REVIEW ARTICLE

TOXIC SUBSTANCES FROM MUSHROOMS

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SUMMARY

Toxic substances from certain species of various genera of the poisonous mushrooms have been isolated, and their chemical structures have been elucidated. Cyclic octapeptides(amatoxins) which derived from several species of *Amanita* and *Galerina* mushrooms seem to be the most toxic fungal toxin presently known. These compounds are very potent nonspecific cytotoxin, producing damages to various organs, notably the liver and the kidney. To make thing even worse, clinician who takes care of the patients with this type of poisoning may be misleading because the patients seem to recover after the initial phase of gastrointestinal disorders; however, serious effects such as acute fatal hepatitis usually occur after four to five days of ingestion. Most patients died unless intensive treatments had been early introduced. Muscimol and psilocybin are two mushroom toxins that primarily affect the central nervous system. Fungi containing these compounds have been used as hallucinogens, and the epidemic of the abuse of these mushrooms have been reported in some countries. Psilocybin also stimulates the sympathetic nervous system leading to mydriasis and tachycardia. Mushroom toxins that act principally on the autonomic nervous system include 1-aminocyclopropanol and muscarine. 1-Aminocyclopropanol possesses a disulfiram-like action, while muscarine stimulates the parasympathetic nervous system. Little is known about the chemical nature and mechanism of action of the gastrointestinal irritants. This group of toxins produces varying degrees of abdominal disturbances, depending on the species of fungi, individual sensitivity, and age of the consumers. Although the incidence of mushroom poisoning in Thailand is relatively low, knowledge of the nature of each type of fungal intoxication may be helpful in treatment of the patients, particularly in amatoxin poisoning.

Mushrooms have been a part of the human diet for many centuries. They can be cooked in a variety of ways, and foods prepared from these fungi are popular, especially among vegetarians. Despite their dietary value, some species of mushrooms are poisonous, and may cause death in intoxicated patients. Cases of mushroom poisoning have been occasionally reported in many countries throughout the world.

As investigated so far, toxic substances derived from poisonous mushrooms can be divided into 4 major groups according to their site(s) and onset of toxic actions (1) as summarized in table 1.

Table 1 Mushroom toxins and some of their characteristics

Group	Toxic substances	Organ affected	Onset of symptoms	Approximate fatality rate
1. Cytotoxins	Amatoxins	Liver, kidney, GI tract, blood, pancreas	12 hrs	50-90 %
	Monomethyl-hydrazine	Liver, kidney, GI tract, blood, pancreas, CNS	6-12 hrs	14.5-34.5 %
2. Toxins principally affecting the ANS	1-Aminocyclo-propanol	ANS (disulfiram-like action)	30mins-4-5 days	None
	Muscarine	ANS (parasympathetic stimulation)	30 mins	6-12 %
3. Toxins principally affecting the CNS	Psilocybin Psilocin	CNS (euphoria, hallucination) ANS (sympathetic stimulation)	30-60 mins	< 1 %
	Muscimol	CNS (GABA agonist)	20-90 mins	< 1 %
4. GI irritants	Unidentified	GI tract	30mins-2hrs	None

Group 1 : Cytotoxins

Mushroom toxins in this group can be divided into 2 subgroups, namely the cyclopeptides and monomethylhydrazine. Most of these compounds are nonspecific cytotoxins causing damages to several organs, including liver, kidney, gastrointestinal tract, pancreas, and blood (1-5). Monomethylhydrazine also possesses central nervous system effect (3). Toxic cyclopeptides are found in several deadly species of at least two mushroom genera, namely *Amanita* and *Galerina* (1). Examples of toxic species containing the cyclopeptides are *A. phalloides*, *A. verna*, *A. virosa*, *G. autumnalis*, and *G. marginata*. In Thailand, poisonous mushrooms of genus *Amanita* are known colloquially as "Ra-ngokhin".

