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Insights into therapeutic potential and practical applications of natural toxins from poisonous mushrooms

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Abstract

Introduction: Mushrooms, belonging to the phyla Ascomycota and Basidiomycota, comprise approximately 14,000 known species, among which a small fraction are toxic. While toxic mushrooms are primarily associated with adverse health effects, recent research highlights their potential as sources of bioactive compounds with promising therapeutic applications.

Methods: A systematic review was conducted using four major electronic databases: Web of Science, Google Scholar, PubMed, and ScienceDirect. The literature search, completed on July 1, 2024, utilized keywords including "Poisonous mushrooms," "Mushroom toxins," "Mycotoxins," "Beta-glucans," "Psilocybin," and "Therapeutic applications." Articles were selected based on specific inclusion criteria, focusing on studies investigating the biochemical, toxicological, and pharmacological properties of toxic mushroom compounds. Studies unrelated to mushrooms, non-peer-reviewed sources, or those with outdated or incomplete data were excluded.

Results: This review examines key toxic mushroom compounds such as amanitins, phallotoxins, ibotenic acid, muscimol, orellanine, and gyromitrin, emphasizing their biosynthesis, structural features, and health effects. Despite their toxicity, compounds like beta-glucans, polysaccharides, lectins, and psilocybin exhibit immune-modulating, anticancer, and neuroprotective properties. These bioactive compounds have shown promise in targeting cancer stem cells and enhancing neurotransmitter activity, positioning them as potential therapeutic agents.

Discussion: Understanding the therapeutic potential of toxic mushroom-derived bioactive compounds bridges toxicology and pharmacology, offering novel avenues for drug discovery. Comparative analysis with existing treatments highlights their unique advantages in modern medicine.

Keywords

Toxic mushrooms, mycotoxins, anticancer agents, immune modulation, biomedical potential

Introduction

Mushrooms are the fleshy, spore-bearing fruiting bodies of fungi belonging to the phyla Ascomycota and Basidiomycota. They are responsible for producing and dispersing spores and typically grow above soil or on nutrient-rich substrates. While some mushroom species are edible, others are toxic and pose significant health risks.[1] Mushrooms are rich sources of structurally diverse secondary metabolites,

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many of which exhibit bioactive properties with potential therapeutic applications in disease treatment.[2] However, certain toxic mushrooms, referred to as poisonous or toxic fungi, produce natural compounds known as toxins. Understanding and classifying these toxic mushrooms is crucial for ensuring the safe consumption of wild mushrooms and advancing scientific research.[3] Of the approximately 14,000 documented mushroom species, only 70–80 species are recognized as toxic (Table 1). Key toxins include amanitins (found in species like the death cap *Amanita phalloides*) and orellanine (produced by mushrooms such as *Cortinarius orellanus* and related webcap species).[4]

In 2019, a classification system was developed to group mushroom poisoning cases into six categories based on clinical features: cytotoxic poisoning, gastrointestinal irritant poisoning, mycotoxic poisoning, endocrine and metabolic toxicity, neurotoxic poisoning, and miscellaneous adverse reactions.[5] Additionally, mushroom toxicity can be classified by toxic compounds, such as amatoxins, ibotenic acid, muscimol, orellanine, and gyromitrin, or by taxonomic groups or genera. Symptoms, including gastrointestinal, neurological, or organ-specific effects, offer another classification approach.[6] These systems aid in identifying toxic mushrooms, facilitating accurate diagnoses and effective treatments.

Proper identification of mushrooms is essential, as many poisonous species closely resemble edible ones. This highlights the importance of understanding local mushroom varieties. Individuals without expertize in mycology are strongly advised against foraging for wild mushrooms and should instead rely on expert guidance or commercially cultivated mushrooms for consumption.[7] The study of mushroom toxins is crucial across scientific, ecological, and practical domains. Its primary importance lies in protecting human health by preventing accidental poisoning and enabling the development of effective treatments.[8] Beyond health, this field provides ecological insights, as mushroom

Table 1. Classification of toxic mushrooms.

Toxic group	Genus	Containing mushroom species	References
Amatoxins	*Amanita*	*Amanita bisporigera*	85
		Amanita brunnescens	
		Amanita ocreata	
		Amanita verna	
		Amanita virosa	
		Amanita phalloides	
	Lepiota	*Lepiota brunneoincarnata*	99,100
		Lepiota brunneolilacea	
		Lepiota castanea	
		Lepiota helveola	
		Lepiota subincarnata	
	Galerina	*Galerina autumnalis*	101
		Galerina steglichii	
		Galerina marginata	
Phallotoxins	*Amanita*	*Amanita phalloides*	42,85,102
		Amanita bisporigera	
		Amanita brunnescens	
		Amanita ocreata	
		Amanita verna	
		Amanita virosa	
Orellanine	*Cortinarius*	*Cortinarius orellanus*	103,104
		Cortinarius rubellus	
Ibotenic acid and muscimol	*Amanita*	*Amanita muscaria*	105–107
		Amanita pantherina	
		Amanita gemmate	
		Amanita aprica	
		Amanita regalis	
Gyromitrin	*Gyromitra*	*Gyromitra infula*	108,109
		Gyromitra esculenta	
GI irritants	*Boletus*	*Boletus miniato-olivaceus*	29,110
		Boletus Satanas	
	Chlorophyllum	*Chlorophyllum molybdites*	
Coprine	*Coprinus*	*Coprinus atramentarius*	111

toxins influence soil microbiota and nutrient cycling, impacting agricultural productivity. Mushroom toxins also hold promises for biomedical research. Compounds such as psilocybin from hallucinogenic mushrooms are being investigated for their therapeutic potential in mental health treatment, while other toxins offer prospects for developing drugs to treat cancers and neurological disorders.[9] Additionally, studying mushroom toxins contributes to mycology by improving species classification and advancing fungal taxonomy and evolutionary research.[10]

Cultural and culinary practices benefit from knowledge about mushroom toxins, ensuring safe foraging and consumption while avoiding toxic species.[11] Additionally, monitoring these toxins can provide insight into ecosystem health and environmental pollution, helping guide conservation efforts for rare and endangered mushroom species.[12]

In summary, studying mushroom toxins covers a wide range of important topics, from human safety to drug development, agriculture, and cultural practices, making it a vital and multidisciplinary field. Studying mushroom toxins is not only important for human safety, but also provides valuable information on ecology, medicine, agriculture, and culture. It highlights the diverse roles fungi play in nature and the need for continued research in this fascinating field. This review article aims to thoroughly explore the diverse aspects of mushroom toxins and their potential applications. It covers the chemistry and biology of mushroom toxins, their toxic effects, practical uses, methods for detection and analysis, environmental impact, safety regulations, future research directions, and challenges. By offering a comprehensive overview, this review seeks to connect scientific knowledge with practical understanding, presenting a well-rounded view of mushroom toxins and their potential for both scientific discovery and practical applications.

Methodology

This study represents a systematic review conducted with a structured approach to designing and implementing systematic reviews. The review process began with an extensive search of the relevant literature and systematic collection of retrieved studies. Each study's quality and potential bias were evaluated using this information to control the quality of the literature. Finally, the findings from the literature were summarized to compile this systematic review.

