ECRONICON OPEN ACCESS

EC EMERGENCY MEDICINE AND CRITICAL CARE
Review Article

Do Mushrooms also Cause Cancer in Human?

Mohammad Shahid Masroor[1]*, Mohammad Salim[2], Shagufta Parween[3] and IP Prajapati[2]

[1]*People's College of Dental Sciences and Research Center, People's Univ., Bhopal (M.P.), India*

[2]*Sanjay Gandhi Smriti Government Autonomous P.G. College, Sidhi, A.P.S. Univ., Rewa (M.P.), India*

[3]*All India Institute of Medical Sciences (AIIMS), Bhopal (M.P.) India*

***Corresponding Author:** Mohammad Shahid Masroor, People's College of Dental Sciences and Research Center, People's Univ., Bhopal (M.P.), India.

Received: November 14, 2020; **Published:** December 10, 2020

Abstract

Mushrooms are not usually known to cause cancer. But this is a poignant truth that some of these poisonous mushrooms containing mycotoxins develop various ailments, diseases and even cancer in human. Peoples are unknowingly consuming the poisonous mushrooms as they are unable to identify them. It appears that no such integrated study has done so far in the past to make the people aware that how some of these mushrooms are toxic in developing cancer in human. The present paper deals with the study of some of these poisonous mushrooms containing mycotoxins causing several ailments, diseases and cancer in human.

Keywords: *Mushrooms; Mycotoxins; Diseases and Cancer*

Abbreviations

AGT: Agaritine; ALF: Acute Liver Failure; RNA: Ribonucleic Acid; DNA: Deoxyribonucleic Acid; MMH: Mono Methyl Hydrazine; CNS: Central Nervous System; mRNA: Messenger Ribonucleic Acid; LD 50: Lethal Dose, 50%; IARC: International Agency for Research on Cancer

Introduction

In the past, mushrooms have never been the part of man's original diet. But, nowadays, they are popular edibles of modern society. How good are they for us? Do they have a positive effect on our health? Some growing reports suggest that some of these mushrooms are not fit for consumption and they harm our health [1]. And, this is all due to a variety of mycotoxins especially the hydrazines found therein [2]. Most of these hydrazines tested so far are either carcinogenic or mutagenic in nature. For example, one of the most common hydrazines is agaritine found in *Agaricus bisporus*, which is metabolized into diazonium derivative, a very potent carcinogen in a very small amount [3]. *Agaricus bisporus* is widely cultivated to produce low-cost mushroom fruiting bodies casting about a multibillion-dollar world industry [4]. It causes lung, bladder and stomach cancer [5-8]. Similarly, the gyromitrin isolated from *Gyromitra* is also hydrolyzed into a more toxic compound monomethylhydrazine (MMH) causing cancer in human and animals [9-12]. Further, the "death cap", *Amantia phalloides* is an extremely poisonous mushroom killing an individual in a very small amount. It contains a variety of amanitins developing liver failure and prostate cancer [13-15]. In addition, the fruiting bodies of *Podostroma cornu-damae* have also been found to be highly toxic as it contains several trichothecenes developing diseases and cancer in human [16-18]. As we have exemplified some of these mushrooms documenting their roles in causing cancer in human, the present review is an attempt to describe them in detail. The basic aim of the paper is to make the people aware of the fact that some of these mushrooms are extremely toxic to human health.

Discussion

Mushroom mycotoxins caused a variety of adverse health effects ranging from acute poisoning to long term effects such as immune deficiency and cancer. Since most mushrooms are rarely eaten, many toxins are poorly documented for their cancer-causing efficiencies. However, some of these mycotoxins found in mushrooms capable of causing cancer are tabulated (Table1) and discussed as under:

