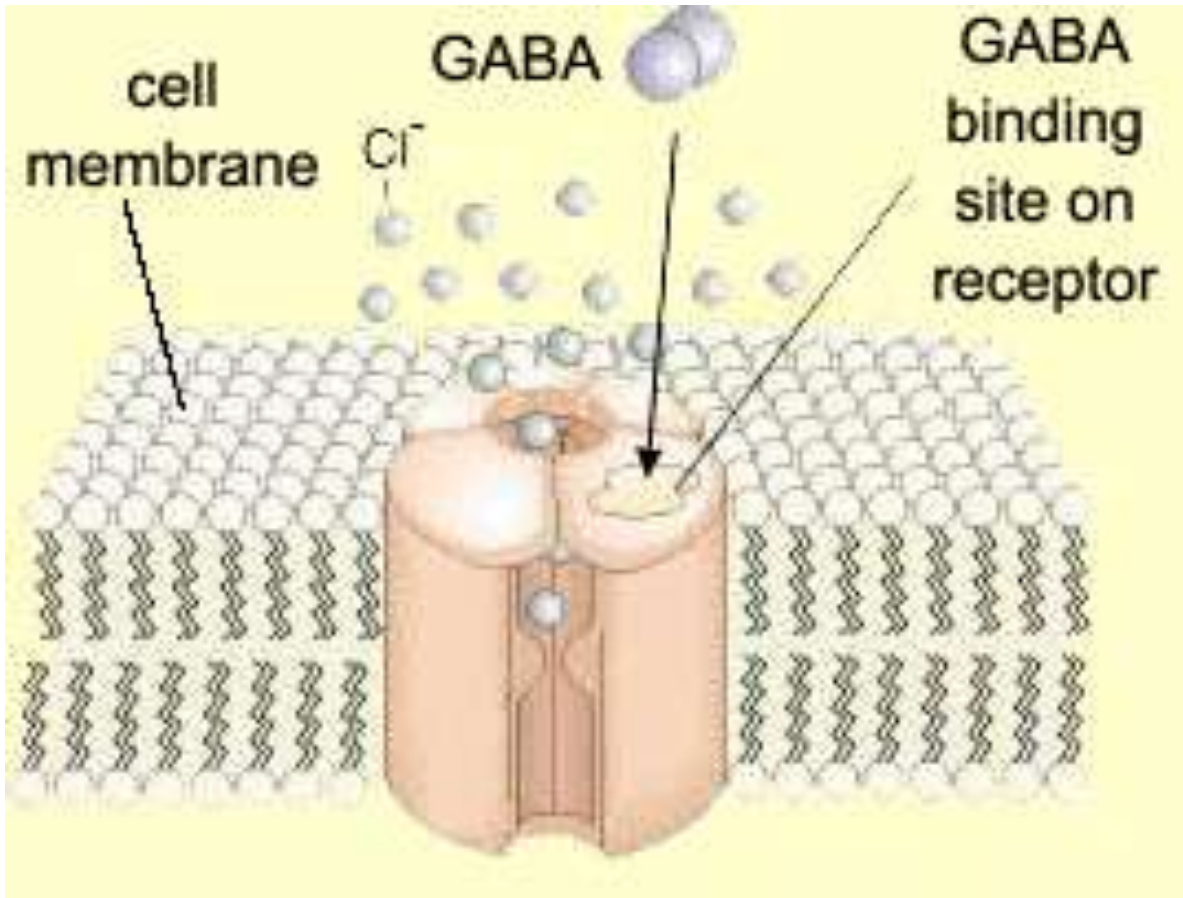
Anemone (銀蓮花屬)

Laburnum (毒豆屬)

Nicotiana (菸草屬)



Gamma-aminobutyric acid (GABA) receptor



Dysrhythmia

Sodium channel activation

Plants:

- Aconitum (烏頭屬)
- Rhododendron (杜鵑花屬)



Pyrrolizidine alkaloid

- Pyrrolizidine injure endothelium of hepatic or pulmonary vasculature leading to Veno-Occlusive Disease and hepatic necrosis.

Plants:

Senecio (千里光屬)

Crotalaria (野百合屬)

Heliotropium

(天芥菜屬)



Toxalbumin

- Protein synthesis inhibitors

Plants:

Abrus (相思子屬)

Ricinus (蓖麻)



- The plant kingdom contains potentially 300,000 species, and the toxic effects of plants serve primarily as defense mechanisms against natural predators.
- Toxicity in humans can result from simply touching as well as ingesting plants to cause a truly wide array of deleterious effects.
- There are many variables that can affect the concentration of a plant's toxin and that can be a major factor in the severity of reaction one will experience on exposure.

These factors include:

what part of the plant exposure is from.

1. The age of the plant.

2. Amount of sun light and soil quality that the plant has grown in

3. Genetic differences within a species.

- Plant toxins falls under a number of different chemical structures, which is useful in understanding related toxins

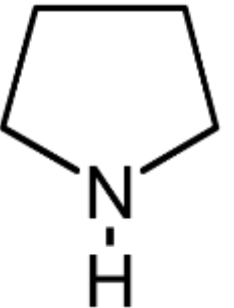
Table 26-2

Chemical Classification of Plant Toxins

| CHEMICAL CATEGORY | GENERA | EXAMPLES |
|-------------------------|---|---|
| Alkaloids | <i>Atropa, Senecio, Nicotinia, Coffea, Papaver, Solanum, Acotinum</i> | Tropines, pyrrolizidines, pyridines, purines, isoquinolines, steroids, diterpines |
| Glycosides | <i>Digitalis, Aesculus</i> | Steroids, coumarins |
| Proteinaceous compounds | <i>Abrus, Amanitin, Lathyrus</i> | Toxalbumins (abrin, ricin), polypeptides (amatoxins, phallotoxins, phalloidin), amines (aminopropionitrile) |
| Organic acids | <i>Caladium, Dieffenbachia, Rheum</i> | Oxalates |
| Alcohols | <i>Cicuta, Eupatorium</i> | Cicutoxin, tremetol |
| Resins and resinoids | <i>Cannabis, Rhus</i> | Tetrahydrocannabinol, urushiol |

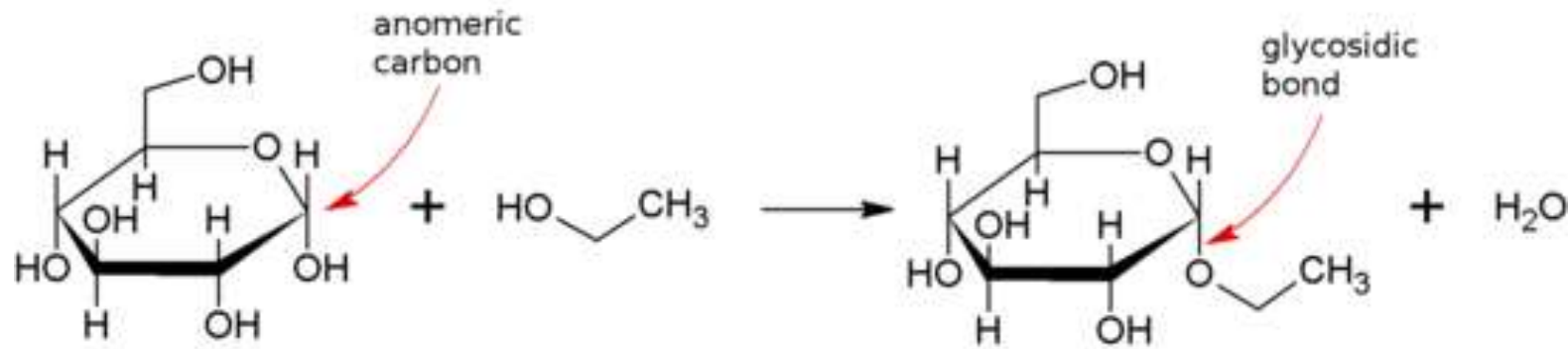
Alkaloid

- A group of naturally occurring chemical compounds (natural products) that contain mostly basic nitrogen atoms.
- Alkaloids are produced by a large variety of organism including bacteria, fungi and animals.
- Many alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications, as recreational drugs, or in entheogenic rituals



Glycosides

- A molecule in which a sugar is bound to another functional group via a glycosidic bond.



- glycoproteins, peptidoglycans and lipopolysaccharides.
- Coumarin (香豆素), a toxicant to Liver and kidney

Glycosides

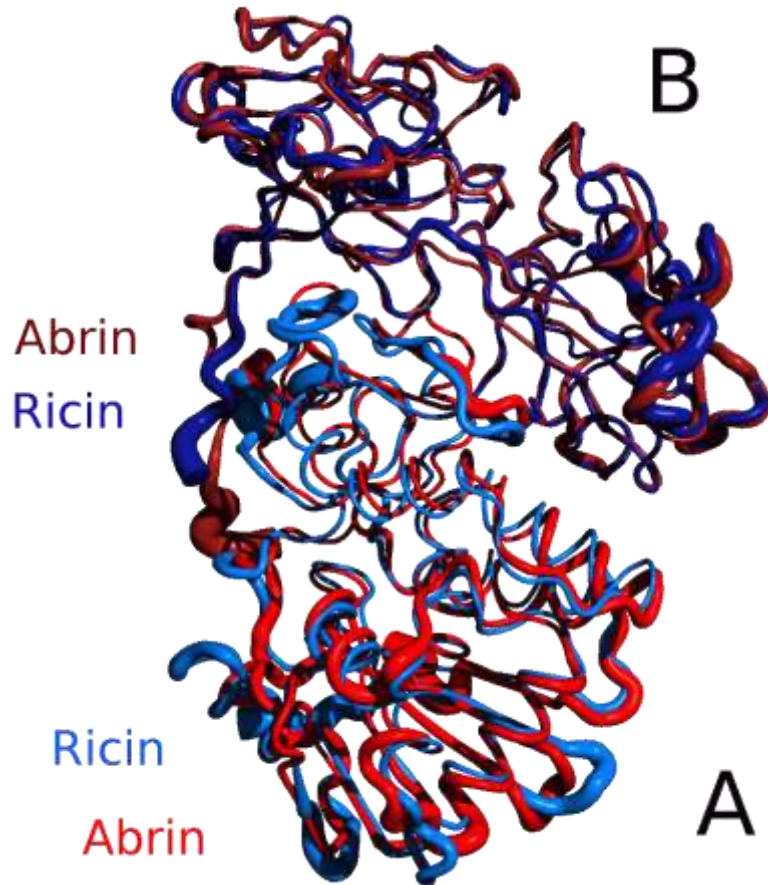
Plants

- Digitalis (毛地黃屬)
- Aesculus (七葉樹屬)

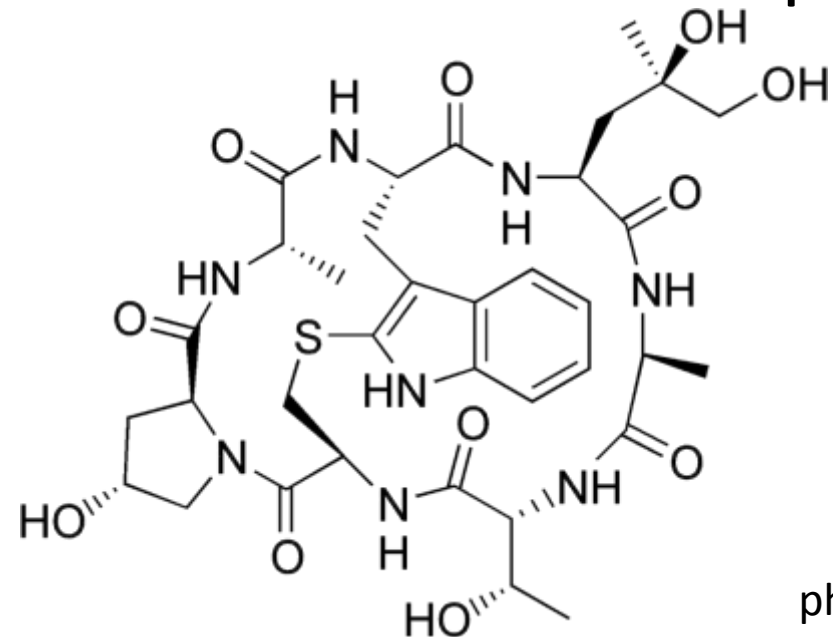


Proteinaceous compounds

- Toxalbumins (abrin, ricin), polypeptides (phallotoxins, phalloidin)



Phallotoxin :consist of at least seven compounds, all of which are bicyclic heptapeptides (seven amino acids), isolated from the death cap mushroom



phalloidin

Proteinaceous compounds

- Plants

Abrus (相思子屬)

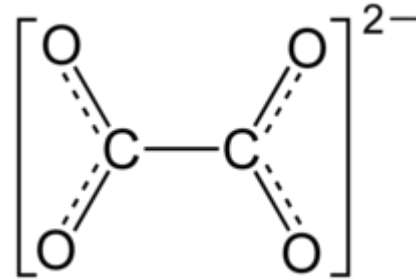
Ricinus (蓖麻)

Amanita phalloides (毒鵝膏) (death cap)



Organic acid

- Oxalate
- Plants:
 - Caladium (五彩芋)
 - Dieffenbachia (萬年青)
 - Rheum (大黃)



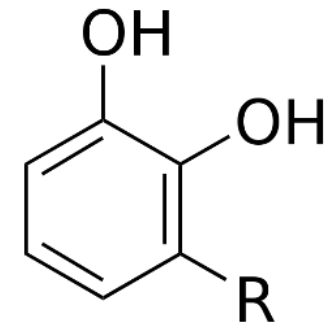
Alcohols

- Cicutoxin: causes death by disruption of the central nervous system.
- Tremetol: milk sickness, individuals who ingest milk from a cow that has fed on white snakeroot, which contains the poison tremetol. Cause trembles

- Plants:
- Cicuta (毒芹屬)
- White snakeroot (白蛇根草)



Resins



- A hydrocarbon secretion of many plants.
- Tetrahydrocannabinol (THC): THC in cannabis is assumed to be involved in self-defense, perhaps against herbivores and UV
- Urushiol: an oily organic allergen found in plants of the family Anacardiaceae, especially Toxicodendron (漆樹)
- Plants
 - Cannabis (大麻屬)
 - Rhus (鹽膚木屬)



TOXIC EFFECTS BY ORGAN: Skin

Allergic Contact Dermatitis

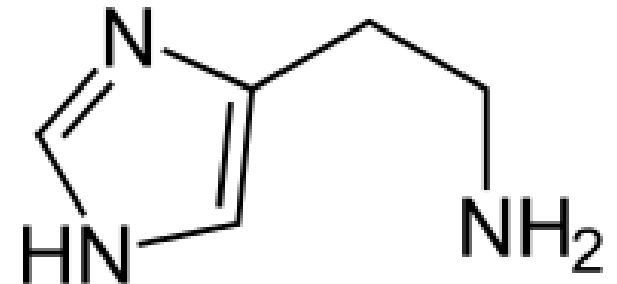
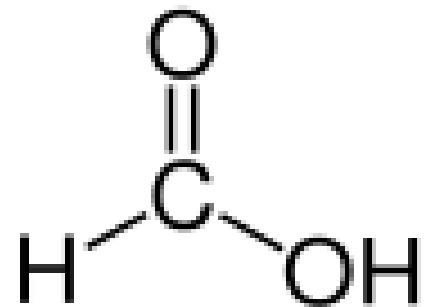
- Plants that cause irritation of the skin on contact are rather common.
- The trichomes (毛狀體) of barb-like hairs found on stinging nettles (*Urtica* species, Urticaceae, 異株蕁麻) puncture skin on contact and release an irritating sap containing a mixture of formic acid, histamine, acetylcholine, and serotonin



Figure 26-1. Stinging hairs of *Urtica ferox* (nettles).



