WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

SJIF Impact Factor 7.421

Volume 7, Issue 11, 184-199 Review Article ISSN 2278 – 4357

MUSHROOMS: MEDICINAL BENEFITS AND TOXICITIES

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Article Received on
05 Sept. 2018,

Revised on 26 Sept. 2018,
Accepted on 16 October 2018

DOI: 10.20959/wjpps201811-12655

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ABSTRACT

Mycology constitutes the study of fungi with diverse phytochemicals that either impart benefit to human health or contribute to toxicities, as reported in literature until date. Ancient Greeks and Romans cultivated mushrooms for medicinal use, initiating a myriad of research into the medicinal value and toxic effects of certain mushrooms. Modern techniques coupled with advanced instrumentation have imparted knowledge of phytoconstituents present in mushrooms, and their respective mechanisms. Researchers have identified secondary metabolites, such as carbohydrates, proteins, fatty acids, and phenolic compounds present in mushrooms, in conjunction with their mechanisms of actions and pharmacological effects. Particular mushrooms exhibit beneficial pharmacological effects, while some contain toxins such as amatoxins, gyromitrin, coprine, psilocybin, choline, and orellanine that cause undesirable toxic effects. Global production, sales, and export of mushroom containing products have contributed to a growing economy for mushrooms. Increasing knowledge of bioactivity and current instrumentation will impart to researchers' evidence of medicinal mushrooms as pharmaceutical agents. The current review discusses the historical practices, global market value, microbiological composition, pharmacological constituents, and their scientific classification.

KEYWORDS: Mushrooms, Metabolites, Phytopharmaceuticals, Fungi, Therapeutic Activities, Toxicity.

1. INTRODUCTION

Mycology, the study of fungi, defines mushrooms as macroscopic filamentous fungi, classified separately due to their cellular organization. They are colloquially called the 'white vegetables' as they contain numerous phytonutrients and secondary metabolites that convey their benefits to human health. Mushrooms have been utilized for their medicinal properties since the time of the Greeks and Romans.[1] Researchers have since expounded on this primitive knowledge of medicinal mushrooms to confirm the validity of ancient literature. Researchers have discovered hepatoprotective, anti-diabetic, immunomodulatory, antiviral, anti-tumor, and antimicrobial constituents of medicinal mushrooms via evidence-based experiments. Research has proven the vital role played by bioactive components and secondary metabolites from mushrooms that include carbohydrates, proteins, fatty acids, and phenols.[2,3,4] *In-vitro* experiments delineate an understanding into the cellular properties of mushrooms associated with human health in alleviating symptoms of the following disorders: obesity, vitamin D deficiency for bone metabolism, immunity, and cognition.[5,6] For medicinal mushrooms to become a widely accepted aspect of Western medicine, research needs to establish their mechanism of action and side effects, through *in-vivo* and *in-vitro* studies followed by clinical trials. Some species of mushrooms are toxic to human health and demonstrate varying levels of symptoms and fatality. Toxic mushrooms including the following toxins: amatoxins, gyromitrin, coprine, psilocybin, choline, and orellanaine.[7] *In-vitro* experiments permit clinical trials to corroborate evidence for the health benefits of certain mushrooms and prove a promising topic for upcoming research.[8]

2. Ancient/Historical Usage of Mushrooms

Used for millennia as a dynamic reservoir in medicine, mushrooms constitute an extensive component of ethnomedicines. Historians discovered an original composition, written in an Egyptian temple: "without leaves, without buds, without flowers: yet they form fruit; as a food, as a tonic, as a medicine: the entire creation is precious".[9] The Greeks believed that mushrooms gave fortitude to warriors in combat, while the Romans believed them to be 'food of the gods.' Ancient Chinese referred to mushrooms as the 'elixir of life'.[10] Hippocrates, the Greek physician, used *Fomes fomentarius* for its anti-inflammatory effects and to seal wounds circa 450 BC. Tao Hongjing, an alchemist from the fifth century, discovered several medicinal mushrooms: *Ganoderma lucidum* and *Dendropolyporus umbellatus*. From modern research instrumentation, scientists have discovered a novel array of chemical constituents via tissue culture methods, confirming literature on ancient medicinal plants.[1]

