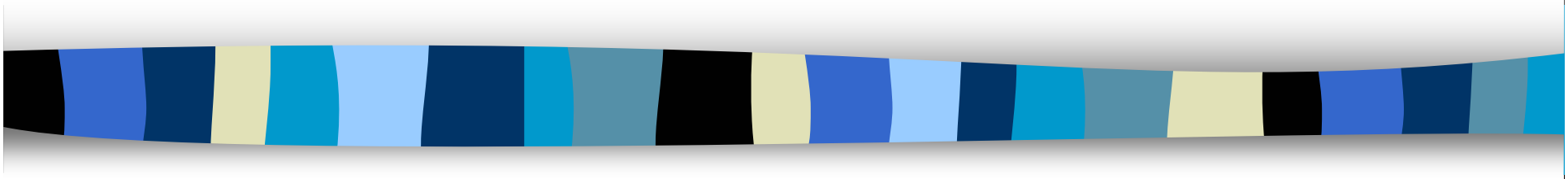
# Fyziologie působení farmak a toxických látek



## Přednáška č.6
## Přírodní toxiny

## Toxiny:

= toxické látky nebo jejich směsi produkované živými organismy;

- mikrobiální toxiny;
- mykotoxiny;
- toxiny produkované řasami a sinicemi;
- toxiny produkované cévnatými rostlinami;
- toxiny živočišného původu.

**Bakteriální toxiny** – proteiny nebo peptidy, mají antigenní vlastnosti – cholera toxin, pertussis toxin, tetanus toxin, botulotoxin, difterotoxin atd. Řada těchto látek je extémně toxická a postihuje především nervový, svalový a kardiovaskulární systém.

Řada bakteriálních toxinů má i praktické využití – př. Cry toxiny produkované Bacillus thuringiensis, využívané jako insekticidy.