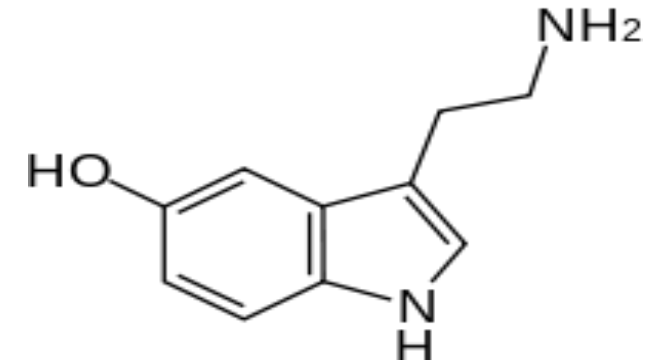
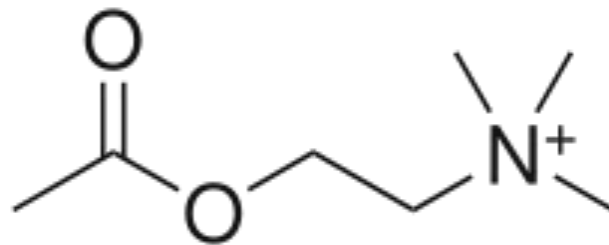
- Formic acid: the simplest carboxylic acid found in ant venom. A major use of formic acid is as a **preservative and antibacterial agent in livestock feed.**
- Histamin: an organic nitrogenous compound involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter. Histamine increases the permeability of the capillaries to white blood cells and some proteins



- Acetylcholine: an organic molecule that **acts as a neurotransmitter** in many organisms, including humans.

In cardiac tissue acetylcholine neurotransmission has an inhibitory effect, which lowers heart rate. However, acetylcholine also behaves as an excitatory neurotransmitter at neuromuscular junctions in skeletal muscle

- Serotonin: a monoamine neurotransmitter, Serotonin's presence in insect venoms and plant spines **serves to cause pain**, which is a side-effect of serotonin injection.



- *Muculla pruriens* (cowhage, 刺毛蒼豆), deploys its toxin via barbed trichomes on contact, may cause pain, itching, erythema, and vesication.

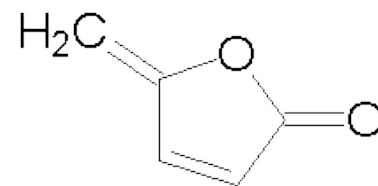
- *Ranunculus* (buttercup, 毛茛屬): contain a compound known as ranunculin, which is enzymatically broken down into the toxin **protoanemonin**.



Once contact with skin, protomoanemonin is converted to anemonin, which is the irritant directly responsible for the resulting dermatitis.

If ingested, protoanemonin may cause severe irritation of the gastrointestinal tract.

anemonin: 銀蓮花素 白頭翁素



Protoanemonin



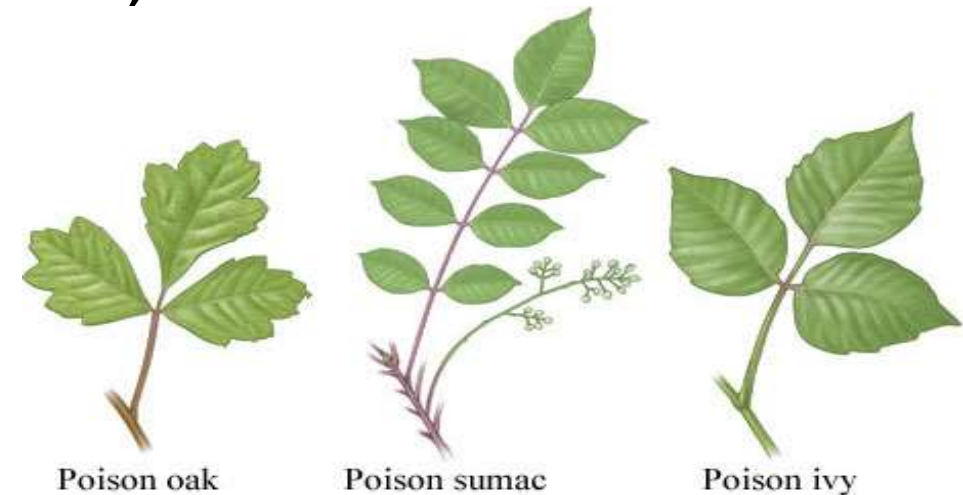
- Damage to the stems or leaves of the genus *Euphorbia* (Euphorbiaceae, 大戟屬) causes exudation of a milky latex that contains diterpene esters that are irritating to the skin.

- *Euphorbia marginata* (snow-on-the-mountain, 銀邊翠), a common plant in the United States that is used in flower arrangements by florists. Dermal contact with its latex can cause skin irritation. Also, serious eye irritation has been reported.

The poinsettia (*Euphorbia pulcherrima*, 一品紅, 聖誕紅), which is ubiquitous at holiday times, may cause contact dermatitis.



- Toxicodendron group of plants (漆屬): *Rhus diversiloba* (poison oak), *Rhus vernix* (poison sumac) and *Rhus radicans* (poison ivy) are all known to cause allergic dermatitis.
- In the *Rhus* species, the allergen is a fat-soluble substance called **urushiol** (漆酚) that can penetrate the stratum corneum (角質層) where it then binds to Langerhans cells in the epidermis (表皮). These haptenated cells then migrate to lymphonodes, where T cells are activated resulting in the allergic response



- Sap of the mango fruit (*Mangifera indica*, Anacardiaceae, 漆樹科) can also cause allergic dermatitis due to the presence of **oleoresins** that, with repeated exposure, will cross-react with allergens of poison ivy (urushiol).
- Oleoresin: a natural mixture of an essential oil and a resin, as found in certain plants.



- Alkaloids present in the sap of daffodils (水仙花), hyacinths (風信子), and tulips (鬱金香) can sometimes cause irritation.
- The major culprit is the compound tulipalin-A, which causes “tulip fingers” from handling tulip bulbs (球根).
- A safe threshold for this allergen is considered to be 0.01 %, the Tulipalin-A can be found in concentrations up to 2%.



- Irritation can also be caused by contact with needle-like crystals of calcium oxalate (草酸鈣), also known as raphides(葉內草酸鈣小晶體), which are present on some plants' bulbs.



- Plants (for examples)

Halogeton glomeratus (saltlover, 鹽生草)

Araceae (天南星科) (黃金葛等)

Palmae (棕櫚科)

Oxalidaceae (酢漿草科)

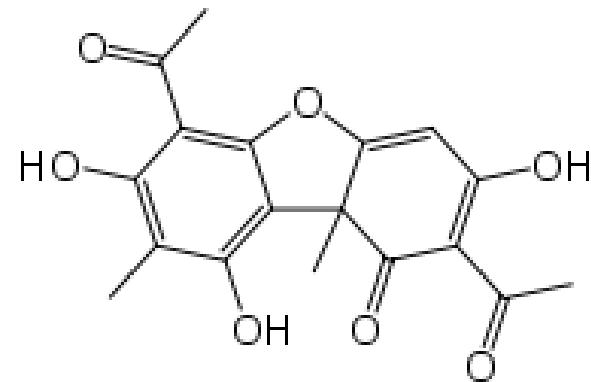


Latex-fruit syndrome

- The result of cross-sensitivity to latex in rubber gloves and some fruits.
- Latex allergy: encompassing a range of allergic reactions to the proteins present in natural rubber latex.
- *Hevea brasiliensis* (the latex tree, 橡膠樹) produces prohevein, a chitin-binding polypeptide that is also found in several plants.
- Individuals who are allergic to rubber latex may become sensitized to fruits containing a chitinase with a hevein-like domain, such as banana, kiwi, tomato, and avocado

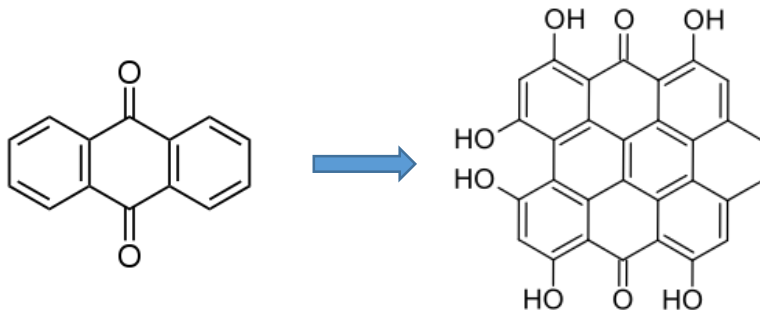
- Lichens (地衣), such as species of Usnea (鬚鬚地衣) is known to cause dermatitis due to the production of **usnic acid**.

Usnic acid has also been implicated in hepatotoxicity following use of certain nonprescription weight loss supplements.



Photosensitivity

- Dermatitis does not necessary have to be caused by skin contact.
- The Consumption of *Hypericum perforatum* (St. John's wort, 金絲桃) by animals can lead to serious dermatitis and even may be life threatening.
- The toxic agent is **hypericin** (a bianthraquinon, 雙蔥醌) that, once ingested and dispersed systematically, causes photosensitization of the animal's skin.



TOXIC EFFECTS BY ORGAN

Respiratory Tract- Allergic Rhinitis

- “Hay fever” or rhinitis from inhalation of plant pollens is a seasonal problem for many individuals.
- Grass species *Poa* (早熟禾) and *Festuca* (羊茅屬) are major contributors along with pollen from several weed genera in the Asteraceae (菊科) (eg, mugwort (艾草) in Europe, and ragweed (豚草) in North America)



- Asthma and rhinitis have been linked to individuals who are exposed to cascara sagrada (*Rhamnus purshiana*) (楊鼠李皮) or worker in greenhouses in which bell peppers (甜椒) are growing.



Respiratory Tract- Cough Reflex

- Workers who process peppers have a significantly increased incidence of coughing when specifically handling *Capsicum annuum* (sweet pepper) and *Capsicum frutescens* (red pepper).
- **Capsaicin** (辣椒鹼) and **dihydrocapsaicin** (二氫辣椒鹼) are two major irritants. Specific nerves in the airway have been found to be capsaicin-sensitive, which leads to the irritation and cough.



Respiratory Tract- Toxin-Associated Pneumonia

- The pneumotoxin, 4-ipomeanol is produced in sweet potato (*Ipomea batatas*, Convolvulaceae 旋花科) by the mold *fusarium solani*.
- 4-*Ipomeanol* is activated by human cytochrome P450s to an intermediate that binds to DNA.
- In cattle and rabbit, the major P450 activator is CYP4B 1 found in the lung that results in pneumonia.
- In the mouse, CYP4B 1 is most abundant in the kidneys that results in renal toxicity and in humans multiple subsets of liver P450 enzymes are responsible for activating 4-ipomeanol.

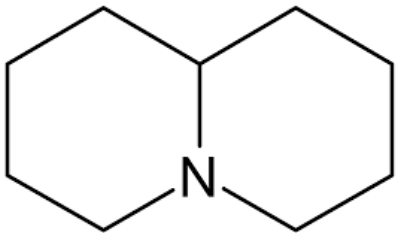


TOXIC EFFECTS BY ORGAN

Gastrointestinal System-direct irritants

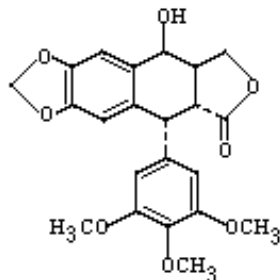
- Ingestion of a toxic plant can cause irritation of the gastrointestinal tract often resulting in nausea, vomiting, and diarrhea.
- Ingestion of **ripe tung nuts** (*Alellrites fordii*) causes abdominal pain, vomiting, and diarrhea. Outbreaks of poisoning are most likely to occur in children

- Toxic quinolizidine alkaloids are found in buffalo beans (毛豆), which grow naturally in the western United States. Ingestion by children causes nausea, vomiting, dizziness, and abdominal discomfort. Also, consumption by livestock of the mature plant with seeds has been reported to be fatal.
- Nuts from *Aesculus hippocastanum* (horse chestnut, 歐洲七葉樹) and *Aesculus glabra* (Ohio buckeye, 俄亥俄七葉樹) contain a glucoside called **esculin**. Ingestion by humans causes gastroenteritis, which increases in severity with the number of nuts consumed



Gastrointestinal system-Antimitotic Effects

- Podophyllotoxin (鬼白毒素) is found in podophyllum peltatum (May apple, Berberidaceae, 鬼白屬), especially in its foliage (葉子) and roots.
- In low doses, mild purgation occurs; however, overdose results in nausea and severe paroxysmal vomiting.
- By binding microtubules, podophyllotoxin blocks mitosis from proceeding.