3. Global Market Trends of Mushroom Consumption and Sale

Mushrooms contribute to the global economy in particular parts of the world and the income of certain cultures depends upon mushrooms. As per The Mushroom Council, the top five mushroom producers include: China, Italy, United States, Netherlands, and Poland. Since 2009, the following percentages reflect mushroom production: China has produced 65%, European Union 24%, the US 5%, Japan 1%, Indonesia 1%, and Canada 1%. During 1980 to 1995, mushrooms demonstrated a five percent growth rate, while 1996 saw a growth rate raised to seven percent. During 1970 to 2011, the global mushroom production excelled from less than one million to 7.7 million metric tons. Further, global mushroom production grew by five hundred percent during 1980 to 2011.[11] During 2011, receipts from mushroom purchases ranked them fifth among vegetables.[12] During the 2012 to 2013 growing season, mushroom sales were at 1.1 billion.[13] Exports of mushrooms constitute a meager portion of United States exports at less than five percent of fresh and processed mushrooms.[14] In the Pacific Northwest region, the value of yearly mushroom harvest equates to the value of lumber produced from the same forests.[15,16] Intensive research is suggested for agricultural and herbal dug manufacturers in the following areas to determine the current and future global market for mushroom consumption: fresh versus processed mushroom market, growth potential of geographical regions, consumer demand, and relation of price and purchase configurations.[17]

4. Bioactive Constituents of Mushrooms

Researchers have discovered high levels of fiber, vitamins, protein, mineral content, bioactive constituents, and all essential amino acids.[18,19] The following conditions affect the bioactive constituents: substrate, strain, cultivation, storage conditions, age, developmental stage, and cooking practices.[20,21] Scientists have discovered the following secondary metabolites in mushrooms: terpenoids, sesquiterpenes, acids, lactones, alkaloids, nucleotide analogs, sterols, vitamins, and metal chelating agents. Mushrooms also contain glycoproteins, polysaccharides, and β-glucans. Extraction of bioactive constituents in conjunction with development of biotechnological methods is vital to obtain such metabolites and determine their phytochemical potential.

4.1 Carbohydrates

Scientists have researched the carbohydrate content of hundreds of mushroom species, namely polysaccharides: fucose, xylose, fructose, mannitol, arabinose, sucrose, glucose, maltose, and trehalose, as reported in table one.[22,23] Polysaccharides that present anti-tumor activity activate immune responses within the host organism, as demonstrated in mice models.[24,25] β-glucans are the principle polysaccharide in mushrooms, as it constitutes half of the fungal cell wall mass.[26,27] β-glucans are not recognized nor synthesized by the human immune system, producing adaptive and innate immune responses. They also demonstrate antioxidant, neuroprotection, anticancer, and anticholsterolemic activity.[28,29] Additionally, they protect from infectious diseases and cancer. Concentrations of β-glucans range from 0.21 to 0.53 g/100 g dry.[29,30]

4.2 Proteins

Mushrooms produce many peptides and proteins that present pharmaceutical potential: fungal immunomodulatory proteins, lectins, antimicrobial proteins, ribosome inactivating proteins, laccases, and ribonucleases.[31] Lectins are nonimmune glycoproteins that bind to cell surface carbohydrates. Lectins, which present antitumoral, antibacterial, antiviral, antifungal, and immunomodulatory activities have been identified by researchers.[32,33,34] Moreover, specific lectins present antiproiferative activity toward selective tumor cell lines: human leukemic T cells, hepatoma Hep G2 cells, and breast cancer MCF7 cells.[31,33] Fungal immunomodulatory proteins have potential applications as adjuvants for tumor immunotherapy as they suppress tumor invasion and metastasis.[31]

