Chapter

Medicinal Mushroom of Potential Pharmaceutical Toxic Importance: Contribution in Phytotherapy

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Abstract

Orthodox medical practice depends greatly on the use of high throughput (HTP) pure pharmaceutical new chemical entities, with a purity that can easily be evaluated and whose efficacy and toxicity can show a dose-dependent, clear structure-activity relationships (SAR). On the contrary, natural products contain mixtures of natural bioactive metabolites that have not undergone any chemical analyses and whose mechanism of action is not known. Medicinal mushrooms have been used throughout the history of mankind for the treatment of various diseases including cancer. Nowadays they have been intensively studied and generated research interest in an attempt to reveal the chemical nature and mechanisms of action of their bioactive molecules. Targeted treatment of diseases, non-harmful for healthy tissues, has become a major objective in recent times and metabolites of fungal origin provide a vast reservoir of potential new chemical entities. There are many examples of mushrooms common for use globally that demonstrate the complex nature of their pharmaceutical potential This review paper attempts to show that some aspects of fungotherapy of the disease have been well studied. We also give an insight into the role of mushroom metabolites for treatment of diseases types that are especially susceptible to the fungal treatments.

Keywords: medicinal mushrooms, fungotherapy, phytotherapy, nutraceutical, bioactive metabolites, cancer

1. Introduction

Medicinal mushrooms and fungi are known to contain more than 120 medicinal properties, which include antitumor, anti-hypercholesterolemic, antiviral, antibacterial immunomodulation, antioxidant, free radical scavenging, cardiovascular, anti-parasitic, antifungal, detoxification, hepatoprotective, and antidiabetic properties [1]. Most of the Basidiomycetes mushrooms contain bioactive metabolites in

fruiting bodies, cultured mycelium, and cultured broth, with special consideration to mushroom polysaccharides [2]. Studies on mushroom polysaccharides and different bioactive metabolites have been done for more than 700 species of higher hetero- and homobasidiomycetes [3]. Many bioactive metabolites from the medicinal mushrooms studied are known to enhance innate and cell-mediated immune responses, and exhibit antitumor activities in animals' models and clinical trials studies in humans [2, 4]. Even though the mechanism of antitumor properties of medicinal mushrooms is yet to be well understood, stimulation and modulation of major host immune responses by these mushroom bioactive are important [5]. Polysaccharides and low-molecular-weight secondary metabolites are very important due to their antitumor and immune-stimulating activities, based on Phase I, II, and III clinical trials. Mushroom compounds have been used extensively and successfully in low medium-income countries for the treatment of many categories of cancers and other pathologies [6]. More exploration has been directed and special emphasis orientated to investigate many important unsolved problems in the study of medicinal mushrooms [7].

1.1 Medicinal mushroom in phytotherapy

From an evolutionary point of view, nature produces vast biodiversity of bioactive molecules, which possess many therapeutic potentials, with respect to the treatment of diseases, such as cancers [1, 8]. Natural products have produced many secondary phytochemical compounds widely used in phytotherapy, whilst the application of such products in folk and traditional medicine has always been an important clue pointing to potential new chemical entities with therapeutic potential. Some examples of plant-based compounds of pharmaceutical importance for cancer treatment include camptothecin derived from the bark and stem of the tree *Camptotheca acuminata* used in Chinese traditional medicine [2], vinca alkaloids derived from *Madagascan periwinkle* [9] or taxanes derived from genus Taxus (yews), paclitaxel (Taxol), and docetaxel (Taxotere) widely used as chemotherapeutic agents [3, 10]. Generally, first-generation natural chemotherapeutic properties are orientated mostly against housekeeping processes (such as DNA replication or microtubule polymerization and stabilization), which are very active against fast proliferating cancer cells, but not cancer specific [11]. The natural products derived from mushrooms may produce potential adverse side effects on ingestion when used in herbal or conventional anticancer treatments, thus could provoke an eventual patient's death when consumed in overdose. Currently, the approaches used in the management and control of cancer pathologies are based on selected or targeted treatment applications with the intention to reduce to healthy uninfected tissues [11]. The discovery and development of potentially bioactive molecules from mushrooms for better selectivity in action to diseases, especially those to act on cancer cells or on tumorigenic processes, are faced with challenges. It is of importance to develop high through put (HTP) methods for the discovery and potential screening of the bioactive compounds of pharmaceutical importance [12].

1.2 Medicinal mushrooms in folk medicine

Mushrooms have been used in folk medicine as far back in ancient times [12]. Mushrooms species used varied in different cultures, in a way that more species have been identified and used in Asian countries than in the Western civilization [5, 13]. It is reported that the difference in usage is linked to the mycophilic and mycophobic nature of the different cultures [14]. In developed countries, the most common species and

possibly the only one that has been identified, at the time of the ancient Greeks, was *Fomitopsis officinalis*. Hippocrates was one of the pioneers to study the medicinal properties of fungi and elucidated their potential uses in the management of certain common diseases, however, it is not certain as to what species he studied. The contribution of Dioscorides, a physician around 55 AD, who was well known and recognized for his work entitled *De Materia Medica*, still stands as the most widely used herbal bioactive natural product during his era and for about 1500 years, he changed in a significant manner the nutraceutical concept of the Western world and played an important role in the use of mushroom as food and medicinal product, which was the onset of the science of nutraceuticals [15]. The work of Pliny and later Galen also studied and concluded that fungi were of medicinal and pharmaceutical importance. Their opinions, however, influenced the mycophobic nature of mushrooms in Western Society that continues, in the current day. However, *F. officinalis* was globally recognized among the medicinal plants that was used to treat various diseases. Other species used for medicinal applications were other bracket fungi; *Fomes fomentarius*, *Phellinus ignarius*, *Fomintopsis pinicola*, and others that were commonly used to stop the bleeding and as wound healing [7, 16]. In China, where mushrooms are known to be a part of the gastronomy and elixir of life, mushrooms have been considered to play an important role in medicine, nutraceutics for as far back as 7000 years. Many species of mushrooms are identified, including *Lentinula edodes*, *Hericium erinaceum*, *Flammulina velutipes*, *Auricularia polytricha*, and *Tremella fuciformis*, etc., and these are species that are very prized for eating [9, 17].

1.3 Mushrooms as a delicacy food in Cameroon

Mushroom is a delicacy for many around the world. In Cameroon, this crop (fungi) is harvested from the wild once a year during the month of April to May. This activity mobilizes many women and youths (girls and boys) who rely on it for income. Harvested mushrooms, mostly the Agaricus and the termitomyces species, are sold on the roadsides and more often by youths as it generates a substantial amount of money that is used to pay part of their school fees, buy school supplies, and even pay medical and telephone bills [18]. Many people in Cameroon solicit mushrooms because of their good taste, medicinal and nutritive value, cheap and available, especially during its peak season. During offseason, it is not the case. Mushrooms are practically absent in the market and very few traders (middlemen) are in possession of some bags of dry mushroom. A bucket (15 L) is often sold between 15,000 and 25,000 FCFA ($30–$50). A plate of mushrooms is very expensive in restaurants and hotels [19].