The chemical nature of toxic cyclopeptides of genus *Amanita* or *Galerina* had been demonstrated by Wieland in 1968 (2). There are two families of cyclopeptides, including amatoxins and phallotoxins. The amatoxins include α-amanitin, β-amanitin, γ-amanitin, ε-amanitin, and amanin. These substances are cyclic octapeptide with molecular weight of about 900 (2). All of them contain two residues of glycine, one of L-isoleucine, one of the unusual L-dihydroxyisoleucine, one of L-asparagine, and one of L-hydroxyproline. In addition, a sulfur atom of cysteine residue is connected to the indole nucleus of a modified tryptophan residue (Fig. 1)

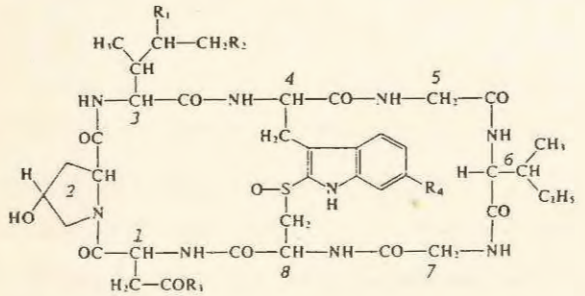
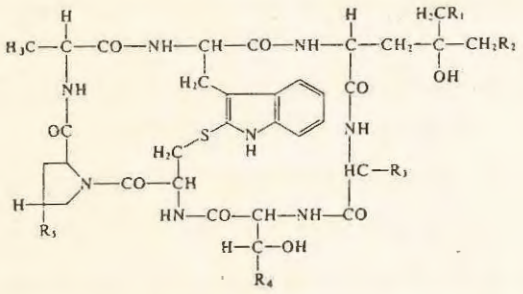


Fig. 1 Chemical Structures of Amatoxins.

	R_1	R_2	R_3	R_4
a α-Amanitin	OH	OH	NH_2	OH
b β-Amanitin	OH	OH	OH	OH
c γ-Amanitin	OH	H	NH_2	OH
d Amanin	OH	OH	OH	H
e Amanullin	H	H	NH_2	OH



	R_1	R_2	R_3	R_4	R_5
a Phalloidin	OH	H	CH_3	CH_3	OH
b Phalloin	H	H	CH_3	CH_3	OH
c Phallisin	OH	OH	CH_3	CH_3	OH
d Phallicidin	OH	H	$CH(CH_3)_2$	CO_2H	OH
e Phallin B (tentatively)	H	H	$CH_2C_6H_5$	CH_3	H

Fig. 2 Chemical Structures of Phallotoxins.

Phallotoxins consist of at least five members (Fig 2) (2). This group of toxins contains seven amino acid residues in their ring structure. Amino acids common to all members of phallotoxins are L-alanine and the coupling product of L-cysteine and L-tryptophan. Other amino acids are present in the different toxins as shown in Fig. 2 (2). Both amatoxins and phallotoxins are stable to heat. Thus, they are not destroyed by boiling or by any form of cooking(1).

Mechanisms of toxicity of amatoxins and phallotoxins have been extensively investigated. The primary targets for toxic actions of amatoxins are the nucleus and the nucleolus. It has been found that amatoxins bind very strongly with the 140-kDa subunit of the nucleoplasmic RNA polymerase II or B, leading to the blockade of transcription (6-11). Nuclear RNA content decreased rapidly within 1 to 2 hours after the administration of pure toxins, but the DNA level was not altered (12). This resulted in cessation of cellular protein synthesis and probably the subsequent cell necrosis.

The impairment in transcription may possibly be responsible for the histological findings of the contracted chromatin and segregation of the nucleolar components seen in both experimental and human liver cells exposed to the toxins (13). Other morphological changes observed in the liver of *Amanita verna* -intoxicated patients include karyolytic nuclei with disrupted nucleoli, fat vacuoles containing filamentous material, focal cytoplasmic degradation, and paracrystalline inclusions in the mitochondria (14).

Kidney is also susceptible to amatoxin intoxication. The primary site of action of the toxins in this organ is the proximal convoluted tubules (15). Amatoxins are filtered through the glomeruli and in turn destroy the tubular cells. The toxins then return to the liver and produce additional hepatic damage (15). However, the proximal tubular cells of some animal species, such as rat, are relatively resistant to the toxins (15). Besides liver and kidney, other tissues that are also sensitive to amatoxins include gastrointestinal epithelium, blood lymphocytes, and pancreas (5).