4.3 Fatty Acids

Edible mushrooms contain polyunsaturated fatty acids, which could reduce serum cholesterol levels.[35,36] The principle sterol is ergosterol, which presents antioxidant activity and can potentially reduce cardiovascular complications.[35,37] Tocopherols, located in the lipidic fraction of mushrooms, are natural antioxidants that remove free radical peroxyl constituents and guard against degenerative malfunctions, cardiovascular disease, and cancer. As an example, linoleic acid, an essential fatty acid, is reported to reduce triglyceride levels, arthritis, cardiovascular disease, and hypertension.[38,39]

4.4 Phenolic Compounds

Phenolic compounds present antiallergenic, antimicrobial, anti-inflammatory, cardioprotective, anti-atherogenic, anti-thrombotic, and vasodilator activity.[38,39] Phenolic compounds are also reported to provide protection against degenerative disorders: cardiovascular disease, cancer, and brain dysfunction.[40] In a study reported by Palacios et al. on eight edible varieties of mushrooms, *B. edulis* and *A. bisporus* were reported to contain the highest content of phenolic constituents. *L. deliciosus* presented high levels of flavonoids, while *A. bisporus*, *C. gambosa*, and *P. ostreatus* presented lower levels.[41]

5. Medicinal Mushrooms

5.1 Antioxidant Activity

The following mushrooms present antioxidant activity, as reported in table 1: *Phellinus rimosus*, *Ganoderma*, *Agaricus bisporus*, and the *Pleurotus* species. *Phellinus rimosus* mushrooms are located in tropical forests and plains and have been utilized in Traditional Chinese Medicine (TCM) as hot water extract.[42,43] *In-vitro* studies proved the reducing, chelating, and antioxidant potential of phenolics and phytoconstituents that dispense oxygen radicals.[44] *Agaricus bisporus*, or button mushroom, are cultivated in North America and Europe. *In-vitro* experiments have confirmed antioxidants in boiled and raw extracts of mushrooms that inhibit oxidation.[45] *Pleurotus*, or oyster mushrooms, present anti-tumor, anti-inflammatory, and antioxidant constituents.[46] Methanolic extract of the fruiting body of *Pleurotus florida* is reported to exhibit free radical scavenging activity and lipid peroxidation inhibition.[46]

5.2 Antimicrobial Activity

Research scientists study novel antimicrobial agents in lieu of drug resistance to commercially available antimicrobial drugs used to treat infections of pathogenic microorganisms.[47] Mycelia and fruiting body extracts contain antimicrobial activity to infectious microorganism.[48] As such, mushrooms must possess antifungal and antibacterial constituents for survival as reported in table one: for example, antifungal proteins, lectins, laccases, and ribonucleases of mushrooms inhibit HIV-1 reverse transcriptase.[48,49] Researchers isolated applanoxidic acid from *G. annulare* and identified its weak antifungal activity against trichophyron mentagrophytes, a fungi[50,51] 5-aergosta-7,22-dien-3b-ol and 5,8 epidioxy-5a,8a-ergosta 6,22- dien 3B-ol, and steroidal constituents have been isolated and are reported to exhibit weak activity towards gram-positive and gram-negative microorganisms.[52] *Lentinula edodes* possesses oxalic acid, which produced antimicrobial effects against *Staphylococcus aureus* and a few other bacteria. Ethanolic extract of mycelium is reported to exhibit anti-protozoal activity against *Paramecium caudatum*.[53] *A. bisporus* is reported to possess antimicrobial activity against gram-positive bacteria and gram-negative bacterium. It also works against the activity of *Bacillus subtilis*.[54]

