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اسم المادة باللغة العربية: السموم السريرية

اسم المادة باللغة الإنكليزية: **Clinical toxicology**

المرحلة: الخامسة

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عنوان المحاضرة باللغة العربية: التسمم بالنباتات.

عنوان المحاضرة باللغة الإنكليزية:**Plant toxicity**

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## Plant toxicity

Herbal product is constituted in general from leafy plant, herbal products, animal products, and/or mineral products.

While many herbal products are harmless or possess minimal toxicity, some contain toxic ingredients that may not be identified on the label. These unidentified ingredients may be unintentionally included in the product (e.g misidentification of a toxic plant as a desired non-toxic plant or contamination with pesticide residues or heavy metals) or introduced for increased effect (e.g addition of a pharmaceutical agent to an herbal preparation).

Dietary supplements, including herbal products, are regulated as a food product, thus does not require to be effective or safe prior to marketing.

The US Food and Drug Administration (FDA) has little control over the marketing of herbal products, but may prohibit sales of herbal products containing pharmaceutical agents. The FDA also may prohibit sale of an herbal product proven to have serious or unreasonable risk under conditions of use on the label or as commonly consumed.

### Pathophysiology

Herbal products are generally heterogeneous, may produce multiple effects, and may affect multiple organ systems, including the nervous, cardiovascular, gastrointestinal, hepatic, renal, and hematologic systems.

Central nervous system:Several herbal products can produce anticholinergic symptoms as

Atropa belladonna, Datura stramonium, Hyoscyamus niger

Kava-kava (Piper methysticum) is a herbal preparation that may be fermented into a beverage. Methysticine and kawain (a local anesthetic) are its main constituents; however, primary effects of kava- kava are anxiolytic, myorelaxant, and sedation. This herbal preparation has also been associated with hepatotoxicity.

Lobelia inflata and Nicotiana products can cause nicotine toxicity with hypertension and CNS excitation. Severe cases may progress to neuromuscular paralysis.

Cardiovascular system

Cardiac glycosides and other cardioactive steroid contaminants may cause toxicity e.g. Digitalis lanata. Ephedra (Ma Huang) and ephedrine-containing products may produce cardiac stimulation, hypertension, peripheral vasoconstriction, chest pain, myocardial infarctions, and intracerebral hemorrhage.

Aconitum species (contain aconitine) and Veratrum species (contain Veratrum alkaloids). These toxins open sodium channels in cardiac myocytes, resulting in conduction blockade, bradycardia, ventricular dysrhythmias and cardiovascular collapse.

Hepatic system

Hepatic toxicity has been reported with pyrrolizidine alkaloids, which are metabolized to alkylating agents that produce hepatomegaly and cirrhosis. Plants that contain these substances include Heliotropium, Senecio, and Symphytum.

Jin Bu Huan is a Chinese herbal preparation (a mixture of 5 herbs) with a long history of use as a sedative, analgesic and decongestant. Some preparations have caused fatal hepatic injury.

Hematologic system

Ginkgo biloba has been reported to increase bleeding times and may have contributed to intracranial hemorrhages.

Yohimbine use has been associated with agranulocytosis.
Jui, a Chinese herbal medication, has been associated with thrombocytopenia.

Contamination and adulteration

Some herbal products contain high concentrations of heavy metals, such as lead, mercury, and arsenic. Use of ayurvedic medications should arouse suspicion of lead contamination. Chinese herbal medications have been an incredible source of contamination, with one study showing that, out of 247 traditional Chinese medicines investigated, a proportion were contaminated with arsenic (5-15%), lead (5%), and mercury (approximately 65%).

Some herbal preparations have been found to be adulterated with drug ingredients. For example, Caffeine, Acetaminophen, Hydrochlorothiazide, Ephedrine, Chlorpheniramine.

Etiology
Adverse effects from herbal preparations can be classified into the following 4 types:

- Type A - Pharmacologically predictable, dose dependent, and preventable by dose reduction

- Type B - Idiosyncratic, pharmacologically unpredictable, toxicity not correlated with dose, often

  immunologically mediated, often serious and potentially fatal

- Type C - Developed over long-term therapy, well-described, and may be anticipated

- Type D - Delayed effects (eg, carcinogenicity, teratogenicity)

Physical Examination
Evaluate the patient for the following:

- Anticholinergic syndromes (ie, mydriasis, dry mucous membranes and axilla, urinary retention, tachycardia, disorientation, hallucinations)

- Cardiac dysrhythmias (suspect cardiac glycoside or aconite toxicity)

- Hepatomegaly and jaundice (suspect pyrrolizidine alkaloids and herbal teas)

Treatment
- Stabilize the airway, assess respiration, and initiate respiratory assistance - Assess blood pressure and pulse
- Supportive care

- Decontamination protocols.