Information sources and search strategy

Four major electronic databases were utilized to collect literature: Web of Science (https://www.webofscience.com/), Google Scholar (https://scholar.google.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), and ScienceDirect (https://www.sciencedirect.com/). The literature search was conducted on July 1, 2024. A set of keywords, including poisonous mushrooms, mushroom toxins, mycotoxins, amanitins, phallotoxins, ibotenic acid, muscimol, orellanine, gyromitrin, beta-glucans, polysaccharides, psilocybin, toxic mushrooms, fungal toxins, mushroom poisoning, gastrointestinal toxins has been used. These keywords were designed to capture studies that explored various aspects of mushroom toxins.

Eligibility and exclusion criteria

The inclusion criteria for research on mushroom toxins focus on studies that investigate the biochemical, toxicological, and pharmacological properties of mushroom toxins, including specific compounds such as amanitins, phallotoxins, ibotenic acid, muscimol, orellanine, and gyromitrin. It also includes research on the classification of mushroom poisoning based on toxic compounds and associated clinical features, as well as studies exploring the therapeutic potential of bioactive compounds like beta-glucans, polysaccharides, and psilocybin in immune modulation, cancer therapy, and mental health treatment. Additionally, studies on the detection and analysis of mushroom toxins, including the application of chemical, immunological, and molecular techniques, are included. Ecological research on the role of mushroom toxins in soil microbiota, nutrient cycling, and agricultural productivity, as well as studies on the monitoring of these toxins in ecosystems, are also relevant. Furthermore, research on cultural practices related to mushroom foraging and consumption safety, global regulations surrounding mushroom toxin use, and safety protocols in handling toxic mushrooms are considered.

Exclusion criteria eliminate studies that are not directly related to mushrooms or their toxins, including those focusing on non-toxic mushrooms, non-peer-reviewed sources, or incomplete and unverified data. Additionally, studies that focus on non-mycological aspects, irrelevant clinical applications, or outdated information are excluded, ensuring that the review remains focused on current, scientifically sound research that advances the understanding of mushroom toxins and their practical applications. Exclusion criteria were applied to ensure that only relevant and high-quality studies were included. These criteria included: (1) Non-systematic and narrative reviews; (2) Articles published in languages other than English; (3) Editorial materials; (4) Studies with limited relevance to the topic; (5) Non-peer-reviewed literature; (6) Duplicate studies that had been published elsewhere; (7) Research that lacked detailed methods, raw data, or results; (8) Studies for which the full text could not be obtained. These eligibility and exclusion criteria ensured a focused and high-quality collection of

literature for analysis. A detailed flowchart illustrating the study selection process is provided.

Mushroom toxins: Types and classification

Research into the chemistry and toxicology of harmful substances found in poisonous mushrooms commenced in the early 19th century. However, significant advancements have taken place since the 1950s. Currently, more than 100 mushroom toxins have been identified and characterized. Nevertheless, numerous toxic compounds remain unidentified in various mushroom species, such as *Amanita neoovoidea*.[13] Certain known mushroom toxins have undergone extensive examination, including investigations into their structures, synthesis from scratch, toxicological effects, swift detection methods, early analysis from blood or urine samples, treatment approaches, their utilization in pharmaceuticals, and other research domains.[14]

Mushroom toxins can be broadly categorized into various groups based on their chemical structures and effects on the human body. There are five primary categories of rapid-onset mushroom poisoning. Each of them is linked to specific symptoms and responsible toxic mushrooms. Those include cytotoxic mushroom poisoning, gastrointestinal irritant mushroom poisoning, mycotoxic mushroom poisoning, endocrine, metabolic, and related toxicity mushroom poisoning, neurotoxic mushroom poisoning, and miscellaneous adverse reactions to mushrooms.[5] Cytotoxic mushroom poisoning is exemplified by the deadly *Amanita* species containing amatoxins which leads to severe liver toxicity with an initial asymptomatic phase followed by gastrointestinal and hepatic failure.[15] Gastrointestinal irritant mushroom poisoning, featuring mushrooms like *Chlorophyllum molybdites*, induces gastrointestinal effects without widespread systemic involvement.[16] Mycotoxic mushroom poisoning is further subcategorized, with muscarinic mushroom poisoning (e.g., *Inocybe* species) causing cholinergic symptoms and rhabdomyolysis-inducing mushroom poisoning (e.g., *Tricholoma* species) presenting with delayed onset fatigue and myalgia.[5,17] Endocrine, metabolic, and related toxicity mushroom poisoning includes diverse subgroups like GABA-blocking, disulfiram-like, polyporic, trichothecene, hypoglycemic, hyperprocalcitoninemia, and pancytopenia mushroom poisonings, each associated with specific toxins and clinical presentations.[5] Neurotoxic mushroom poisoning involves mushrooms like *Inocybe* and *Clitocybe* species, leading to hallucinations and delirium.[17,18] Lastly, miscellaneous adverse reactions encompass diverse syndromes, such as shiitake mushroom dermatitis, erythromelalgic-like poisoning from *Paralepistopsis acromelalga/amoenolens*, Paxillus syndrome causing autoimmune hemolytic anemia, and encephalopathy syndrome linked to hydrocyanic acid (HCN) poisoning from mushrooms like *Pleurocybella porrigens*.[5,19] This comprehensive classification aids healthcare professionals in identifying and managing mushroom poisoning based on distinct toxic profiles and clinical features.

Mushroom toxins can also be classified based on their chemical structure. This classification provides insights into the types of compounds responsible for the toxic effects. Common structural classifications of mushroom toxins include peptides. Many mushroom toxins fall into this category, including amatoxins, phallotoxins, and virotoxins. These are small proteins that can have severe physiological effects on the body.[20] Ibotenic acid and muscimol are examples of compounds in this category. They are responsible for the psychoactive effects observed in certain mushrooms.[21] Gyromitrin, found in gyromitra species, is a hydrazine compound. These toxins can lead to neurological symptoms and are extremely toxic.[22] Cyclopeptides group includes toxins like the cyclic peptides found in the genus *Galerina*. They can cause liver and kidney damage.[23]

Besides there are some of the key types of mushroom toxins. One category is called microchemical. These are compounds produced by mushrooms that may or may not be toxic which are easily separated from other constituents by their high molecular weights. Some mycochemicals have medicinal or pharmacological properties and are not necessarily harmful when consumed in moderation. Examples include simple phenols, phenolic acids, phenylpropanoids, flavonoids, flavonols, flavones, stilbenes, lignans, polysaccharides, terpenoids, and beta-glucans.[24] The field of mycochemistry has evolved into a unique area of study dedicated to the vast array of chemical compounds known as "mycochemicals" that are produced and stored by mushrooms. Mycochemicals have significant implications for human and animal well-being, nutrition, and their role as functional food.[24] The term "phenolic compounds" encompasses a diverse array of mycochemicals known for having an aromatic ring with one or more hydroxyl groups attached. Within mushrooms, phenolic acids are the primary type of phenolic substances present. They are categorized into two main groups such as hydroxybenzoic acid (HBA) and hydroxycinnamic acid (HCA).[25] While it has been stated that mushrooms don't naturally produce flavonoids, various edible mushrooms have been found to contain flavonoids, including substances such as catechin, myricetin, chrysin, hesperetin, naringenin, naringin, formometin, biochanin, resveratrol, quercetin, pyrogallol, rutin, and kaempferol.[26] Lectins represent another category of mycochemicals, comprising complexes of polysaccharides with proteins or peptides. Lectins derived from mushrooms demonstrate various beneficial properties, such as their ability to inhibit cell proliferation, modulate the immune system, exert anti-tumor effects, inhibit HIV-1 reverse transcriptase, regulate cell growth, and possess several other valuable characteristics.[27] Research has

unveiled the significant potential of mushrooms in generating mycochemicals, which serve as a valuable reservoir for the development of pharmaceuticals, nutraceuticals, and functional foods. These mycochemicals which have been isolated and characterized from mushrooms, encompass a diverse array of bioactive compounds that belong to various chemical classes.[24]