- Found in the bulbs of *Colchicum autumnale* (autumn crocus, Liliaceae, 秋水仙屬), colchicine (秋水仙素)(blocks the formation of microtubules ultimately preventing successful mitosis).
- Ingestion of these bulbs causes severe gastroenteritis (nausea, vomiting, diarrhea, and dehydration).
- Severe poisoning can result in confusion, hematuria, neuropathy, renal failure and cardiotoxicity.

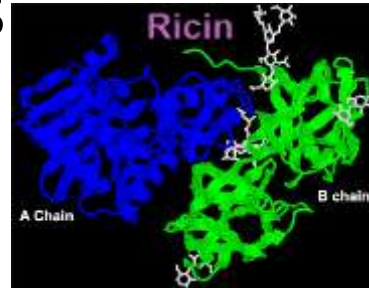


Gastrointestinal System-Protein Synthesis Inhibition

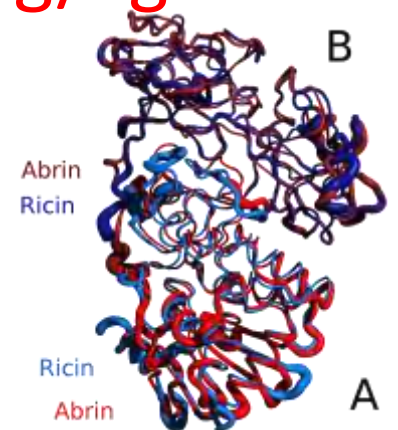
- The family Euphorbiaceae (大戟科) contains several genera that are known to be very toxic.
- The castor bean (*Ricinus communis*, 蓖麻) is an ornamental (decorated) plant that produce seeds that, if eaten by children or adults, causes no symptoms of poisoning for several days after ingestion. Gradually, gastroenteritis develops resulting in some loss of appetite, with nausea, vomiting, and diarrhea



- A fatal dose for a child can be as few as five seeds and may be as low as 20 seeds for an adult.
- The toxic agents are two lectins found in the beans: ricin I and ricin II of which ricin II is more toxic.
- Ricin II is made up of an A-chain and a B-chain. The B-chain is responsible for helping the A-chain get inside the cell.
- Once in cell, the A-chain inactivates the 60s ribosomal subunit of cells by catalytic depurination of an adenosine residue within the 28s rRNA, thereby blocking protein synthesis



- The seeds of *Abrus precatorius* (jequirity bean, Leguminosae, 雞母珠) contain lectins known as abrins.
- Abrin-a, one of four iso-abrins produced by the plant, has the highest inhibitory effect on protein synthesis and consists of an A-chain and a B-chain. Similar to ricin, the A-chain directly inhibits protein synthesis while the B-chain is responsible for getting the A-chain inside the cell.
- The LD50 of abrin when injected in mice is less than $0.1\mu\text{g}/\text{kg}$ making abrin one of the most toxic substances known.



- Plants that produce only A-chains are not nearly as toxic as those that pair them with a B-chain.
- Young shoots of pokeweed (*Phytolacca americana*, Phytolaccaceae, 垂序商陸) can be ingested without toxicity, however, consumption of mature leaves and berries may cause nausea and diarrhea.
- The plant produces three enzymes of single-chain lectins that are capable of inhibiting protein synthesis in cells only with the aid of virus.



TOXIC EFFECTS BY ORGAN

Cardiovascular System-cardioactive glycoside

- The best known cardioactive glycoside is *Digitalis purpurea* (foxglove, Scrophulariaceae, 毛地黃屬).
- However, others exist in the lily family, such as squill (*scilla maritima*, 海葱), which contains scillaren, and lily of the valley (*convallaria majalis*, 鈴蘭), which contains convallatoxin in the bulbs, that have actions similar to digitalis.



- The cardiac glycoside desglucouzarin in *Asclepias asperula* (馬利筋, 金鳳花), like digitalis, inhibits Na^+ , K^+ -ATPase.
- *Thevetia peruviana* (yellow oleander, 黃花夾竹桃) is a common ornamental plant in the United States whose seeds contain the highest concentration of cardiac glycosides. The fatal dose to an adult is eight to 10 seeds.



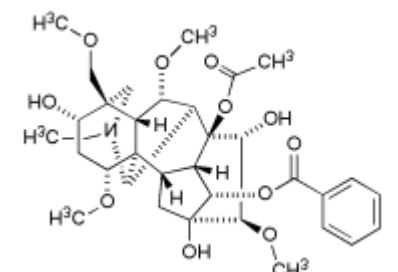
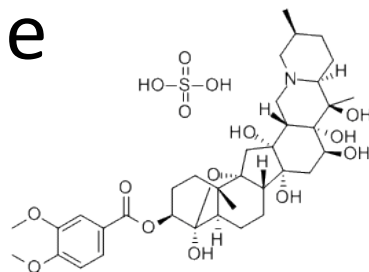
Cardiovascular System

Actions on Cardiac Nerves

- Toxic alkaloids found in *Veratrum viride* (American hellebore, Liliaceae, 美國藜蘆, 百合科), *Veratrum album* (European hellebore, 白藜蘆), and *Veratrum californicum* cause nausea, emesis, hypotension, and bradycardia on ingestion.
- *Veratrum album* has been used for centuries to “slow and soften the pulse.”



- The mixture of alkaloids includes protoveratrine (藜蘆鹼), veratramine (藜蘆胺), and jervine (白藜蘆鹼) that affects the heart by causing a repetitive response to a single stimulus resulting from prolongation of the sodium current.
- Aconitum species (烏頭屬), which have been used in western and Eastern medicine for centuries, produce the toxic alkaloids aconitine (烏頭鹼), mesaconitine (美沙烏頭鹼) and hypoaconitine(烏頭次鹼)
- The alkaloids work by causing a prolonged sodium current with slowed repolarization in cardiac muscle



Cardiovascular System

Vasoactive Chemicals

- Both phoratoxin(槲寄生毒肽)(produced by American mistletoe, 美槲寄生) and viscotoxin (produced by European mistletoe, 槲寄生) cause hypotension, vasoconstriction (血管收縮) of the vessels in skin and skeletal muscle, and braycardia resulting from negative inotropic actions(負性肌力作用)on heart muscle.



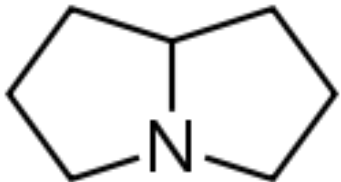
- Ingestion of the fungus *Claviceps purpurea* (ergot, 麥角), which grows on grains that are used for food, causes vasoconstriction.
- Ergot poisoning was called "St. Anthony's fire (聖安東尼火)" due to the blackened appearance of the limbs of some victims.



TOXIC EFFECTS BY ORGAN

Liver-Hepatic damage

- Pyrrolizidine alkaloids can be found in Senecio (千里光屬)(groundsel, Asteraceae, 菊科) and within four genera of Boraginaceae (紫草科): Echium (bugloss, 牛舌草), Cynoglossum (hound's tongue, 倒提壺), Heliotropium (heliotrope, 向日葵), and Symphytum (comfrey, 聚合草).
- These alkaloids causes liver damage in the form of hepatic venoocclusive (靜脈閉塞)disease associated with lipid peroxidation



Liver-Mushroom Toxins

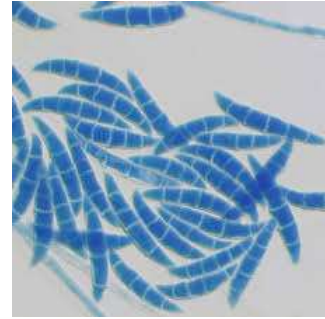
- Repeated ingestion of the false morel (假羊肚菌), *Gyromitra esculenta* (鹿花菌), has been found to cause hepatitis.
- Two types of toxin, phalloidin and amatoxins, can be found within *A. phalloides* (毒鵝膏)
- Phalloidin is binding actin in muscle cells; however, it is not readily during digestion, which limits its harmful effects



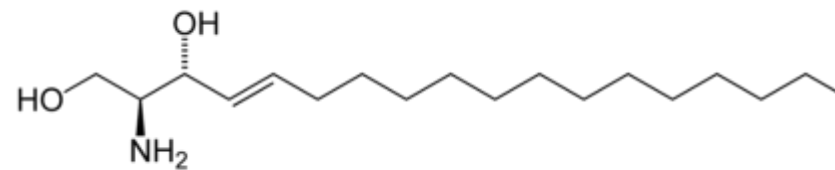
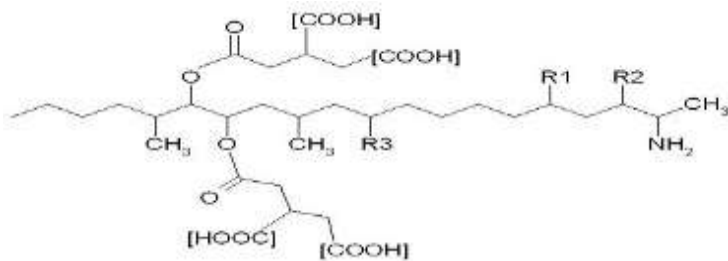
- α - , β -, and γ -amanitins are absorbed due to being molecularly much smaller than phalloidin.
- α -amanitin is the most toxic as it inhibits synthesis in hepatocytes by binding to RNA polymerase II.
- In addition to liver, intestinal mucosa and kidney are also affected
- α -amanitin also irreversibly inhibits acetylcholintransferase

Liver-Mycotoxins

- Fumonisin (鏟孢毒素) toxins are produced by the fungus *Fusarium* (鏟刀黴菌) that is known to grow on corn.



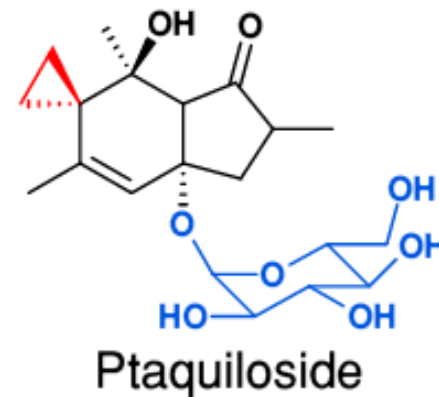
- Liver is the most affected organ by fumonisins.
- Ingestion in humans has been suggested to be associated with esophageal cancer.
- Fumonisin is structurally similar to sphingosine that is responsible for their toxicity as they block the enzymes involved in sphingolipid biosynthesis.



TOXIC EFFECTS BY ORGAN

Kidney and Bladder-carcinogens

- The bracken fern (*P. aquilinum*, 歐洲蕨), which is extremely common worldwide, is the only higher plant known to be carcinogenic in animals under natural feeding condition.
- Ptaquiloside (原蕨苷), a norsesquiterpene glucoside (雙環苷), is the known carcinogen present in the fern and it has been found to alkylate adenines and guanines of DNA.



Kidney Tubular Degeneration

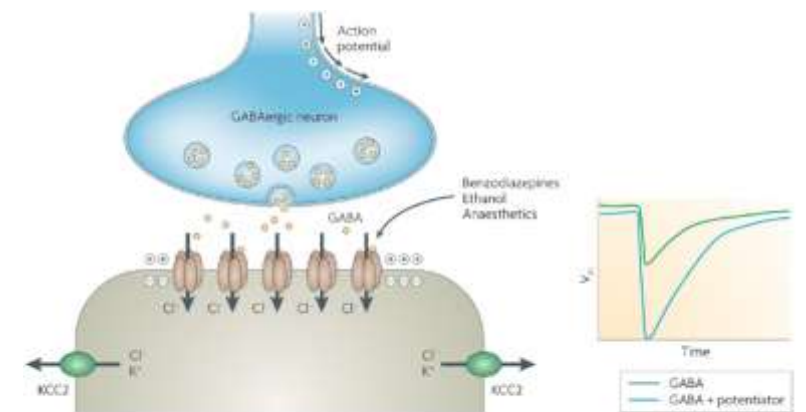
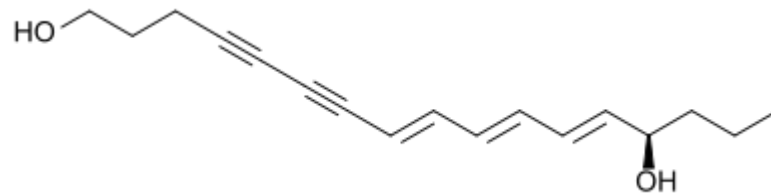
- Species of *Xanthium* (蒼耳子)(cocklebur, Asteraceae) have been found to contain the toxin **carboxyatractyloside** (羧化蒼耳苷), which causes microvascular hemorrhages in multiple organs including kidney.
- *Cortinarius orellanus* and *C. rubellus* (毒丝膜菌屬) contain the deadly toxin **orellanin** (蘑菇毒素), which triggers renal failure.



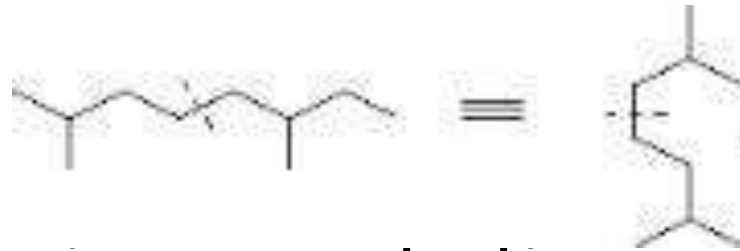
TOXIC EFFECTS BY ORGAN

Nervous System- Seizures

- The freshy tubers (塊莖) of *Cicuta maculata* (water hemlock, 水毒芹) produce neurotoxic cicutoxin (毒芹素).
- Consumption of a single tuber can result in fatal poisoning, characterized by **tonic-clonic convulsion** (僵直陣攣驚厥), owing to the cicutoxin binding to GABA (胺基丁酸)-gated chloride channels.