The structural requirements for the toxicity of amatoxins have recently been revised by Wieland et al (16). From the studies of the comparative inhibitory effect of various synthetic analogs of α-amanitin on RNA polymerase B from calf thymus, it was concluded that the following groups or side chains are necessary for toxicity (16): a β-branched chain with at least three carbon atoms and a γ-hydroxyl group (R_1 = OH) at position 3 (Fig. 1); a hydroxyl group in proline ring (position 2); an isoleucine side chain in position 6 and the absence of a side chain in position 5. Thioether linkage connecting cysteine residue to tryptophan residue is also a prerequisite for toxicity, since treatment of the toxins with Raney-nickel yields nontoxic dethio derivatives (2).

The inhibition of RNA polymerase II by amatoxins is possibly correlated with their toxicity. It was previously suggested by Buku et al (17) that there is a parallelism between the in vivo toxicity of the various amatoxins and their in vitro inhibition of rat liver RNA polymerase B. This was confirmed by Cochet-Meilhac and Chambon (8). Wieland et al (16) pointed out that LD_{50} values of amatoxins parallel their inhibitory constant (K_i). Alpha amanitin and their synthetic analogs with K_i values below 0.008 μM show parenteral LD_{50} in mice of about 0.3-0.5 mg/kg, whereas compound with K_i of 0.02 μM has LD_{50} of 15 mg/kg. None of the analogs with K_i above 0.02 μM had a lethal effect on the experimental animals. It is interesting that amanullin

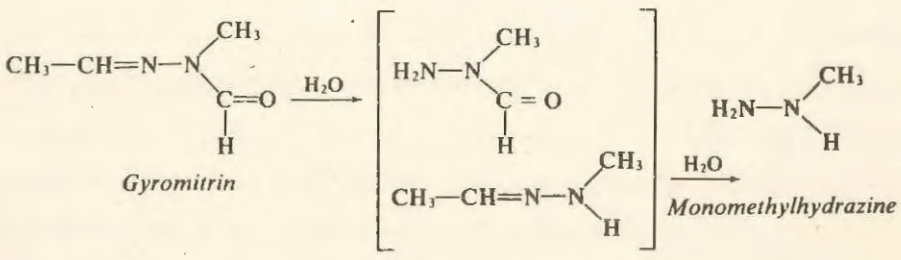
binds effectively with the enzyme in vitro (K_i = 0.01 μM), but it is not toxic in vivo. This may be due to permeability problem, probably related to the hydrophobicity of its nonpolar isoleucine side chain as suggested by Cochet-Meilhac and Chambon (8). Recently, it was found that wheat germ RNA polymerase II that binds very tightly with α-amanitin can be reactivated by monochromatic 314 nm irradiation. The enzyme recovers virtually all of the activity that an uninhibited control exibits (18). These findings, therefore, rule out the possibilities that the toxins inhibit the polymerase by catalyzing a cleavage of the polypeptide backbone, by permanently driving the enzyme into an inactive conformation, or by permanently dislodging a subunit of the enzyme (18). Thus, the exact molecular inhibitory mechanism of amatoxins on the polymerase remains to be elucidated.

The destructive mechanism of phallotoxins is different from that of amatoxins. Phallotoxins act selectively on hepatocytes and, except in the rat, on the proximal convoluted tubules (19). In the liver, these toxins bind to the plasma membrane and to membranes of subcellular organelles, including endoplasmic reticulum and lysosomes (15,20). These bindings induce disruptions of the membranes which are followed by protrusion of the cell membrane of isolated hepatocytes (20), massive efflux of potassium ions, and leakage of lysosomal enzymes (21). The latter phenomenon precedes severe liver injury (22,23).