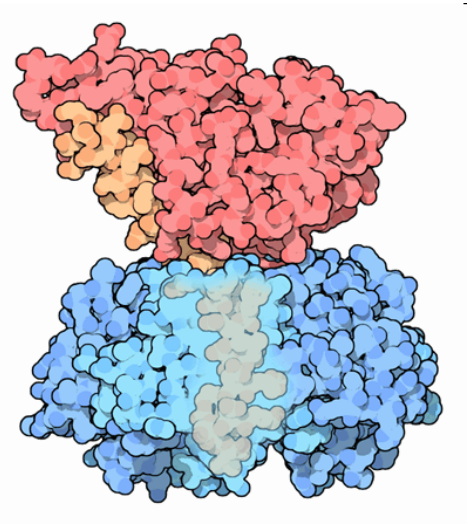
# Enterotoxins

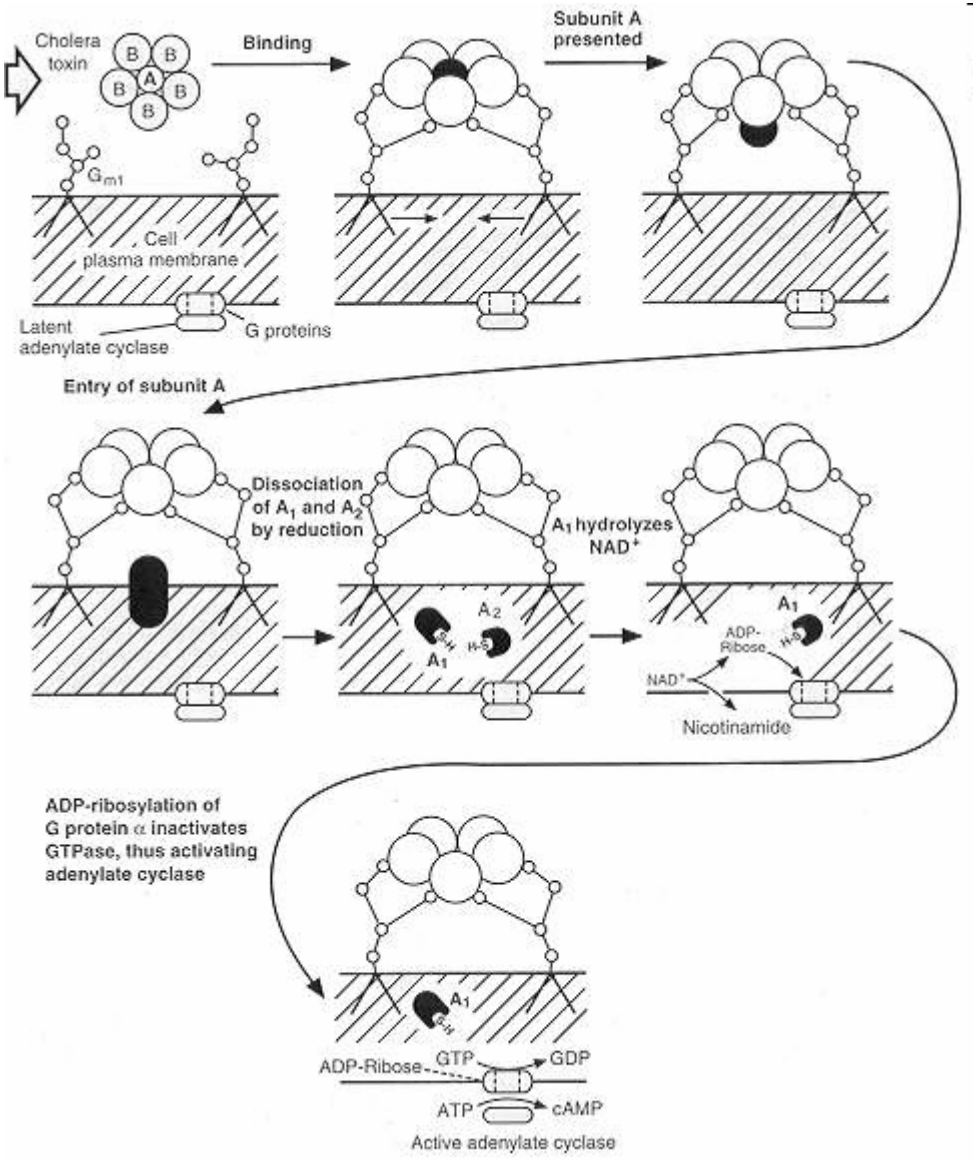
**TABLE 95-1 Toxin-Producing Bacteria Associated With Diarrheal Disease**

| Microorganism | Action of Toxin | | |
|---|---|---|---|
| | Adenylate Cyclase | Cytotoxic | Guanylate Cyclase |
| *Vibrio cholerae* | + | | |
| *E coli* (heat-labile toxin) | + | | |
| *E coli* (heat-stable toxin) | | | + |
| *Shigella* | | + | |
| *Staphylococcus aureus* | | + | |
| *Clostridium perfringens* | | + | |

**Medical Microbiology, 4th ed., 1996**

Cholera is caused by *V cholerae*, which is usually ingested in contaminated water. Vibrios that survive passage through the stomach colonize the surface of the small intestine, proliferate, and elaborate the enterotoxin. Cholera toxin acts via adenylate cyclase to stimulate secretion of water and electrolytes from the epithelial cells into the lumen of the gut. The duodenum and upper jejunum are more sensitive to the toxin than the ileum is. The colon is relatively insensitive to the toxin and may still absorb water and electrolytes normally. Thus, cholera is an "overflow diarrhea," in which the large volumes of fluid produced in the upper intestine overwhelm the resorptive capacity of the lower bowel.






Medical Microbiology, 4th ed., 1996

Mechanism of action of **cholera enterotoxin**. Cholera toxin approaches target cell surface. B subunits bind to oligosaccharide of GM1 ganglioside. Conformational alteration of holotoxin occurs, allowing the presentation of the A subunit to cell surface. The A subunit enters the cell. The disulfide bond of the A subunit is reduced by intracellular glutathione, freeing A1 and A2. NAD is hydrolyzed by A1, yielding ADP-ribose and nicotinamide. One of the G proteins of adenylate cyclase is ADP-ribosylated, inhibiting the action of GTPase and locking adenylate cyclase in the "on" mode

Crystal (Cry) and Cytolitic (Cyt) protein families are a diverse group of proteins with activity against insects of different orders—Lepidoptera, Coleoptera, Diptera and also against other invertebrates such as nematodes. Their primary action is to lyse midgut epithelial cells by inserting into the target membrane and forming pores.