- Members of the mint family (Labiatae, 唇形科) such as pennyroyal (Hedeoma, 胡薄荷), sage (Salvia, 鼠尾草) and hyssop (Hyssopus, 神香草) are well known for their essential oils containing monoterpenes (單萜).



- Ingestion of monoterpenes in concentrations much higher than those used for flavoring can cause tonic--clonic convulsions. In particular, menthol is a selective modulator of inhibitory ligand-gated channels.



Nervous system-Excitatory Amino Acids

- The fungi *Amanita muscaria* (fly agaric, 毒蠅傘) produce the excitatory amino acid ibotenic acid (isoxazole amino acid, 鵝膏蕈氨酸).
- Poisoning produces central nervous system depression, ataxia (失調), hysteria (歇斯底里) and hallucinations (幻覺).



Psilocybe

Nervous system -Parasympathetic Block

- Atropine(阿托平), L-hyoscyamine(莨菪鹼), and scopolamine(東莨菪鹼) are belladonna (顛茄) alkaloids that can be found in varying concentrations in several genera of Solanaceae (茄科) such as Datura stramonium (jimson weed, 曼陀羅花) and Atropa belladonna (deadly nightshade, 顛茄).
- These alkaloids all effectively block the muscarinic receptor, essentially turning off the parasympathetic drive at the target organ.



Nervous system -Skeletal Muscle Damage

- Livestock grazing on *Thermopsis montana* (**golden pea**,) develop locomotor depression and recumbency due to areas of necrosis in skeletal muscle that have been found on autopsy.
- White snakeroot (*Ageratilla aftissima*, Asteraceae 白蛇根, 菊科), a common plant in the central and western United States, can be accidentally eaten by grazing cattle. On ingestion, the cattle exhibits tremors and humans who drink the milk of an affected cow can get “milk sickness”.
- The toxic effects are attributed to tremetone (白蛇根毒素) a benzofuran, which blocks gluconeogenesis from lactate, resulting in acidosis, and ultimately death



TOXIC EFFECTS BY ORGAN

Reproduction and teratogen- Abortifacients

- Swainsonine (苦馬豆素), the active alkaloid in the legumes (莢果) Astragalus (黃耆) and Oxytropus(棘豆屬), also causes abortions in pregnant livestock that accidentally ingest locoweeds.
- Foliage(葉子) and seeds of *Leucaena leucocephala* (銀合歡) and *Mimosa pudica* (含羞草) contain a toxic amino acid, mimosine, which on ingestion by cattle leads to reproductive disturbances including infertility and fetal death.
- Mimosine has been found to arrest the cell cycle in late G I phase that helps explain its toxic effects.



Reproduction and teratogen- teratogen

- Ingestion of *V. californicum* (California false hellebore, Liliaceae, 假藜蘆, 百合科) by pregnant sheep is known to cause malformations in its offspring including cyclodia (獨眼), exencephaly (露腦畸形), microphthalmia (大小眼畸形).
- Many other species of animals are susceptible to *V. californicum* poisoning including cows, goats, chickens, rats rabbit, hamsters ,mice, lambs, and rainbow trout embryos.
- The toxic alkaloid called jervine (白藜蘆鹼) causes teratogenesis by blocking cholesterol synthesis that, among other things, prevents a proper response of fetal target tissue to the sonic hedgehog gene



CLINICAL STUDY OF PLANT POISONS

- Recent research has shown that Uzara root extract reduced chloride secretion by the gut specifically by inhibiting Na^+ , K^+ -ATPase. This effect was seen even in the presence of cholera toxin that causes potent diarrhea by increasing chloride secretion in the gut.
- Anemonin (銀蓮花素), which is the active skin irritant produced by species of *Ranunculus* (buttercup, 毛茛), has been found to show potent anti-inflammation effects under certain conditions.



INTRODUCTION TO ANIMAL VENOMS

- The venom is the sum of all natural venomous substances produced in the animals. Conversely, poisonous animals have no specific mechanism or structure for the delivery of their poisons, and poisoning usually takes place through ingestion.
- Animal venom may play a role in offense (as in the capture and digestion of food), in the animal's defense (as in against predators or aggressors), or in both functions.
- The venom is not primarily designed to kill the prey, but only to immobilize the organism for feeding.

- Poisonous animals on the other hand, usually derive their toxins through the food chain. As such, is often a metabolite produced by microorganisms, plants, or animals.
- Poisons are sometimes concentrated as they pass through the food chain from one animal to another.
- Venoms are very complex, containing polypeptides, high- and low-molecular-weight protein, amimes, lipids, steroids, aminopolysaccharides, quinones (醌), glucoside, and free amino acids, as well as serotonin, histamine and other substances

- The bioavailability of a venom is determined by its composition, molecular size, amount or concentration gradient, solubility, degree of ionization, and the rate of blood flow into that tissue, as well as the properties of the engulfing surface itself.
- The venom can be absorbed by active or passive transport, facilitated diffusion, or pinocytosis, among other physiologic mechanisms.
- Besides the bloodstream, the lymph circulation not only carries surplus interstitial fluid produced by the venom but also transports larger molecular components and other particulates back to the bloodstream.

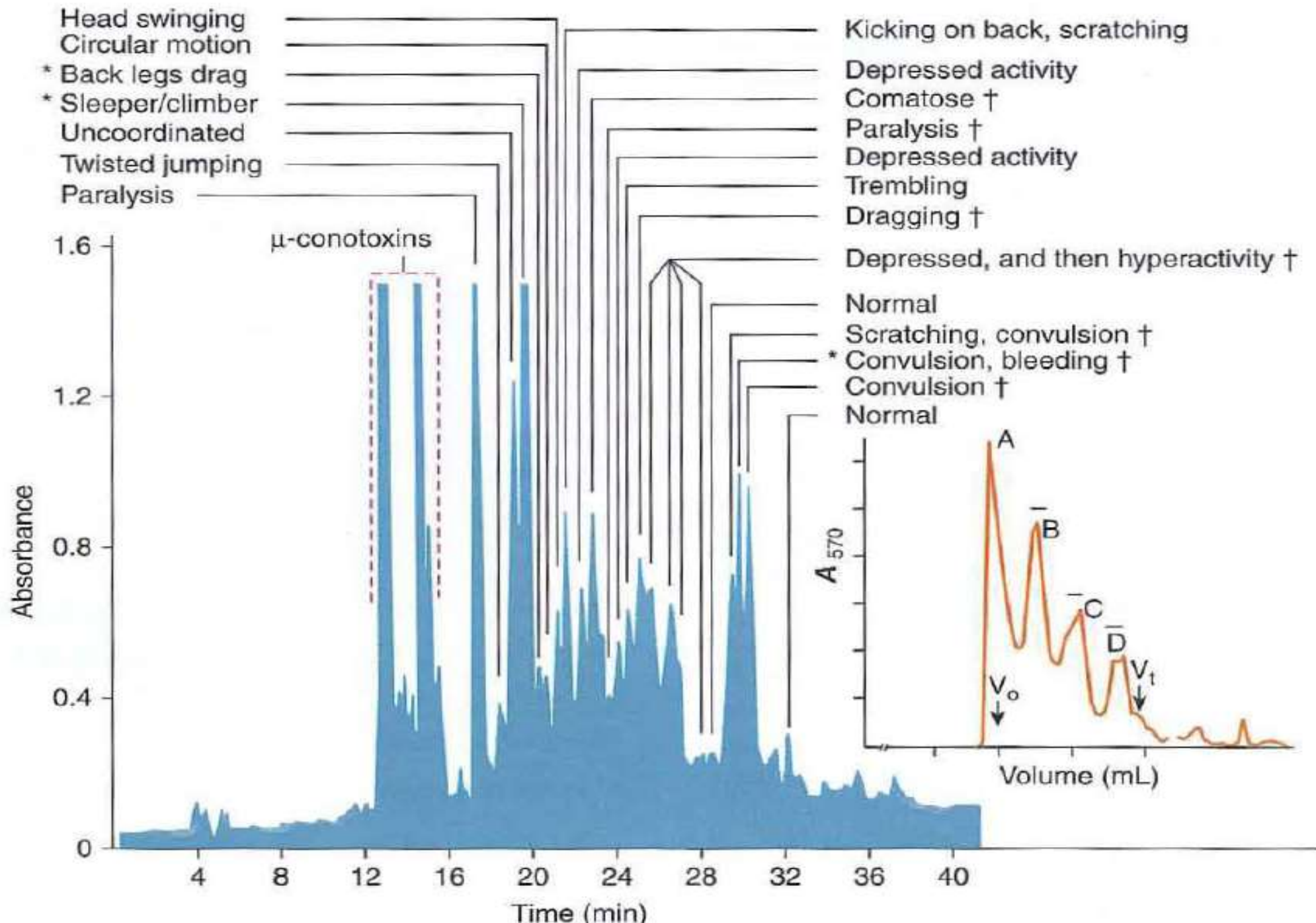


Table 26-9

**Intravenous LD₅₀ Values of Selected Toxins
Determined in Mice**

| TOXIN SOURCE | COMMON NAME | LD ₅₀ (μg/kg) |
|---------------------------------|------------------------------|--------------------------|
| <i>Clostridium botulinum</i> | Botulinum toxin | 0.0003 |
| <i>Crotalus viridis helleri</i> | Southern pacific rattlesnake | 1.3 |
| <i>Crotalus adamanteus</i> | Eastern diamondback | 1.5 |
| <i>Oxyuranus scutellatus</i> | Australian taipan | 2 |
| <i>Crotalus atrox</i> | Western diamondback | 2.2 |
| <i>Agkistrodon piscivorus</i> | Eastern cottonmouth | 4 |
| <i>Agkistrodon contortrix</i> | Copperhead | 11 |
| <i>Androctonus australis</i> | North African scorpion | 17 |
| <i>Notechis scutatus</i> | Australian tiger snake | 25 |
| <i>Naja siamensis</i> | Indochinese spitting cobra | 75 |

SOURCES: Data from Mebs (2002) and Russell (2001).



肉毒桿菌素



響尾蛇

鑽紋響尾蛇

太攀蛇



鑽紋響尾蛇

棉口蛇



ARACHNIDA-Scorpions

- Many scorpion venoms contain low-molecular-weight proteins, peptides, amino acid, nucleotides, and salts.
- *Centruroides vittatus* (條紋木蠍), the striped bar scorpion is commonly involved in envenomation but fatal fatalities are rare.
- After sting, the area becomes sensitive to touch, and merely pressing lightly over the injury will elicit an immediate retraction. Usually there is little or no local swelling and only mild erythema.



Spiders

- Of the 30,000 or so species, at least 200 have been implicated in significant bites on humans.
- All spiders except the Uloboridae family possess a venom apparatus that produces neurotoxins designed to paralyze or kill prey.
- Spider venoms are complex mixtures of low-molecular weight components, including inorganic ions, polypeptides, salts, free acids, amines, and neuron transmitters

- The acylpolyamines, composed of a hydrophobic aromatic carboxylic acid linked to a lateral chain of one to nine aminopropyl, aminobutyl, or aminopentyl units, are **voltage-dependent open-channel blockers** (sodium, calcium, and potassium channels) and/or blockers of the ion channel associated with **glutamate receptors**.
- The acylpolyamines possess insecticidal activity and induce fast insect paralysis via a reversible block of the insect neuromuscular junction
- Peptide toxins from spiders have proved useful in discrimination between different cellular components of native ion channel currents and for the molecular isolation and designation of cellular receptors

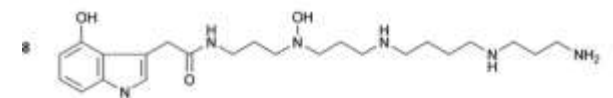
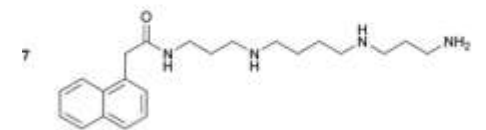
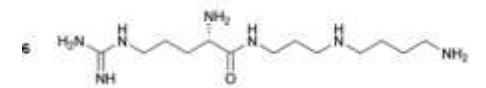
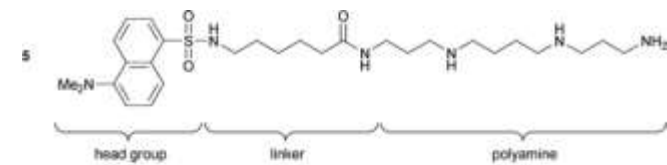


Table 26-11

Some Significant Spiders, Their Toxins, and the Targets of the Toxins

| SPIDER | PEPTIDE | TARGET* |
|---------------------------------|---------------------|------------------|
| <i>Acanthoscurria gomesiana</i> | Gomesin | PLM |
| <i>Agelenopsis aperta</i> | ω -AfaI-IVA | Ca^{2+} |
| | μ -Afatoxin 1-6 | Na^+ |
| <i>Grammostola spatula</i> | HaTx1,2 | K^+ |
| | GsMTx2,4 | MS |
| | GSTxSIA | Ca^{2+} |
| <i>Hadronyche versuta</i> | ω -ACTX-Hv1a | Ca^{2+} |
| | ω -ACTX-Hv2a | Ca^{2+} |
| | δ -ACTX-Hv1a | Na^+ |
| <i>Heteroscodra maculate</i> | HmTx1,2 | K^+ |
| <i>Ornithoctonus huwena</i> | Huwentoxin I | Ca^{2+} |
| | Huwentoxin IV | Na^+ |
| <i>Psalmopoeus cambridgei</i> | PcTx1 | ASIC |
| <i>Phrixotrichus auratus</i> | PaTx1,2 | K^+ |
| <i>Thrixopelma pruriens</i> | ProTxI,II | Na^+ |



巴西白頭膝蜘蛛

草蜘蛛屬



大蘭多蜘蛛





Table 26-12

Comparison of Clinical Effects of Bites by Some Spiders of Australia

| CLINICAL EFFECTS | LACTRODECTUS REDBACK SPIDERS | STEATODA CUPBOARD SPIDERS | LAMPONIDAE WHITE-TAIL SPIDERS | MYGALOMORPHAETWS, MOUSE SPIDERS, TRAPDOOR SPIDERS |
|--|---------------------------------|------------------------------|----------------------------------|--|
| Severe pain (%) | 62 | 26 | 27 | 49 |
| Duration of pain | 36 h | 6 h | 5 min | 60 min |
| Fang marks (%) | 6 | 17 | 17 | 58 |
| Initial erythema | 74 | 96 | 83 | 36 |
| Swelling (%) | 7 | 9 | 8 | 13 |
| Itchiness (%) | 38 | 48 | 44 | 0 |
| Nausea, vomiting, headache, malaise (%) | 35 | 30 | 9 | 36 |
| Distal limb bite (%) | 46 | 52 | 82 | 91 |

SOURCE: Data from Ialister and White (2004)

(hands and feet)

寡婦蛛屬
紅背蜘蛛

肥腹蛛屬

白尾蛛

土蜘蛛

Agelenopsis Species (American Funnel Web Spiders)



- 漏斗網蜘蛛 棚蛛屬
- The American funnel web spider (*Agelenopsis aperta*) contains three classes of agatoxins that target ion channels.
- The α -agatoxins appear to be noncompetitive antagonists of the glutamate receptor channels.
- The μ -agatoxins cause increased spontaneous release of neurotransmitter from synaptic terminals and repetitive action potentials in motor neurons.
- The action of the α -agatoxins is synergized by the μ -agatoxins causing channels to open at the resting potentials.