Mycotoxins are toxic compounds produced by certain fungi, including mushrooms that can cause harm when ingested. They are typically associated with mold-contaminated food and can have severe health consequences.[28] The principal toxin groups are cyclopeptide, orellanine, monomethylhydrazine, disulfiram-like, hallucinogenic indoles, muscarinic, isoxazole, and GI-specific irritants. Cyclopeptides are among the most infamous toxic compounds found in certain mushrooms.[29]

Chemistry of toxins

Amanitins. Amanitins are a subgroup of toxins found in *Amanita* mushrooms which are responsible for the majority of mushroom poisoning deaths worldwide. They specifically target the liver and kidneys leading to organ failure.[30] They are a class of cyclic peptides that serve as the primary toxins with the infamous Death Cap mushroom (*Amanita phalloides*) being a prominent example. These cyclic peptides are composed of eight amino acids intricately arranged within a distinctive cyclic structure.[31] Amatoxins are extremely potent toxins and even a tiny amount of 0.1 mg per kilogram of body weight can be deadly for adult humans. Consuming a mature phalloides mushroom weighing 20–25 g would result in exposure to 5–8 mg of amatoxins, which could be fatal.[32] Children are generally considered to be more susceptible to amatoxins, but this sensitivity may be attributed to the relationship between the dose and body weight.[33] The process of amanitin biosynthesis entails the incorporation of various amino acids into the cyclic peptide structure. In *Amanita* species, this complex biochemical pathway is orchestrated by a set of enzymes and gene clusters that work in tandem to synthesize these toxic compounds.[34] One of the most renowned members of the amanitin family is alpha-amanitin. This compound exerts its toxicity by disrupting a fundamental biological process. Specifically, alpha-amanitin functions as an inhibitor of RNA polymerase II, an enzyme crucially involved in the transcription of genetic information into RNA, a pivotal step in protein synthesis.[35] The consequences of inhibiting RNA polymerase II are profound. By interfering with this process, amanitins like alpha-amanitin effectively halt the production of essential proteins that are vital for the functioning and survival of cells.[36] The repercussions of this disruption are particularly severe in organs like the liver and kidneys, where the rapid synthesis of proteins is indispensable for proper functioning. The ensuing cellular damage and impairment can ultimately lead to organ failure and pose a significant threat to an organism's overall health. Figure 1 illustrates different types of poisonous mushrooms that cause toxicity in humans.[37]

Understanding the mechanism of action of amanitins is essential in recognizing their dangerous impact on organisms and the severe consequences of their ingestion.[35] It is a thermally stable bicyclic octapeptide that hinders the function of RNA polymerase II, consequently disrupting DNA transcription. This disruption leads to the cessation of protein synthesis and ultimately results in cell necrosis.[29] Amanitins are predominantly eliminated from the body through urine, with a smaller proportion being excreted through bile. Notably, there is a significant enterohepatic circulation of amanitins. In a study utilizing a dog model, it was observed that about 85% of amanitin could be recovered in the urine within 6 hours following ingestion.[38] In summary potent toxicity of amanitins arises from their ability to inhibit RNA polymerase II, disrupting the critical process of protein synthesis and causing cell death, particularly in vital organs like the liver and kidneys.

Phallotoxins. Phallotoxins are a group of toxins primarily found in the *Amanita* genus of mushrooms, such as *Amanita phalloides* (Death Cap). Phallotoxin is known for its hepatotoxicity, meaning it can cause severe damage to the liver. It is not readily absorbed from the intestine in animal studies, and its impact on human toxicity is considered to be relatively low. Phallotoxins represent yet another class of cyclic peptides discovered within *Amanita* species. Their structural composition bears resemblance to amanitins. They consist of seven amino acids intricately organized into a unique cyclic arrangement.[39] In terms of their synthesis, the process of phallotoxin formation closely parallels that of amanitins, encompassing a sequence of enzymatic reactions pivotal to crafting the cyclic peptide structure. Expanding upon their mode of action, phallotoxins predominantly exert their effects on cellular membranes.[40] They achieve this by binding tightly to actin filaments within the cell. This binding interaction leads to a disruption in the structural integrity of the cell membrane. The consequences of this disruption are particularly pronounced in organs such as the liver, where the structural integrity of cells is paramount for their normal functioning. The impact of phallotoxins on the cell membrane is noteworthy.[41] By interfering with the stability of the membrane through actin binding, these toxins induce cellular damage, potentially compromising the liver's ability to perform essential functions. This disruption of cell membrane integrity can have far-reaching consequences, ultimately posing a significant threat to an organism's overall health, particularly in instances of mushroom poisoning.[42] In summary, phallotoxins are cyclic peptides primarily affect cell membrane integrity by binding