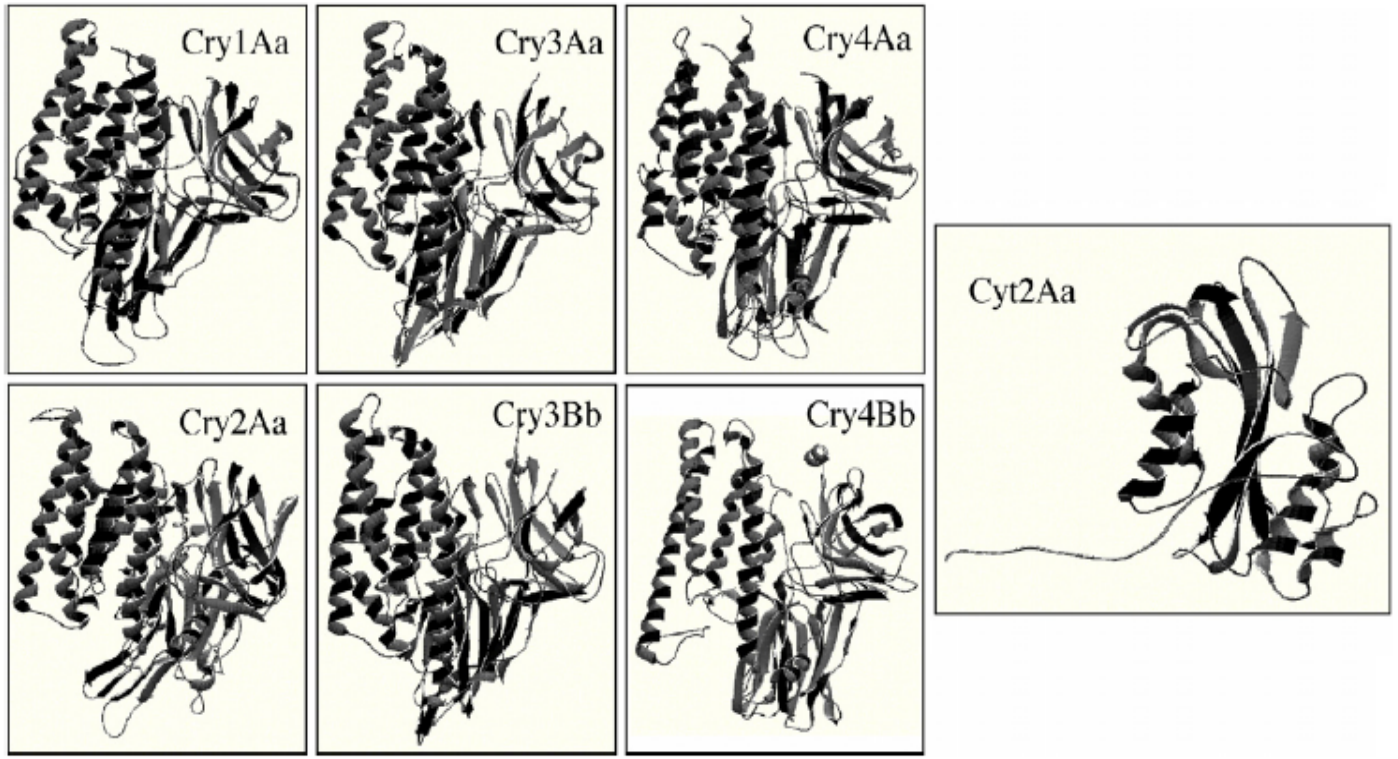



Fig. 1. Three-dimensional structures of insecticidal toxins produced by *Bacillus thuringiensis* Cry1Aa, Cry2Aa, Cry3Aa, Cry3Bb, Cry4Aa, Cry4Bb and Cyt2A.