- Specific treatments depend on the substance ingested e.g. specific antidotes for suspected cardiac glycoside toxicity (immune fab), N -acetylcysteine for hepatotoxicity, chelating agent for heavy metal poisoning.

Plant poisoning

The plant species most frequently reported in human exposures were Philodendron, Caladium and Dieffenbachia species. they are commonly found in homes, offices, and waiting rooms.

Pathophysiology

Philodendron, Dieffenbachia, and Caladium contain calcium oxalate crystals packaged into bundles called raphides. Also the presence of proteolytic enzymes, in addition to specialized cells that forcibly expel the raphides, seems to be necessary to cause injury. When the person accidentally eat the plant leaf, then the person will usually develop immediate burning, irritation and swelling of the oral mucosa, which generally deters any further exposure.

Cutaneous exposure can cause redness and irritation but is not nearly as common as oral exposure caused by chewing.

Ocular exposure may result in eye pain, redness, and lid swelling.

**Treatment**

- All pieces of Caladium, Dieffenbachia, or Philodendron should be removed and the mouth gently rinsed with water to eliminate all residual components.

- Induced emesis and gastric lavage are not indicated.
- Ingesting demulcifying agents, such as cold milk or ice cream, may help.

- Based on severity of pain, analgesics, including acetaminophen, ibuprofen, or codeine derivatives, may be necessary.

- Steroids may be beneficial for severe cases.
- Antihistamines may improve patient comfort in moderate or severe cases. - Ophthalmology follow-up should be arranged for ocular injuries.
- Antibiotic eye drops, steroids, or both may be prescribed.

**Mushroom poisoning**

Mushrooms are the fruiting bodies of a group of higher fungi, mushroom toxicity occurs after the ingestion of mushrooms that contain toxins which are similarly appearing to non-toxic mushrooms. They are widely distributed throughout the world. There are thousands of species of mushrooms, but only about 100 species of mushrooms cause symptoms when eaten by humans, and only 15-20 mushroom species are potentially lethal when ingested. No simple rule exists for distinguishing edible mushrooms from poisonous mushrooms. In more than 95% of mushroom toxicity cases, poisoning occurs as a result of misidentification of the poisonous mushroom from edible mushroom.

The severity of mushroom poisoning may vary, depending on the geographic location where the mushroom is grown, growth conditions, the amount of toxin delivered, and the genetic characteristics of the mushroom. Boiling, cooking, freezing, or processing may not alter some mushroom's toxicity.

**Pathophysiology**

Each poisonous mushroom species contains 1 or more toxins, which may be classified on the basis of the mushroom's physiologic and clinical effects in humans, the target organ toxicity, and the time to symptom onset. The clinical spectrum and toxicity vary with the following factors:

- Species consumed
- Amount consumed
- Season
- Geographic location where the mushroom was grown

- Preparation method
- Individual response to the toxins

mushroom poisoning can be classified into the following 3 categories on the basis of the time from ingestion to the development of symptoms :

- Early symptom category – Symptoms generally appear within the first 6 hours of mushroom ingestion and include gastrointestinal, allergic, and neurologic syndromes
- Late symptom category – Signs and symptoms begin to appear between 6 - 24 hours after ingestion and may include hepatotoxic and nephrotoxic syndromes
- Delayed symptom category – Symptoms appear more than 24 hours after ingestion and include mostly nephrotoxic syndromes

Mushroom toxins include the followin:

- Cyclopeptides - Amatoxin
- Gyromitrins (monomethylhydrazine)
- Orellanine
- Muscarine
- Psilocybin
- Muscimol and ibotenic acid
- Coprine
- Nephrotoxins (norleucine)
- Myotoxins
- Immunoactive toxins
- Hemolytic toxins
- GI irritants

Amatoxins, gyromitrins, and orellanine are the toxins most commonly implicated in fatal mushroom poisonings worldwide.

Amatoxins

Amatoxins, are cyclic octapeptides that are synthesized by Amanita species. At least 5 subtypes of amatoxins are known, the only significant human toxin being alpha-amatoxin, which inhibits RNA polymerase II and protein synthesis.

Gyromitrins
Gyromitrin is a volatile hydrazine derivative synthesized by Gyromitra esculenta.

In the stomach, gyromitrin is rapidly hydrolyzed into acetaldehyde and N-methyl-N-formyl hydrazine (MFH), which is then slowly converted to N-methylhydrazine (MH). MFH inhibits a number of hepatic systems, including cytochrome P-450 and glutathione, and causes hepatic necrosis.

MH inhibits pyridoxine kinase and interferes with all the pyridoxine-requiring enzymes in the body, including those involved in the synthesis of gamma-aminobutyric acid (GABA). The reduction of GABA concentrations in the brain leads to CNS hyperexcitability and convulsions.