S.N.	Name of Mushroom	Mycotoxins Produced	References
1.	*Agaricus bisporus*	Agaritine	Toth *et al.* 1982[6], Hashida *et al.* 1990[7], Walton *et al.* 1997[21], Schulzova *et al.* 2002[19], Nagaoka *et al.* 2006[2], Kondo *et al.* 2008[8], Schulzova *et al.* 2009[20]
2.	*Gyromitra esculanta*	Gyromitrin	Pyysalo 1975[9], Lampe 1979[30], Braun *et al.* 1981[10], Coulet and Guillot (1982)[27], Meierbratschi *et al.* 1983[28], Bergman and Hellenas 1992[29], Karlson and Person 2003[11], Dart 2004[12]
3.	*Amanita phalloides, Conocybe, Galerina, Lepiota*	Amanitins	Horgan *et al.* 1978[39], Piqueras 1989[13], Meinecke and Meinecke 1993[40], Karlson and Persson 2003[11], Andler *et al.* 2013[14], Hechler and Andler 2015[15]
4.	*Podostroma cornu-damae*	Trichothecenes	Yoko *et al.* 2001[42], Ahn *et al.* 2013[41], Kim *et al.* 2016[43], Park *et al.* 2016[16], Sanggil *et al.* 2018[17], Lee *et al.* 2019[18]

Table 1: *A List of some Mushroom Mycotoxins Causing Cancer in Human.*

Agaritine

Agaritine (AGT) is produced by a mushroom named as *Agaricus*. This is worldwide in occurrence and popularly known as the button white or table mushroom. *A. bisporous* is a very popular species of *Agaricus*. This is one of the most consumed mushrooms of the world being cultivated in more than seventy countries [19,20].

Agaritine is an aromatic, hydrazine derivative and IARC Group 3 carcinogen (Figure 1) [2,7,19]. It causes lung and bladder cancer [5,7]. Agaritine has also been shown to be a mutagen by Ames test [21]. It covalently binds with DNA *In vivo* [22]. This is metabolized in kidney and toxic metabolites thus produced can cause stomach cancer in mice [6,8].

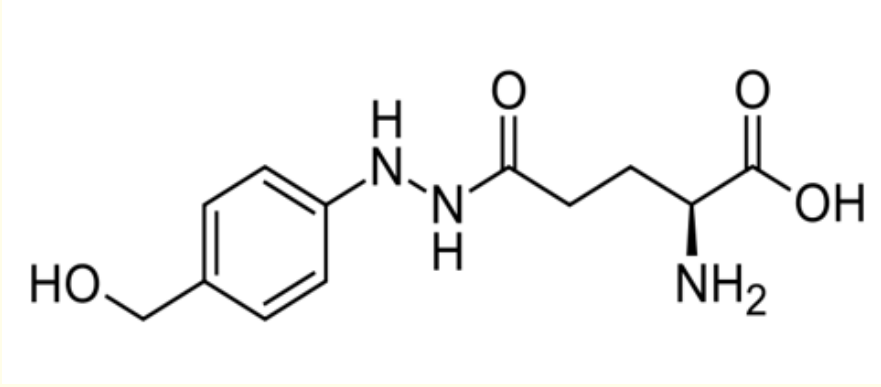

Figure 1: *Skeletal Formula of Agaritine.*

Though agaritine causes cancer in human and animals, their clinical implications have also shown to inhibit the cell proliferation of HL-60 leukaemia cells via the induction of apoptosis [23,24]. Similarly, it has some antiviral properties against HIV too [25]. Clinically, this is observed that *Agaricus brasiliensis* has some advantageous effects on the human to decrease the body weight, fat, blood glucose and cholesterol significantly. It activated the immune system and normalize the liver function [26].

Gyromitrin

Gyromitrin is produced by several species of *Gyromitra* especially reported from *G. esculanta*. This is one of the false morels and an edible mushroom mostly found in America and Europe. Gyromitrin is a volatile, water-soluble and unstable compound. It can easily be hydrolyzed into rather more toxic compound monomethylhydrazine (MMH) [9]. Several hydrazines have been isolated from *G. esculanta.* The raw mushroom of *G. esculanta,* gyromitrin, methylformylhydrazine and its precursor, all have been reported to cause cancer in experimental animals [10,11,27-29]. Their effects are cumulative and even in a very small amount it could be carcinogenic in future (Figure 2) [12]. Its toxicity from raw mushroom can be removed by cutting into small pieces and repeatedly boiling with adequate water under good ventilation. Prolong period of air drying also reduces the level of toxin.