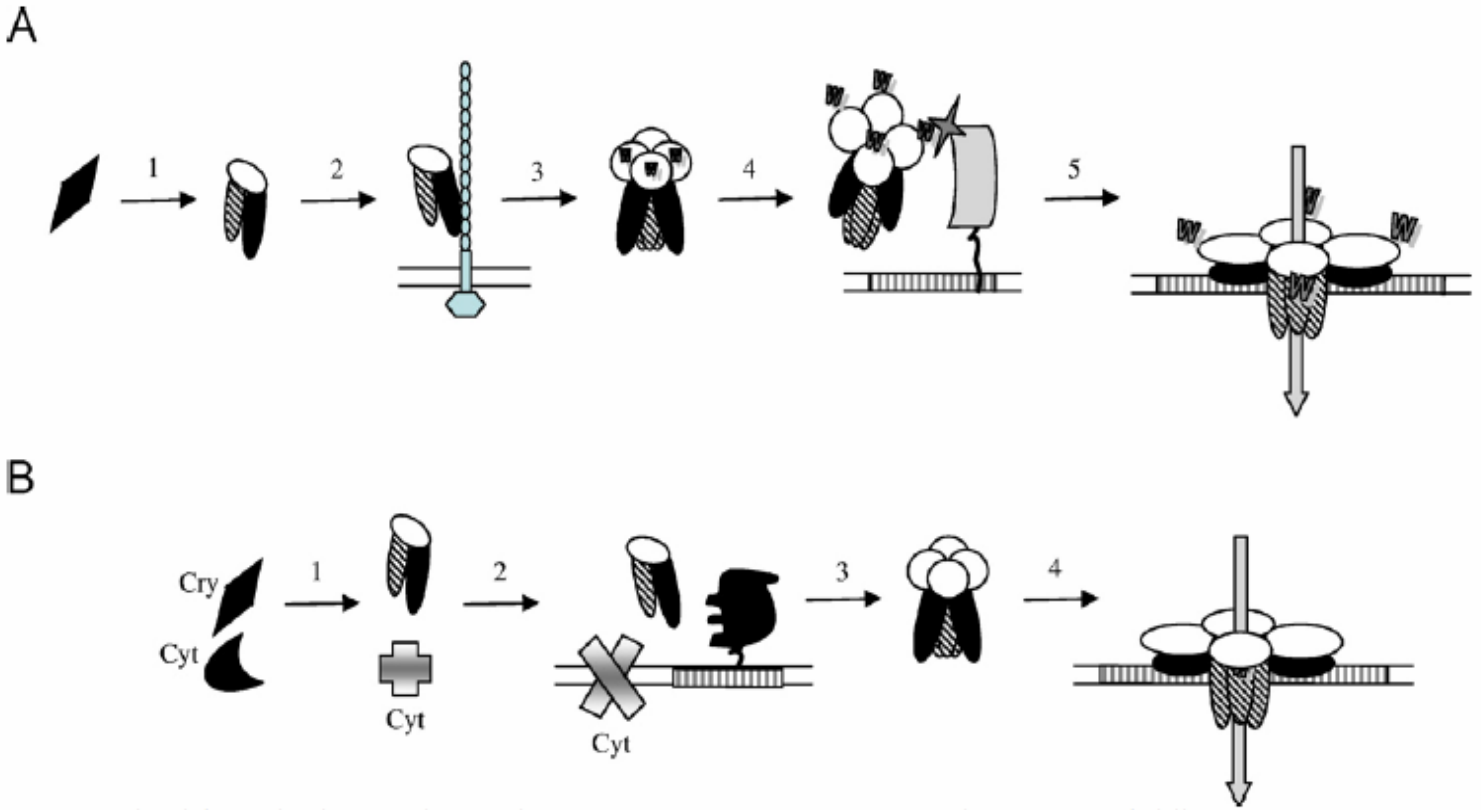


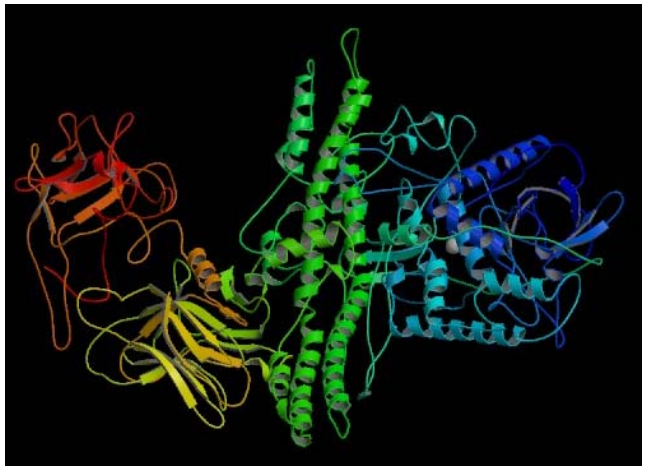

Fig. 4. Model of the mode of action of Cry and Cyt toxins. (A), sequential interaction of Cry toxins with different receptor molecules in lepidopteran larvae. (1) Solubilization and activation of the toxin; (2) binding of monomeric Cry toxin to the first receptor (CADR or GCR), conformational change is induced in the toxin and α-helix 1 is cleaved; (3) oligomer formation; (4) binding of oligomeric toxin to second receptor (GPI–APN or GPI–ALP), a conformational change occurs and a molten globule state of the toxin is induced; (5) insertion of the oligomeric toxin into lipid rafts and pore formation. (B), Role of Cyt and Cry toxins in the intoxication of dipteran larvae. (1) Cry and Cyt toxins are solubilized and activated; (2) Cyt toxin inserts into the membrane and Cry toxin binds to receptors located in the membrane (ALP or Cyt toxin); (3) oligomerization of the Cry toxin is induced; (4) oligomer is inserted into the membrane resulting in pore formation.