Latrodectus Species (Widow Spider)

- 寡婦蛛屬
- Mature **Latrodectus mactans** (黑寡婦) females range in body length 10 to 18 mm, whereas male range from 3 to 5 mm.
- The toxins named **latrotoxins** are synthesized as large precursors containing around 1000 amino acid (around 132-156 kDa) that undergo proteolytic processing to 130 kDa and activation in the lumen of the venom gland.
- alpha-latrotoxin is the most studied protein that is toxic only to vertebrates and not to insects or crustaceans.



- α -latrotoxin exerts its toxic effects on the vertebrate central nervous system depolarizing neurons by increasing intracellular $[Ca]^{2+}$ and by stimulating exocytosis of neurotransmitters from nerve terminals.
- α -latrotoxin acts presynaptically to release neurotransmitter acetylcholine, norepinephrine and GABA from vertebrate sensory and motor neurons, as well as endocrine cells.
- The toxin acts as nerve ending to prevent relaxation of muscles, causing tetany-constant, strong and painful muscle contractions.

Loxosceles Species (Brown or Violin Spiders)



- 棕色遁蛛
- This spider has six eyes grouped in three dyads. Females average 8 to 12 mm in body length, whereas males average 6 to 10 mm. Both males and females are venomous.
- The venom of Loxosceles spiders appears to contain phospholipase, protease, esterase, collagenase, hyaluronidase, deoxyribonuclease, and ribonuclease.
- The venom has coagulation and vasoconstriction properties and it causes selective vascular endothelial damage

Ticks (蜱)

- The tick bite involves insertion of cutting, tube-like mouthparts through the host's skin with anchoring so that the tick can feed for hours, days, or weeks.
- Ticks are known to organisms causing Lyme disease, Q fever, tick-borne encephalitis, etc.
- Tick saliva contains a number of active constituents. For example, apyrase (ATP-diphosphohydrolase), which hydrolyzes ADP—that is released at the bite site thereby inhibiting ADP-induced platelet aggregation.



- kininase (ACE-like protein or angiotensin-converting enzyme-like protein), which hydrolyzes circulating kinins and reduces the host inflammatory response.
- serine protease inhibitors, which inhibit coagulation enzyme. An anticomplement protein that inhibits an enzyme in the alternative pathway for complement
- Potentially 50 species of ticks are associated with clinical paralysis. As tick bites are often not felt, the first evidence of envenomation may not appear until several days later.
- The saliva of *Ixodes holocyclus* (硬蜱科) has yielded a peptide holocyclotoxin-1 that may cause paralysis.

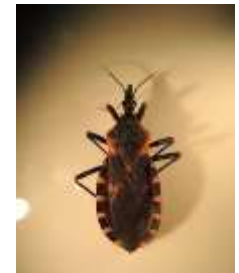
CHILOPODA (CENTIPEDES) 蜈蚣

- Centipedes range in length from 3 to almost 300 mm.
- Centipede venom contain high-molecular-weight proteins, proteinases, esterases, histamine, lipids and polysaccharides.
- The venom also contains a heat-labile cardiotoxic protein of 60 kDa that produces, in humans, changes associated with acetylcholine release.
- The bite produces two tiny punctures, sharp pain, immediate bleeding, redness, and swelling often lasting for 24 hours. Localized tissue changes and necrosis have been reported.



INSECTA: Heteroptera (True Bugs) 異翅亞目

- 異翅亞目包括蝽象、水蠅、紅娘華、水螳螂等昆蟲
- The clinically most important of the true bugs are the Reduviidae(獵蝽科).
- The venom of these bugs appears to have apyrase activity and to lack 5-nucleotidase, inorganic pyrophosphatase, phosphatase, and adenylate kinase activities, but it contains omega-conotoxins and is fairly rich in protease properties and inhibits collagen-induced platelet aggregation.
- The bites of *Triatoma* species (kissing bug, 錐鼻蟲) are painful and give rise to erythema, pruritus, increased temperature in the bitten part, localized swelling.



Hymenoptera (膜翅目)-Ants

- Most ants have stings, but those that lack them can spray a defensive secretion from the tip of the gaster, which is often placed in the wound of the bite.
- Clinically important stinging ants are the harvesting ants (*Pogonomyrmex*, 毛收割家蟻), fire ants (*Solenopsis*, 火蟻), and little fire ants (*Ochetomyrmex*, 小火蟻).
- The venoms of the ants vary considerably. Formicinae ant venom contains about 60% formic acid. Fire ant venoms are poor in polypeptides and proteins, but are rich in alkaloids.
- In multiple stings there may be nausea, vomiting, vertigo, increased perspiration, respiratory difficulties, cyanosis, coma, and even death



Apidae (Bees)

- The commonest stinging bees are **Apis mellifera** and the Africanized bee, **Apis mellifera adansonii**.
- The venom of the Africanized bee is not remarkably different from that of the European bee, *A. mellifera*. The former bee is smaller and gives less venom, but its aggressiveness is such that attacks of 50 to hundreds of bees are not unusual.
- The venom contains biologically active peptides, such as melittin, apamine, mast cell-degranulating peptide, as well as phospholipases A, hyaluronidase and histamine.



蜂毒反應

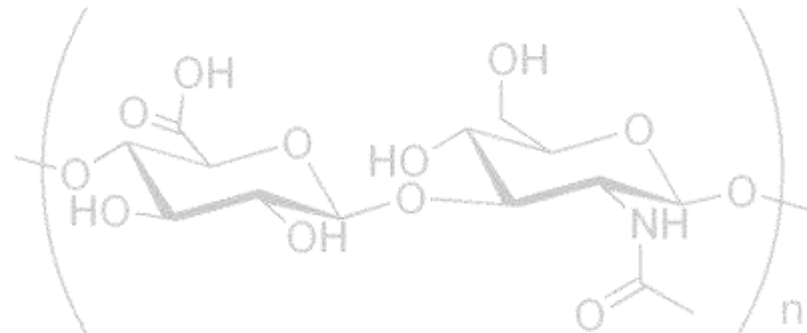
- 人被螫刺後會出現紅腫、熱疼並伴有搔癢感的局部反應，經 2 ~ 3 天腫脹自行消退
- 有極少數人會產生過敏反應，在螫刺後 1 小時內發生全身搔癢、胸悶、血壓下降、 臉色蒼白等過敏症狀，
- 通常被螫刺在 2 0 0 隻以上才會引起明顯中毒反應。

多數學者認為蜂螫致死量為 5 0 0 ~ 1 0 0 0 隻。

透明質酸酶 (hyaluronidase)

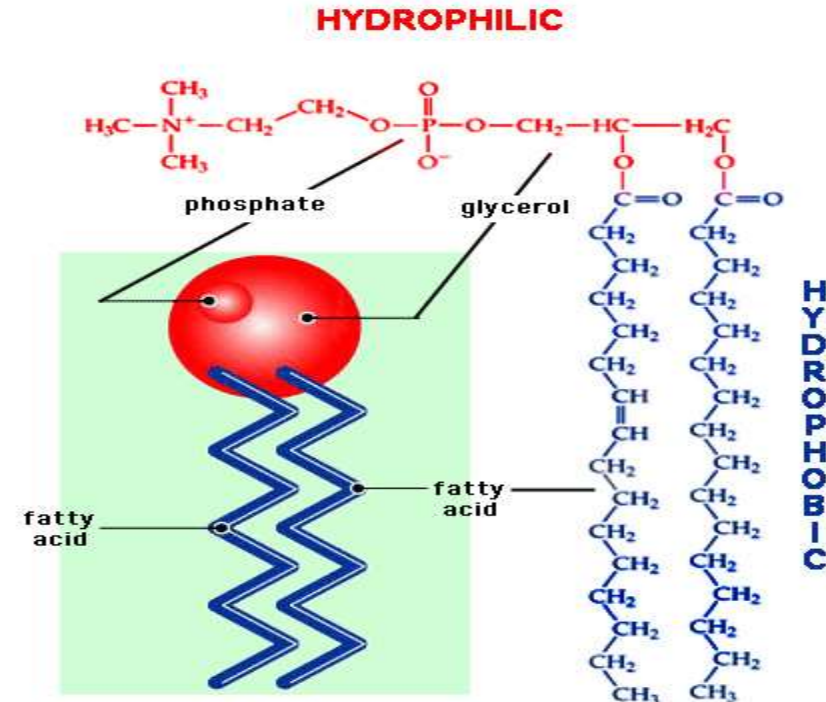
分子量為 **35,000**。主要功能為促進透明質酸(重複性雙糖結構複合體)的分解。

生物活性很強，無直接毒性，能促使蜂毒成分在局部組織間滲透及擴散，是動物性毒素中普遍存在的一種。



磷脂酶A2 (phospholipase A2)

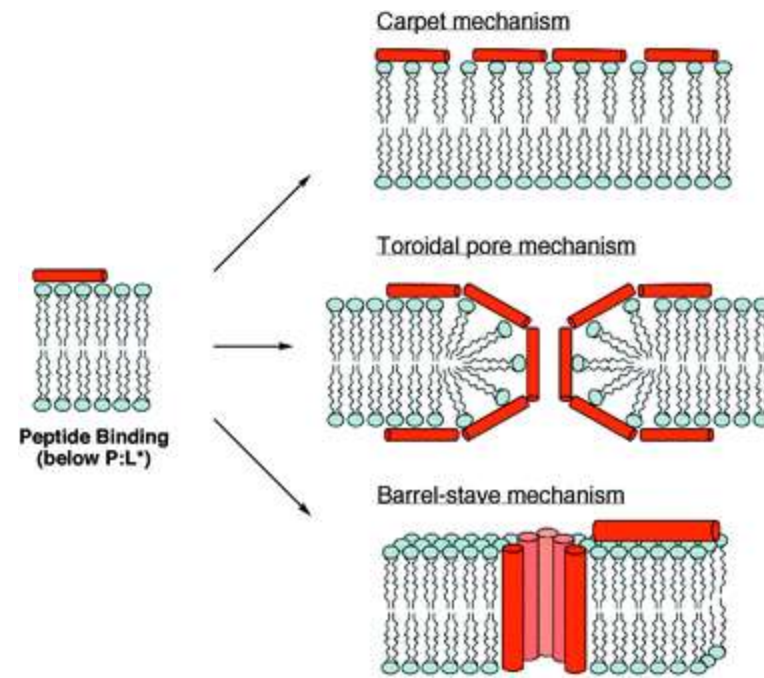
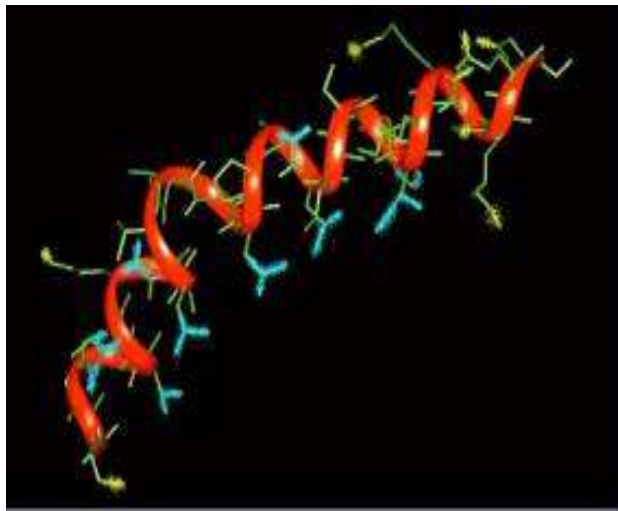
佔12%。分子量為14,500。由129個胺基酸組成。能夠迅速水解生物膜，發揮蜂毒的生物活性，有很強的間接溶血作用。



蜂毒肽 (mellitin) :

又稱蜂毒溶血肽、蜂針素、蜂毒溶血素。是蜂毒中的主要活性物質約佔50%。分子量為2,840，由26個胺基酸組成的單體，單體又聚合為四聚體，四聚體解離為具有高度活性的單體。