Cultivating mushrooms is a good business owing to its short production cycle and poor farmers or youths can easily start up a small farm if trained. This will put mushrooms on the table and in the market all year round generating a substantial amount of income to prospective growers. The government has not been very supportive of this activity and we still struggle to import mother spawns to produce base 2 cultured spawns that farmers use to grow mushrooms. In addition, many people are unaware of the different types of edible mushrooms, so there is inadequate sensitization. The absence of financial and technical support also contributes a great deal.

1.4 Usage of medicinal mushrooms

Most of the benefits of mushrooms studied and investigated through the scientific method are those that have been recognized to produce bioactive metabolites that

Mushroom	Immunomodulating compound
Lentinula edodes	Lentinan
Schizophyllum commune	Schizophyllan
Grifola frondosa	D-fraction
Coriolus versicolor	PSP (polysaccharide peptide) and PSK (also called Krestin)
Ganoderma lucidum	Polysaccharide (GLPS) fractions

Table 1.
Mushroom with immunomodulating bioactive compound [3, 19].

inhibit or can destroy cancer cells development [18]. Most species that produce these bioactive compounds do so by the process of immunomodulation, the modification, by suppressing or enhancing the immune system, and is used in the treatment of cancerous growth [3, 19]. These compounds as illustrated in **Table 1** include Lentinan, Schizophyllan, D-fraction to name but a few.

Just a few species containing these bioactive metabolites have been studied, and over 30 species of mushrooms studied have been shown to have anticancer properties in animals [20]. PC-SPES, which includes a GLPS fraction, has been demonstrated to control adenocarcinoma of the prostate cancer cell line by inhibition of the cell division and growth of their cells [21, 22, 24]. This is a very simple and logical explanation of the mechanism. Various species of mushrooms have been reported as nutritious and tasty food in many parts of the world and have been documented by many researchers [24–26]. The nutritious property of mushrooms is also another means by which they can be beneficial to the health of the person consuming mushrooms [27].

Many researchers have demonstrated the medicinal and nutraceutical properties of mushrooms' bioactive compounds, for the management of different illnesses [28]. Despite the bioactive activity demonstrated none of the phytoactive compounds have had approval by the Food and Drug Administration (FDA) of USA, and therefore still considered under the category of dietary supplements, as opposed to the drugs approved by FDA that are prescribed or used as over-the-counter drugs, failing to have undergone any clinical trials studies [29–31]. This category of supplements is marketed with the condition to carry the label of not being approved for use by the FDA [32].

2. Some example species of mushrooms that have been studied for medicinal properties

The examples of mushroom species indicated used in folk medicine do not have any demonstrated medicinal efficacy, and therefore the description of their usage is mostly non-evidence based [33].

2.1 *Coriolus versicolor*

This mushroom is under the species of bracket fungus that is widely referred to as Turkey tail. This common species is ubiquitous, but mostly in the temperate regions of the world [3, 34]. The fruiting body has many useful medicinal secondary metabolites, such as the immunoactive polysaccharopeptide (PSP) and polysaccharide-K (PSK) and especially the antitumor polysaccharide called coriolan [35]. The PSK and PSP are known to inhibit the growth of cancer cells and are administered by intravenous route or

Figure 1.
Coriolus versicolor *(Turkey Tail) [38].*

enterally in clinical studies of cancer volunteers. They have shown promising anticancer activities for the management of many forms of cancer, synergistically in combination with radiation therapy through improving the sensitivity of cancer cells to radiation. The survival of the treatment of PSK has shown the potential to increase the survival rate within 5 years by 21 and 52%, respectively [36]. In *Materia medica* within the traditional Chinese pharmacopeia, *C. versicolor*, is promising for the inhibition of phlegm, management of pulmonary disorder, energy booster for the treatment of chronic diseases [11, 37]. Medicinal mushrooms in Mexico used in traditional folk medicine, are applied for the treatment of ringworm [38]. *C. versicolor* is well illustrated in **Figure 1**.

2.2 Lentinula edodes

The shiitake belongs to the group of mushrooms mainly used for thousands of years, in Japan and China, for its food value and is very prized for its medicinal properties [39]. It is considered as the world's second most widely cultivated and consumed mushroom. In traditional medicine, shiitake has been widely studied, with many clinical studies reported [40]. It has the polysaccharide, lentinan, as well as other polysaccharides that have antitumor properties. Some studies have shown that the shiitake can inhibit bacteria resistant to bacteria [15]. For instance, studies show that clinical trials volunteers that were exposed to antibiotic-resistant strains of *Mycobacterium tuberculosis*, the causal agent of tuberculosis, showed recorded improved conditions when lentinan was administered to them and inhibited relapses of tuberculosis in the lungs [41]. The treatment for cancerous liver tumors in rats, liver protection increased the production of antibodies against hepatitis B, lowered cholesterol blood levels, lipids, and blood pressure [16, 42]. *Lentinula edodes* is illustrated in **Figure 2**.

2.3 *Tremella fuciformis*

These are particular species of jelly fungus that are commonly called the snow fungus. This species grows on hardwood trees, but it is not a wood decomposer as has been considered in the past. It is parasitic on hosts belonging to the order Xylariales, of the phylum Ascomycota [43]. Before understanding its true nature, the cultivation of this species was very challenging. This species belongs to the many Chinese traditional medicinal mushrooms important in the treatment of diseases, used mostly

Figure 2.
Lentinula edodes *(Shiitake) [42].*

as an immune tonic, stops asthma and coughing, reduces phlegm, supports the liver and exhaustion, cosmetics, anti-inflammatory, gastric ulcer, constipation, abnormal menstrual cycles, and many others [11, 44]. This species is common on hardwood in tropical and temperate areas, throughout the world.

From clinical trials studies, it has been shown to improve the level of blood cells as a result of losses from radio and chemotherapy treatment of cancer patients, to boost the immune system through the stimulation of white blood cell activity [45]. Ethnopharmacology studies indicate medicinal mushroom use in lowering cholesterol and the treatment of cardiovascular diseases, such as arteriosclerosis and abnormal clotting [46]. *Tremella fuciformis* has been illustrated in **Figure 3**.

2.4 *Ganoderma lucidum*

This mushroom variety commonly known as the Ling-Zhi in China and Reishi in Japan is considered one of the bracket fungi. However, contrary to most species, it is characterized by a long slender stalk attached to the side of the "cap" of the fruiting body [47]. This species is widely distributed in North and South America, Europe, and part of the African dense humid forest, where they grow on the hardwood. The species is very popular and widely used in Chinese and Japanese traditional pharmacopeia in the past 4000 years, for the treatment of multiple diseases of the liver, hypertension, gastric ulcer, arthritis, chronic hepatitis, insomnia, bronchitis, and asthma [9, 48].

A number of anti-cancer bioactive constituents have been isolated from *G. lucidum*, as illustrated in **Figure 4**. These compounds have shown immune-stimulating, anti-tumor activities [22]. *In vitro* studies have demonstrated that this species possess anti-allergic, bronchitis preventive effect, anti-inflammatory, antibacterial properties against a broad spectrum of bacteria isolate, lowers blood pressure, and has antioxidant properties [49]. Clinical studies have shown the beneficial potential in treating a variety of disorders.

