THE POISONOUS MUSHROOMS IN JAPAN

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ABSTRACT: *Of mushrooms found in Japan, approximately 35 species are classified as poisonous mushrooms. The mushroom poisonings caused by these mushrooms are classified as three types according to the symptoms and their toxic constitutents. The first type is the cholera–like symptom which is induced mainly by the toxic constitutents such as cyclopeptide and gyromitrin. The second type is the neurological manifestations induced by muscarine (cholinergic), muscimol (delirium), psilocybin (hallucinogenic) and coprine (antabuse–like). The third type is the gastrointestinal irritation which is induced by illudin and fasciculol. Antidotes to these toxins have been listed; i.e., thioctic acid and aucubin to amanitin, pyridoxine to monomethylhydrazine, atropine to muscarine, physostigmine to muscimol, and chloropromazine to psilocybin.*

Keywords: *Poisonous mushroom, Poisoning, Symptomatology, Toxic constituent, Antidotes.*

INTRODUCTION

Many species of mushrooms are found in Japan. In recent years, there has been a notable increase in the number of people consuming wild mushrooms as foods. Consequently, the number of poisonings caused by poisonous mushrooms are increasing. The mushroom poisonings in Japan have been reported to number about 100 cases annually (1,2), but the number of cases that actually happen is estimated to be more than that officially reported (3).
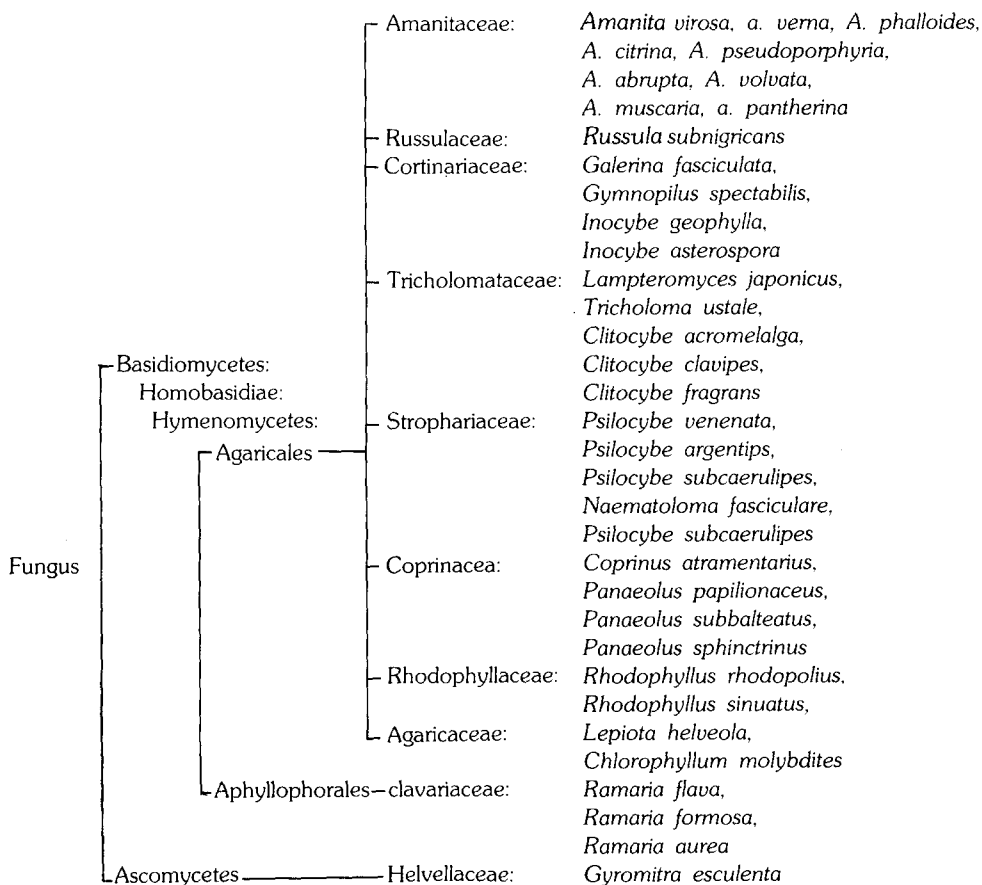
The knowledge on mushroom posioning has not been sufficiently accumulated hence the mechanisms of mushroom poisonings have not been fully elucidated. In addition, the toxic constitutents in most of the poisonous mushrooms remain unidentified.

