# Mushroom Poisoning

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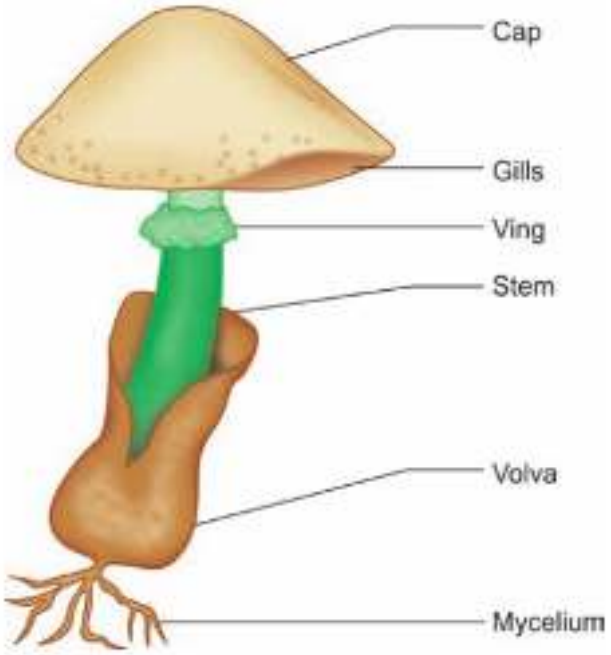


Parts of a mushroom

# Introduction

- The term "mushroom" actually refers to the reproductive portion of a fungus which grows up from an underground mycelium,

- Mushrooms are a recognized component of the human diet, with versatile medicinal properties.

- Some mushrooms are popular worldwide for their nutritional and therapeutic properties.


- However, some species are dangerous because they cause toxicity.
- Of the numerous species of mushrooms, less than 5% are poisonous
- All toxic mushrooms belong to two divisions: Basidiomycetes and Ascomycetes

**Table 33.6:** Common Names of Common Mushrooms

| Species | Common Name |
|---|---|
| *Amanita muscaria* | Fly agaric |
| *Amanita pantherina* | Panther cap/False blusher |
| *Amanita phalloides* | Death cap |
| *Amanita virosa* | Destroying angel |
| *Clitocybe dealbata* | Sweater |
| *Coprinus atramentarius* | Inky cap |
| *Galerina autumnalis* | Deadly galerina |
| *Gyromitra esculenta* | False morel/Beefsteak mushroom |
| *Panaeolus foenisecii* | Mower's mushroom |
| *Psilocybe caerulipes* | Blue foot |
| *Psilocybe semilanceata* | Liberty cap/Magic mushroom |

*Amanita virosa*

**Table 2.** Molecular properties and mechanism of toxicity of different toxins found in various mushroom species

| Toxin name | Sources | Molecular properties | Mechanism of toxicity | Reference |
|---|---|---|---|---|
| Ostreolysin | *Pleurotus ostreatus* | A 16-kDa acidic protein, is a member of the aegerolysin protein family. It contains 137 residues of amino acids 13 positively and 16 negatively charged residues. | Transient increase in arterial blood pressure and then a progressive fall to mid-circulatory pressure accompanied by bradycardia, myocardial ischemia, and ventricular extrasystoles. The hyperkalemia resulting from the hemolytic activity probably plays an important role in its toxicity. | [29, 30] |
| Amatoxin | Different species of *Amanita* | Thermostable bicyclic octapeptide. Nine amatoxins have been identified and α-amanitine is the most active. | Inhibit RNA polymerase-II and thus transcription of DNA occurs by protein synthesis and cell necrosis. | [16, 31] |
| Phallotoxin | *Amanita phalloides* | Peptides containing bicyclic-skeleton with a transannular thioether bridge. | Specific binding of the toxin to F-actin in liver cells, which consequently inhibits the depolymerization of F-actin into G-actin. | [32] |
| Agaritin | *Agaricus bisporus* | Is an L-glutamic acid (b-N-(g-L(+) glutamyl)-4-hydroxymethyl) phenylhydrazine). | Agaritine can be enzymatically activated to a mutagenic metabolite and can bind with DNA and form adducts. | [33, 34] |