2.5 *Auricularia auricula* and *Arabis polytricha*

Commonly referred to as Jew's Ear that according to folklore is linked to Judas Iscariot, the biblical story of his betrayal of Jesus Christ, who later committed suicide

Figure 3.
Tremella fuciformis *(Snow Fungus) [46].*

Figure 4.
Ganoderma lucidum *[22].*

by hanging on an elder tree. The ear-like shape of the mushroom is linked to the returned spirit of Judas, which serves as a reminder of his betrayal [27, 50]. This species is widely distributed in the temperate zones as opposed to *A. polytricha* that is located in the sub-tropical to tropical regions. The other species have a variety of common names, however, all of them contain the word "ear" in their name due to

Figure 5.
Morphology of Auricularia polytricha *(Pepieau) [42].*

the fact that they have ear-shaped basidiocarp, as shown in **Figure 5** [50]. In Hawaii, for example, the species is referred to as the "pepeiao," the Hawaiian name for the ear. Both species belong to the Basidiomycota known as the "jelly fungi" due to the consistency of their fruiting body [51].

Both species in China, have been used in folk medicine for the past thousands of years for the treatment of hemorrhoids and as a stomach tonic [52]. In Europe, *A. auricula* is traditionally used in a boiled liquid form for the treatment of inflammation of the throat and eye irritation. Studies have also shown more evidence of *A. auricula* wide use for the improvement of the immune system [53]. The potential uses in the lowering of blood cholesterol, as an anticoagulant and potential anti-diabetic activity has been demonstrated [54].

2.6 *Boletus edulis*

This species is widely considered as *King Bolete* and also as the *Cepe* in Italy. It is a mycorrhizal fungus associated with conifers and other hardwood trees [33, 54]. There are many known species of Boletus, but this variety of interest is the most valuable edible species and is recorded as the only species in the genus to have antitumor activities [55]. Boletus species has been widely used in Chinese traditional folk medicine for the treatment of lumbago, leg pains, numbness in limbs, and tendon complications [12, 56]. *Boletus edulis* is illustrated in **Figure 6**.

2.7 *Cordyceps sinensis*

This species is commonly called the Caterpillar Fungus and is probably the most extensively studied species. It is a parasitic species with the caterpillar as its primary host [19]. *C. sinensis* is also included in some food recipes in addition to its medicinal

Figure 6.
Boletus edulis *(Cepe or King Bolete) [37].*

use. It has activities similar to ginseng, antioxidant, anti-inflammatory, and very potent. The first documented use of *C. sinensis* was in 620 AD, during the Tang Dynasty, used for strengthening of the body after exhaustion or long term illness, impotence, backaches, and an antidote for opium poisoning [56]. Cordycepin is the active molecule in *C. sinensis*, as illustrated in **Figure 7**. Cordycepin or 3′-deoxy-adenosine, is a derivative of the nucleoside adenosine. It was initially extracted from the fungus *Cordyceps militaris* [9], but is now produced synthetically. It is also found in other *Cordyceps* species as well as *Ophiocordyceps sinensis* [27].

Based on the similarity of cordycepin to adenosine acting as an analog, some enzymes have affinity but cannot discriminate between the two bioactive compounds [57]. Cordycepin can participate in some biochemical reactions like, 3-dA for example, can provoke the premature termination of mRNA synthesis [34, 58], by acting as an adenosine analog [59]. Cordycepin has been shown to produce rapid, strong imipramine-like antidepressant effects in animal models of depression, and these effects, similar to those of imipramine, are dependent on the enhancement [60]. A photo of a mature *Cordyceps sinensis* in its natural habitat is illustrated in **Figure 8**. The AMPA receptor (AMPA-R) is a subtype of the ionotropic glutamate receptor coupled to ion channels that modulate cell excitability by gating the flow of calcium and sodium ions into the cell [61].

Many studies have been done on this fungus but with little confirmatory result [62]. In traditional Chinese medicine, Cordyceps has been used in the treatment of respiratory and pulmonary diseases, such as renal, liver, and cardiovascular diseases [3, 29]. It has been used in the treatment of immune disorders in association with cancer chemotherapy treatments and surgery [9]. It is also used as a remedy for impotence, fatigue and as a "rejuvenator" for the increase in energy [57]. Successful

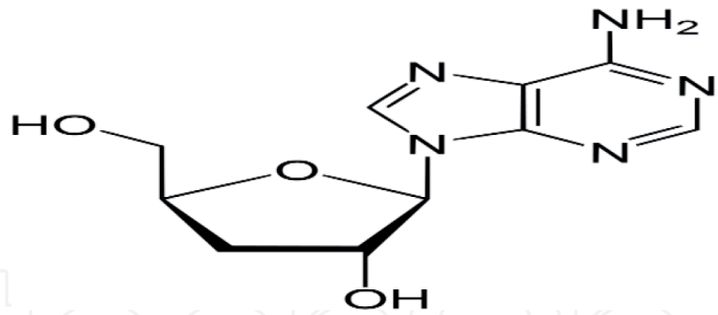

Figure 7.
Structure of cordycepin.

Figure 8.
A mature Cordyceps sinensis *in its natural habitat [39].*

treatment for impotence, acting as an aphrodisiac has also been reported in clinical trials testing. This fungus is considered to be a miracle mushroom [19].

2.8 *Fomitopsis officinalis*

This is a bracket fungus, commonly known as white agaric, agaric, puring agaric, and larch agaric [21, 46]. Apart from its medicinal properties, it is also known to be used as tinder and with the common names as tinder and touchwood [17]. This species is considered as the oldest traditional medicinal mushroom in Asia that has been used by both the Greeks and Romans. It was used in ancient times as an antidote for poisoning [36]. In the past century, it was recorded for use as a laxative, in preventing flatulence and to treat the intestine of worms and parasites [53]. It has contributed to Africa and the tropics for the successful treatment of malaria. Just prior to the mid-twentieth century, it was still used as a tonic for bronchial asthma and night sweats in tuberculosis patients [48, 55]. *Fomitopsis officinalis* is illustrated in **Figure 9**.

Fomitopsis officinalis species are among the most studied species for their medicinal properties. Although bioactivity studies for disease treatment have been done in most

Figure 9.
Fomitopsis officinalis *(White agaric) [30].*

cases this species is not highly recognized to be of pharmaceutical importance for the treatment of the diseases studied and therefore not approved by the FDA [21]. In addition, for its use as dietary supplement/nutraceuticals more research is needed before a strong consideration for use as a supplement, as some species have been reported to show toxicity if consumed more than the recommended established doses [34].