This review deals with the recent advances in the study on poisonous mushrooms; taxonomy of the poisonous mushrooms in Japan, classification of mushroom poisonings and poisonous mushrooms according to symptoms, biochemical toxicology and toxic constitutents in the mushrooms. The clinical treatment of mushroom poisoning is also described.

TAXONOMY

Approximately more than 2000 speices of mushrooms seem to grow in Japan. Some of them are poisonous; however, most of them are considered nontoxic and some of them are consumed as food and medicine, in both wild and cultivated forms. It is known that most of

Table 1. Taxonomic positionof representative poisonous mushrooms in Japan.

	Amanitaceae:	*Amanita virosa, a. verna, A. phalloides,* *A. citrina, A. pseudoporphyria,* *A. abrupta, A. volvata,* *A. muscaria, a. pantherina*
	Russulaceae:	*Russula subnigricans*
	Cortinariaceae:	*Galerina fasciculata,* *Gymnopilus spectabilis,* *Inocybe geophylla,* *Inocybe asterospora*
	Tricholomataceae:	*Lampteromyces japonicus,* *.Tricholoma ustale,* *Clitocybe acromelalga,* *Clitocybe clavipes,* *Clitocybe fragrans*
Basidiomycetes: Homobasidiae: Hymenomycetes: Agaricales	Strophariaceae:	*Psilocybe venenata,* *Psilocybe argentips,* *Psilocybe subcaerulipes,* *Naematoloma fasciculare,* *Psilocybe subcaerulipes*
	Coprinacea:	*Coprinus atramentarius,* *Panaeolus papilionaceus,* *Panaeolus subbalteatus,* *Panaeolus sphinctrinus*
	Rhodophyllaceae:	*Rhodophyllus rhodopolius,* *Rhodophyllus sinuatus,*
	Agaricaceae:	*Lepiota helveola,* *Chlorophyllum molybdites*
Aphyllophorales−clavariaceae:		*Ramaria flava,* *Ramaria formosa,* *Ramaria aurea*
Ascomycetes	Helvellaceae:	*Gyromitra esculenta*

Fungus

the mushroom poisonings are caused by a limited number of mushrooms, about 35 species, of which fewer than a dozen are considered to be deadly. Among the mushroom poisonings in Japan, about 70% were caused by *Lampteromyces japonicus* and *Rhodophyllus rhodopolius.* Both of them are not deadly poisonous.

Representative poisonous mushrooms in Japan are shown in Table 1 and Fig. 1. It is noted that most of deadly poisonous species belong to the genus *Amanita.*

Identification of poisonous species is very important, not only in toxicology of mushroom poisoning, but also in natural product chemistry. The following is the very complicated, but very instructive example in which taxonomy played an important part.

Dr. Takemoto and his co-workers (4) isolated biologically active (fly–killing) amino acid called ibotenic acid from *Amanita* species growing in the coastal pine forests around Sendai City, Northern Honshu, Japan. This *Amanita* is called "Ibotengutake" in Japanese by the natives around there, and it was identified as *Amanita strobiliformis.* Afterward Benedict *et al.* (5) tried to isolate ibotenic acid from American *Amanita strobiliformis.* But it was never detected. According to Bas (6), *A. strobiliformis* is a edible mushroom, growing only in Europe, and does not exist in the United States. One of the authors, Yokoyama is now reinvestigating this poisonous *Amanita* called "Ibotengutake". *Amanita pantherian* is the

Amanita virosa
(Jpn. name: Dokutsurutake)

Amanita pseudoporphyria
(Kotengutakemodoki)

Amanita abrupta
(Tamashiroonitake)

Amanita volvata
(Fukurotsurutake)

Amanita muscaria
(Benitengutake)

Galerina fasciculata
(Koreatake or Dokuajirogasa)

Fig. 1. Photographs of some poisonous mushrooms in Japan.