## Botulotoxin

a neurotoxic protein produced by the bacterium *Clostridium botulinum*. It is the most toxic protein known. The toxin is a two-chain polypeptide with a 100-kDa heavy chain joined by a disulfide bond to a 50-kDa light chain. This light chain is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular junction, preventing vesicles from anchoring to the membrane to release acetylcholine. By inhibiting acetylcholine release, the toxin interferes with nerve impulses and causes flaccid (sagging) paralysis of muscles in botulism as opposite to the spastic paralysis seen in tetanus.

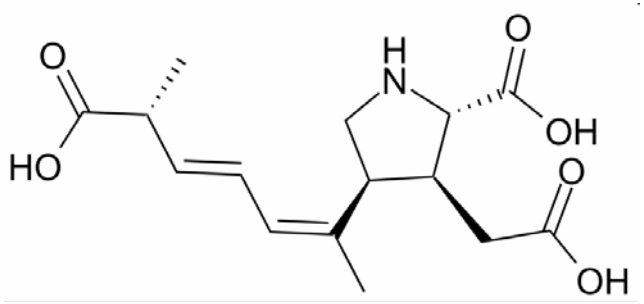
## Tetanospasmin

is the neurotoxin produced by the vegetative spore of *Clostridium tetani* in anaerobic conditions. The action of the A-chain stops the affected neurons from releasing the inhibitory neurotransmitters gamma-aminobutyric acid and glycine by degrading the protein synaptobrevin. The consequence of this is dangerous overactivity in the muscles from the smallest stimulus-- the failure of inhibition of motor reflexes by sensory stimulation. This causes generalized contractions of the agonist and antagonist musculature, termed a tetanic spasm.



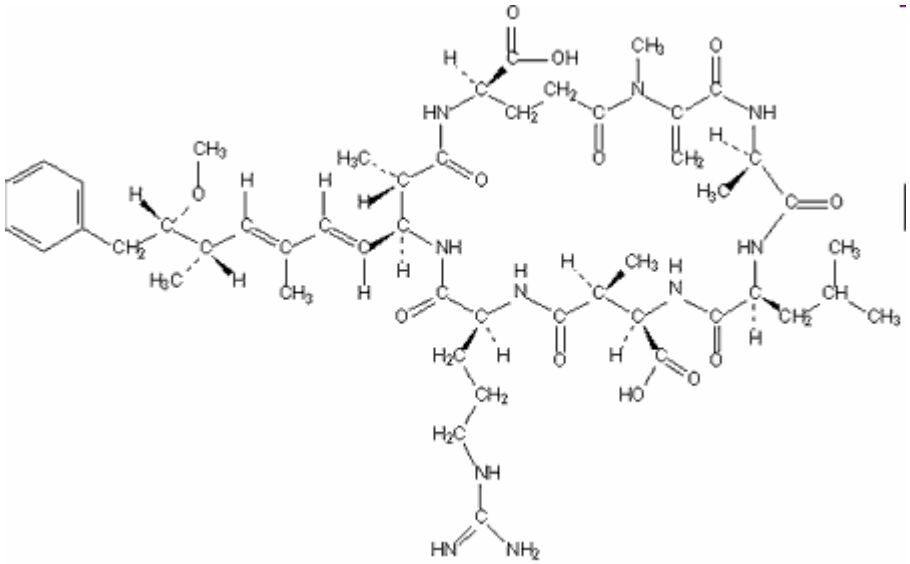
# **Toxiny řas a sinic** – různé typy nízkomolekulárních látek odvozených od sinic, rozsivek nebo bičíkovců – neobvyklé typy aminokyselin

*Amnesic Shellfish Poisoning (ASP)* was first identified in 1987 from Prince Edward Island, Canada after four people died from eating contaminated mussels. It is caused by domoic acid produced by several species of *Pseudonitzschia* diatoms. The main contamination problems include mussels, clams, and crabs of the Pacific Northwest of the United States and Canada.