2.9 *Pleurotus ostreatus*

Pleurotus ostreatus, commonly called the oyster mushroom, oyster fungus, or hiratake, is a widely consumed edible mushroom [63]. It was first cultivated in Germany in subsistence farming to support food sources for the population during the World wars [63], and is currently widely cultivated on a commercial large-scale production worldwide for sustainable food production. It is closely related to the widely cultivated king oyster mushroom. This species of mushrooms is industrially used for mycoremediation purposes [9, 64]. The oyster mushroom is considered as one of the most widely sought-after wild mushrooms, even though they are highly cultivated on straw and other substrate media. It produces the bittersweet aroma of benzaldehyde, which is a characteristic of bitter almonds [15, 65]. The species of Pleurotus are shown in **Figure 10**.

The gastronomic effects are described by the addition of either the dried fruiting bodies of the oyster fungus *P. ostreatus*, or the ethanolic extract, to the diet of normal Wistar male rats and a strain with hereditary hyper-cholesterolemia. The addition of the dry oyster fungus to the diet is linked to a two-fold significant increase of the triacylglycerol (TAG) level in the plasma of both treatment groups of rats when

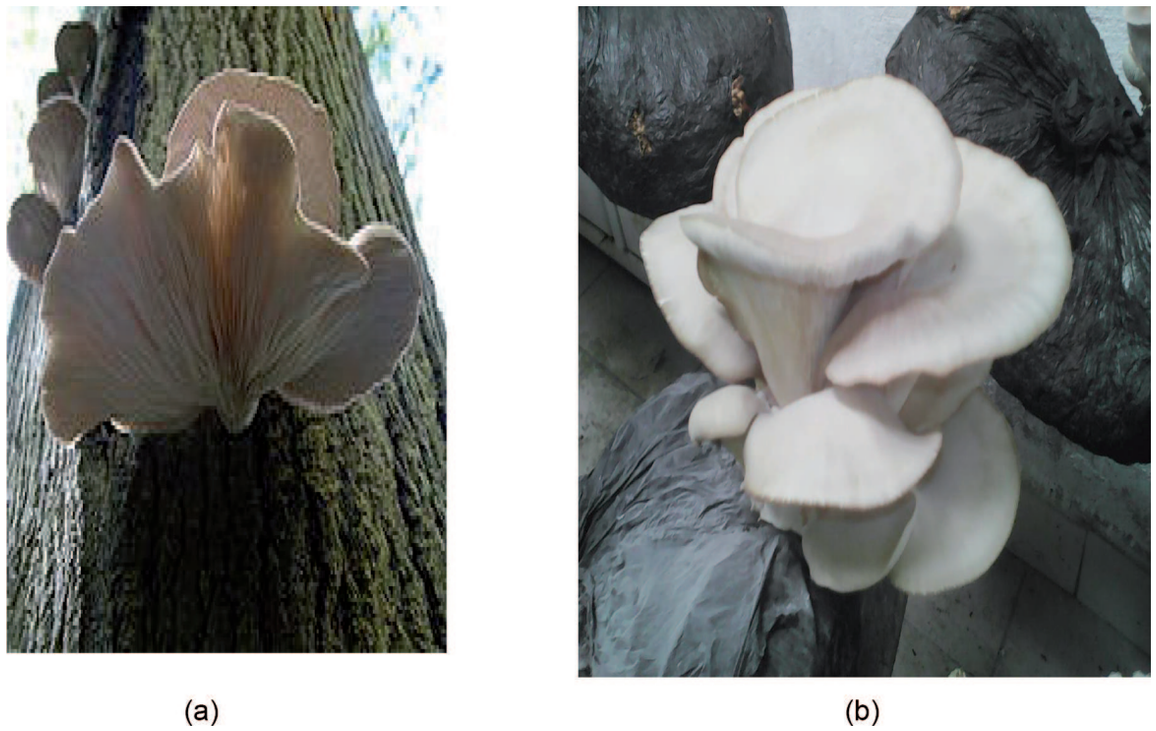

Figure 10.
(a) Pleurotus ostreatus *growing on a tree trunk. (b)* Pleurotus ostreatus *cultivated in Cameroon.*

compared with their respective controls [66–68]. On the contrary, the ethanolic extract alone did not significantly increase TAG levels. There was no significant change for total cholesterol and its high- and low-density lipoprotein fractions in the plasma, as well as the calculated atherogenic index.

3. Carnivorous fungi

They are fungi that are able to obtain most of their nutrients from trapping and eating microscopic animals [69]. They can develop a strong carnivorous feeding mechanism, and more than 200 species are well studied and documented. They belong to either the phyla Ascomycota, Mucoromycotina, or basidiomycota [70]. They are soil-dwelling mycorrhizal fungi and many species are capable of trapping the soil nematodes (nematophagous fungus), while others can invade amoeba or collembola [66].

This group of fungi species can grow on the epidermis, hair, skin, nails, or feathers of living or dead animals and thus known as dermatophytes instead of carnivores. Furthermore, fungi in orifices and the digestive tract of animals are neither carnivorous in nature, nor considered as internal pathogens [71]. The insects' pathogens that invade and colonize insects are called carnivorous if the fungal thallus is mainly in the insect as in the case of Cordyceps, or if it attaches to the insect-like in the case of the Laboulbeniales [72].

3.1 Common toxic mushrooms

Most common mushroom species, such as *Amanita phalloides*, produce bioactive compounds that are toxic in nature, antibiotic, antiviral, hallucinating, or have the bioluminescent potential [73]. Although only a small number of deadly species have

been reported, several other mushrooms have the potential to cause serious and unpleasant adverse effects. Mushroom toxicity can play a role in the protection of the function of the basidiocarp and the mycelium can possess considerable energy and protoplasmic material to develop a structure for spore distribution efficiency [42]. One major setback for the consumption of mushrooms is the production of toxins that makes the mushroom not suitable for consumption, by either causing side effects or symptoms like vomiting after the meal [74]. In addition, a report in 2008, on the ability of mushrooms to absorb heavy metals, radioactive substances, is an indication that some European mushrooms may have included toxicity from the 1986 Chernobyl disaster and many studies are still in progress [23].

3.2 Psychoactive mushrooms

Most mushrooms with psychoactive activities are known to play a vital role in traditional folk medicine worldwide. Psychoactive mushrooms have been used as a sacrament in rituals for mental and physical healing, and to facilitate visionary functions [24, 75]. One such ritual practice is the velada ceremony. A tradi-practitioner of mushroom use is called the *shaman* or *curandera* associated with a priest healer [76]. An example of a psychoactive mushroom *Psilocybe zapotecorum*, a hallucinating mushroom, is shown in **Figure 11**.