It is noteworthy that phallotoxins are about 20 times less toxic than amatoxins(15). When administered parenterally to experimental animals, phallotoxins in high doses can cause death within one or two hours, while lethal effect of amatoxins does not appear until about 15 hours after injection (15). However, phallotoxins are probably nontoxic orally (15). Thus, these toxins should not be responsible for death in patients intoxicated with poisonous mushrooms of genus *Amanita* or *Galerina*. In man, the LD_{50} of amatoxins is possibly less than 0.1 mg/kg. Thus, ingestion of only one cap of the fresh mushroom weighing about 50 grams may be lethal in adult, since this amount of the fungus contains approximately 7 milligrams of amatoxins (1).

The clinical pictures of amatoxin poisoning can be divided into three phases (24). The first phase characterized by nausea, vomiting, abdominal pain, and cramps are seen within twelve hours of ingestion. These are followed by the second phase of clinical improvement which may be misleading. During this phase, patient seems to recover, but laboratory features reveal a marked hepatic damage resemble those of CCl_4 intoxication. Serum transaminases are strikingly elevated in some patients (13, 25-27) and only modestly increased in others (28). The levels of lactic dehydrogenase increase significantly with a marked elevation in LDH isoenzymes of fractions IV and V (29). Hyperbilirubinemia is characteristic, and abnormal values for the flocculation tests have been reported (25). The levels of clotting factors involved in coagulation, notably factors V, VII, and VIII, decrease simultaneously, leading to a bleeding tendency after the first two days of intoxication (25). Hypoglycemia and lactic acidosis may develop lately after the exhaustion of glycogen storage (30). Neurological signs may appear as a result of hepatic encephalopathy (19). This phase may last from hours to three or four days (24). Acute hepatic necrosis with its complications characterize the final phase. Estimated mortality rates are quite high, ranging from 50% to 90% (31).

Cytotoxin present in mushroom *Gyromitra esculenta*(false morel) is gyromitrin (acetaldehyde N-methyl-N-formylhydrazone) (1). This compound is hydrolyzed under the acidic conditions of the stomach to monomethylhydrazine (Fig. 3) (32).



Gyromitrin *Monomethylhydrazine*

Fig. 3 Chemical Structure of Gyromitrin and Monomethylhydrazine.

Monomethylhydrazine is believed to be responsible for the toxicity of *Gyromitra esculenta* (33,34). It should be noted that toxic effect of the mushroom can be diminished by boiling, since gyromitrin and monomethylhydrazine are rapidly extracted into hot water (35). However, toxicity may develop if one consumes the boiled mushroom with the broth. The boiling point of monomethylhydrazine is 87.5°C. Thus, cook may be intoxicated with the vapor of monomethylhydrazine while cooking the fungus (1).

Poisoning from *Gyromitra esculenta* is usually characterized by nausea, vomiting, diarrhea, abdominal cramps, weakness, dizziness, severe headache, and muscle cramps. These symptoms occur after a relatively long latent period of 6 to 12 hours (1). In some cases, acute hepatitis, convulsions, and coma may develop which may result in death. Approximate mortality rates from *Gyromitra* poisoning range from 14.5% to 34.5% (36,37). Monomethylhydrazine has been reported to produce tumors in mice and in hamsters (38-40). However, tumorigenicity of this compound is still controversial (3). Mechanism of cytotoxic action of monomethylhydrazine and related hydrazine derivatives remains unclear. It has been suggested that these agents or their metabolites may bind covalently to macromolecules, such as proteins, leading to cell damage (41).

Group 2 : Toxins principally affecting the autonomic nervous system

Toxins in this group have profound effects on the autonomic nervous system (1). However, they are less dangerous than fungal toxins in Group 1. Coprine and muscarine are two major toxins in this group. Coprine is present in *Coprinus atramentarius* (inky cap), while muscarine is found in clinically significant concentrations in a number of species of *Inocybe* and *Clitocybe* mushrooms (1). Coprine (N^5-(1-hydroxycyclopropyl)-L-glutamine, Fig. 4) possesses a disulfiram-like action, sensitizing the mushroom consumer to toxic effects of

acetaldehyde (1). This compound was found to be converted to 1-amino-cyclopropanol, a potent inhibitor of aldehyde dehydrogenase (42). This enzyme catalyzes the dehydrogenation of acetaldehyde to acetic acid, therefore, inhibition of the enzyme activity causes an elevation of blood acetaldehyde after ethanol consumption (43).