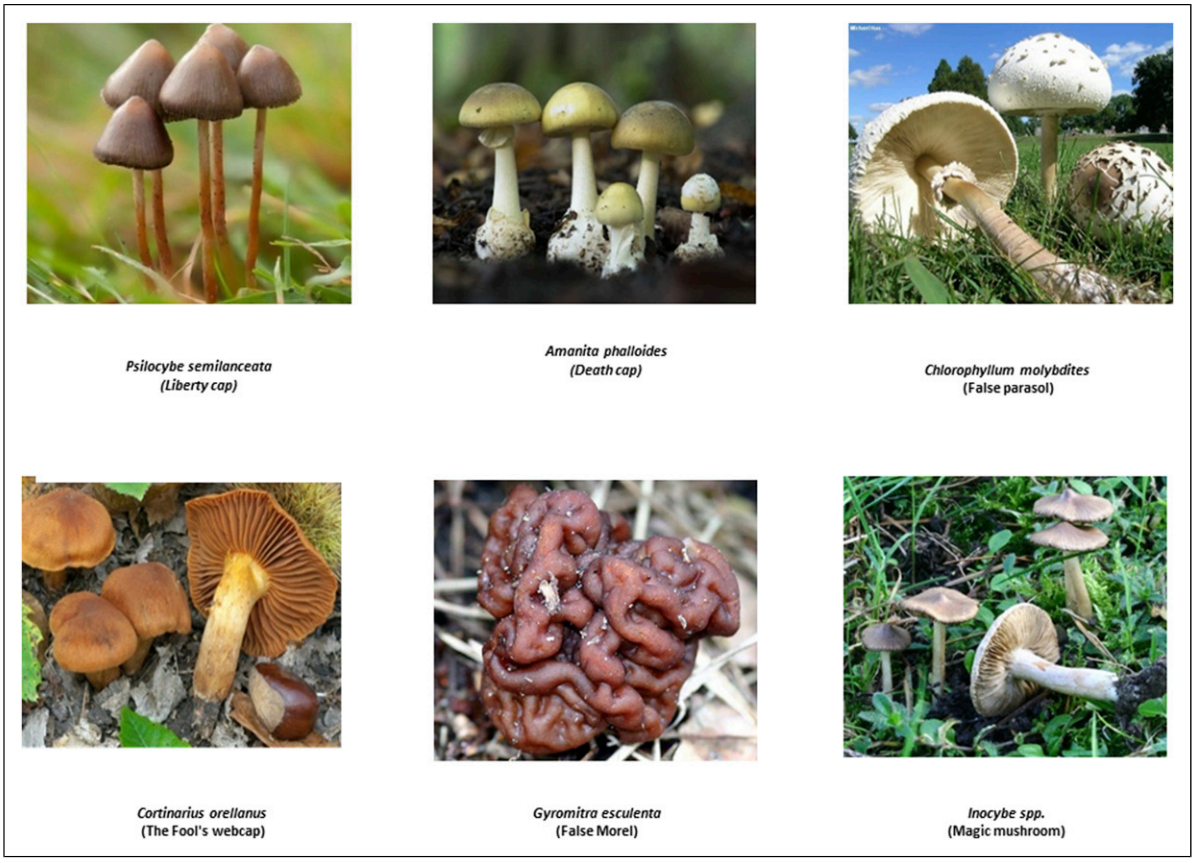

Figure 1. Different types of poisonous mushrooms (Source: https://www.first-nature.com/fungi/~id-guide.php).

to actin filaments, causing cell damage, particularly in the liver. Understanding the mechanisms by which phallotoxins operate is crucial in comprehending their toxic impact on cells and organs when encountered in *Amanita* mushrooms. Figure 2 illustrates the chemical structures of different mushroom toxins.

Ibotenic acid and muscimol. These compounds are found in mushrooms like *Amanita muscaria* (Fly Agaric) and *A. pantherina*. They can induce hallucinogenic effects, affecting the central nervous system.[43] Ibotenic acid is classified as a carboxylic acid, whereas muscimol is its decarboxylated counterpart. It's important to note that these compounds have a distinct chemical structure compared to cyclic peptides.[44] These compounds are believed to originate from the amino acid tryptophan through enzymatic processes occurring within the mushroom. Ibotenic acid undergoes decarboxylation to transform into muscimol. Ibotenic acid possesses the ability to induce neurological effects by functioning as an agonist at glutamate receptors in the brain. This activity results in symptoms such as hallucinations, delirium, and muscle spasms.[45] Muscimol, its decarboxylated form, exhibits similar effects. In summary, ibotenic acid, initially derived from the amino acid tryptophan through enzymatic processes, can produce neurological effects by acting as an agonist at glutamate receptors in the brain. This activity leads to symptoms such as hallucinations, delirium, and muscle twitching. Muscimol, which is formed through the decarboxylation of ibotenic acid, shares these effects and is also responsible for the psychoactive properties associated with these mushrooms.[46]

Orellanine. Orellanine is a hydrazine compound found in specific mushrooms belonging to the *Cortinarius* genus. Certain mushrooms contain orellanine which can lead to kidney damage when ingested. Symptoms may not appear until days or weeks after consumption.[47] It is characterized by a chemical structure centered on a hydrazine core with various substituents adorning it. While the exact process of orellanine's biosynthesis remains somewhat mysterious, it is postulated to involve a series of enzymatic reactions occurring within the mushroom.[48] These enzymatic processes culminate in the formation of the distinctive

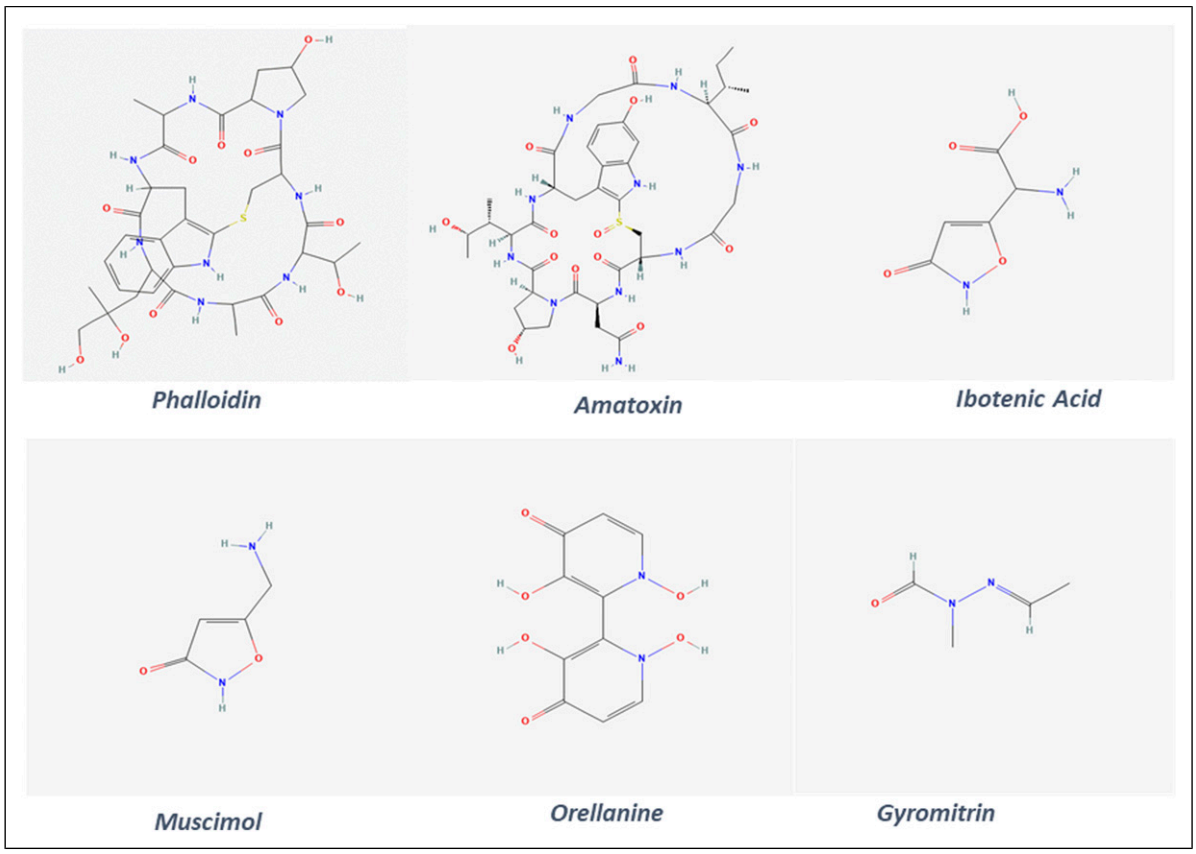

Figure 2. Chemical structures of different mushroom toxins. (National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 125121811, Amatoxin. Retrieved October 16, 2023 from https://pubchem.nc).

hydrazine core that defines orellanine. Orellanine is notorious for its detrimental impact on kidney tubules, potentially leading to delayed kidney failure. Although its adverse effects on the kidneys are well-documented, the precise mechanism through which it exerts its toxic effects remains only partially understood. Although the biosynthesis of orellanine is not comprehensively understood, it likely involves multiple enzymatic steps within the mushroom.[49] However, the precise mechanisms responsible for its toxicity necessitate further research for full elucidation.