The Psilocybin mushrooms are also referred to as psychedelic mushrooms possessing psychedelic activity known as "magic mushrooms" or "shrooms." They are widely available in smart shops worldwide, or on the black market in countries that have outlawed their sale [11, 76]. Psilocybin mushrooms have been reported to facilitate a profound and life-changing effect often referred to as mystical experiences. Some scientific works have backed up these claims, as well as the long-lasting effects of the induced spiritual experiences [24, 77]. There are more than 100 psychoactive mushroom species of genus Psilocybe distributed worldwide. Psilocybin, a naturally occurring chemical in certain psychedelic mushrooms such as *Psilocybe cubensis*, has been studied for its ability in the treatment of psychological disorders, such as obsessive-compulsive disorder [77]. Small amounts have been shown to inhibit migraine headaches [78]. A double-blind study, done by the Johns Hopkins Hospital, showed psychedelic mushrooms promising potential to provide people an experience with substantial personal meaning and spiritual

Figure 11.
Psilocybe zapotecorum *(hallucinogenic mushroom) [23].*

Species	Compound/derivative	Targets/mechanisms of action	Cancer types affected	Experimental models	References
Fomitopsis pinicola	Methanol extract	Cytotoxicity	Hepatocarcinoma, cervical cancer	Cell lines	[24]
	Chloroform extract	ROS-mediated apoptosis	Colorectal cancer	Cell lines	[14]
		Metalloproteinase-mediated migration inhibition	Colorectal cancer	Cell lines	[35]
	Ergosterol	ROS-mediated apoptosis	Colorectal cancer	Cell lines	[14, 70]
	Ethanol extract	Tumor growth arrest	Sarcoma	Mouse xenograft tumors	[9]
Hericium erinaceus	Ethanol extract	Tumor growth arrest	Gastric, liver, colon cancer	Cell lines, mouse xenograft tumors	[70]
	Water extract	Metalloproteinasemediated migration inhibition, suppression of ERK and JNK kinase activation	Colon carcinoma	Mouse xenograft tumors	[11, 45]
		NK cells and macrophages stimulation, arrest of angiogenesis	Colon carcinoma	Mouse xenograft tumors	[72]
		Apoptosis via downregulation of antiapoptotic proteins	Leukemia	Cell lines	[21]
	Polysaccharides	Immunostimulation,	—	Mouse models	[45]
	Erinacine A (ditherpenoid)		Gastrointestinal	Cell lines, mouse xenograft tumors	[21]
		ROS-mediated cell cycle cancer, colorectal arrest cancer antiinvasive			
	Cerebroside E	Angiogenesis blocker		HUVEC cell line	[58]
	HEP3 protein	Immuno-stimulation via adenocarcinoma gut microbiota		Mouse xenograft tumors	[73]
	HEG-5 glycoprotein	Proapoptotic stimulation	gastric cancer	Cell lines	[47]
	Ethanol extract	Gastric ulcer cytoprotective (carcinogenic condition)		Rat model	[52]

Species	Compound/derivative	Targets/mechanisms of action	Cancer types affected	Experimental models	References
	1-(5-chloro-2-hydroxyphenyl)-3-methyl-1-butanone,2,5-bis(methoxycarbonyl) terephthalic acid	Gastric ulcer *Helicobacter pylori* (carcinogenic growth inhibition condition)		*In vitro* bacterial growth models	[13]
Inonotus obliquus	Water extracts	Colon cancer, cytotoxic/cytostatic liver cancer		Cell lines	[40]

Table 2.
The metabolites found in medicinal mushrooms and their therapeutic potential against cancer.

significance. In the study, one-third of the volunteers reported that the ingestion of psychedelic mushrooms was the single most spiritually significant event of their lives [79].

3.3 Mushroom bioactive metabolites of therapeutic potential

Potential bioactive metabolites studied in medicinal mushrooms and their therapeutic potential against cancer are illustrated in **Table 2**. Secondary metabolites of higher fungi (mushrooms) are an underexplored resource compared to plant-derived secondary metabolites. An increasing interest in mushroom natural products has been noted in recent years [34, 80]. The divergent biosynthetic pathways from farnesyl pyrophosphate to sesquiterpenoids are also described. Selected triterpenoids with novel structures and promising biological activities, including lanostanes and ergostanes, ergosterol are reported from the genus Ganoderma, and the fungi *Antrodia cinnamomea* and *Poria cocos* [81].

4. Therapeutic potential of mushrooms

The major importance of mushrooms is attributed to their medicinal potential that has generated a lot of research interest on a global scale. The great pharmacological and physiological properties of mushrooms are linked to the immune enhancement, maintenance of homeostasis and regulation of biorhythm, management, and prevention of various diseases, quality of life improvement from life-threatening diseases, such as cancer and cardiovascular diseases [19, 27, 82]. Many activities of mushrooms have been reported, such as hypotensive and renal effects [ref], immunomodulatory and antitumor properties of polysaccharide-protein complex (PSPC) from mycelial cultures [9, 14] immunomodulatory and antitumor activities of lectins from edible mushrooms. Due to the great potential benefits of mushrooms to humans, many scientific publications are available to the extent that a database of scientific evidence is available about the specific health effects of mushrooms and their bioactive molecules. These potential benefits include the following:

4.1 Pharmacological properties of mushrooms

4.1.1 Antioxidant property of medicinal mushrooms

The reactive oxygen (ROS) and reactive nitrogen species (RNS) produced from the normal cellular metabolism are generally very reactive as studied for most organic compounds, [11, 33]. They could have either adverse or beneficial effects on living or biological systems [80]. ROS are free radicals made of atoms or molecular fragments with one or more unpaired electrons in their atomic or molecular orbitals [33, 83]. They are naturally produced in the body, especially in organelles like the mitochondria, as intermediates in a variety of normal biochemical and physiological processes, contributing a significant role in many normal cellular processes [30]. However, at high doses, ROS and RNS contribute to the oxidative damage of biological macromolecules, such as DNA, proteins, and lipids of the cell membranes. The damage to cells initiated by the free radicals, especially the damage to DNA, may lead to a significant development of many diseases, such as cancer and other metabolic disorders [22, 69].

Free-radical scavengers are chemicals with the potential to react with free radicals and then neutralize them, thus reducing the damages caused by those

reactive species [55]. Most living body cells produce antioxidant and repair systems that can protect the body against oxidative damage; however, these substances are not enough to prevent or repair the damage completely [30]. The body, therefore, requires the introduction of more antioxidant agents from the diet, which is fundamental for maintaining cell homeostasis and a stable a healthy organism [84]. Although synthetic antioxidants, such as butylhydroxytoluene (BHT), propyl gallate (PG) butylhydroxyanisole (BHA), and *tert*-butylhydroquinone (TBHQ), have been generally used as antioxidant additives in foods for many years, their safety has always been of great public health concern [38], the reason for increased interest in natural antioxidants research.

Many researchers have studied antioxidant activities on extracts and isolated secondary metabolites from edible mushrooms using different tests *in vitro* to evaluate the total antioxidant activity, lipid peroxide inhibitory property, reducing power capacity, the 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity, hydroxyl radical scavenging properties, the ferric reducing antioxidant power, the nitric oxide (NO) scavenging activity, and the ABTS radical scavenging, and the superoxide radical, [13, 49]. A large number of results in the data mining, therefore, clearly indicates that several edible mushrooms have significant antioxidant properties due to their bioactive metabolites, such as polyphenols, polysaccharides, carotenoids, vitamins, and minerals nutrients [11, 19, 53].