5.3 Anticancer Activities

Mushrooms demonstrate anticancer activity and have potential to be pharmaceutical products. Polysaccharides found in mushrooms possess anticancer and immunostimulating potential by activating different immune responses. T-cell constituents and thymus dependent immune metabolism are required to exert their antitumor abilities.[55] The following mushrooms are reported to exhibit anticancer activity: *Phellinus linetus*, *Agaricus bisporus*, *Pleurotus* species, *Pleurotus florida*, *Grifola frondosa*. *Phellinus linetus* is a basidiomycete fungus located in Asia, Africa, and America, as reported in table one.[56] Numerous constituents have been isolated: polysaccharides, acidic proteoheteroglycans with mixed alpha and beta linkage and a [1-6]-branched type [1-3]-glycan.[57] Such complex polysaccharides demonstrate immunostimulatory and antitumor potential.[55] Traditional medicine practitioners use polysaccharide extract of *Agaricus bisporus*, commonly called the button mushroom, as an immunostimulatory agent, anti-cancer agent, and kidney tonic. It is also suggested as a principle dietary component to reduce hormone-dependent breast cancer.[58,59] Isolated constituents from the *Pleurotus* species demonstrate anti-hypertensive and anti-hypercholestremic properties.[60,61] Scientists demonstrated that the methanolic extract of the fruiting bodies of *Pleurotus florida* present antitumor activity in Ehrlich's ascites carcinoma cell line.[62] Lentinan was the first compound isolated by research scientists to present anti-tumor and anti-proliferative properties.[63] Its cytostatic effect is due to the activation of host immune responses. *Grifola frondosa* have shown antitumor potential in xenografts via the B D glucan and glycoprotein complexes. Researcher's report immuno-modulating and antitumor effects using animal models with a purified extract of β-glucan [β-1, 6 glucan branched.[64] Chemical structures of beneficial constituents are provided in Fig. 1.

Figure Legends:

Fig. 1: Chemicals reported from medicinal mushrooms.

Fig. 2: Toxic constituents in mushrooms.

Tables:

Table 1: Selected reported bioactivities of mushrooms.

Table 2: Clinical manifestations, sites of toxicity, and toxicity potential of mushrooms.

Table 1: Selected reported bioactivities of mushrooms.

Reported Activity	**Species**	**Activity**
Antioxidant	*Phellinus rimosus*	TCM hot water extracts.[42,43]
	Agaricus bisporus	Boiled and raw extracts, exhibit oxidation.[45]
	Pleurotus species	Constituents reported to exhibit anti-tumor, anti-inflammatory, and antioxidant activities.[46]
Antimicrobial	*G. annulare*	Applanoxidic acid isolated, exhibits weak antifungal activity against trichophyron mentagrophytes.[50,51]
	Lentinula edodes	Oxalic acid isolated, produced antimicrobial effects against *Staphylococcus aureus.*[53]
	A. bisporus	Reported activity against gram positive bacteria, gram-negative bacterium, and *Bacillus subtilis.*[54]
Anticancer	*Phellinus linetus*	Polysaccharides, acidic proteoheteroglycans with mixed alpha and beta linkage and a [1-6]-branched type [1-3]-glycan isolated, exhibit antitumor potential.[55,56,57]
	Agaricus bisporus	Polysaccharide extract acts as anti-cancer agents, immunostimulatory agent, and a principle dietary component in breast cancer reduction.[58,59]
	Pleurotus florida	Exhibit antitumor activity in Ehrlich's ascites carcinoma cell line.[62]
	Grifola frondosa	Exhibit antitumor potential in xenografts via the B D glucan and glycoprotein complexes, immuno-modulating and antitumor effects in animal models with purified extract of β-glucan [β-1, 6 glucan branched.[64]