Gyromitrin. Gyromitrin, which is found in *Gyromitra* species, is a hydrazine compound. These toxins can lead to neurological symptoms and are extremely toxic.[50] Its chemical structure consists of a hydrazine core complemented by a methyl group and a formyl group. The exact mechanism behind the biosynthesis of gyromitrin remains uncertain. However, it is believed to involve a series of enzymatic reactions within the *Gyromitra* mushroom.[22] These enzymatic processes are thought to culminate in the creation of the hydrazine core, along with its accompanying methyl and formyl groups. Gyromitrin undergoes a transformation into the toxic compound hydrazine when ingested. Hydrazine disrupts various cellular processes, resulting in symptoms such as seizures, coma, and liver damage. Gyromitrin ingestion can result in the release of toxic fumes and cause neurological symptoms. It's important to note that some people have attempted to detoxify these mushrooms through various methods, but they remain extremely dangerous.[51]

The chemical characteristics and stability of mushroom toxins exhibit notable variability. Some toxins, such as amanitins and phallotoxins, exhibit relatively high stability and can endure exposure to cooking temperatures. Conversely, others such as gyromitrin, may degrade when subjected to heat, potentially emitting harmful fumes.[52] Solubility also varies among these toxins, with some being water-soluble while others are not, impacting their extractability or removal during food preparation. The unique chemical properties of these toxins dictate their specific toxic effects on the human body. For instance, amanitins primarily target the liver and kidneys, while gyromitrin affects the nervous system.[53] The body's ability to detoxify or eliminate these toxins can differ among individuals and toxins, adding further complexity. Analytical methods such as high-performance liquid chromatography

(HPLC) and mass spectrometry rely on the chemical properties of these toxins for their detection and analysis.[54] It's crucial to recognize that the detailed chemical structures, biosynthesis pathways, and properties of mushroom toxins are continually evolving areas of research. The most effective strategy to prevent mushroom poisoning remains the accurate identification and avoidance of toxic mushrooms, as ingestion of these toxins can result in severe and potentially life-threatening consequences.[55]

Health implications of mushroom poisoning

Toxicological effects

Mushroom poisoning can have severe toxicological effects on humans and animals, depending on the specific mushroom toxin ingested. The manifestations and potential health hazards linked to mushroom poisoning can exhibit considerable variation contingent upon the specific toxin involved and the quantity consumed.[56] Commonly observed symptoms and associated health risks encompass the following. Firstly, individuals may experience gastrointestinal distress, marked by symptoms such as nausea, vomiting, abdominal discomfort, and diarrhea, which are prevalent in numerous instances of mushroom poisoning.[57] Secondly, certain toxins, as exemplified by those present in *Amanita muscaria* mushrooms, have the capacity to induce hallucinations, delirium, muscle spasms, and alterations in mental states, constituting neurological symptoms. Thirdly, the ingestion of amanitins and select other toxins can inflict substantial harm on the liver and kidneys, often presenting with telltale signs like jaundice (characterized by the yellowing of the skin and eyes) and the emission of dark urine.[45] Fourthly, in scenarios involving orellanine and gyromitrin poisoning, symptoms may remain dormant for extended periods, sometimes emerging days or even weeks following consumption by rendering diagnosis a formidable challenge. Lastly, in severe instances of mushroom poisoning, the consequences can be dire, potentially culminating in organ failure, particularly involving the liver and kidneys, thereby posing a life-threatening threat to the afflicted individual.[58]

Figure 3 illustrates the toxic mechanism of α-AMA which is a robust toxin, showing resilience to both high and low temperatures. Once ingested, it is swiftly taken up from the digestive system, entering the bloodstream in approximately 90 to 120 min and targeting specific organs like the liver and kidneys. Even though it doesn't attach to plasma proteins, its involvement in the enterohepatic circulation prolongs its half-life and the duration of its toxic impact. The water-soluble form of α-AMA is eliminated through urine.[59]

Consuming toxic mushrooms can lead to a wide range of health implications, with outcomes varying from mild digestive discomfort to life-threatening organ failure. The specific impact hinges on the particular type of poisonous mushroom and the mycotoxin it contains. Among the potential health implications are gastrointestinal distress, characterized by symptoms like nausea, vomiting, abdominal pain, and diarrhea.[60] Neurological symptoms may also arise, especially with mushrooms like the Amanita species, causing confusion, hallucinations, seizures, and, in severe cases, even coma. Some toxic mushrooms harbor hepatotoxic mycotoxins, resulting in liver damage that can manifest as jaundice, liver failure, and, in the worst scenarios, death.[61] Kidney damage and acute kidney injury (AKI), cardiovascular effects like irregular heartbeats and low blood pressure, rhabdomyolysis leading to muscle pain and weakness, and even respiratory distress necessitating mechanical ventilation in intensive care units are possible health implications of mushroom poisoning.[62] In severe cases, often involving Amanita species, multiple organ failure can lead to death, which might occur within days or weeks post-ingestion. The severity of these implications depends on several factors, including the type and quantity of toxin ingested, the individual's age and overall health, and the promptness of medical intervention.[63] Hence, swift medical attention is essential for anyone suspected of having consumed toxic mushrooms.

Positive health effects

Certain compounds found in specific mushrooms are currently being studied for their potential therapeutic benefits, and it's important to distinguish them from traditional toxins (Table 2). These compounds, rather than being harmful, are bioactive substances that exhibit promising health properties.[64] For instance, beta-glucans, present in mushrooms like shiitake (*Lentinula edodes)*, are the subject of research for their potential immune-boosting properties and their role in fortifying the body's natural defense mechanisms.[65] The potential anti-cancer properties of mushroom-derived compounds are investigated with a particular focus on their impact on cancer stem cells (CSCs). These CSCs are instrumental in tumor development and are often unresponsive to conventional cancer treatments, making them a critical target for therapeutic interventions.[66] The investigation delves into how various mycochemicals derived from dietary and non-dietary mushrooms might disrupt the signaling pathways involved in the growth and regulation of CSCs. It is observed that certain mushroom compounds possess the capacity to indirectly modulate the immune response directed against CSCs, notably through polysaccharides and polysaccharopeptides.[67] These compounds have the potential to influence the pathways associated with CSC stemness and their proliferation.