4.1.2 Hypocholesterolemic effects

One of the common metabolic disorders such as cardiovascular disease is associated with atherosclerosis, low-density lipid (LDL) oxidation, and hypercholesterolemia, play a role in the regulation of the cholesterol level which is vital for the prevention and treatment of this disease [42, 83]. Edible mushrooms are important food for the management of atherosclerosis due to their high fiber content and low-fat content [16]. In addition, the incorporation of edible mushrooms in a natural hypocholesterolemic and anterosclerotic diet is commonly used in traditional medicine [85]. Studies on the cholesterol-lowering activities of mushrooms were studied in Japan in the early 1960s, and it was demonstrated that rats fed with high fat and high-cholesterol diet supplemented with 5% water of the fruiting bodies of *Lentinus. edodes* for 10 weeks, had a significant dose-dependent decrease in plasma cholesterol concentrations of the animals [31, 82]. The adenosine derivative lentinacin or lentysine, also known as eritadenine [2(R), 3(R)-dihydroxy-4-(9-adenyl)-butyric acid, was later isolated and identified to be one of the active hypocholesterolemic secondary metabolites in the shiitake mushroom [86]. Studies also showed that Eritadenine has been shown to reduce the serum cholesterol level in mice by the acceleration of the excretion of ingested cholesterol and its metabolic breakdown [9, 17, 86]. Eritadenine affects the metabolism of cholesterol, phospholipids, and fatty acids in rats [87]. The dietary supplementation of eritadenine is also considered to decrease phosphatidylcholine biosynthesis through the alteration of the phosphatidylethanolamine concentration [47, 88].

4.1.3 Mushrooms as hypoglycemic agents

Advanced research for traditional plant treatments for diabetes has shown that identified edible mushrooms are an ideal food for the dietetic prevention of hyperglycemia due to their high dietary fiber and protein and low-fat content [69, 89]. Studies have been conducted on the hypoglycemic activity of whole mushrooms and their

fruiting bodies and on mushroom bioactive molecules, including polysaccharides [24] and lectins [90] isolated from the fruiting bodies. In addition, the endo and exopolymers produced in submerged mycelial cultures have been reported to have a hypoglycemic effect [91]. The most common widely used animal models for the study of the hypoglycemic effects of mushrooms are rats and mice with insulin-dependent diabetes mellitus (IDDM), induced by streptozotocin (STZ), and genetically modified diabetic mice with non-insulin [13, 92].

4.1.4 Anticancer activity of mushroom steroids, phenols, and dietary fiber

Within the group of mushroom steroids, the glycosylated form of ergosterol peroxide obtained from the methanol extract of *Cordyceps sinensis* has been shown to be an inhibitor of the proliferation of cell lines, such as the WM-1341, HL-60, K562, Jurkat, and RPMI-8226 tumor cell lines [22, 93]. Anticancer sterol from *Sarcodon aspratus* shows inhibition of the growth of HT29 cancer cells, but not the WI38 normal human fibroblasts [48]. Studies on the anticancer mechanism have indicated that the sterol can induce expression of the cyclin-dependent kinase inhibitor 1A, thereby causing cell cycle arrest and apoptosis in HT29 cells [41, 78, 94]. Phenols can also show anticancer activity as a preventive agent with antioxidant activities that can trigger direct cytotoxicity on cancer cells. Quantitative and qualitative analysis of mushroom mycelia depends on various cultivation conditions, especially considering the substrate for cultivation. Synthetic culture media are known to suppress the generation of important secondary metabolites [50]. Consequently, there is the need for the selection of the most suitable cultivation media for obtaining the most active secondary metabolites of fungal mycelia [51]. **Table 3** illustrates mushroom antitumor polysaccharides and polysaccharide-protein complexes that have progressed to clinical trials studies.

4.1.5 Antiviral properties of mushrooms

Diseases caused by viruses are not treated by common antibiotics and therefore require target-specific drugs. Antiviral properties have been studied not only for whole extracts of mushrooms but also for isolated secondary metabolites derived compounds. These antiviral compounds may act directly through the inhibition of viral enzymes, synthesis of viral nucleic acids, or adsorption and uptake of viruses into the mammalian cells [87, 95]. The direct antiviral activities are effectively demonstrated by smaller molecules. Indirect antiviral activities are due to the immune-stimulating

Taxa origin of isolation	Trade name	Chemical structure	Reference
Grifola frondosa	Fruiting bodies and mycelium polysaccharopeptide (PSP)	D and MD fractions β-D-glucan	[7]
Lentinus edodes	Fruiting bodies polysaccharide krestin (PSK)	Lentinan β-D-glucan	[8]
Trametes versicolor	Mycelial mass PSP, PSK (krestin)	Polysaccharide protein complexes	Polysaccharide protein complexes
Schizophyllum commune	Cultured media broth	Schizophyllan β-D-glucan	[8]

Table 3.
Mushroom antitumor polysaccharide and polysaccharide-protein complexes that have passed clinical trials.

activity of polysaccharides or other complex compounds [33]. Small molecular bioactive compounds with antiviral properties, several triterpenes from *Ganoderma lucidum* such as ganoderiol F, ganodermanontriol, ganoderic acid B, all act as antiviral agents against human immunodeficiency virus IHIV) type 1 (HIV-1) [9, 51, 82]. *In vitro* antiviral activity for influenza viruses type A and B was shown for mycelial extracts of *Kuehneromyces mutabilis* [14], and two isolated phenolic compounds from *Inonotus hispidus* [64, 96] and also ergosterol peroxide identified in several mushrooms.

4.1.6 Mushrooms as antibacterial and antifungal agents

Mushrooms are capable of producing antibacterial and antifungal secondary bioactive compounds as an adaptive defense system to survive in their natural environment. Therefore, they are potential sources of natural antibiotics and many of the external bioactive compounds from extracellular secretions by the mycelium, that can inhibit bacteria [72, 99] and viruses [3, 19]. Several metabolites compounds extracted from mushrooms have been demonstrated to have antifungal and antibacterial properties, especially against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* [24, 49, 79]. The European-derived *Ganoderma* species, *Ganoderma pfeifferi* are known to inhibit the growth of methicillin-resistant *S. aureus* and other bacteria by a new compound sesquiterpenoid hydroquinones [19]. It has also been demonstrated that whole aqueous extracts of this mushroom can inhibit the growth of microorganisms linked to skin problems, such as *Staphylococcus epidermidis*, *Pityrosporum ovale*, and *Propionibacterium acnes* [33].

Infectious diseases caused by microorganisms, such as bacteria, viruses, fungi, or parasites, are among the most serious agents of global morbidity and mortality [23]. Currently, many pathogenic infections are often caused by multi-resistant microorganisms resulting in disease resistance and difficulty for drug therapy; with a well-known example like coronavirus (COVID-19), which is the latest pandemic killing millions of people worldwide. Consequently, the pharmacoeconomic of healthcare costs are on a rapid increase, and of public health concern in many countries [9, 24]. This pandemic situation has led to an increasing search for new chemical entities (lead compounds) of antimicrobial agents from different sources. Several researchers have studied the antimicrobial potential of natural or synthetic compounds of pharmaceutical importance [27]. Thus, natural sources of bioactive compounds mushrooms, are constantly on investigation for finding novel antimicrobial bioactive compounds [23, 38].