Orellanine
Orellanine is a nephrotoxic compound that is synthesized by Cortinarius mushrooms.

Orellanine is colorless and crystalline in nature and may be converted into orelline, which itself may be toxic. Its main effects are on the renal tubular system, where it causes necrosis with relative sparing of the glomerular apparatus.

Norleucine

These mushrooms cause vomiting and diarrhea 1-12 hours after ingestion, followed by a transient elevation of transaminases, then oliguric renal failure in 3-6 days. It is important to note that renal failure occurs within days of ingestion, as opposed to orellanine-induced renal failure that has an onset over 1-2 weeks.

Psilocybin

Psilocybin and psilocin are serotonin (5-HT2) agonists and, when ingested, cause psychological effects similar to those of lysergic acid diethylamide (LSD).

Ibotenic acid and muscimol
Both are excitatory neurotoxins and may be mildly hallucinogenic.

Ibotenic acid is structurally similar to glutamic acid and acts as an agonist at the glutamic acid receptors in the CNS. Ibotenic acid is decarboxylated in vivo to muscimol which is structurally similar to GABA and acts as a GABA-receptor agonist.

Muscarine

Muscarine stimulates M1 and M2 types of postganglionic cholinergic receptors (muscarinic receptors) in the autonomic nervous system. This action results in parasympathetic stimulation similar to that caused by the release of endogenous acetylcholine at postganglionic receptors of smooth muscle and exocrine gland Muscarine-containing mushrooms typically produce cholinergic symptoms such as sweating, facial flushing, salivation, lacrimation, vomiting, abdominal cramps, diarrhea, urination, and miosis; occasionally, bradycardia, hypotension, and dizziness develop. Symptoms typically occur within 1 hour of

ingestion and last for 4-24 hours. In most cases, they resolve without drug therapy or with a dose of atropine.

Coprine

Coprine is an amino acid that is metabolized to 1-aminocyclopropanol in the human body. This metabolite blocks acetaldehyde dehydrogenase, and in the presence of alcohol, acetaldehyde accumulates, resulting in a disulfiram reaction.

Involutin

Ingestion of Paxillus involutus may result in the acute onset of abdominal pain, nausea, vomiting, and diarrhea within 30 minutes to 3 hours of ingestion, followed by an immune complex-mediated hemolytic anemia with hemoglobinuria, oliguria, anuria, and acute renal failure.

GI toxins

Hundreds of mushrooms contain toxins that can cause GI symptoms (nausea, vomiting, diarrhea, and abdominal pain) similar to those observed with more dangerous mushrooms. They include Chlorophyllum, Boletus, and Agaricus.

Complications of mushroom toxicity include the following:

- Respiratory – Aspiration pneumonia may occur with mushroom poisonings and involves loss of airway protective reflexes

- Neurologic – Convulsions are common in gyromitrin poisoning, but they also may be due to hypoxia, acidosis, and metabolic abnormalities; cerebral edema may be a complication of hypoxia, acidosis, trauma, and hepatic failure

- Hepatic – hepatic failure and hypoglycemia are complication of amatoxin and gyromitrin poisonings

- Renal – Renal failure is a common complication of norleucine and orellanine poisoning but also may be due to hypoperfusion and shock

- Hematologic – Methemoglobinemia and hemolysis may complicate gyromitrin poisoning

- Trauma may complicate hallucinogenic mushroom poisoning

- Hypovolemia and electrolyte disturbances may complicate any mushroom poisoning

Treatment

- Early volume resuscitation (fluid rehydration) is important for liver and renal toxic syndromes.

- Gut decontamination, including whole-bowel irrigation.

- multiple doses of activated charcoal (regardless of the timing of presentation) should be administered repeatedly to interrupt enterohepatic circulation of these toxins.

- Endotracheal intubation is recommended in all patients at risk of aspiration, and mechanical ventilation should be initiated in all patients with hypoxia, acidemia, and shock.

- Agitation, commonly observed with hallucinogenic mushrooms, is treated with benzodiazepines.

- Severe muscarinic symptoms may be treated with the infusion of small doses of atropine.

- Patients with severe poisoning from disulfiram-containing mushrooms may benefit from fomepizole which blocks alcohol dehydrogenase and, hence, the formation of the toxic aldehyde.

- Renal failure, commonly observed with norleucine and orellanine poisoning, may have to be treated with hemodialysis.

- Conventional indications for dialysis include fluid overload (with pulmonary edema), severe hyperkalemia, and acidosis.

- Blood transfusions may be required in patients with hemorrhagic diarrhea, blood loss, and severe hemolytic anemia.

- Blood pressure support with dopamine and norepinephrine may be required when crystalloids and colloid infusions fail.

-Hypoglycemia is treated with infusions of 10% dextrose.