Lampteromyces japonicus
(Tsukiyotake)

Clitocybe acromelalga
(Dokuazirogasa or Yakedokin)

Psilocybe argentipes
(Hikageshibiretake)

Naematoloma fasciculare
(Nigakuritake)

Panaeolus subbalteatus
(Senbonsaigyougasa)

Rhodophyllus rhodopolius
(Kusaurabenitake)

most probable species according to the field work, the information from the natives and judging from the photograph in the journal presented by Takemoto (7).

CLASSIFICATION OF POISONINGS AND POISONOUS MUSHROOMS BY SYMPTOMS AND TOXIC CONSTITUENTS

We classify mushroom poisonings to 3 major types according to the symptoms which appear following the ingestion of the mushrooms, and poisonous mushrooms are divided

Phallotoxins

	R_1	R_2	R_3	R_4
Phalloidin	OH	H	CH_3	CH_3
Phalloin	H	H	CH_3	CH_3
Phallisin	OH	OH	CH_3	CH_3
Phallacin	H	H	$CH(CH_3)_2$	COOH
Phallacidin	OH	H	$CH(CH_3)_2$	COOH
Phallisacin	OH	OH	CH(CH)	COOH

Amatoxins

	R_1	R_2	R_3
α-Amanitin	CH_2OH	NH_2	OH
β-Amanitin	CH_2OH	OH	OH
γ-Amanitin	CH_3	NH_2	OH
ε-Amanitin	CH_3	OH	OH
Amanin	CH_2OH	OH	H

Virotoxins

	X	R	R
Viroisin	SO_2	CH_2OH	$CH(CH_3)_2$
Viroidin	SO_2	CH_3	$CH(CH_3)_2$
Deoxo-viroidin (Ala)	SO	CH_3	$CH(CH_3)_2$
viroidin (Ala)	SO_2	CH_3	CH_3
Deoxo-Viroidin	SO	CH_3	CH_3
Deoxo-viroisin	SO	CH_2OH	$CH(CH_3)_2$

Fig. 2. Cyclopeptide toxins

into 7 groups. Biochemical toxicology and the toxic constitutents in the mushrooms are described hereafter.

On the average, mushrooms consist of about 90% water, 3% protein, and some other nitrogen compounds, carbohydrates, fat and ash. The proteins and nitrogen compounds in mushrooms play an important role in mushroom poisoning.

During the past decade, identificational studies of the toxic constitutents in the mushrooms have progressed markedly. But human bioassay of the toxins identified is impossible. Therefore, it is the most difficult problem in this kind of research to identify the toxic principles causing the poisoning.

(A) Cholera–like symptoms–causing type

Species:*Amanita virosa, A. verna, A. phalloides, A. abrupta,f A. volvata, Gyromitra esculenta, Galerina fasciculata, Russula subnigricans*

After a latent period of 6–24 hr between ingestion of the mushroom and the first symptoms, there is a sudden onset of abdominal pain, nausea, violent vomiting and watery diarrhea. Then abdominal pains recur with dehydration, collapse, convulsions, coma and result in death (8–10). These mushrooms cause the damage of liver and kidney. The fatality rate is 50–90%. These mushrooms account for over 90% of all cases of fatal mushroom poisoning.

The level of blood glucose progressively decreases in the early phase of the poisoning, and depletion of liver glycogen and the inhibition of β–oxidation of fatty acids occur (11). The activities of serum transaminases and the level of blood urea nitrogen (BUN) increase markedly, and the elevated activities or level is maintained thereafter (12,13). In *Gyromitra esculenta* poisoning, methemoglobin is detected in blood (14).

As for the toxic constitutents of these mushrooms, phallotocins (cyclic heptapeptides) and amantoxins (cyclic octapeptides) have been isolated from *A. virosa, A. verna, A. phalloides* (10,15), and other polypeptides with a much higher molecular weight, named virotoxins, have been isolated from *A. virosa* (16).

These toxins are all intracellular poisons in man (16–18). Amanitin is about 20 times more toxic than phalloidin (19). Amatoxins have been shown to interfere with both DNA and RNA transcription by inhibiting RNA polymerase; the end result is termination of protein synthesis and cell death (20,21).