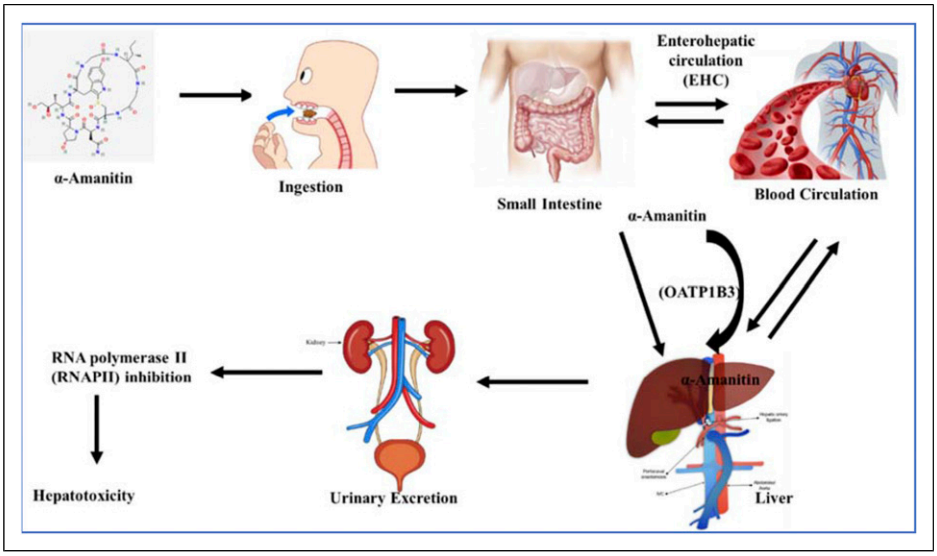

Figure 3. Representation of the pharmacokinetics and the mechanism of toxic effects caused by α-amanitin (α-AMA). Involves enterohepatic circulation (EHC), the organic anionic transporter peptide 1B3 (OATP1B3), and RNA polymerase II (RNAPII).

Among the well-recognized mushroom-derived components, β-glucans stand out for their robust anti-tumor and immunomodulatory attributes. While they may not directly induce cell death in cancer cells, they exhibit the ability to stimulate both humoral and cellular immunity.[68] They also inhibit cancer growth and impact factors such as vascular endothelial growth. Moreover, β-glucans have shown promise in reducing the size of cancerous tumors, and when used alongside other immune-boosting agents, they may enhance the effectiveness of chemotherapy.[65] Furthermore, it is suggested that extracts from medicinal mushrooms possess the capability to directly impede tumor growth. This is achieved by inhibiting cancer cell adhesion, reducing integrin expression, and slowing down the proliferation of tumor cells. The potential synergy between β-glucans and other mushroom-derived compounds in promoting anti-cancer effects is emphasized.[67] These findings contribute to out how mushroom-derived compounds can influence the growth and regulation of cancer stem cells. They provide valuable insights into potential strategies for cancer treatment, particularly in the context of addressing the challenges posed by CSCs and drug resistance.

Psilocybin, a compound found in psychedelic mushrooms like *Psilocybe cubensis*, has garnered attention in clinical studies due to its potential in addressing conditions such as depression, anxiety, and post-traumatic stress disorder (PTSD).[69] The anti-depressant effects of psilocybin, found in certain psychedelic mushrooms, are believed to be associated with its complex interactions with brain systems. Psilocybin reacts with serotonin 5-HT2A receptors, leading to a unique "mystical-like" hallucinatory experience.[70] This experience is linked to changes in brain activity, particularly in the prefrontal cortex, which is thought to mediate its anti-depressant and anti-anxiety effects.[71] One possible mechanism involves the deactivation or normalization of the hyperactivity of the medial prefrontal cortex (mPFC), a region typically overactive in depression. Psilocybin also influences the amygdala, a brain area responsible for processing emotions.[69,72,73] In cases of depression, individuals often lose their responsiveness to emotional stimuli, and psilocybin may help restore positive emotional responsiveness. Furthermore, psilocybin's effects on brain connectivity involve the disintegration of certain networks and the integration of sensory function networks, possibly mediating the subjective effects of unconstrained cognition.[74] It has been proposed that psilocybin's impact on the brain's reward system including the dopamine pathway contributes to its anti-depressant potential. While the exact mechanisms are not definitively understood, psilocybin's ability to alter brain dynamics, affect connectivity within specific brain regions, and influence emotional processing may contribute to its anti-depressant properties.[75] This research may offer new insights into the treatment of depression and related mood disorders. It's important to note that the use of psilocybin for treating depression should be conducted under professional supervision and is still an area of ongoing research. However, it's crucial to emphasize that the use of psilocybin is strictly regulated and should only occur under medical supervision. Additionally, mushrooms such as Lion's mane (*Hericium erinaceus*) contain compounds known as hericenones and erinacines, which are being explored for their ability to stimulate nerve growth and support brain health.[76] This research may have

Table 2. Mechanisms of different bioactive compounds in poisonous mushrooms.

Bioactive compound	Research models	Dose	Target molecular mechanism	Results	References
Beta-glucans	Female, 8-week-old BALB/c mice were injected with glucan (IL-2 secretion experiment)	100 μg of beta-glucan	Secretion of IL-2 (Interleukin-2) by the purified spleen cells. This mechanism is related to the immune response and indicates the potential immune-modulating properties of beta-glucans	In the IL-2 secretion experiment, the results involved testing the presence of IL-2 in the collected supernatants. The presence of IL-2 indicated the potential immunomodulatory effects of beta-glucans	[112]
Beta-glucans	The study used C57BL/6JNarl mice Dose: A fixed dose of 1×10^6 Lewis lung carcinoma cells (LLC1) was administered subcutaneously into the right inner thighs of each mouse	Mice were tube-fed with either distilled water, celecoxib, or mushroom beta-glucan continuously for 12 days	The administration of Lewis lung carcinoma cells (LLC1) and subsequent treatment with different substances (distilled water, celecoxib, or mushroom beta-glucan) affects molecular and physiological responses in C57BL/6JNarl mice	Tumor formation was observed 2 days after the injection, and the study continued for 12 days. At day 14, the mice were euthanized	[113]
Psilocybin	Participants ingested varying doses of psilocybin	Psilocybin in the form of 3 mg capsules	5-HT2A receptor (5-HT2AR) occupancy: The study aimed to understand the relationship between subjective psychedelic effects and 5-HT2AR occupancy by psilocybin's active metabolite, psilocin. Psilocybin and its metabolites are known to interact with the serotonin 2A receptor, which is thought to be central to the psychoactive effects of serotonergic psychedelics	The research indicates that psilocybin's effects on the human brain are closely tied to its interaction with 5-HT2A receptors, with plasma psilocin levels influencing both receptor occupancy and the subjective psychedelic experience	[114,115]

implications for managing conditions such as depression, anxiety, and cognitive function.

It's essential to remember that ongoing research is needed to fully understand the medicinal properties of these compounds, and they should not be viewed as exclusive or guaranteed treatments for medical conditions. Any use of such compounds or mushrooms for health purposes should be conducted under the guidance of a qualified healthcare professional to ensure safety and effectiveness. Furthermore, self-experimentation with wild mushrooms is risky due to the potential for severe poisoning from toxic varieties. Therefore, individuals should exercise caution and seek reliable expert advice when exploring the potential health benefits of mushroom compounds.

Clinical management, and practical applications of mycotoxins

Mycotoxins, commonly known as mushroom toxins, hold a broad spectrum of practical applications in various fields,

Table 3. Symptoms causing for human and antidotes for different toxins found in poisonous mushrooms.