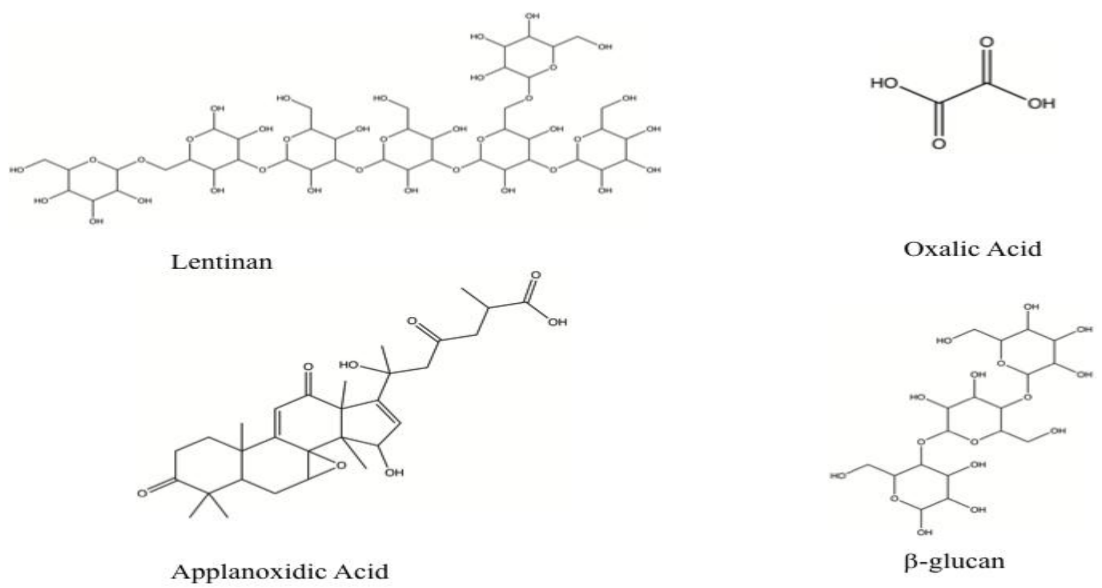

Figure 1: Phytoconstituents reported from medicinal mushrooms.

6. Mushroom Toxicities: Toxic Constituents

Mushrooms represent a significant constituent of diet in certain regions of the world, with diverse nutritional benefits. Nevertheless, some are toxic to human health and cause the following delirious conditions: bradycardia, chest pain, seizures, liver failure, intestinal fibrosis, gastroenteritis, renal failure, rhabdomyolysis, and erythromelalgia.[65,66] Researchers classify toxic mushrooms into seven categories, determined by the toxins present in each species: amatoxins (cyclopeptides), orellanus (*Cortinarius* species), gyromitrin (monomethylhydrazine), muscarine, ibotenic acid, psilocybin, and coprine, as reported in Table 2.[67] Structures of toxic constituents are illustrated in Fig. 2.

6.1 Amatoxins

Fungi that contain amatoxins are derived from the families of Cortinariaceae, Amanitaceae, and Agaricaceae. Amatoxins are bicyclic octapeptides and thermostable poisons.[68] Scientists have identified nine amatoxins, with alpha-amanitine being the strongest. Symptoms of amatoxins poisoning include: drowsiness, euphoria, ataxia, gastrointestinal disturbances, motor depression, dizziness, muscle twitches, and alterations in mood and feelings.[69] Amatoxins prevent DNA-dependent RNA polymerase-II. Over time, mRNA levels decrease; protein synthesis decreases, and cells experience apoptosis or necrosis.[68,70] Certain species of Amanita, such as *A. phalloides, Amanita virosa*, *A. ocreata*, *A. verna*, *A. suballiacea*, *A. tenuifolia*, *A. bisporigera*, and *A. hygroscopica*, present many amatoxins. Clinicians use a detoxification treatment, as well as benzodiazepines or phenobarbitone for seizures due to mushroom intoxication.[71,72] Liver transplant may accompany acute poisoning.[68]

6.2 Gyromitrin

The toxin, called gyromitrin, is a constituent of certain species of *Gyromitra*. Symptoms include: fatigue, diarrhea, vertigo, vomiting, ataxia, tremor, and nystagmus. Hepatic disorders and hemolysis may also develop. When gyromitrin is hydrolyzed in the stomach post-ingestion, hydrazines are produced and have cytotoxic and irritant properties.[73,74] Pyridoxine is the antidote for gyromitrin.