Gyromitra esculenta contains the specific toxin, gyromitrin, which on hydrolysis produces monomethylhydrazine a highly toxic compound.
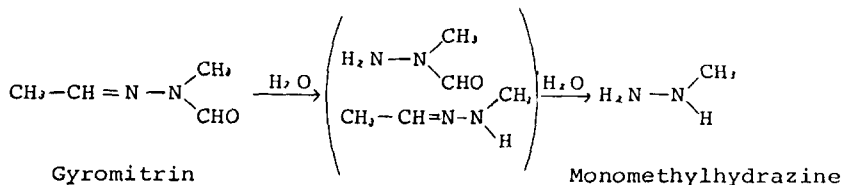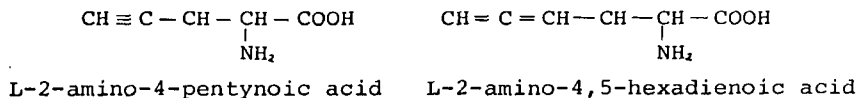

Fig. 3. Gyromitrin and monomethylydrazine

Fig. 4. Amino acids

Monomethylhydrazine is a hemoloytic toxin and inhibits the transaminases which have pyridoxal phosphate as a co–factor (22).

Recently, two amino acids, L–2–amino–4–pentynoic acid and L–2–amino–4,5–hexadienoic acid have been isolated from *A. abrupta* and *A. pseudoporphyria* (23,24).

The former causes the changes of glucose metabolism and hepatotoxic action (23) and inhibits the enzymes involved in methionine and cystathionine metabolism in liver (25,16). The latter causes decrease in respiratory depth, pilomotor erection and hypothermia (27).

(B) Neurological symptoms–manifestating type

1) Stimulus of parasympathetic nervous system

Species: *Clitocybe* spp., *Inocybe* spp., (*A. muscaria, A. pantherina*)

The poisoning by these mushrooms causes a characteristic syndrome of constricted pupils, excessive perspiration, salivation and lacrimation within 30 min–2 hr after ingestion. These are followed by blurring of vision and painful abdominal cramps. In severe cases, a fall in blood pressure to critical levels and loss of consciousness may occur. The fatality rate is less than 10%.

The activity of serum cholinesterase decreases. the level of blood glucose increases in the early phase, but it decreases in the later phase (28).

L–(+)–muscarine, muscaridine and acetylcholine in these mushrooms have a cholinergic effect. Muscarine has not fully been shown to produce a psychotropic action.

2) Depression of parasympathetic nervous system

Species: *amanita muscaria, A. strobiliformis*, Tricholoma muscarium*

Opened pupils and dizziness are early signs induced by this type of poisoning. In severe cases, this ataxia may progress to muscular twitching, hyperkinetic activity and spasms. The fatality rate is less than 1%.

The levels of BUN and ammonia in blood increase, and liver glycogen decreases within 3 hr after administration (28).

Isoxazole compounds, ibotenic acids, muscimol and muscazone have been isolated from these mushrooms (29,30,31).

All these compounds have delirium effects. Ibotenic acid is found in the highest concentration in the mushroom, but it is very unstable and is readily converted into muscimol which
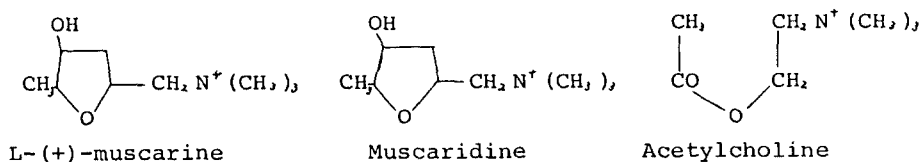

L-(+)-muscarine   Muscaridine   Acetylcholine

Fig. 5. Quaternary ammonium compounds

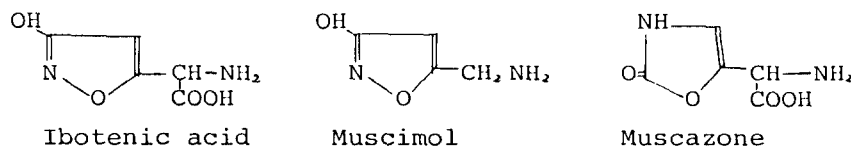Ibotenic acid   Muscimol   Muscazone

Fig. 6. Isoxazole derivatives

*See the taxonomical part of this paper.

is 5–fold as potent as ibotenic acid in its effect on the nervous system.