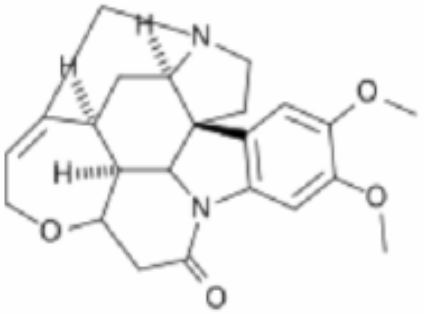

In mammals, including humans, domoic acid acts as a neurotoxin, causing short-term memory loss, brain damage and, in severe cases, death. In the brain, domoic acid especially damages the hippocampus and amygdaloid nucleus. It damages the neurons by activating AMPA and kainate receptors, causing an influx of calcium. Although calcium flowing into cells is a normal event, the uncontrolled increase of calcium causes the cell to degenerate. Because the hippocampus may be severely damaged, long-term memory loss occurs.

**Microcystins** are cyclic nonribosomal peptides produced by cyanobacteria. They are cyanotoxins and can be very toxic for plants and animals including humans. Their hepatotoxicity may cause serious damage to the liver. Microcystins consist of several uncommon non-proteinogenic amino acids such as dehydroalanine derivatives and the special β-amino acid ADDA ((all-S,all-E)-3-Amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-diene acid).



Microcystin LR

# **Rostlinné toxiny** – proteiny, peptidy, alkaloidy – produkty sekundárního metabolismu



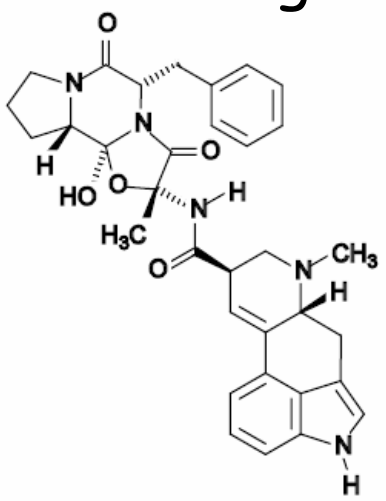

The large array of toxic chemicals produced by plants (phytotoxins), usually referred to as secondary plant compounds, are often held to have evolved as defense mechanisms against herbivorous animals, particularly insects and mammals. They include sulfur compounds, lipids, phenols, alkaloids, glycosides, and many other types of chemicals. Many of the common drugs of abuse such as cocaine, caffeine, nicotine, morphine, and the cannabinoids are plant toxins. Many chemicals that have been shown to be toxic are constituents of plants that form part of the human diet. For example, the carcinogen safrole and related compounds are found in black pepper. Solanine and chaconine, which are cholinesterase inhibitors and possible teratogens, are found in potatoes, and quinines and phenols are widespread in food. Livestock poisoning by plants is still an important veterinary problem in some areas.

**Toxiny hub a plísní** – nízkomolekulární látky, peptidy
- produkty specializovaného metabolismu hub

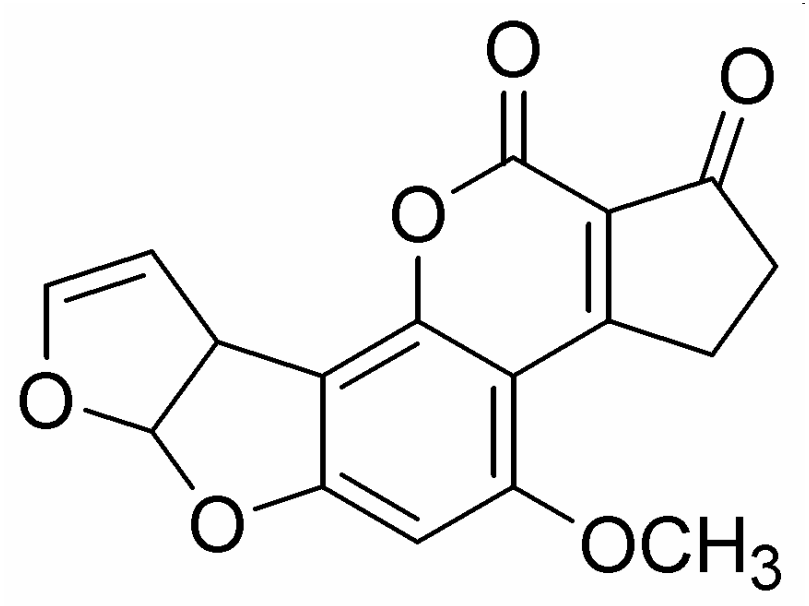
**Paličkovice nachová** (*Claviceps purpurea*)