| Toxin name | Sources | Molecular properties | Mechanism of toxicity | Reference |
|---|---|---|---|---|
| Orellanine | *Pleurotus ostreatus* and *Cortinarius orellanus* | Is a heat-stable bipyridine N-oxide. Orellanine chemically resembles the pyridine herbicides paraquat and diquat and is deoxidized to orelline that is non-toxic. | *In vitro* data strongly suggest that orellanine generates oxygen radicals at the target site through redox cycling and/or redox activation of iron. Further data from cellular systems indicate that a metabolite of the toxin can inhibit protein synthesis. | [35] |
| Gyromitrin | *Gyromitra esculenta* | Gyromitrin is a volatile liquid, which is quite unstable, oxidizes at room temperature, and exists free or bonded with glucosides. | The hydrazines are convulsants, and they react with pyridoxal phosphate to form a hydrazine, which results in the decreased activity of glutamic acid decarboxylase and diminished formation of GABA. | [36] |
| Acromelic acid | *Clitocybe acromelalga* | Is a member of kainoid family, a group of non-proteinogenic pyrolidine dicarboxylic acids. | Acromelic acid A exhibits neuroexcitatory activity, can bind glutamate receptors, mimics glutamic acid, causes characteristic behavior changes, and induced selective damage to the interneurons in the lower spinal cord when tested in an animal model. | [37] |

| Toxin name | Sources | Molecular properties | Mechanism of toxicity | Reference |
|---|---|---|---|---|
| | | | model. | |
| Ibotenic acid | *Amanita muscaria* and *A. pantherina* | Is an α-amino-3-hydroxy-5-isoxazole acetic acid. | An NMDA receptor agonist. Because of the acidic property of the isoxazole moiety, it is similar to glutamic acid and mimics its effects in animals. | [14, 15] |
| Muscimol | *Amanita muscaria* and *A. pantherina* | It is a decarboxylated product of ibotenic acid. | This substance shows structural resemblance to GABA and imitates the action of this inhibitory neurotransmitter in the CNS. | [14, 15] |
| Muscarine | *C. serussata*, *C. dealbata*, *C. phyllophilla*, *C. rivulosa* and *A. muscaria* | It is tetrahydro-4-hydroxy-*N*,*N*,*N*-5-tetramethyl-2-furanmethanaminium. | Muscarine's structure is very similar to that of acetylcholine and it binds to the same receptors. It is not hydrolyzed by cholinesterase causing a parasympathomimetic symptomatology. | [31] |
| Psilocybin and psilocin | - | Component of the tyramine type, 4-phosphoryloxy-*N*,*N*-dimethyltryptamine | Cleavage of the phosphoric ester group by alkaline phosphatase and unspecific esterases indicates that psilocybin acts as a prodrug and that its hydroxyl metabolite psilocin the active agent. Activity of psilocybin is due to the activation of serotonin 2-A receptor. | [38, 39] |

GABA, gamma-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; CNS, central nervous system.

- of all the toxins, phalloidin appears to be the most rapid acting, while amanitin causes more delayed manifestations.

| Toxic syndrome | Toxins | Sites of toxicity | Species | Mortality rate |
|---|---|---|---|---|
| Acute gastroenteritis without liver failure | GI irritants | GIT | *Chlorophyllum molybdites*, *Clitocybe nebularis*, *Omphalotus illudens* | Rare |
| Hallucinogenic | Psilocybin, psilocin | CNS (hallucinogenic effects) | *Psilocybe cubensis*, *P. mexicana*, *Conocybe cyanopus*, *G. aeruginosa* | Rare |
| CNS excitation and depression (stupor, coma, delirium, agitation, hallucinations and seizures) | Ibotenic acid, muscimol | CNS (depressant and excitatory effects) | *Amanita muscaria*, *A. pantherina*, *A. gemmata* | Rare |
| Cholinergic excess (vomiting, diarrhea, bradycardia, bronchorrhea, tearing, bronchospasm, salivation) | Muscarine | Autonomic nervous system (muscarinic receptors) | *Clitocybe dealbata*, *C. illudens*, *I. fastigiata*, *Boletus calopus* | Rare |
| Flushing, headache, tachycardia, chest pain, anxiety | Coprine | - | *Coprinus atramentarius* | Rare |