6.3 Coprine

Coprine, when combined with alcohol, can become addictive. Mushrooms that contain coprine accumulate in blood due to the breakdown of alcohol. Certain species of *Clitocybe* cause muscarinic syndrome. Muscarine is present in the following species: *C. dealbata*, *C. rivulosa*, *C. phyllophila*, *C. cerussata*, and *C. candicans*. Symptoms include: increased breathing and pulse rate, vomiting, dizziness, headache, gastrointestinal disturbances, hypersecretion, miosis, and, in acute cases, bradycardia. Symptoms presented upon muscarinic poisoning are sweating, tearing, vomiting, drooling, diarrhea, and shortness of breath due to its exertion on the parasympathetic nervous system. Clinically, atropine is administered to counterweight its effects.[75]

6.4 Psilocybin

The genus *Psilocybe* contains psilocybin and includes the following species: *P. semilanceata, P. bohemica, P. baeocystis, P. cubensis*, and *P. Mexicana*.[76,77] Symptoms present visual impairment, nausea, anxiety, hypertension, motor incoordination, asthenia, vertigo, and disorientation, thirty minutes post ingestion. Children can experience additional symptoms that include: seizures, coma, and hyperthermia.[76] Mushrooms containing indole derivatives are typically blue. Toxicity symptoms include poor comprehension, visual and auditory hallucinations, and tongue anxiety. Mushroom that possess this toxin include: *Panaeolus sphinctrinus*, *Panaeolus papilionaceus*, and *Panaeolus subbalteatus*. The antidote for poisoning due to these mushrooms is chlorpromazine. *Lampteromyces japonicas* contains lampterol and results in the following toxicity symptoms: diarrhea, vomiting, and abdominal discomfort.[78]

6.5 Choline

Choline is also present within some mushrooms and is reported to cause toxicity. When humans ingested choline, the body coverts it into acetylcholine. The resultant toxicity symptoms include the following: pupil contraction, increased blood flow and blood pressure, decreased heart rate, and increased activity of the digestive system.[12] Examples of such mushrooms include: *Russula emetic*, *Rhodophyllus rhodopolius*, and *Lactarius chrysorrheus*.[12]

6.6 Orellanine

Orellanine, a nephrotoxic bipyridine N-oxide, is a constituent of *C. orellanus* and *C. speciosissimus*. Researchers postulate that quinone compounds assemble in renal tissue upon oxidation of orellanine and the covalent binding to biological constituents produce cell injury. Symptoms of orellanine toxicity include: abdominal discomfort, chills, nausea, thirst, oliguria or polyuria, and anuria. Hemodialysis treatment can restore renal function.[79] Scientists have shown via *in-vitro* data, that orellanine creates oxygen radicals via the redox initiation of iron and, moreover, protein synthesis can be subdued by a metabolite of orellanine.[80,81]

Table 2: Clinical manifestations, sites of toxicity, and toxicity potential of mushrooms.

Toxin	Identified Species	Symptoms	Reported Mechanisms
Amatoxin	Cortinariaceae, Amanitaceae, Agaricacea	Drowsiness, euphoria, ataxia, gastrointestinal disturbances	Preventing DNA-dependent RNA polymerase-I, mRNA levels decrease, protein synthesis decrease, apoptosis or necrosis.[68,69,70]
Gyromitrin	*Gyromitra*	Diarrhea, vertigo, vomiting, ataxia, tremor, nystagmus	Hydrolyzed in stomach post-ingestion, hydrazines produced.[73,74]
Coprine	*Clitocybe*	Vomiting, dizziness, gastrointestinal disturbances, hypersecretion, miosis, bradycardia	Parasympathetic nervous system.[75]
Psilocybin	*Psilocybe*	Nausea, anxiety, hypertension, motor incoordination, asthenia, vertigo, disorientation.[76,77,78]	--
Choline	*Russula emetic, Rhodophyllus rhodopolius, Lactarius chrysorrheus*	Pupil contraction, increased blood flow and blood pressure, decreased heart rate.[12]	--
Orellanine	*C. orellanus C. speciosissimus*	Abdominal discomfort, chills, nausea, thirst, oliguria or polyuria, anuria	Creates oxygen radicals via the redox initiation of iron.[79,80,81]