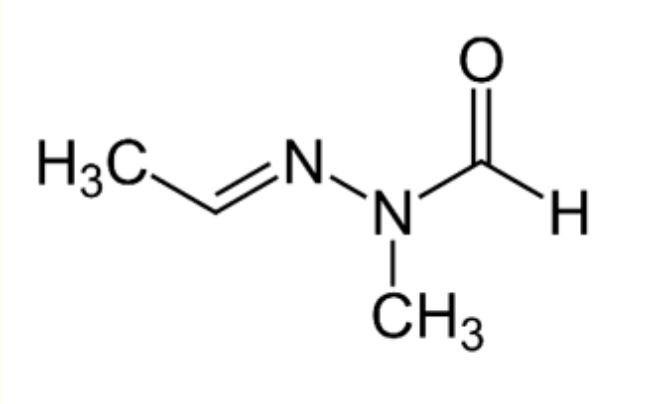

Figure 2: *Skeletal Formula of Gyromitrin monomethylhydrazine.*

A poisoned person may usually recover within 2 to 6 days having a mortality rate of about 10% [30]. Its toxicity may result in stomach cramps, nausea and vomiting, diarrhoea, CNS disturbances with convulsions, jaundice, coma and death. It also causes liver and kidney damage, methemoglobinemia, cyanosis and respiratory arrest [11]. Recently, this is observed that gyromitrin can develop amyotrophic lateral sclerosis [4].

Clinical systemic symptoms of poisoning are often delayed. The patient is kept under supportive care and the symptomatic relief is given. The stomach is emptied as soon as possible. And, the charcoal blood filtration therapy is also performed. As Gyromitrin decomposes in the stomach to form rather more toxic and irritating monomethylhydrazine which reduces pyridoxine in the central nervous system, the high dose of pyridoxine is given in cases of severe CNS toxicity. The patient is also treated with benzodiazepine-like diazepam for the control of seizers [31-35].

Amatoxins (Amanitins)

Amanita phalloides is one of the most poisonous toadstools known to science. Originally found in Meghalaya, this is popularly known as the "Death Cap" mushroom. This is an extremely poisonous mushroom to such an extent that only one death cap is enough to kill an individual and their toxicity is not even reduced by cooking, freezing or drying [13].

Amatoxins include at least eight related mycotoxins produced by the death cap, *Amanita phalloides* and several other members of the same genus as well as some other mushrooms like *Conocybe, Galerina* and *Lepiota*. They are- α-amanitin, β-amanitin, ϒ-amanitin, Σ-amanitin, amanullin, amanullinic acid, amaninamide and amanine. They were for the first time isolated in 1941 by Heinrich O. Wieland and Rudolf Hallermayer and are oligopeptides made of eight amino acids. They are very lethal and thermostable mycotoxins. The main target organs of amatoxins poisoning are liver, heart and kidney failure (Figure 3) [12,13,15].

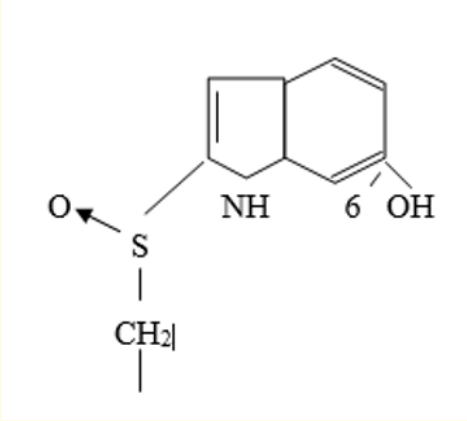

Figure 3: *Chemical Structure of alpha Amanitin.*

The Clinical picture of amanitin intoxication ranges from a mild subclinical presentation to a lethal fulminant course. Gastrointestinal decontamination is a preliminary step to be followed immediately after ingestion. The gastrointestinal phase is characterized by nausea, vomiting, diarrhoea abdominal cramp and hematuria. Acute liver failure (ALF) is caused by the poisoning of amanitins followed by kidney involvement [36]. Currently, the most important antidote used to *Amanita phalloides* mushroom poisoning is an antioxidant silybin [37].