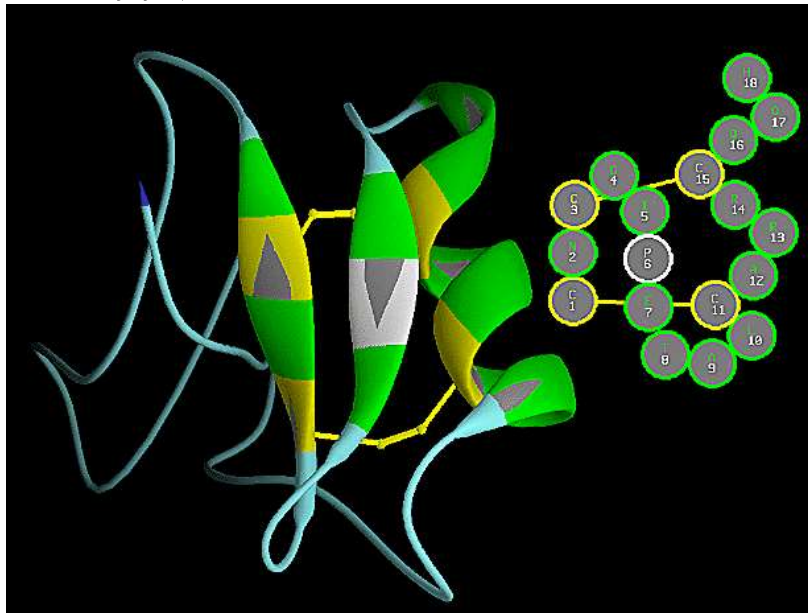
主要干擾生物膜上的磷脂分子，促使細胞膜分解成很多部份，最後使紅血球溶解具有抗凝血作用。



蜂毒神經肽（apamin）

由**18** 個胺基酸組成的多肽類。是一種很強的神經毒素，是動物神經毒素中分子最小的神經毒，可通過各種給藥途徑穿過血腦屏障，作用於中樞神經，目前已經可用人工合成。

Apamine主要是抑制 中樞神經系統 **Calcium-activated potassium channels**的作用



組織胺（histamine）：

蜂毒中的含量與蜜蜂的日齡有關，約佔蜂毒重量的0.1~1.5%。主要引起平滑肌和骨骼肌的緊張收縮，使皮膚灼痛，並引起氣喘 休克等急性徵狀。

組織胺主要儲存在體內各組織的肥大細胞(mast cells)中，次要地方。

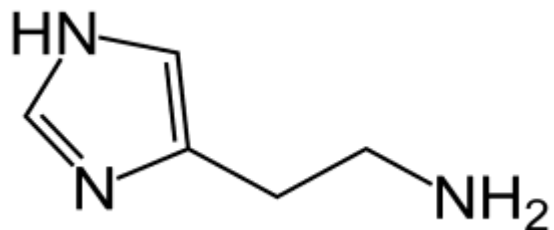
組織胺受體:

目前已被發現的組織胺受體至少有三種亞型： H_1 、 H_2 、 H_3

A. H_1 受體: 分佈於平滑肌、內皮細胞、腦部

B. H_2 受體: 分佈於胃黏膜、心肌、肥大細胞、腦部

C. H_3 受體: 分佈在突觸前、腦部、腸肌叢和其他的神經元



Lepidoptera (Caterpillars, Moths, and Butterflies)

- The toxic material found in the venom glands of lepidoptera contains aristolochic acids, cardenolides, krein, and histamine among other substances.
- Contacts with larvae of the saturniid moths (天蠶蛾) in South America (***Lonomia achelous*** and ***lonomia oblique***) can cause severe coagulopathy, due to inhibition of clotting factor XIII by a venom component called lonomine V.



- Severe envenomation can cause cerebral hemorrhage and death

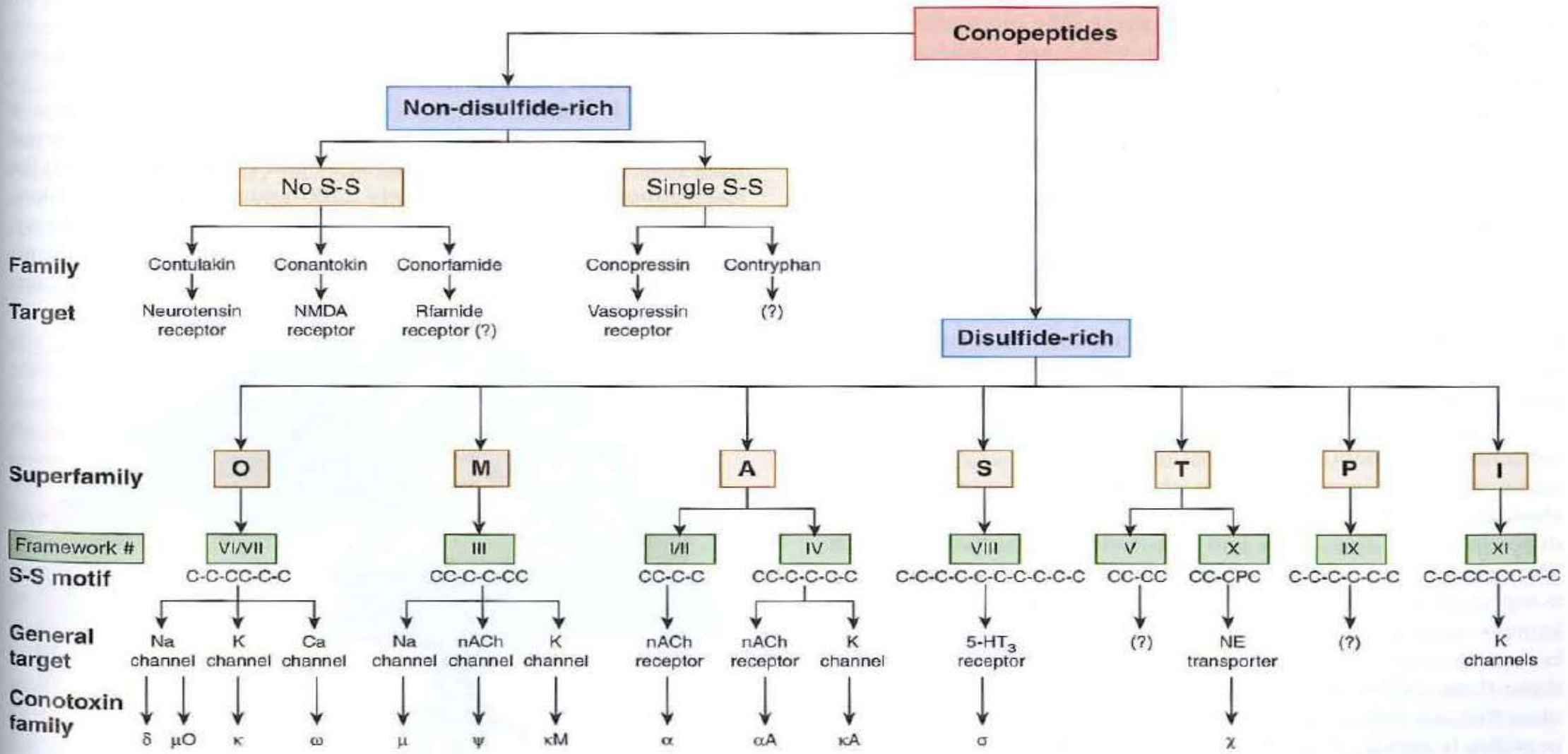
MULLOSCA (CONE SNAILS) 芋螺

- Cone snails have a venom duct for synthesis and storage of venom and hollow harpoon-like teeth for injection of the venom.
- Components have become known as conotoxins, which may be rich in disulfide bonds, and conopeptides.
- Molecular targets include G-protein-coupled receptor, neuromuscular transmitters, and ligand- or voltage-gated ion channels. Some components have enzymatic activity



- The two major divisions of Conus toxins are the disulfide-rich conotoxins and the peptides that lack multiple disulfide cross-links
- Most disulfide-rich conotoxins are small and consist of 12 to 30 amino acids. These toxins contain an unusually diverse complement of posttranslationally modified amino acids.
- Apparently, the posttranslational modification enzyme-carboxylase is present in their venom ducts.
- After injection, multiple conopeptides act synergistically to affect the targeted prey.
- The term **toxin cabal** has been applied to this coordinated action of the conopeptide mixture

- The fish hunting species *Conus purpurascens* apparently has two distinct phases whose effects differ in time and space.
- The “ lightning-strike phase” causes immediate immobilization of the injected prey because various venom components inhibit voltage gated sodium channel inactivation and block potassium channels, resulting in massive depolarization of axons in the vicinity of the injection site and a tetanic state.
- The second physiologic phase the “motor phase,” acts more slowly as conotoxins must be distributed throughout the body of the prey.
- Various conopeptides inhibit presynaptic calcium channels that control neurotransmitter release, the postsynaptic neuromuscular nicotinic receptors, and the sodium channels involved in the muscle action potential



α-CTX的靶點是煙鹼型乙酰膽鹼受體、ω-CTX為電壓敏感型鈣通道的阻斷劑
 μ-CTX是鈉通道的阻斷劑 δ-CTX可使延遲型鈉通道失活劑
 κ-CTX則是鉀通道的抑製劑 ψ-CTX是煙鹼型乙酰膽鹼受體的非競爭性拮抗劑

芋螺毒素的應用

| 毒素名稱 | 類型 | 種族 | 作用 | 開發情況 |
|--------------|------------|------------------------|-------|--------|
| Vc1.1 | α | <i>Conus victoriae</i> | 神經性疼痛 | 臨床前 |
| CVID | ω | <i>C. catus</i> | 神經性疼痛 | II期臨床 |
| MVIIA | ω | <i>C. magus</i> | 癌症疼痛 | III期臨床 |
| MrtA/B | κ | <i>C. mannoreus</i> | 神經性疼痛 | 臨床前 |
| Contutokin-G | Contutokin | <i>C. geographus</i> | 慢性疼痛 | II期臨床 |
| Conantokin-G | Conantokin | <i>C. geographus</i> | 癲癇 | 臨床前 |

REPTILES-Lizards

- The Gila monster (*Heloderma suspectum*, 美國毒蜥) and the Mexican beaded lizards (*Heloderma horridum*, 串珠蜥蜴) are divided into five subspecies.
- The venom of these lizard has serotonin, amine oxidase, phospholipase A, a bradykinin releasing substance, helodermin, gilatoxin, and low-proteolytic as well as high-hyaluronidase activity, but lacks phosphomonoesterase and phosphodiesterase, acetylcholinesterase, nucleotidase, ATPase, deoxyribonuclease, ribonuclease, amino acid oxidase, and fibrinogenocoagulase activities.



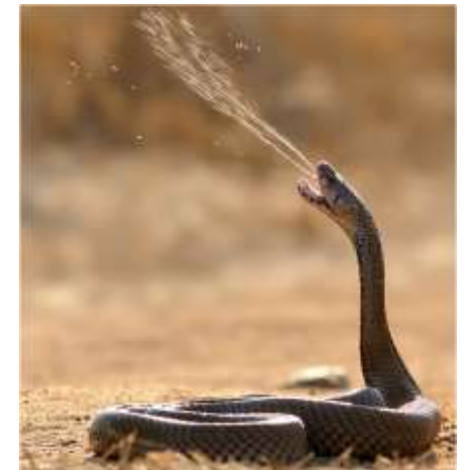
- The clinical presentation of a helodermatid bite can include pain, edema, hypotension, nausea, vomiting, weakness, and diaphoresis. No antivenin is commercially available. Treatment is supportive.
- The venom has been shown to contain a 25-kDa protein, **helothermine**, containing 223 amino acids and four pairs of disulfide bonds, which appears to inhibit Ca^{2+} flux from the sarcoplasmic reticulum.
- A fraction causing hemorrhage in internal organs and the eye, a glycoprotein of 210 amino acid residues with plasma **kallikrein**-like properties, has also been described.

SNAKES

- Of the approximately 2700 known species of snakes, about 20% are considered to be venomous.
- Venomous snakes primarily belong to the following family: Viperidae (vipers) (蝮蛇科, 蝰蛇科, 響尾蛇科), Elapidae (蝙蝠蛇科), Atractaspidae (穴蝰科) and Colubridae(游蛇科).
- Overall, the Colubridae are considered the largest venomous family, and are composed of nearly 60% of all snakes.



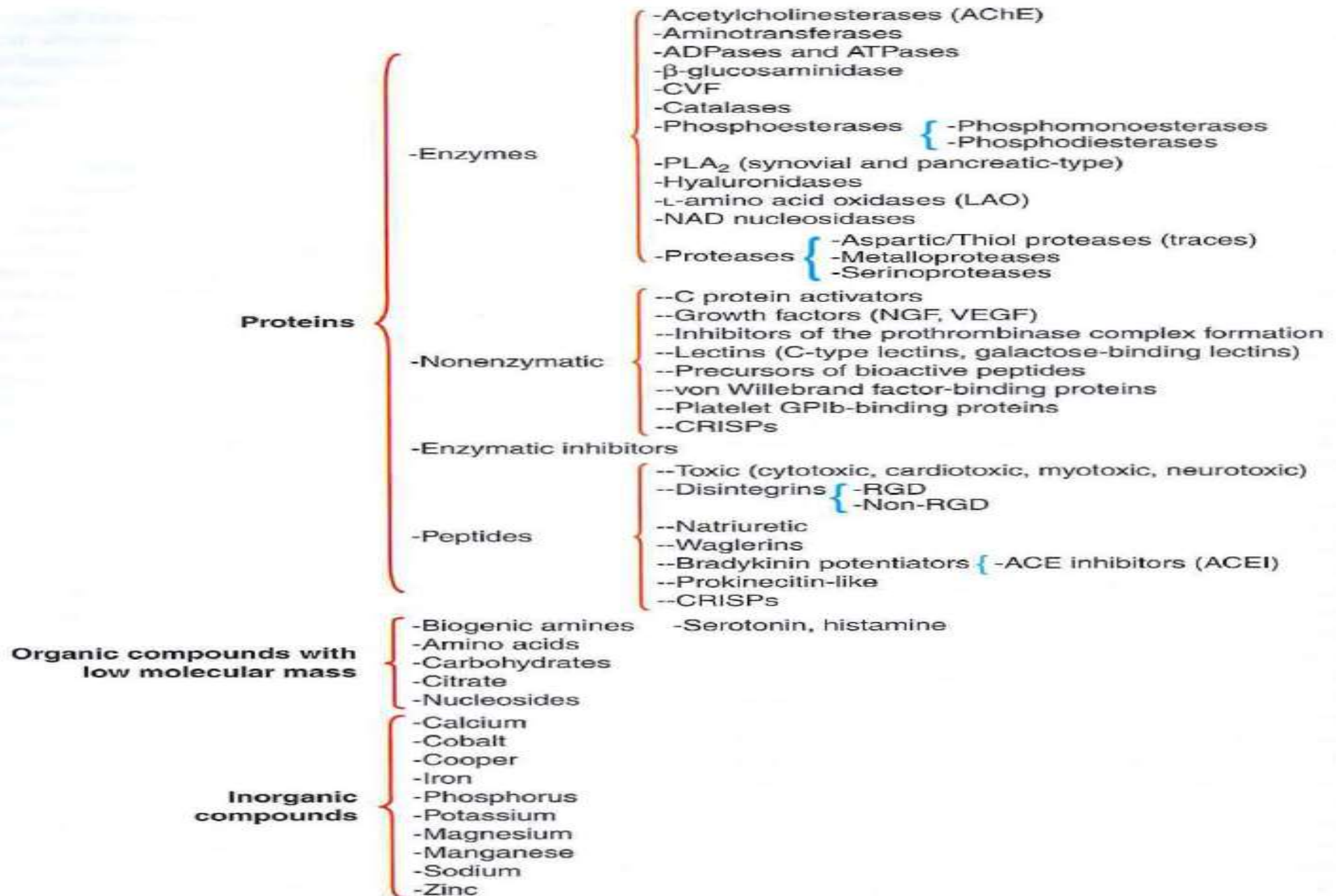
- Scale pattern and coloration provide distinct boundaries in the wild and often carry unspoken warnings based on a reputation for snake venom toxicity for a given species.
- The Viperidae fang structure is regarded as the most developed and efficient means of venom, or toxin, delivery to prey
- The venom gland is positioned at the base of a long (-30 mm) hollow retractable fang.
- Another highly developed venom delivery apparatus is characteristic of the spitting cobras, aptly named for their ability to project venom via glands that protrude from the base of the fang opening.