Toxin	Symptoms	Antidote	Reference
Amatoxins	Insidious onset of liver failure (48 hours post-exposure), jaundice, abdominal pain, vomiting; disruption of mRNA transcription leads to hepatocyte dysfunction, nucleolar disintegration, and centrilobular hepatic necrosis	N-acetylcysteine: IV treatment for potential liver injury; provides glutathione Penicillin: High-dose IV may compete with liver uptake of amatoxin Silymarin: Available as IV formulation (Europe) or OTC milk thistle extract (North America); doses are 1 gm orally four times daily or silibinin IV (5 mg/kg over 1 hour, followed by 20 mg/kg/day infusion); inhibits OAT-P transporter, slowing amatoxin entry into the liver Activated charcoal: May reduce absorption if given early (1 g/kg every 2-4 hours); prevents enterohepatic recirculation Cyclosporine: Inhibits OAT-P transporter	116
Phallotoxins	Hepatotoxicity characterized by cholestasis and cytotoxicity due to selective uptake by hepatocytes, where phallotoxins bind to F-actin and prevent its depolymerization, leading to liver damage and gastrointestinal distress	Silymarin (milk thistle) contains silybin, which has antioxidant properties. It may help protect the liver by inhibiting the uptake of phallotoxins and promoting regeneration N-acetylcysteine (NAC) while primarily used for acetaminophen overdose, it may offer some hepatoprotective benefits due to its role in replenishing glutathione Activated charcoal administered within a few hours of ingestion to reduce absorption of toxins. Dosing typically is 1 g/kg every 2-4 hours Penicillin limited studies suggest that high-dose benzylpenicillin may have some efficacy in reducing hepatotoxicity, though evidence is variable	4,117
Orellanine	Vomiting, polydipsia, lumbar pain, nausea, abdominal pain, headache, polyuria, asthenia, diarrhea, anorexia, myalgia, faintness, paresthesia, constipation, chills, somnolence, vertigo, dysgeusia, sweats, tinnitus, burning in mouth, fatigue, thirst, dry mouth, visual defects, loin pain Renal phase: Myalgias, intense lumbar pain, flank pain, oliguria, leukocyturia, hematuria, proteinuria, anuria, glucosuria, leukocytosis, increased serum creatinine, potassium, and urea	Corticosteroids, diltiazem, dopamine, selenium, N-acetylcysteine	48
Ibotenic acid and muscimol	Gastrointestinal upset: nausea, vomiting, diarrhea, abdominal pain, hallucinations, myoclonic jerks, irritability, polydipsia, lumbar pain, headache, polyuria, asthenia, faintness, paresthesia, chills, somnolence, vertigo, dysgeusia, sweats, tinnitus, burning in mouth, fatigue, thirst, dry mouth, visual defects	Benzodiazepines, anticonvulsant	105
Gyromitrin	Gastrointestinal irritation: nausea, vomiting, abdominal pain, diarrhea; renal injury: potential nephrotoxicity; CNS effects: seizures (due to GABA depletion), excitatory state, possible encephalopathy; liver failure: jaundice, elevated liver enzymes	Pyridoxine (vitamin B6), benzodiazepines	118

including traditional medicine, pharmaceuticals, and biotechnology (Table 3). Traditional medicine has incorporated specific mushroom toxins into its practices for centuries, with examples like *Amanita muscaria* being used in Siberian shamanic rituals due to its hallucinogenic and therapeutic properties.[2] In the pharmaceutical realm, some mushroom toxins, such as psilocybin from magic mushrooms, are being investigated for their potential in treating mental health conditions, while others, like those from venomous creatures, offer prospects for neurological medications and antibiotics.[69,77] Additionally, mycotoxins have found their place in biotechnology and agriculture, serving as natural pesticides, agents for bioremediation, and sources of enzymes with applications in food production, biofuels, and bio-based chemicals.[78] It's essential to recognize that the use of mushroom toxins carries risks of severe toxicity and even fatality if not handled with care. Consequently, research and development in these areas require rigorous safety protocols to ensure secure and controlled utilization. Additionally, it's crucial to note that the legality and regulatory framework surrounding the use of specific mushroom toxins for medicinal and pharmaceutical purposes can vary significantly by region.[79]

The clinical management and treatment of mushroom poisoning encompass several essential steps. Firstly, it is imperative to seek immediate medical attention if mushroom poisoning is suspected or if symptoms manifest. Providing comprehensive information about the ingested mushroom, including its physical characteristics, is crucial.[3] Secondly, the focus of treatment often revolves around symptom management and supportive care. This entails measures such as administering intravenous fluids to ensure proper hydration, using antiemetic drugs to control nausea and vomiting, and prescribing medications to address specific symptoms like seizures.[80] Thirdly, in select cases, activated charcoal might be administered to aid in the absorption of toxins within the digestive tract and prevent further uptake. Fourthly, for certain types of mushroom poisoning, specific antidotes may be employed; for instance, in severe instances of *Amanita* poisoning, silibinin, an antidote for amatoxin poisoning, may be administered.[81] Fifthly, when severe kidney damage is evident, hemodialysis may become necessary to effectively filter toxins from the bloodstream and support kidney function. Lastly, in cases of exceedingly severe liver failure resulting from amanitin poisoning, a liver transplant may emerge as the sole viable treatment option.[82] Preventing mushroom poisoning is paramount. Proper identification of edible mushrooms, avoidance of foraging without expert knowledge, and immediate medical attention in case of suspected poisoning are critical for minimizing health risks associated with toxic mushrooms.

However, translating these findings into clinical practice presents several challenges. Toxicity and safety concerns remain a significant hurdle, as many mushroom-derived compounds have a narrow therapeutic window, requiring precise dosing and rigorous clinical trials to minimize adverse effects.[33] Regulatory and legal barriers also limit research progress, particularly for psychoactive compounds like psilocybin, which faces strict legal restrictions despite promising antidepressant and anxiolytic properties.[75] Additionally, the complexity of bioactive compounds in mushrooms presents challenges in extraction, isolation, and large-scale pharmaceutical synthesis, requiring further research into biosynthetic pathways and molecular mechanisms.[83,84] Another major limitation is the lack of extensive human clinical trials, as most studies on mushroom toxins rely on in vitro and in vivo models, restricting the understanding of their pharmacodynamics and pharmacokinetics in humans.[85] Moreover, drug formulation and delivery issues must be addressed to enhance stability, bioavailability, and targeted therapeutic effects, with nanotechnology-based systems offering a potential solution.[78] Finally, public perception and stigma surrounding toxic and psychoactive mushrooms remain a barrier to acceptance in the medical community, necessitating greater public education and scientific outreach to foster awareness of their medicinal value.[86]