Amatoxins are a group of complex cyclic polypeptides which damage tissues by inhibiting the RNA synthesis within each cell [38]. Amatoxins are potent inhibitors of RNA polymerase II, a vital enzyme for the synthesis of mRNA. In the lack of mRNA, protein synthesis does not progress, cell metabolism stops and lysis takes place [11,39]. α-Amanitin is a cyclic polypeptide of eight amino acids and is the most poisonous of all amatoxins. The oral LD50 of amanitin is approximately 0.1 mg/kg for rats. This is also an inhibitor of polymerase II and III [40]. Inhibition of RNA polymerase II, amanitin binding not only leads to apoptosis of dividing cells but also of slowing the growing cells, which is often observed in prostate cancer [14,15].

Trichothecenes

Trichothecenes are produced by the mushroom *Podostroma cornu- damae*. The mushroom was first discovered from China in 1895 and was originally described as *Hypocrea cornu – damae.* Later on, a Japanese mycologist described it as *Podostroma cornu- damae* [41]. This is native to Korea, Japan, China and Java and has been a rare deadly fungal species of Ascomycetes belonging to the family Hypocreaceae. Its fruiting bodies are highly toxic containing trichothecenes as roridin E, verrucarin J and satratoxin H. Researchers have further identified the trichothecenes as satratoxin H, H12, H12-acetate, H13-acetate and H13-diacetate (Figure 4) [42,43].

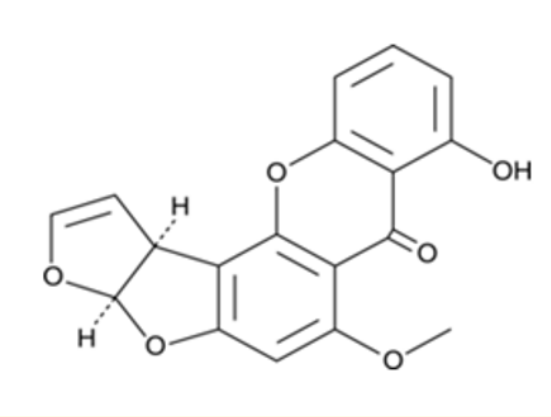

Figure 4: *Skeletal Formula of a Trichothecene, roridin E.*

Several fatalities of *Podostroma cornu- damae* intoxication have been reported in Japan but none from Korea up to 2013. This is easily mistaken either for a healthy traditional food of *Cordyceps sobolifera* or an antler *Ganoderma lucidum* [41]. While early clinical symptoms of intoxication of this mushroom are gastrointestinal disturbances such as dehydration, nausea and vomiting, diarrhoea, anuria, polypnea, unconsciousness and multiple organs failures, the late symptoms are alopecia, desquamation of palms and soles, anaemia, leukocytopenia, thrombocytopenia, pancytopenia and sepsis leading to death. The main cytotoxic and malignant effects of *Podostroma cornu-damae* are inhibition of cell division, protein biosynthesis and apoptosis [16-18].

Conclusion

Among thousands of species of mushrooms worldwide, only a few of them are known to be fatally poisonous. And, due to some of these poisonous mushrooms, the entire population is blamed causing it as an atypical dish worldwide. One of the most toxic mushrooms is *Amanita phalloides,* the death cap containing amatoxin [17,43]. The paper is an attempt to describe some of these cancer-causing mushrooms found in nature. Mushrooms contain potent mycotoxins mainly developing multiple organs failure causing death in those unlucky enough to consume them. And, if survived, in the long run, they usually found to suffer from cancer. Further, this is advisable to consume them with caution as peoples are quite unable to differentiate them perfectly and only an expert can do the job safely. The pieces of information given in the paper might be useful for better treatment in future for patients showing the symptoms of mushroom poisoning as mycetism, pancytopenia with desquamation of scalp, palms and soles. The physicians should also consider the possibility of ingesting any poisonous mushroom when such symptoms appear.