3) Depression of central nervous system

Species:*Psilocybe venenata, P. argentipes, P. subcaerulipes, Panaeolus papilionaceus, Pa. subbalteatus, (Gymnopilus spectabilis)*

A hallucinogenic dysphoric state occurs 30 min–3 hr after ingestion. The psychological state may be pleasant or filled with anxiety. The hallucinations and illusions may also be acoustic or gustatory. Vertigo, ataxia, muscle weakness and drowsiness would last for about 6 hr after ingestion.

Psilocybin, psilocin baeocytin and norbaeocystin have been isolated from these mushrooms (32,33).

These indole derivatives which are similar to D–lysergic acid (LSD) in their chemical structure exert their effects on the central nervous system to produce hallucination.

4) Disulfiram–alcohol (Antabuse–like) syndrome

Species:*Coprinus atramentarius, Clitocybe clavipes*

The peculiar features of the poisoning by these mushrooms are the disulfiram like symptoms; flushing of the face and neck, nausea, vomiting. These symptoms appear 30 min–1 hr after drinking alcohol if the mushroom has been taken in advance, or may occur with alcohol consumption even 6 days after taking the mushroom. In severe cases, vertigo, confusion and coma occur.

It has been clarified that the mushroom inhibits the activity of hepatic aldehyde dehydrogenase, which induces an increase of acetaldehyde level in blood, thus enhancing the toxicity of alcohol (34,35).

Coprine, N^5–(1 hydroxycyclopropyl)–L–glutamine have been isolated from *Coprinus atramentarius* (36).

Coprine is converted into 1–aminocyclopropanol which has chelating properties similar to those of disulfiram, binding to molybdenum, and resulting in the inhibition of acetaldehyde dehydrogenase (10).
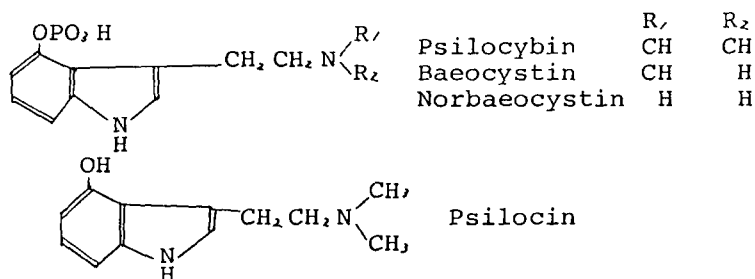

	R_1	R_2
Psilocybin	CH	CH
Baeocystin	CH	H
Norbaeocystin	H	H

Psilocin

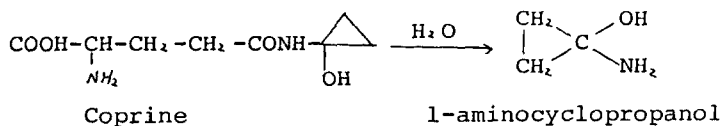Fig. 7. Indole derivatives

Coprine   1-aminocyclopropanol

Fig. 8. Coprine and 1–aminocyclopropanol

5) Stimulus of motoric peripheral nerve system

Species:*Clitocybe acromelalga*

Nausea may occur several hours after ingestion. Acromelalgia appears followed by a feeling of swelling and paresthesia in the hands and feet 3 to 5 days later (12 days in some cases). this symptom may last for a month or more.

As for the toxins in the mushroom, clitidine and acromelic acid have been isolated (37,38,39).

(C) Gastrointestinal irritating type:

Species: *Lampteromyces japonicus, Tricholoma ustale, Naematoloma fasciculare, rhodophyllus rhodopolius* etc.

Onset of nausea, vomiting an abdominal cramps with diarrhea may occur within 30 min–2 hr after ingestion. In most cases, symptoms subside in 3–6 hr, and the patients would recover within a day. But N. fasciculare is more toxic and there have been some victims by this mushroom (1).