Detection and analysis of mushroom toxins

The detection and analysis of mushroom toxins play a pivotal role in ensuring food safety, identifying potentially harmful species, and supporting research across various domains. Several key aspects are associated with the detection and analysis of mushroom toxins. One of the primary methods for detecting and quantifying mushroom toxins involves chemical testing, with techniques like HPLC frequently used to separate and quantify individual toxins based on their chemical properties. This method is widely employed for analyzing mushroom toxins.[87] Mycochemicals are typically analyzed using various chromatographic methods, including thin layer chromatography (TLC), gas chromatography (GC), and HPLC. Additionally, techniques such as Fourier-transform infrared spectroscopy (FT-IR), mass spectrometry, and different forms of nuclear magnetic resonance (NMR) experiments, such as 1D ^{1}H and ^{13}C NMR, as well as 2D NMR methods like H–H COSY, TOCSY, HMQC, HMBC, and NOESY, are valuable in providing information for elucidating the chemical structures of mycochemicals.[24] The identification and quantification of phenolic acids and flavonoids in selected mushroom species (including *P. ostreatus*, *P. eryngii*, *Agaricus bisporus*, *Cyclocybe aegerita*, *Russula cyanoxantha*, *R. virescens*, *Macrolepiota procera*, *Boletus edulis*, *Lactarius deliciosus*, *Coprinus comatus*, and *Tuber melanosporum*) were carried out using HPLC coupled with mass spectrometry (HPLC–MS). The identification of these compounds was based on their retention times, UV–Vis absorption spectra, mass spectral data, and comparison with available reference data.[88] Immunological assays, such as the enzyme-linked immunosorbent assay (ELISA), employ antibodies to swiftly and sensitively detect specific toxins in a sample, offering an effective screening approach. Molecular methods, like polymerase chain reaction (PCR), can

detect the DNA of toxic mushroom species and their associated toxins, enabling the identification of potentially hazardous mushrooms.[89] Mass spectrometry, particularly liquid chromatography-mass spectrometry (LC-MS), stands as a powerful technique for both qualitative and quantitative analysis of mushroom toxins. This enables precise identification and quantification.[90] Additionally, NMR spectroscopy can be employed to scrutinize the chemical structure of toxins and confirm their identity.[91] Bioassays, which use living organisms like mice or fruit flies, are valuable for assessing the toxicity of mushroom samples, although they are less specific compared to chemical methods.[92]

Advancements in analytical techniques have further enhanced the detection and analysis of mushroom toxins. High-resolution mass spectrometry (HRMS) enables more accurate mass measurements, improving compound identification in complex mixtures such as mushroom extracts. Metabolomics, which involves the comprehensive analysis of all metabolites in a sample, provides a holistic understanding of the chemical composition of mushrooms and their toxins.[93] Next-Generation Sequencing (NGS) contributes to the identification of mushroom species and their genetic potential to produce toxins, facilitating early detection and risk assessment. Lastly, developments in data analysis and bioinformatics tools simplify the interpretation of complex analytical data, streamlining the identification and quantification of mushroom toxins.[94]

Challenges in toxin identification and analysis and future directions

The identification and analysis of mushroom toxins come with a set of challenges. Firstly, mushroom toxins can exhibit variability in their composition and concentration due to factors such as species, growth conditions, and environmental influences, making consistent analysis a complex task.[95] Moreover, the morphological similarities between toxic and non-toxic mushroom species can render visual identification unreliable. In cases involving less studied or emerging toxins, the absence of reference standards can hinder accurate quantification. Mushroom samples often contain a diverse array of compounds, including non-toxic ones, further complicating the analysis and interpretation process.[96] Strict regulatory requirements from governing bodies regarding toxin detection and quantification in food and pharmaceuticals necessitate robust and validated analytical methods. Additionally, the continuous discovery of new mushroom toxins requires ongoing research and updated analytical methods to detect these emerging toxins.[53]

Beyond therapeutic applications, mushroom poisoning remains a global health concern, with thousands of reported cases annually, particularly in regions where foraging is common.[85] The global burden of mushroom poisoning is exacerbated by misidentification of toxic species, limited access to rapid diagnostic tools, and inadequate treatment options, leading to high morbidity and mortality rates in severe cases.[78] The development of standardized classification systems for mushroom toxins, coupled with advancements in molecular diagnostics, could significantly enhance the accuracy of poisoning diagnosis and risk assessment. Improved biochemical and toxicological profiling of mushroom toxins could also facilitate the discovery of novel antidotes and targeted detoxification strategies, reducing the fatality rate of toxic ingestions.[86]

Mushroom toxin research is a continually evolving field, replete with emerging trends, promising areas for further exploration, and the potential for groundbreaking applications. The following outlines future directions and research challenges in the realm of mushroom toxin research.[83] The investigation of psychoactive compounds found in specific mushrooms, notably psilocybin, is witnessing a resurgence of interest due to their potential therapeutic applications in addressing mental health issues and enhancing overall well-being.[97] Research on the ecological implications of mushroom toxins, encompassing their roles in nutrient cycling and interactions with other organisms, is gaining significance, particularly in the context of ecosystem health and conservation.[86]

The development of rapid and sensitive detection methods for mycotoxins in food and agricultural products is a growing research area, aimed at ensuring food safety and quality. The exploration of potential biotechnological and medical applications of specific mushroom toxins, such as antimicrobial or anticancer properties, is a notable area of interest.[98] A deeper comprehension of the biosynthetic pathways and regulatory mechanisms responsible for mushroom toxin production is essential for manipulating toxin production or identifying novel toxins. Elucidating the mechanisms by which mushroom toxins affect various organisms at the molecular and cellular levels can provide insights into their toxicology and potential therapeutic applications.[84] Further research is necessary to evaluate the long-term ecological consequences of toxins produced by mushrooms, especially concerning changing environmental conditions and habitat loss. Research into the cultivation of non-toxic or low-toxin mushrooms for food, medicine, and biotechnology applications holds practical benefits.

Conclusions

In conclusion, the study of mushroom toxins is a multifaceted field that holds significant importance in various domains. This comprehensive review article has shed light on the diverse aspects of mushroom toxins, emphasizing their profound significance and practical relevance. From

understanding the chemistry and biology of these toxins to their toxicological effects, practical applications, detection methods, and ecological impact, this research provides a holistic view of mushroom toxins and their potential for scientific discovery and real-world applications. The classification of mushroom toxins into various categories, such as mycochemicals and mycotoxins, reveals the complexity and diversity of these compounds. Mycochemicals which encompassing various chemical classes like phenolic compounds, flavonoids, and lectins, have implications for human and animal health, nutrition, and functional foods. On the other hand, mycotoxins, including cyclopeptides, phallotoxins, ibotenic acid, muscimol, orellanine, and gyromitrin, are toxic compounds produced by certain fungi, some of which can cause severe harm when ingested. Understanding mushroom toxins is crucial for safeguarding human health and safety, preventing accidental poisoning, and ensuring public well-being. Moreover, it provides valuable insights into ecological relationships, pharmaceutical potential, agricultural applications, taxonomic studies, cultural practices, and environmental monitoring. The study of mushroom toxins underscores the multifaceted roles of fungi in the natural world and highlights the need for ongoing research in this intriguing field. In summary, the exploration of mushroom toxins is not only vital for human safety but also offers valuable contributions to ecology, medicine, agriculture, culture, and more. This review article serves as a comprehensive resource for researchers, scientists, educators, and the public, aiming to bridge the gap between scientific knowledge and practical understanding of mushroom toxins and their potential applications.

Author contributions

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