PLATE XXXVII.—*Claviceps purpurea* (Rye ergot). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

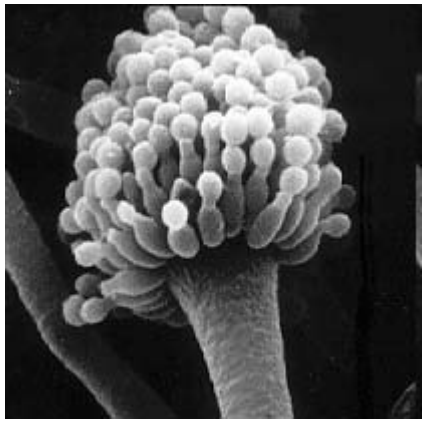
ergotamin




Ergotismus – konvulzívní a gangrenózní forma, horčka sv. Antonína




Aflatoxin B1



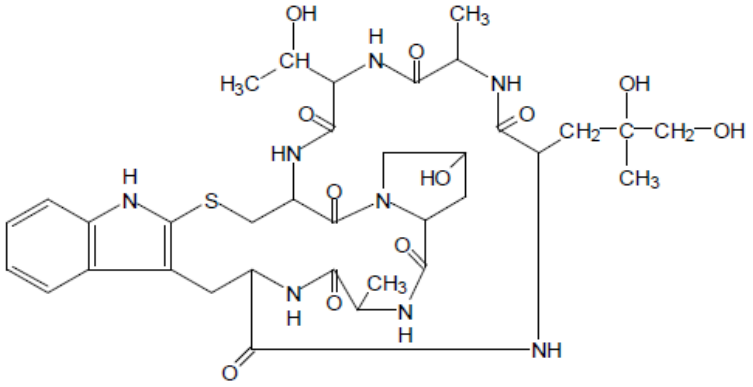
Aspergillus sp.

Hepatic necrosis, fibrosis

Even at low doses – DNA adducts – mutations; primary risk factor for hepatocellular carcinoma in developing countries

# Amanita phalloides

## phalloidin

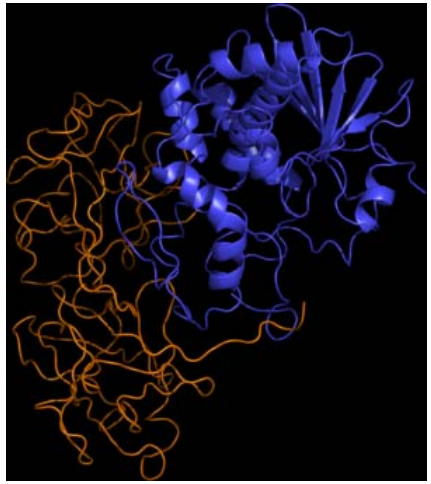



Phalloidin is a fungal toxin isolated from the poisonous mushroom *Amanita phalloides.* Its toxicity is attributed to the ability to bind F actin in liver and muscle cells. As a result of binding phalloidin, actin filaments become strongly stabilized. Phalloidin has been found to bind only to polymeric and oligomeric forms of actin, and not to monomeric actin. The dissociation constant of the actin-phalloidin complex has been determined to be on the order of $3 \times 10^{-8}$ M.[6] Phalloidin differs from amanitin in rapidity of action; at high dose levels, death of mice or rats occurs within 1 or 2 hours.[1]

# Ricin

The seeds of the castor bean (Ricinus communis L.) have been recognised for their toxicity since times immemorial. As so many poisonous plant materials, their seeds have been extensively used in folkmedicine against a variety of illnesses and also for criminal purposes. Castor beans were used in classical Egyptian and Greek medicine. The main product obtained from the castor bean is castor oil. It is produced by hot extraction of the beans, a procedure that destroys the toxin. A minor amount of the oil production is used in medicine as a laxative, but the major part is used in industry for its favourable lubricating properties. The ingestion of about five beans appears to be lethal. This represents a considerable amount of toxin, but being a protein, ricin is to a large extent destroyed in the intestinal tract. Therefore, the toxin is about 100 times more toxic when administered parenterally.