In the food industry, contaminants by bacteria and fungi may be a result of exposure to sources of contamination during post-harvest processing (harvesting, processing, and/or packaging process) [12, 64]. Food additives are now widely used in the food industries to enhance and increase the shelf life of food and to prevent the optimal proliferation conditions of microorganisms [14]. It is for this reason that natural antimicrobials, including those isolated from mushrooms, are increasingly popular as potential alternatives to synthetic preservatives, whose safety and impact on human health are still challenging [19, 78]. However, proof of the safety of many natural antimicrobials has been generally recognized in Europe, USA, and in Asia as opposed to sub-Saharan Africa where research is limited [34, 72].

4.1.7 Mushrooms as anti-inflammatory agents

Studies on the ethanolic extracts and a proteoglycan from *P. linteus* have shown potential anti-inflammatory activity some *in vitro* tests, such as in the

collagen-induced arthritis, the croton oil-induced ear edema test in mice, and antinociceptive effect in the writhing test [69, 71, 83]. Other bioactive compounds effectively elucidated in the writhing test include the ganoderic acids A, B, G, and H, isolated from *G. lucidum*. These compounds demonstrated a stronger anti-inflammatory activity in the animal model than acetylsalicylic acid [12, 45]. Methanolic extract of *Pleurotus pulmonarius* fruiting bodies at doses (500 and 1000 mg/kg) reduced carrageenan-induced and formalin-induced paw edema in mice. The activity was comparable to the reference diclofenac (10 mg/kg). The IC50 value for hydroxyl-radical scavenging was recorded as 476 mg/ml and for lipid peroxidation inhibition 960 mg/ml [11, 89]. The edible mushroom *Gaylussacia frondosa* is known to contain ergosterol, ergosta-4-6-8, 22-tetraen3-one, and 1-oleoyl-2-linoleoyl-3-palmitoylglycerol, which can potentially inhibit cyclooxygenases I and II activity [76].

4.1.8 Mushrooms as hepatoprotective agents

Early studies on bioactive compounds, ganoderic acids R and S and ganosporeric acid A from *Gonaderma lucidum* have shown *in vitro* antihepatotoxic activity in the galactosamine-induced cytotoxic test using primary cell-cultured rat hepatocytes [2, 44]. Further *in vivo* study of two fractions of total triterpenoids extract of *G. lucidum* (75% ethanol) demonstrated a protective activity in mice against hepatic necrosis induced by chloroform and D-galactosamine, respectively. The hepatoprotective properties were more associated with the scavenging promoting capacity of enzymes for hepatic free radicals in mice, and hence the increase in the antioxidant activity in mice [44, 45]. In addition to the widely investigated psychoactive mushrooms like *Amanita muscaria* or *Psilocybe* spp., some bioactive compounds mushroom extracts have shown special central nervous effects of pharmacological interest. Phenol-analogous compounds like (hericenons C, D, E, F, G, H) from *Holothuria erinaceus* are capable of inducing the synthesis of nerve growth factors, potential improved effect in Alzheimer's dementia [48]. Erinacin E from *Hericium coralloides* fermentation broth is a highly selective agonist at the kappa opioid receptor with (IC50 of 0.8 mM, receptor binding at the m opioid receptor with an I 50 of >200 mM). These metabolites could exhibit antinociceptive activity without little side effects observed with m receptor agonists like morphine [35]. Biochemical screening of selected basidiomycetes has shown inhibitory effects of *G. applanatum*, *H. annosum*, *P. betulinus*, *Fomitopsis pinicola*, and *Daedaleopsis confragosa* on neutral endopeptidase (enkephalinase) (IC50 values between 40 and 55 mg/ml) [93].

4.1.9 New approaches for cancer therapy with mushroom bioactive compounds (vaccinotherapy)

Vaccine preparations with preventive activities against liver and cervical cancer associated with hepatitis B and human papillomatosis infections have been developed in Belgium and USA [66]. Currently, there is no commercialized vaccine for the protection of existing tumors, metastases, or relapses [3, 19]. The addition of immunomodulating substances of natural and synthetic origin to vaccines has shown promising potential to sufficiently enhance their anticancer properties. Therefore,

there were high doses and schemes of *L. edodes* polysaccharide fraction administration in combination with a vaccine based on autological glycopeptides of Ehrlich's carcinoma, Sarcoma 37, LLC, L1210, and B16 cell lines [66]. Such preparations were prepared to improve the cytolytic activity of lymphocytes, the metabolic activity of peritoneal macrophages, and the cytolytic activation of blood plasma serum in the presence of complement in intact animals and in sarcoma-bearing animals [3, 47]. The recent identification of an immunomodulating protein Ling Zhi-8 has been reported from mycelia of *G. lucidum* with stimulatory activity on dendritic cells [67]. Industrial amplification of recombinant protein Ling Zhi-8 has been elucidated using a well-developed patented yeast system.

5. Mushroom toxicity

Since prehistoric times humans have heavily consumed mushrooms for nutritional and therapeutic use. Mushroom toxicity has also been known since man started the consumption of mushrooms, and has been the cause of death of many historical figures, including the Roman Emperor Claudius [3, 77]. Currently, several mushrooms are cultivated commercially, but foraging for mushrooms has gained popularity as a form of recreational activity in the community. Mushroom poisonings increasingly are common due to a lack of knowledge by foragers to identify and distinguish a poisonous mushroom species from edible species, and in some cases, problems occur as intentional ingestions [9, 31, 86]. Mushroom poisonings may an indication from a benign symptom of generalized gastrointestinal upset to very devastating outcomes that include liver failure, kidney failure, and neurologic disorders. Up to 14 described syndromes are documented, which manifest depending on the mushroom species, toxins, and quantity ingested [11, 94]. The mushroom poisoning symptoms are related to the toxin ingested, which include amatoxin, psilocybin, muscarine, coprine, allenic norleucine, gyromitrin, etc. [3, 7, 89]. Within the several mushroom species, there are about 100 species that are toxic in nature. Annual ingestion is recorded at a level of about 6000 ingestions yearly alone in the United States, and out of these, over 50% of the exposures are pediatric in nature, recorded in children under 6 years of age [88]. Most poisonings exhibit symptoms mainly of gastrointestinal upset, which is a common feature across several toxidromes, and this is most likely to occur with ingestions of small quantities of toxic mushrooms. Severe mushroom poisonings that take place, are primarily a consequence of misidentification by adults foraging for wild mushrooms who consume them as food [3, 14]. A summary table of Mushroom toxicity effects, symptoms, and examples of Mushrooms having the toxin has been illustrated in **Table 4**.

5.1 Pathophysiology of mushroom poisoning

The clinical presentation differs depending on the species of mushroom and toxin ingested. For **Acute gastroenteritis**: Most often secondary to one of a variety of "backyard mushrooms" such as *Chlorophyllum molybdites*. In most cases are developing symptoms of nausea, vomiting, gastrointestinal upset like abdominal cramping and possibly diarrhea associated with ingestion accounting for most of the reported poisonings [31, 90]. The symptoms of poisoning are manifested usually or typically within 1–3 hours of ingestion [3].