Snake Venoms

- Snake venoms are complex mixtures: proteins and peptides, consisting of both enzymatic and nonenzymatic compounds, make up over 90% of the dry weight of the venom.
- Snake venoms also contain inorganic cations such as sodium, calcium, potassium, magnesium, and small amounts of zinc, iron, cobalt, manganese, and nickel.
- For example, zinc ions appear to be necessary for anticholinesterase activity, and calcium may play a role in the activation of phospholipase A and the direct lytic factor.

- A simplistic approach would group toxin components as neurotoxins, coagulants, hemorrhagins, hemolytics, myotoxin, cytotoxin, and nephrotoxins.
- At least 26 different enzymes have been isolated from snake venoms, which can be a sequence of 150 to 1500 amino acids.
- No single snake venom contains all 26 enzymes.
- Proteolytic enzymes that catalyze the breakdown of tissue proteins and peptides include peptide hydrolases, proteases, and peptidase.
- The proteolytic enzymes have molecular weights between 1,000 and 95,000. Some are inactivated by ethylenediaminetetraacetic acid (EDTA) and reducing reagent.

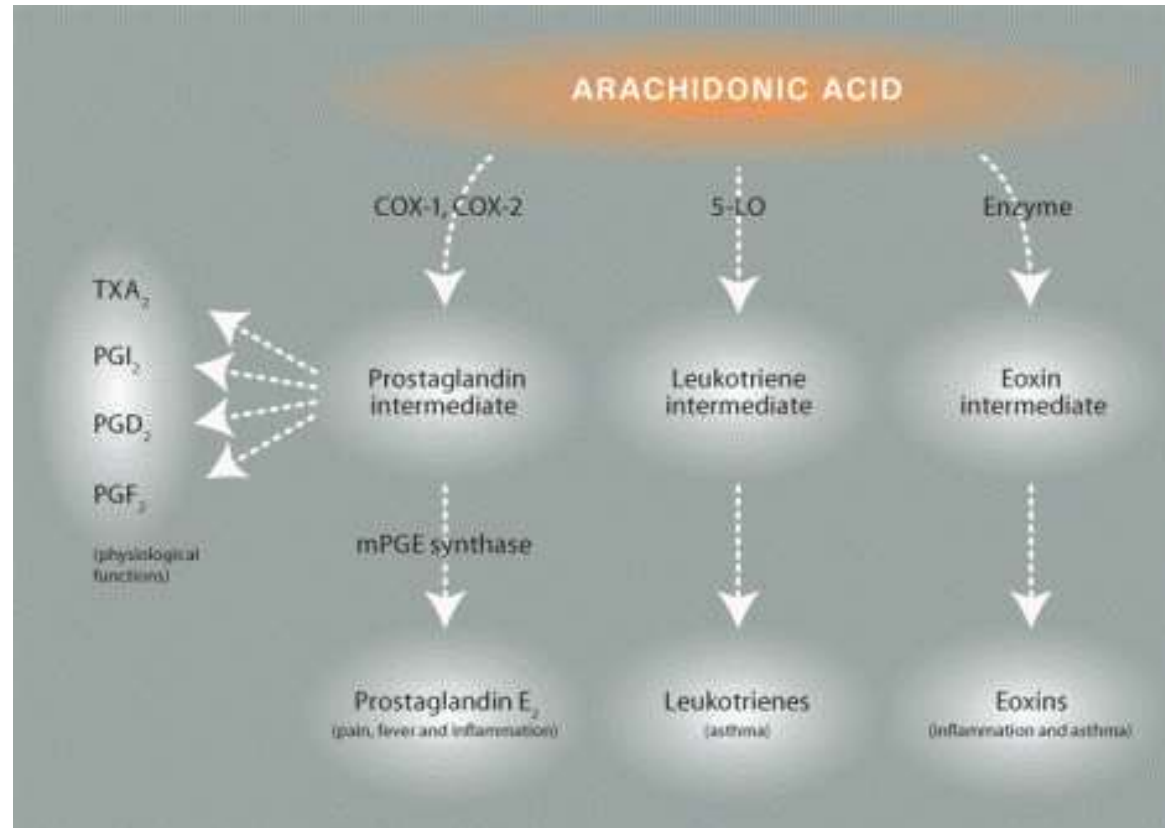
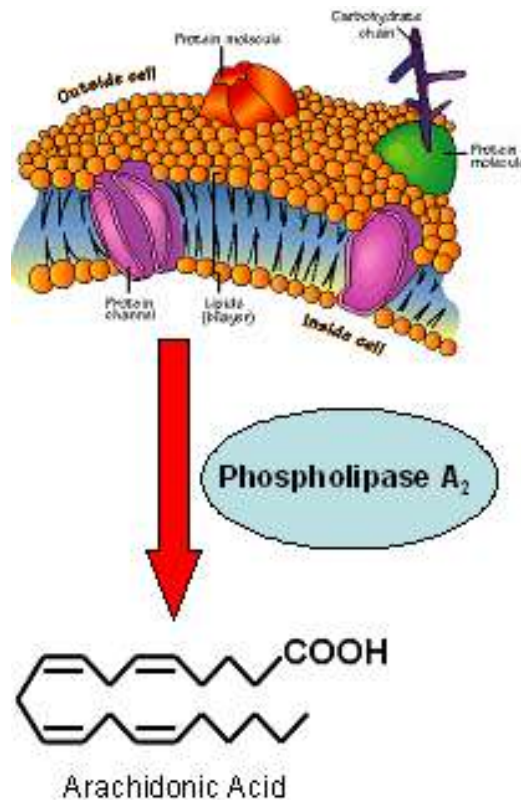


- Collagenase is a specific kind of proteinase that digests collagen. This activity has been demonstrated in the venoms of a number of species of crotalids and viperids. The venom of **Crotalus atrox** (西部菱背響尾蛇) digests mesenteric collagen fibers but no other proteins. EDTA inhibits the collagenolytic effect, but not the arginine esterase effect.
- Hyaluronidase cleaves internal glycoside bonds in certain acid mucopolysaccharides resulting in a decrease in the viscosity of connective tissues.
- The breakdown in the hyaluronic barrier allows other fractions of venom to penetrate the tissues, causing hyaluronidase to be called “spreading factor”.



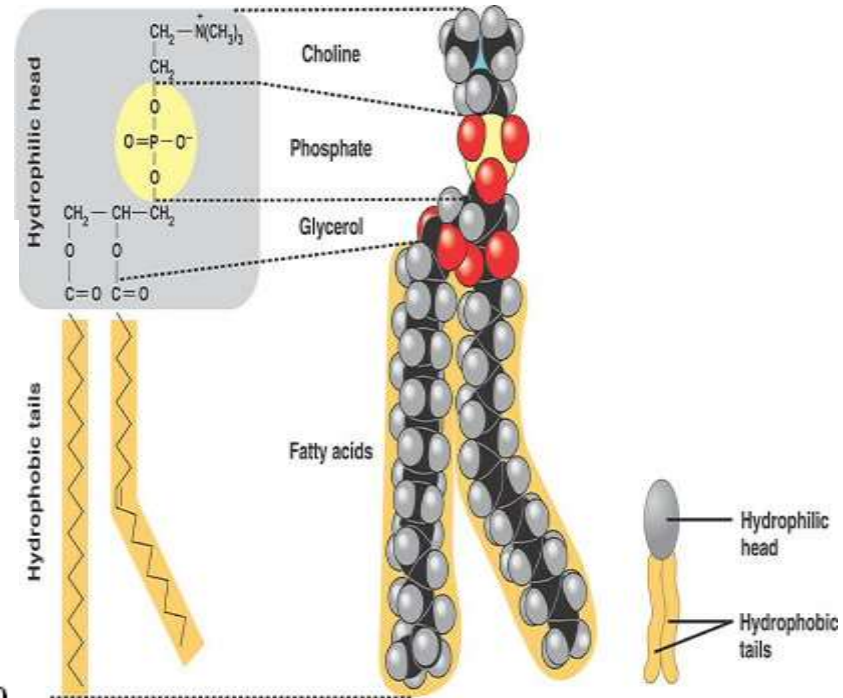
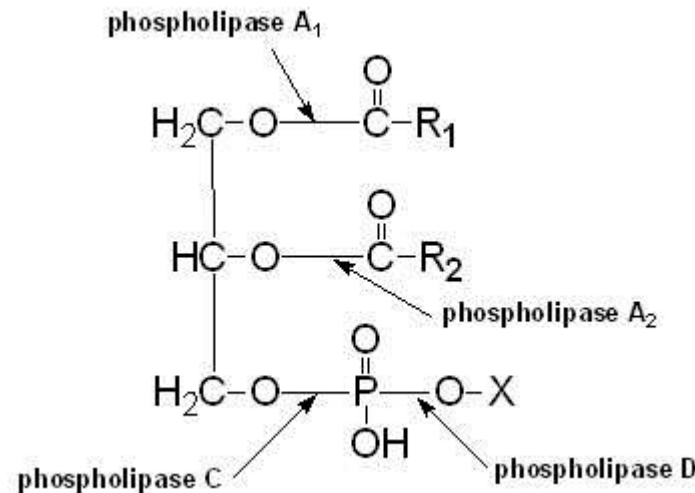
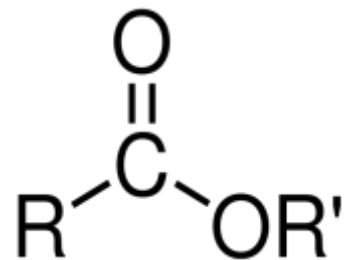
Phospholipase A2

- **Phospholipases A2** (PLA2s) are upstream regulators of many inflammatory processes.



Phospholipase A₂

- Phospholipase A₂ (PLA₂) catalyzes the hydrolysis of the fatty acid ester at the 2-position of diacylphosphatides, forming lysophosphatides and fatty acids, primarily unsaturated.
- Snake venoms are the richest sources of PLA₂ enzymes.
- The enzyme is widely distributed in the venoms of
 - *Elapids*
 - *Vipers*
 - *Crotalids*
 - *Sea snakes*
 - *Colubrids*

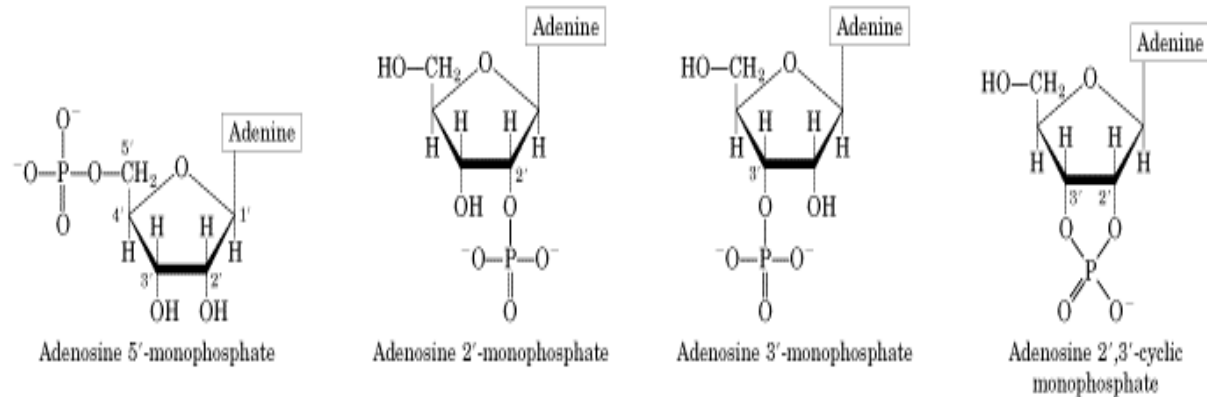


- Pharmacological effects of PLA₂ including
 - hydrolysis of membrane phospholipids
 - liberation of pharmacologically active products
 - effects independent of enzymatic action

- Snake venom PLA₂ enzymes can be separated into three major groupings depending on their pharmacological activities
 - Low-toxicity ($LD_{50} > 1 \text{ mg/kg}$)
 - High-toxicity ($1 \text{ mg/kg} > LD_{50} > 0.1 \text{ mg/kg}$)
 - Presynaptically acting toxins (*β -bungarotoxin*)