| Toxic syndrome | Toxins | Sites of toxicity | Species | Mortality rate |
|---|---|---|---|---|
| Gastroenteritis and delayed onset renal failure | Allenic norleucine | Kidney, GIT | *Amanita smithiana* | Rare |
| Delayed liver toxicity and delayed gastroenteritis | Amatoxins, phallotoxins | GIT, liver, kidney | *Amanita phalloides*, *A. virosa*, *A. verna*, *A. bisporigera*, *Galerina autumnalis*, *G. marginata*, *G. venenata*, *Lepiota helveola* | 2~30% |
| Seizures, delayed gastroenteritis, and liver toxicity | Gyromitrin | GIT, CNS, liver and blood | *Gyromitra esculenta*, *G. infula*, *Sarcosphaera coronaria*, *Chrysina macropus* | 0~10% |
| Delayed renal failure, cellular and oedematous intestinal fibrosis | Orellanine, orellinine, cortinarin | Kidney, GIT | *Cortinarius orellanus*, *C. speciosissinus*, *Mycena pura*, *O. orarius* | Rare |
| Delayed rhabdomyolysis | Unknown | Muscle | *Tricholoma equestre* | 25% |
| Erythromelalgia | Acromelic acid | Peripheral nerves, skin | *Clitocybe acromelalga* | Rare |
| Delayed encephalopathy (patients with renal failure) | Unknown | Encephalopathy | *Pleurocybella porrigens* | 27% |
| Abdominal pain, diarrhea, and intense sweating | - | - | *Clitocybe rivulosa* | - |

GI, gastrointestinal; GIT, gastrointestinal tract; CNS, central nervous system.

# Clinical features

| Phase I: | Phase II: | Phase III: |
| --- | --- | --- |
| **Abdominal pain, nausea, vomiting, diarrhoea fever, tachycardia, hypoglycaemia, hypotension and electrolyte imbalance, lasting for about a day.**<br><br>**Diarrhoea is often severe, watery, and cholera-like (up to 2 to 4 litres/day).**<br><br>**Metabolic acidosis may occur.** | **Treacherous phase of remission, during which the patient may be considered to have recovered and may even be sent home, only to return soon thereafter.** | • **Two to three days after ingestion- hepatic, renal, and (occasionally) pancreatic failure**<br><br>• **7 to 10 days- Hepatotoxicity manifests in the form of elevations of AST, ALT, and bilirubin levels, hypoglycaemia, jaundice, encephalopathy with convulsions coma, and death.** |

# Clinical features

| Phase I: | Phase II: | Phase III: |
| --- | --- | --- |
| | | • Coagulation defects with hypofibrinogenaemia and hypoprothrombinaemia occur in hepatic failure-local or general bleeding.<br>• Lactic acidosis and metabolic acidosis<br>• Hypoglycaemia is a grave marker signifying poor prognosis and C-peptide concentrations are elevated in many patients. Amanita toxins appear to be able to induce a direct insulin-releasing effect, and also have a cytotoxic effect on beta cells.<br>• Cardiovascular collapse usually accompanies severe hepatic failure at the terminal stage |

# Clinical features

| Phase I: | Phase II: | Phase III: |
| --- | --- | --- |
| | | • Adult respiratory distress syndrome (ARDS) may develop in the later stages of cyclopeptide mushroom poisoning, in conjunction with severe hepatic impairment and coagulopathies.<br><br>• Polyneuropathy<br><br>Two kinds of renal failure are observed in Amanita poisoning.<br>• During the gastrointestinal phase,-characterised by hypovolaemia, and is secondary to fluid losses and hypoperfusion of the kidneys<br>• Acute renal failure with anuria occurs in the third phase of poisoning, and may be accompanied by severe hepatitis with hepatic coma and haemorrhages. This is part of the hepatorenal syndrome |

# Usual Fatal Dose

- 2 to 3 mushrooms (A. phalloides).
- 5 to 15 mg of amatoxins per gram of dried mushroom have been found, which is equivalent to one Amanita cap.
- 0.1 mg/kg of amatoxin may be a lethal dose for human adults.
- About 15 to 20 Galerina caps could kill a healthy adult, as will about 30 Lepiotas.

# Diagnosis

- The Meixner test-unfortunately gives false positive reactions
- Melzer's test can be done to detect an amyloid reaction in cyclopeptide containing Amanitas.
- Hepatic and renal function tests.
- Serum electrolytes, urea, creatinine, and glucose levels
- A drop of material, Mushroom dish, gastric contents, or stools placed on slide and observed under high power (450X–500X) magnification, reveal spores
- Detection of toxins in gastric aspirate, serum, urine, stool, and liver and kidney biopsies, using HPLC, TLC, or RIA
- Monitor coagulation parameters (INR or PT)

# Diagnosis

- Elevated AST, ALT, LDH, and serum bilirubin are the earliest and best indicators of liver damage, while glucose, fibrinogen, and prothrombin time are the best indicators of established hepatocellular failure

- Patients with prothrombin values less than 10% have high fatality rate.