The clinical features of coprine poisoning may appear one-half to one hour after drinking alcohol if patient has eaten the mushroom for four to five days before (1). However, the symptoms may develop when the fungus is consumed simultaneously with large amounts of alcohol (1). The patient may show flushing of the face and neck, paresthesia in the hands and feet, metallic taste, tachycardia, and chest pain. These are followed by nausea, vomiting, and sweating. Vertigo, visual disturbance, weakness, hypotension, confusion, and cardiac arrhythmias may occur in severe cases. The patient usually recovers spontaneously within two to four hours (1).

The inhibitory mechanism of 1-aminocyclopropanol on aldehyde dehydrogenase is still unclear. This compound may inhibit the enzyme by different mechanism from that of disulfiram, since the structure of the two agents differs markedly. Recently, it has been proposed that disulfiram inhibits human liver aldehyde dehydrogenase E_1 by binding at a specific site and oxidizing essential enzyme sulfhydryl groups to form internal disulfide bonds (44).

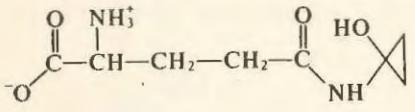
Another toxin in this group is muscarine (Fig. 4). This compound is found in physiologically significant amounts in various species of *Inocybe* and *Clitocybe* fungi, but only in minute quantities in *Amanita muscaria* (0.00025 % by weight of the fresh specimens) (1,2). Muscarine has the parasympathomimetic properties of acetylcholine but lacks the sympathomimetic and voluntary muscle effects (45). Symptoms of muscarine poisoning usually appear within 30 minutes after ingestion (1). Excessive sweating, salivation, and lacrimation are characteristic and may occur rapidly. Other early signs include pupil constriction,

hypotension, and slow pulse. In severe cases, nausea, vomiting, abdominal pain, diarrhea, and difficulty in breathing may be evident (1,19). Normally, the symptoms will subside, even without treatment, within two hours (19). Parenteral atropine should be given if severe cholinergic effects are present (1). Children with cardiac or pulmonary disease are particularly vulnerable to muscarine (1). Estimated mortality rates of muscarine intoxication range from 6 % to 12 % (46,47).

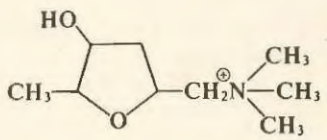
Group 3 : Toxins principally affecting the central nervous system

Several mushroom toxins are capable of producing toxic effects on the central nervous system. Some species of fungi containing these toxins have been employed as hallucinogens by the Indians of Meso-America for thousands of years (1). Even nowadays, many cases of the abuse of indigenous hallucinogenic fungi in Britain have been reported (48,49).

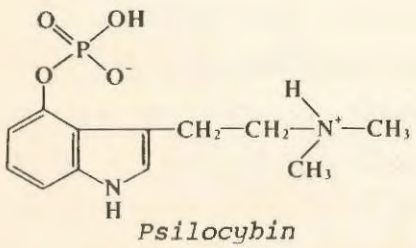
There are at least two groups of mushroom toxins that primarily affect the central nervous system (1). The first group includes psilocybin, psilocin, baeocystin, and norbaeocystin (1). The structures of some of these compounds are shown in Fig. 4. The toxins are present



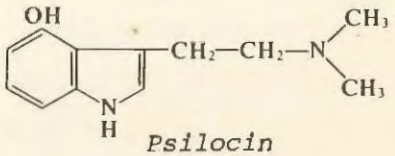
Coprine



Muscarine



Psilocybin



Psilocin

Fig. 4 Chemical Structure of Coprine, Muscarine, Psilocybin, and Psilocin.