Statistically most of the mushroom poisonings are caused by these mushrooms Many investigators on the toxic constitutents in the mushrooms of this type have not been successful in identifying specific toxins. Illudin S (lampterol) from *L. japonicus* (40), fasciculol E and F from *N. fasciculare* have been isolated (41).
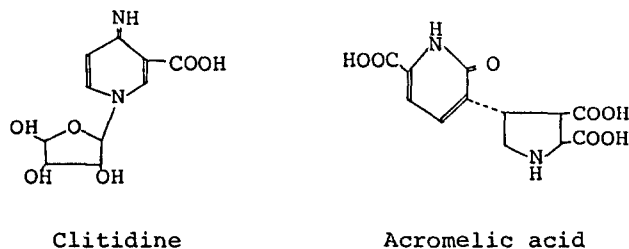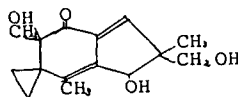
Clitidine   Acromelic acid

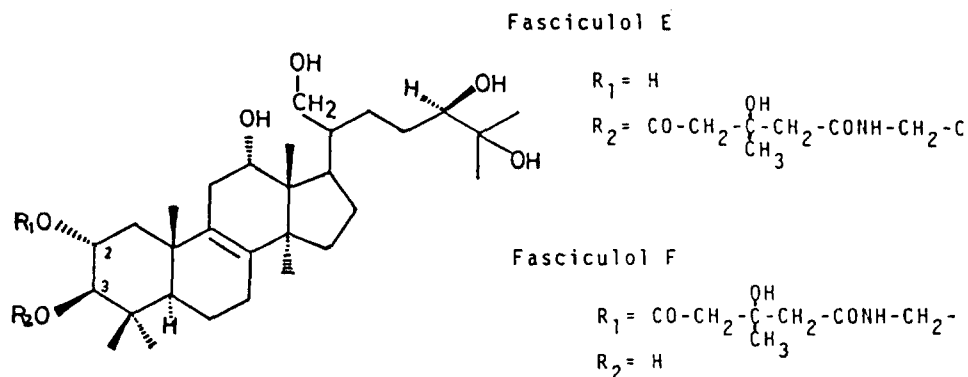**Fig. 9.** Clitidine and acromelic acid

Fig. 10. Illudine S

Fig. 11. Fasciculol E and F.

CLINICAL TREATMENTS AND ANTIDOTES

The accurate diagnosis of mushroom poisoning from symptoms alone is virtually impossible, since many cases present only nausea, vomiting and diarrhea which are typical symptoms in general food poisoning. There is certainly no definite method in physical examination which might suggest mushroom poisoning. The clinician should suspect mushroom poisoning when encountered with unusual manifestations of gastroenteritis and should examine liver parameters which might suggest serious mushroom poisoning. In most cases treatment would be required before the mushroom species or the toxin could be identified.

The general treatment of mushroom poisoning can be summarized as follows:

Reducation of absorption

Administration of emetic followed by large amounts of water is one of the most effective treatments. If the patient is in coma or convulsion, intubation of a gastric tube into stomach and oral administration of activated charcoal to adsorb the toxins might be useful.

Enhancement of excretion

If catharsis is not adequate, use of a purgative might give some good results. Hemodialysis (extracorporal circulation through charcoal filter) is the best treatment of liver and renal failures.

The treatment of mushroom poisoning varies according to the kind of toxins involved. Antidotes may be administered only when the type of poisoning is diagnosed and the toxin is identified (Table 2).

Table 2. Efficient antidotes to the toxins.

Toxins	Antidotes
Amanitins	Thioctic acid; Fineston, A. (1972). Aucubin; Chang, I.−M. (1984). Penicillin−G; Hazani, E. (1983)
Monomethylhydrazine	Pyridoxine; Kirklin, J.K. (1976).
Muscarine	Atropine Eugster, C.H. (1969).
Ibotenic acid, muscimol	Physostigmine; Rumack, B.H. (1973)
Psilocybin, psilocin	Chlorpromazine; Keeler, M.H. (1967)

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