Acknowledgements

This piece of research work is dedicated to the memory of my paternal grandmother marhooma Mariam. The authors are also deeply appreciating the institutions concerned for providing us with the necessary facilities during this research work.

Conflict of Interest

The authors have declared no conflict of interest. They have approved the final version of the manuscript contributing equally.

Financial Support

No financial support was granted during this research work.

Bibliography

1. Mas A. "Mushrooms". *Journal of Hepatology* 42.2 (2005): 166-169.
2. Nagaoka MH., *et al.* "Measurement of a genotoxic hydrazine, agaritine and its derivative by HPLC with fluorescence derivatization in the Agaricus mushroom and its products". *Chemical and Pharmaceutical Bulletin* 54.6 (2006): 922-924.
3. Saviuc P and Danel V. "New syndromes in mushroom poisoning". *Toxicological Reviews* 25.3 (2006): 199-209.
4. Emmeline L and Jean PV. "Warning on false or true morels and button mushrooms with potential toxicity linked to hydrazinic toxins: an update". *Toxins* 12.8 (2020): 482-492.
5. Toth B., *et al.* "Tumor induction with the N- acetyl derivative of 4- hydroxymethylphenylhydrazine, a metabolite of agaritine of Agaricus bisporus". *Cancer Research* 38.1 (1978): 177-180.
6. Toth B., *et al.* "Gastric tumorigenesis by a single dose of 4- (hydroxymethyl) benzenediazonium ion of Agaricus bisporus". *British Journal of Cancer* 46.3 (1982): 417-422.
7. Hashida C., *et al.* "Quantities of agaritine in mushrooms (Agaricus bisporous) and the carcinogenicity of mushroom methanol extracts on the mouse bladder epithelium". *Nihon Koshu Eisei Zasshi* 37.6 (1990): 400-405.
8. Kondo K., *et al.* "The metabolisms of agaritine, a mushroom hydrazine in mice". *Food and Chemical Toxicology* 46.3 (2008): 854-862.
9. Pyysalo H. "Some new toxic compounds in false morels. Gyromitra esculanta". *Naturwissenshaften* 62.8 (1975): 395.
10. Braun R., *et al.* "Consideration on the carcinogenicity of the mushroom poison gyromitrin and its metabolites". *Journal of Applied Toxicology* 1.5 (1981): 243-246.
11. Karlson-Stiber C and Person H. "Cytotoxic fungi- an overview". *Toxicon* 42.4 (2003): 339-349.
12. Dart RC. "Mushrooms". Medical Toxicology, Philadelphia, P.A.: Williams and Wilkins (2004): 1719-1735.
13. Piqueras J. "Hepatotoxic Mushroom poisoning: diagnosis and management". *Mycopathologia* 105.2 (1989): 99-110.
14. Andler J., *et al.* "Antibody-Drug conjugate payloads". *Methods in Molecular Biology* 1045 (2013): 51-70.
15. Hechler T and Andler J. "Amanitin based ADCs with an improved therapeutic index". Poster #633, AACR Annual Meeting (2015).
16. Park JS., *et al.* "Four cases of successful treatment after Podostroma cornu-damae intoxication". *Hong Kong Journal of Emergency Medicine* 23.1 (2016): 55-59.
17. Sanggil C., *et al.* "Identification of trichothecene- type mycotoxins in toxic mushroom Podostroma cornu- damae and biological specimens from a fatal case by LC- QTOF/MS". *Forensic Science International* 291 (2018): 234-244.
18. Lee SR., *et al.* "Macrocyclic trichothecene mycotoxins from a deadly poisonous mushroom, Podostroma cornu- damae". *Journal of Natural Products* 82.1 (2019): 122-128.
19. Schulzova V., *et al.* "Influence of storage and household processing on the agaritine content of the cultivated Agaricus mushroom". *Food Additives and Contaminants* 19.9 (2002): 853-862.

20. Schulzova V., *et al.* "Agaritine content of 53 Agaricus species collected from nature". *Food Additives and Contaminants* 26.1 (2009): 82-93.