in several species of *Psilocybe*, *Panaeolus*, and *Gymnopilus* (1). These compounds are indolylalkylamines of varying psychotropic potency. Their chemical structure is quite similar to that of a well-known hallucinogen LSD, but have only about 1 % of the potency of LSD (50). Psilocybin is relatively more resistant to oxidation than psilocin, therefore, its toxicity is retained in dried mushrooms (19). Two major components of neurological symptoms are evident in patients deliberately ingested *Psilocybe semilanceata* as reported by Young et al. (49). These include sympathomimetic stimulation (mydriasis and tachycardia) and euphoria and/or visual hallucinations (49). It has been estimated that about 30 to 40 fresh specimens of this mushroom (equivalent to 3 to 4 grams of dry material) are required to produce the complete range of hallucinogenic effects (48). The symptoms usually appear within 30 to 60 minutes of ingestion (1), However, fatality rate from psilocybin intoxication is relatively low, probably less than 1 % (1). The mechanism of psychotropic effects of these toxins in not well understood. It has been suggested that the toxins may alter the levels of some brain neurotransmitters, especially serotonin, and thus interfering with the processes of information processing and perception (51).

Another group of psychotropic fungal toxins consists of ibotenic acid and muscimol (Fig. 5). These compounds are 3-isoxazole derivatives with zwitterionic structures (52,53). Ibotenic acid is converted nonenzymatically in the mushrooms to muscimol (54). These toxins are found in various species of genus *Amanita*, including *A. muscaria*,

Ibotenic acid *Muscimol*

Fig. 5 Chemical Structure of Ibotenic Acid and Muscimol.

A. pantherina, *A. gemmata*, and *A. cothurnata* (1). Muscimol is five to ten times more potent than ibotenic acid, therefore, the former compound should play a more important role in producing the central nervous system effects (1,19).

Symptoms of muscimol poisoning may develop within 20 to 90 minutes after ingestion (19). Patients may experience drowsiness, dizziness which may sometimes be associated with sleep, and muscle incoordination (1,19). In severe poisoning, this ataxia may progress to muscle twitchings, hyperkinetic activity, muscle cramps, and spasms (1). Echo pictures, micropsia, confused identities, or even manic excitement may occur (19). Tonic-clonic convulsions and coma may be found in children who were severely intoxicated with the mushrooms (19). Approximate mortality rate of this type of poisoning is possibly less than 1% (1).

The exact mechanism of psychotropic effects of muscimol is not clearly understood. Several lines of evidence suggest that this compound may act on the central inhibitory GABA transmission (55). Muscimol has multiple effects at GABA synapses, including an in vitro high affinity binding to postsynaptic GABA receptors (56,57) and also to the presynaptic autoreceptors (58,59), an in vivo activating of GABA receptors (60,61), and the interactions with the GABA transport systems (62). These diverse effects of muscimol on the functions of central GABA-mediated synapses may contribute to the observed psychotropic effects of this compound (55).

Group 4 : Gastrointestinal irritants

Toxins in this group have been known collectively as gastrointestinal irritants. Chemical structure and mechanism of gastroenteric irritation of these toxins have not been clearly characterized yet (1). The irritants have been found in certain species of various genera of fungi, including *Agaricus*, *Amanita*, *Boletus*, *Chlorophyllum*, *Entoloma*, *Hebeloma*, *Ramaria*, and so on (1). Among these, *Chlorophyllum molybdites (Lepiota*

morganii) is a common cause of this type of poisoning, and characteristics of its toxin had been investigated (63). It should be noted that the severity of gastrointestinal toxicity produced by this group of toxins is variable, depending on the type of mushrooms, individual susceptibility, and age of the consumers (1,19). Generally, the toxins may produce abdominal discomfort within 30 minutes to two hours of ingestion (1). Patients may experience nausea, vomiting, and abdominal cramps with varying degrees of diarrhea (1). In severe cases, marked dehydration, electrolyte loss, and hypovolemic shock may occur, notably in children (19). Besides the above symptoms, gastrointestinal bleeding may be found in *Chlorophyllum molybdites* poisoning (64,65). This effect may possibly be attributed to disseminated intravascular coagulation induced by the toxin (65). Patients may recover spontaneously within one or two days, however, fluid and electrolyte replacements as well as other symptomatic treatments may be required in severe cases (1).

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