RTA cleaves a glycosidic bond within the large rRNA of the 60S subunit of eukaryotic ribosomes. RTA specifically and irreversibly hydrolyses the N-glycosidic bond of the adenine residue at position 4324 (A4324) within the 28S rRNA, but leaves the phosphodiester backbone of the RNA intact. The depurination event rapidly and completely inactivates the ribosome, resulting in toxicity from inhibited protein synthesis.

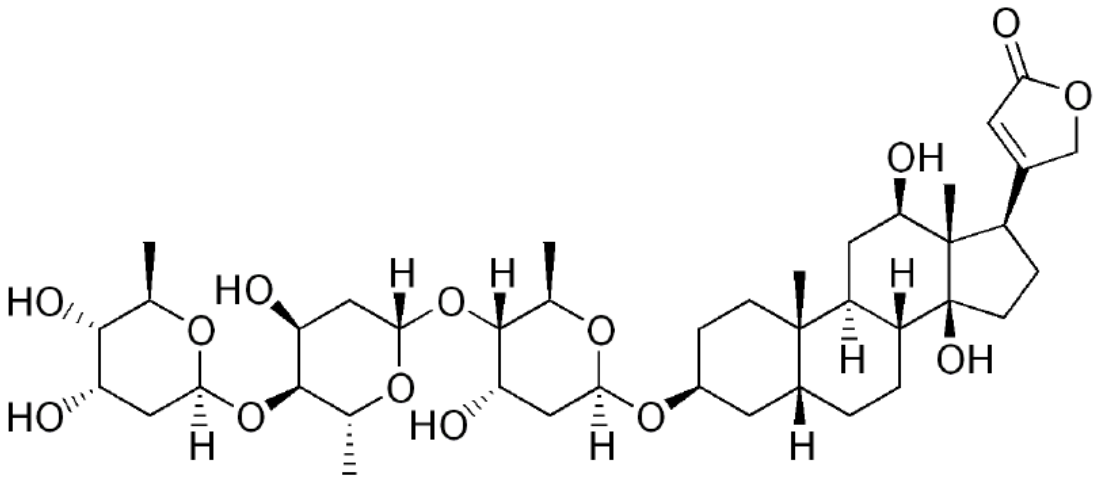


# Digoxin

pharmacological effects of digoxin are on the heart. Extracardiac effects are responsible for many of the adverse effects.

Its main cardiac effects are

* A decrease of conduction of electrical impulses through the AV node, making it a commonly used antiarrhythmic agent in controlling the heart rate during atrial fibrillation or atrial flutter.
* An increase of force of contraction via inhibition of the Na+/K+ ATPase pump (see below).



The chemistry of **animal toxins** extends from enzymes and neurotoxic and cardiotoxic peptides and proteins to many small molecules such as biogenic amines, alkaloids, glycosides, terpenes, and others. In many cases the venoms are complex mixtures that include both proteins and small molecules and depend on the interaction of the components for the full expression of their toxic effect.

**Table 5.5 Some Components of Bee Venom**

| Compound | Effect |
|---|---|
| Biogenic amine | |
| Histamine | Pain, vasodilation, increased capillary permeability |
| Peptides | |
| Apamine | CNS effects |
| Melittin | Hemolytic, serotonin release, cardiotoxic |
| Mast cell degranulating peptide | Histamine release from mast cells |
| Enzymes | |
| Phospholipase A | Increased spreading and penetration of tissues |
| Hyaluronidase | |

The venoms and defensive secretions of insects may also contain many relatively simple toxicants or irritants such as formic acid, benzoquinone, and other quinines, or terpenes such as citronellal.

**Snake venoms** have been studied extensively; their effects are due, in general, to toxins that are peptides with 60 to 70 amino acids. These toxins are cardiotoxic or neurotoxic, and their effects are usually accentuated by the phospholipases, peptidases, proteases, and other enzymes present in venoms. These enzymes may affect the blood clotting mechanisms and damage blood vessels.

Many **fish species**, over 700 species worldwide, are either directly toxic or upon ingestion are poisonous to humans. A classic example is the toxin produced by the puffer fishes (*Sphaeroides* spp.) called tetrodotoxin (TTX). Tetrodotoxin is concentrated in the gonads, liver, intestine, and skin, and poisonings occurs most frequently in Japan and other Asian countries where the flesh, considered a delicacy, is eaten as "fugu." Death occurs within 5 to 30 minutes and the fatality rate is about 60%. TTX is an inhibitor of the voltage-sensitive Na channel; it may also be found in some salamanders and may be bacterial in origin.

http://www.toxinology.com/