Phosphomonoesterase

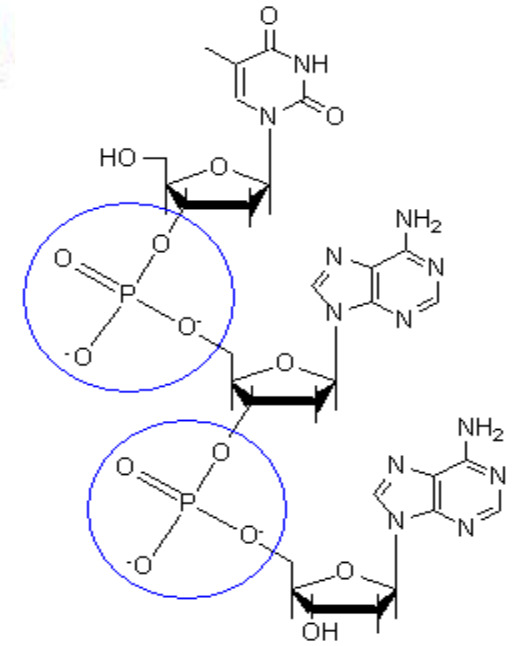
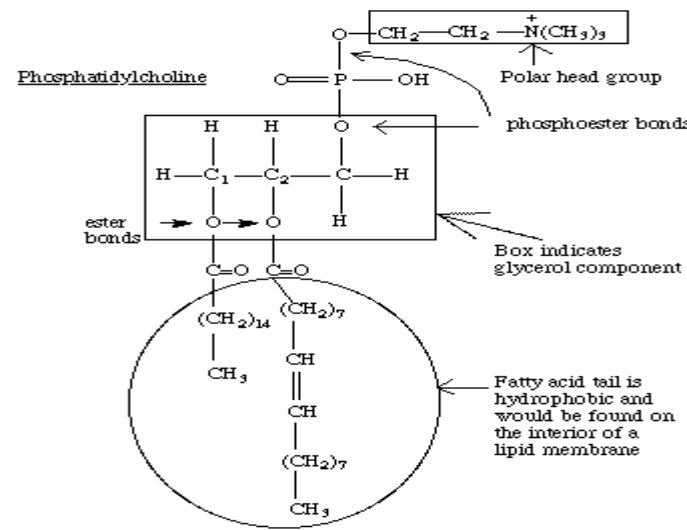
- Phosphomonoesterase (phosphatase) is widely distributed in the venoms of all families of snakes except the colubrids.
 - Acid phosphatase (pH 5.0)
 - Alkaline phosphatase (pH 8.5)



responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins, and alkaloids.

Phosphodiesterase

- Phosphodiesterase has been found in the venoms of all five families of poisonous snakes
- It releases 5-mononucleotide from the polynucleotide chain and thus acts as an exonucleotidase, attacking DNA RNA



Polypeptides

- Snake venom polypeptides are low-molecular-weight proteins that do not have enzymatic activity.
 - Neurotoxins (α -bungarotoxin)
 - Platelet aggregation inhibitors:
 - Disintegrins
 - Platelet aggregation inducers
 - Trimucytin (龜殼花)
 - Aggretin (馬來亞腹蛇)

Less than 50 amino acids

Fibrinogenolytic enzymes

- Two types of fibrinogenolytic enzymes including metalloproteinases and the serine proteinases, have been isolated from venom of Viperidae, Elapidae, and Crotalidae snake families.
- The snake venom hemorrhagic metalloproteinases (SVMP) are enzymes that disrupt the hemostatic system.
- SVMPS degrade proteins such as laminin, fibronectin, type IV collagen, and proteoglycan from the endothelial basal membrane; degrade fibrinogen enhancing the hemorrhagic action, and inhibit platelet aggregation and stimulate release of cytokines.

Table 26-13**Miscellaneous Properties of Some α -Chain and β -Chain Fibrin(ogen)ases**

| PROPERTIES | α -CHAIN FIBRINOGENASE | β -CHAIN FIBRINOGENASE |
|----------------------|----------------------------------|---------------------------------|
| Common name | Fibrolase | β -Fibrinogenase |
| Class of enzyme | Metalloproteinase | Serine protease |
| Chain length | 203 amino acids | 232 amino acids |
| Molecular weight | ~22.7 kDa | ~26 kDa |
| pI | 6.8 | ~3 |
| Carbohydrate content | None | >30% |
| pH optimum | 7.1–7.4 | 8.5–9.5 |

SOURCE: Data from Swenson and Markland (2005).

The coagulation process

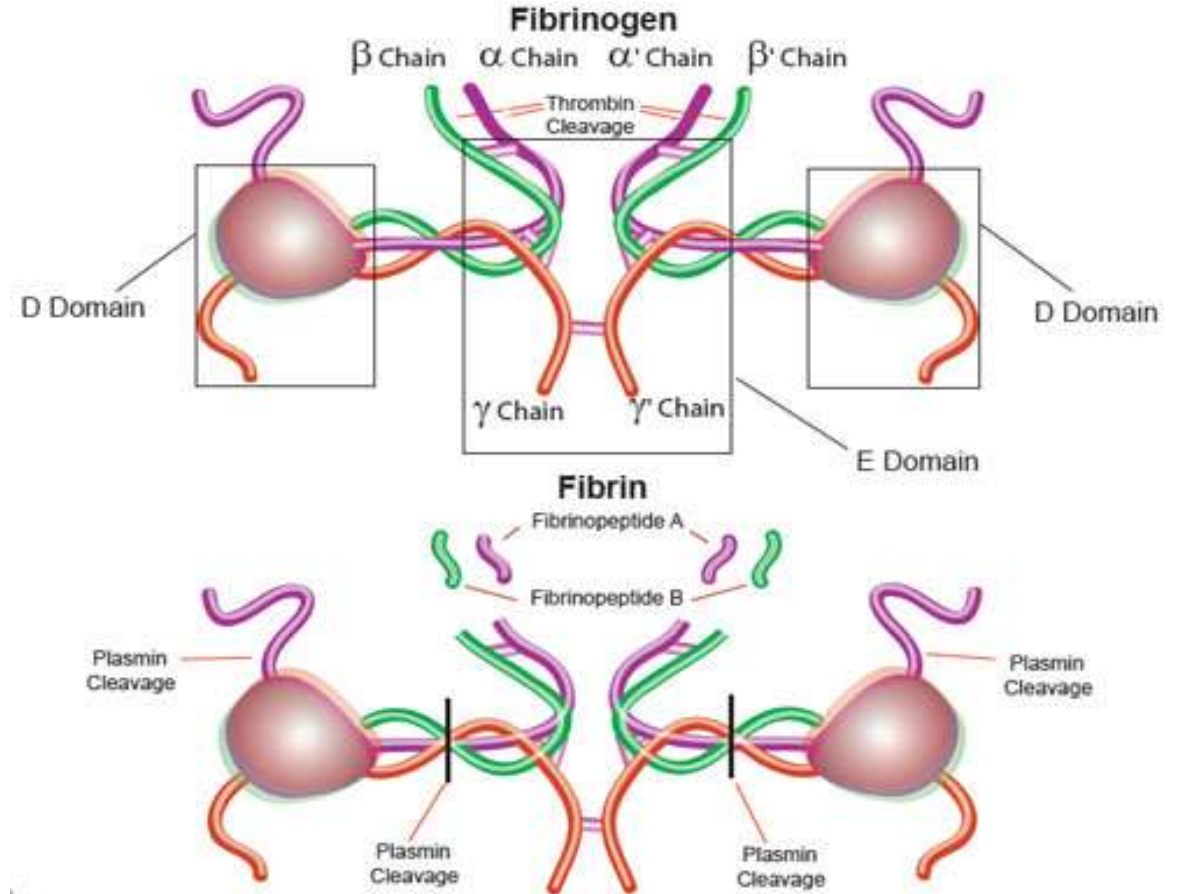
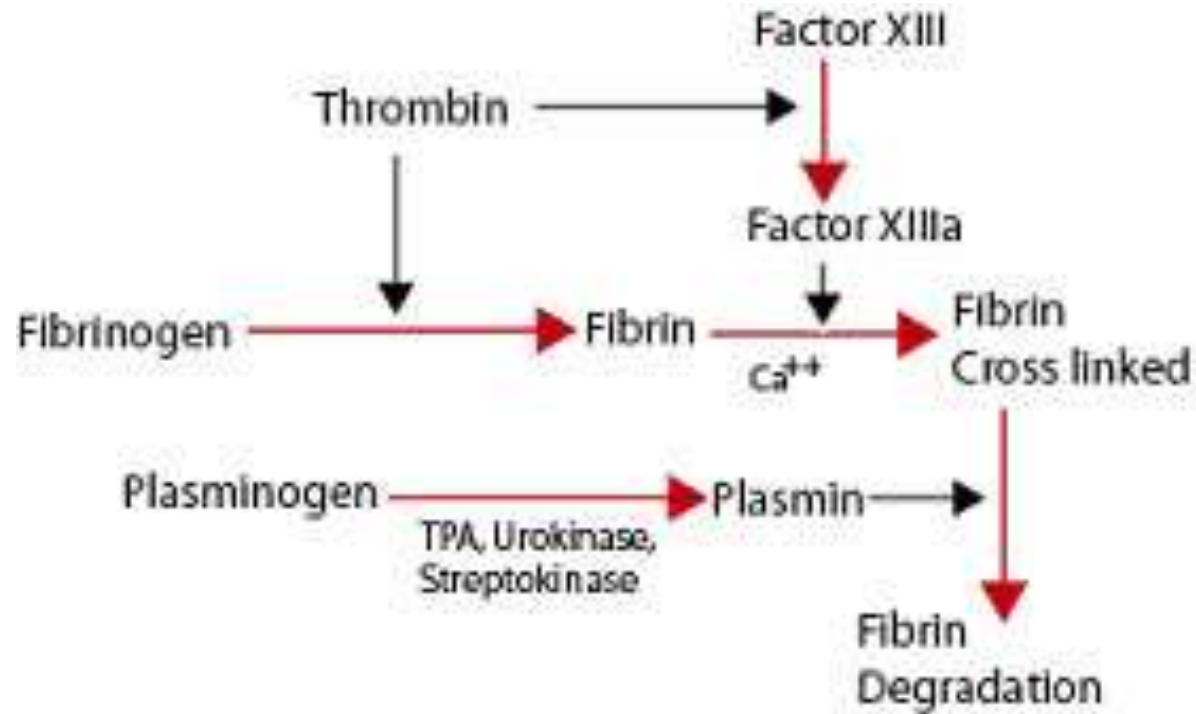


Table 26-15

Comparison of Thrombin and Thrombin-like Snake Venom Enzyme Actions

| ENZYMES | ACTION ON HUMAN FIBRINOGEN | | | | |
|--|-----------------------------|---|------------------------------|----------------------------------|-------------------------------------|
| | FIBRINOPEPTIDES RELEASED | CHAIN DEGRADATION | ACTIVATION OF FACTOR XIII | PROTHROMBIN FRAGMENT CLEAVAGE | PLATELET AGGREGATION AND RELEASE |
| Thrombin | A – B | $\alpha(A)$ | Yes | Yes | Yes |
| Thrombin-like enzymes | A [*] | $\alpha(A)$ [†] or $\beta(B)$ [‡] | No | Yes or no [§] | No |
| <i>Agkistrodon c. contortrix</i> venom | B | ND | Incomplete | ND | No |
| <i>Bitis gabonica</i> venom | A + B | ND | Yes | ND | ND |

ND, not determined.

^{*}Includes ancrod, batroxobin, crotalase, and the enzyme from *T. okinavensis*.

[†]Ancrod (batroxobin degrades $\alpha(A)$ chain of bovine but not human fibrinogen).

[‡]Crotalase.

[§]Fragment I released by crotalase and *Agkistrodon contortrix* venom, but not by ancrod or batroxobin.

SOURCE: Data from Russell (2001).

Table 26-17**Snake Venom Proteins Active on the Hemostatic System**

| GENERAL FUNCTIONAL ACTIVITY | SPECIFIC BIOLOGICAL ACTIVITY |
|------------------------------------|---|
| Procoagulant | Activates factors II, V, IX, X, and protein C Fibrinogen clotting |
| Anticoagulant | Factor IX/factor X-binding protein Thrombin inhibitor Phospholipase A |
| Fibrinolytic | Fibrin(ogen) degradation Plasminogen activation |
| Vessel wall interactive | Hemorrhagic |

SOURCES: Data from Markland (1998) and Russell (2001).

Table 26-18**Basal Bioactivities of Some Toxin Types**

| TOXIN | ACTIVITY |
|--------------------|---|
| 3FTx | α -Neurotoxicity, blocks nicotinic acetylcholine receptor |
| ADAM | In Viperidae venoms, proteolytic cleavage of C-terminal domains results in direct fibrinolytic activity, liberation of disintegrins, which inhibit platelet aggregation |
| Cobra venom factor | Causes unregulated activation of complement cascade, hemolysis, cytolysis |
| Crotamine | Myonecrosis, modifies voltage-gated sodium channels |
| Factor V | In taipan and brown snake venom, combines with toxic form of factor X to convert prothrombin to thrombin |
| Kallikrein | Increases vascular permeability, stimulates inflammation, and reduces blood pressure |

| | |
|----------------------|--|
| Kunitz | Inhibits plasmin and thrombin and other serine proteases, blocks L-type calcium channels |
| L-Amino oxidase | Induces apoptosis, decreases platelet aggregation, inhibits blood factor IX |
| PLA ₂ | Releases arachidonic acid from phospholipids, resulting in inflammation and tissue destruction |
| VEGF | Increases permeability of vascular bed causing hypotension and shock |
| Whey acidic proteins | Inhibit leukoproteinases |

SOURCE: Data from Fry (2005).

CONCLUSION

- The myriad toxins produced by plants and animals range from relative simplicity of small chemical agents to the exceedingly complex proteinaceous toxins.
- The effects of these compounds amazingly diverse and can range from local irritation to systematic destruction and death.
- As laboratory techniques become more sophisticated and new methods are developed, research concerning toxins and their effects will continue to grow