21. Walton K., *et al.* "Bioactivation of the mushroom hydrazine, agaritin, to intermediates that bind covalently to proteins and induce mutations in the Ames test". *Carcinogenesis* 18.8 (1997): 1603-1608.

22. Shephard SE and Schlatter C. "Covalent binding of agaritine to DNA *In vivo*". *Food and Chemical Toxicology* 36 (1998): 971-974.

23. Roupas P., *et al.* "Mushrooms and agaritine: A mini review". *The Journal of Functional Foods* 2.2 (2010): 91-98.

24. Mostafa E. "Chemical profile, agaritine and selenium of Agaricus bisporous". *Brazilian Archives of Biology and Technology: An International Journal* 55.6 (2012): 911-920.

25. Gao WN., *et al.* "Agaritine and its derivatives are potential inhibitors against HIV proteases". *Medicinal Chemistry* 3.3 (2007): 221-226.

26. Ying L., *et al.* "Immunomodulating activity of Agaricus brasiliensis KA21 in mice and human volunteers". *Evidence-Based Complementary and Alternative Medicine* 5.2 (2008): 205-219.

27. Coulet M and Guillot J. "Poisoning by Gyromitra: a possible mechanism". *Medical Hypothesis* 8.4 (1982): 325-334.

28. Meierbratschi A., *et al.* "Methylation of DNA in the rat by the mushroom poison gyromitrin". *Journal of Agricultural and Food Chemistry* 31.5 (1983): 1117-1120.

29. Bergman K and Hellenas KE. "Methylation of rat and mouse DNA by the mushroom poison gyromitrin and its metabolite monomethylhdrazine". *Cancer Letters* 61.2 (1992): 165-170.

30. Lampe KF. "Toxic fungi". *Annual Review of Pharmacology and Toxicology* 19 (1979): 85-104.

31. Kirklin JK., *et al.* "Treatment of hydrazine- induced coma with pyridoxine". *New England Journal of Medicine* 294.17 (1976): 938-939.

32. Toth B and Erickson J. "Reversal of the toxicity of hydrazine an analogue by pyridoxine hydrochloride". *Toxicology* 7.1 (1977): 31-36.

33. Michael AM., *et al.* "Gyromitra mushrooms". *Clinical Toxicology Review* 23.5 (2001): 1-2.

34. Xia Y., *et al.* "Mushroom toxins: chemistry and toxicology". *Journal of Agricultural and Food Chemistry* 67 (2019): 5053-5071.

35. Horowitz Km., *et al.* "Gyromitra mushroom toxicity". In: Stat pearls (Internet) Treasure Island (FL), Stat Pearls Publishing (2020).

36. Garcia J., *et al.* "Amanita phalloides poisoning. Mechanism of toxicity and treatment". *Food and Chemical Toxicology* 86 (2015): 41-55.

37. Zheleva A., *et al.* "Free redical reactions might contribute to severe alpha amanitin hepatotoxicity- a hypothesis". *Medical Hypotheses* 69.2 (2007): 361-367.

38. Hallen H., *et al.* "A gene family encoding the major toxins of lethal Amanita mushrooms". *Proceedings of the National Academy of Sciences* 104.48 (2007): 19097-19101.

39. Horgan PA., *et al.* "The insensitivity of mushroom nuclear RNA polymerase activity to inhibition by amatoxins". *Archives of Microbiology* 118.3 (1978): 317-319.

40. Meinecke B and Meinecke - Tillmann S. "Effects of α-amanitin on nuclear maturation of porcine oocytes *In vitro*". *Journal of Reproduction and Fertility* 98.1 (1993): 195-201.

41. Ahn JY., *et al.* "Two cases of mushroom poisoning by Podostroma cornu- damae". *Yonsei Medical Journal* 54.1 (2013): 265-268.

42. Yoko S., *et al.* "Toxic principles of a poisonous mushroom Podostroma cornu- damae". *Tetrahedron* 57.39 (2001): 8277-8281.

43. Kim HN., *et al.* "Two cases of incidental Podostroma cornu-damae poisoning". *Clinical and Experimental Emergency Medicine* 3.3 (2016): 186-189.

Volume 5 Issue 1 January 2021