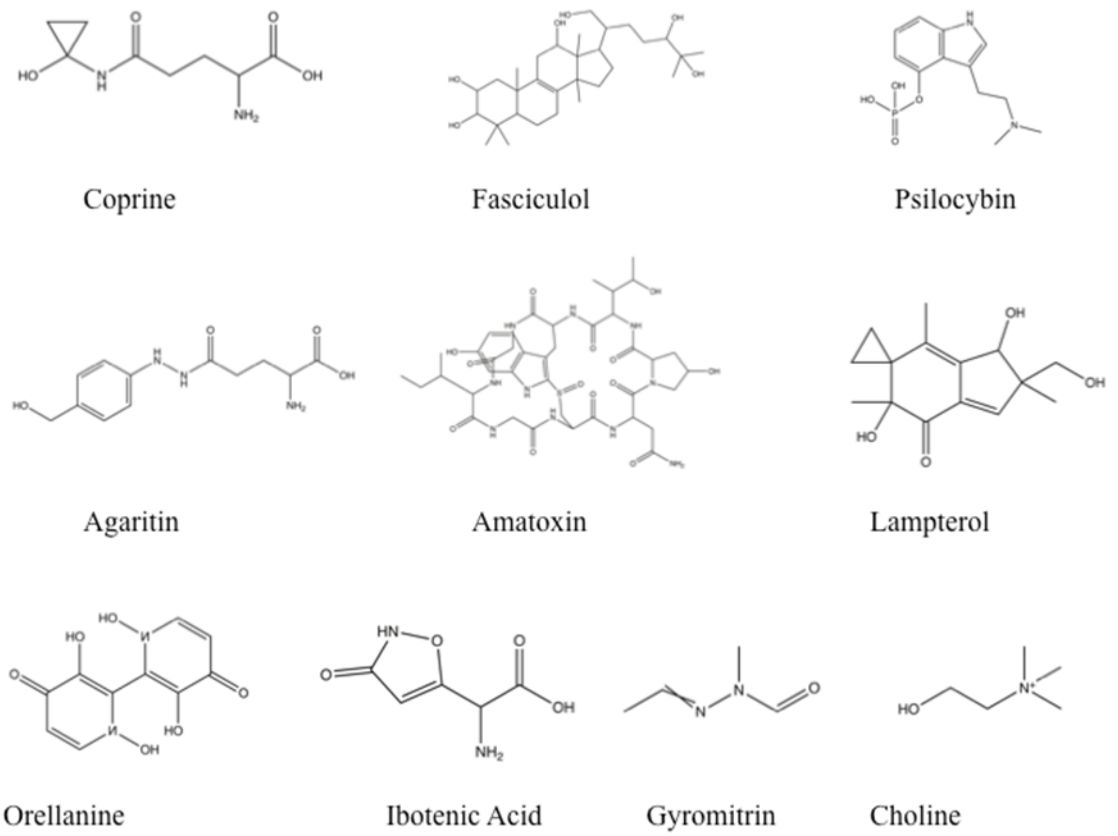

Figure 2: Toxic constituents in mushrooms.

7. Conclusion and Future Prospects

Mushrooms have recently gained significant interests by researchers in the arena of phytopharmaceuticals. Researchers studying mycology have since identified and purified novel myochemicals via *in-vitro* experiments that show great potential to alleviate human disease, deeming mushrooms as functional foods. Not all mushrooms are deemed medicinal; some contribute to disorders, disease, and some are fatal. Additional clinical trials are necessary for insights into the cellular workings of said phytonutrients to guarantee the efficacy of mushrooms as nutritional sources and pharmaceutical medication. Knowledge of the mushroom genome aids this process. Mushrooms, and their respective phytoconstituents present a promising avenue for pharmaceuticals compounds and dietary supplements in the future.

Conflicts of Interest: The authors declare to have no conflict(s) of interest.

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