# Severity Classification

- Grade 1: GI upset
- Grade 2: All signs of intoxication, with a mild to moderate rise in transaminases (less than 500 units/L).
- Grade 3: Severe hepatic damage with a great increase in transaminases (> 500 units/L), plus an impaired plasma clotting function
- Grade 3a: Bilirubin rise is mild or absent.
- Grade 3b: Bilirubin rise is steep and continuous (> 5 mg/ dL). dL). These patients are at risk and should be transferred to a facility where liver transplant is possible

# Severity Classification

- Grade 4: Steep rise in transaminases, accompanied by a steep decline in clotting function, a steep rise in bilirubin, and the onset of kidney dysfunction.
- These patients have a poor prognosis, and many die in spite of intensive care

# Treatment

- Stabilisation
- Decontamination
- Antidotes:
- Treatment of acute liver failure

# Stabilization

- Restoration of fluid
- IV glucose
- Due to coagulation defect Clinical haemorrhage is present, give vitamin K (50 to 100 mg/day IV) and fresh frozen plasma.
- Correction of hypokalaemia (by potassium chloride diluted in solutions of dextrose 5%, or NaCl 0.9%),and of metabolic acidosis (by sodium bicarbonate solution 1.4%)

# Decontamination

- Activated charcoal in the usual manner and Multiple dose activated charcoal is supported
- Forced diuresis (6 to 9 L/day) may therefore help if the patient is seen within 24 to 48 hours because significant amounts of amatoxins are eliminated in urine, especially during the first 48 hours following ingestion
- Haemoperfusion beneficial if performed within 24hrs( risk of bleeding due to decreased platelets)
- Charcoal plasmaperfusion (CPP) and continuous venovenous haemofiltration (CVVH) was successful

# Antidote

- Benzyl penicillin at a dose of 300,000 to 1,000,000 units per day is said to be effective in displacing amatoxin from plasma protein-binding sites allowing for increased renal excretion
- Thioctic acid (alpha-lipoic acid) was initially thought to be beneficial in the treatment of hepatic damage but presently its use discouraging
- Silybinin is being investigated for its reported beneficial effects in countering hepatotoxicity,- No evidence so far of clear-cut advantage.
- Cimetidine (4 to 6 gm/day) a potent cytochrome P450 system inhibitor may have hepatoprotective effects against alphaamanitin
- N-acetylcysteine (NAC) has been investigated in some patients with various degrees of amanita poisoning.
- Root of Indian plant Picrorhiza kurroa (Kutkin) contains an iridoid glycoside mixture that has been shown to be hepatoprotective in certain situations.
- Aucubin is an iridoid glycoside obtained from the leaves of Aucuba japonica-protective against Amanita intoxication (when tested in dogs).

# Treatment of acute liver failure

- General symptomatic treatment
- Treatment of hepatic encephalopathy -Lactulose, Dietary protein withdrawal, Metronidazole or neomycin
- Treatment of cerebral oedema-
    - ICP monitoring
    - Osmotic diuretics such as mannitol (1 gm/kg, as rapid IV infusion of 20% solution).
    - Barbiturates such as IV thiopentone (3 to 5 mg/ kg) infused slowly over 15 minutes until signs of raised ICP resolve
    - Corticosteroids may not help in relieving cerebral oedema due to acute liver failure.
    - Proper positioning of the patient, i.e. head upright

# Treatment of acute liver failure

- Treatment of infection-Treating with antibiotics aggressively or prophylactically depending on situation
- Treatment of coagulopathy -Fresh frozen plasma for serious or persistent bleeding.
- Liver transplantation -recommended in following situations
    - Grade II encephalopathy and beyond.
    - Prolonged prothrombin time (greater than two times normal), despite administration of fresh-frozen plasma.
    - Serum bilirubin greater than 25 mg%.
    - Azotaemia.
    - Evidence of acidosis, hypoglycaemia, GI haemorrhage and hypofibrinogenaemia.

# Treatment of acute liver failure

- Molecular Absorbent Regenerating System (MARS)
  - It's a short-term extracorporeal hepatic support -so-called 'liver dialysis'
  - MARS is a method of removing protein bound substances in patients with liver failure and hepatic encephalopathy
  - It employs an albumin-impregnated highly permeable dialyser with albumin-containing dialysate recycled in a closed loop with a charcoal cartridge, an anion exchange resin absorber, and a conventional haemodialysis membrane.
  - MARS appears to be a promising bridging technique until the patient's liver can spontaneously recover, or until liver transplantation can occur.