Class of toxins	Toxicity	Effects and examples of mushrooms having the toxin
Alpha-amanitin	Death	Main causes of fatal liver damage a day after ingestion. The principal toxin is the death cap (*Amanita phalloides*)
Phallotoxin	Non-lethal	Main cause of the severe gastrointestinal disorder. Common in most mushrooms eg *Gomphus automnalis*
Orellanine	Deadly	A redox cycler similar to pesticide paraquat. Main cause of kidney failure mostly 3 weeks after ingestion. Principal example is the genus Continarius
Monomethylhydrazine (MMH)	Deadly	Causes brain damage, seizures, gastrointestinal disorder, hemolysis. And metabolic poison. Principal toxin associated in genus Gyromitra. Antidote is administration of large doses of intravenous pyridoxine hydrochloride
Coprine	Not lethal	Causes adverse effects when consumed in combination with alcohol. Principal toxin in genus is coprinus
Ibotenic acid	Potentially lethal	Excitotoxin. Principal toxin in *Amanita muscarin*. *A pantherina*. *A gemmata*
Muscimol	Phytoactive	Causes central nervous depression and hallucination. Principal toxin in *Amanita muscaria*, *A pahtherina*, and *A gemmate*.
Psilocybin and psilocin	Phytoactive	Causes CNS activation and hallucinations. Principal side effects are from psilocybin mushrooms, many of which belong to the genus Psilocybin (often used as recreational drugs
Arabitol	Non-lethal	Causes diarrheal in some subjects.
Bolestatine	Non-lethal	Causes stomach upset, nausea and vomiting.
Ergotamine	Deadly	Affect the vascular system and can lead to loss of limb, cardiac arrest. Found in the genus Claviceps.

Table 4.
Of mushroom toxicity effects, symptoms, and examples of mushrooms having the toxin [12, 86, 95].

Hallucinations: The main cause is produced by the bioactive compounds from psilocybin and psilocin from the mushroom species such as *Psilocybe*, *Conocybe*, *Gymnopilus*, and *Panaeolus*. These chemically bioactive compounds act as agonists or partial agonists at 5-hydroxytryptamine (5-HT) subtype receptors [19, 40]. These species of mushrooms are cultivated for recreational purposes as substances of abuse, although they can grow naturally in warm, moist climates. The mushroom can be ingested as fresh mushroom caps or dried mushrooms preparations and can cause altered sensorium and euphoria occurring 30 minutes to 2 hours after ingestion that can last for about 4–12 hours, depending on the quantity ingested [24].

Cholinergic toxicity: This is caused by muscarine-containing mushroom in the genera *Clitocybe* and *Inocybe*. *Amanita muscari* contains small amounts of muscarine, but the concentrations are generally low to cause a cholinergic effect. Cholinergic effects, however, of diaphoresis, salivation, lacrimation, bronchospasm, abdominal cramping, bronchorrhea, and bradycardia generally may occur within 30 minutes of ingestion, and the duration is dose-dependent and usually short-lived as compared to other pesticide-related cholinergic poisoning [95].

Disulfiram-like reaction: Caused by coprine-containing species such as *Coprinus atramentarius*, known as inky cap mushrooms. The toxin's bioactive metabolites can result in the inhibition of aldehyde dehydrogenase causing headache, nausea,

vomiting, flushing, tachycardia, and in rare cases hypotension. The adverse effect is very obvious and only occurs in cases where alcohol is ingested a few hours to days after the consumption of coprine-containing mushrooms. Co-ingestion of alcohol and the toxin can lead to reduced toxic effects due to slower metabolism of coprine to its toxic secondary metabolites [8, 15].

5.2 Mushroom liver toxicity

Toxicity from different species can be caused by amatoxin observed in species like *Galerina*, *Lepiota* and particularly *Amanita* [41]. The toxins can disrupt RNA polymerase II, resulting in cellular level protein deficiency. The toxicity consists of three distinct phases. Gastrointestinal effects can be observed typically 6–12 hours after ingestion, followed by a quiescent phase of 24–36 hours after ingestion with a symptomatic improvement [8, 14, 69]. During the quiescent phase, there may be clinical signs of hepatotoxicity. After 48 hours of ingestion, hepatic damage increases, leading to liver failure and other related clinical complications. Lethal occurrence recorded in mushroom toxicity may occur within a week in severe cases or require liver transplantation.

5.3 Nephrotoxicity

Nephrotoxic agent orellanine is produced by the genus *Cortinarius* producing renal complications in which the symptoms may be delayed for 1–2 weeks after ingestion [75]. Nephrotoxicity can lead to the production of allenic norleucine usually observed in *Amanita smithiana*, but this can also be seen in other *Amanita* species. *Amanita smithiana* is well distributed in the United States [94], and their typical toxic symptoms include acute gastroenteritis leading to renal injury within 12–24 hours. Although some subjects with toxicity may require hemodialysis, in most patient's full recovery with appropriate supportive care is possible [8, 27]. Cases of seizures can be due to the presence of gyromitrin in *Gyromitra*, *Paxina*, and *Cyathipodia micropus* species, although can be less common in the latter two. Mushroom foragers in search for morel (*Morchella esculenta*) may accidentally ingest *Gyromitra* and toxicity could result from a metabolite, monomethylhydrazine, that may potentially lead to secondary product pyridoxine (B6) and up with GABA depletion. With GABA depletion, the occurrence of seizures may be intractable to anticonvulsant therapy and may require supplemental treatment including pyridoxine [78, 82].

Other manifestations due to the wide range of mushrooms that foragers could accidentally several other clinical manifestations have been documented and reported such as vertigo, somnolence, headaches, palpitations, dysrhythmias, rhabdomyolysis (*Tricholoma equestre*), methemoglobinemia, hemolysis (*Paxillus involutus*), erythromelalgia (acromelic acid), dermatitis (shiitake mushrooms), and cramping [4, 22, 55].

5.4 Toxicity evaluation, treatment, and management

Toxicity evaluation is usually guided by many regulatory and clinical presentations, and may include:

Systematic and regular observation without testing in asymptomatic low-risk subjects, Serum electrolytes, kidney function testing, urinalysis, Serum creatinine kinase (CK), Liver enzymes, coagulation analysis, and complete blood count study

[37, 44, 91]. In critical highly symptomatic subjects, target specific studies based on the symptoms of hepatic failure, altered mental status, hypoxia or respiratory distress can be performed [44]. Treatment of many possible symptoms mainly consists of supportive care. Depending on the period or time of ingestion, activated charcoal or chelating agents may be used for clinical intervention to provide some health benefit [82]. Acute gastrointestinal manifestation may benefit from rehydration and antiemetics in response to correction of any electrolyte imbalance [12, 20, 92]. For most patients showing adverse hallucinations, benzodiazepines administration may provide anxiolysis. Cholinergic toxicity may be managed from the administration of anticholinergic agents such as glycopyrrolate or atropine [76], with consideration of the administration of Atropine 0.5–1 mg IV adults or 0.01 mg/kg for cases of pediatric patients [29, 55].

In some specific cases, patients with refractory seizures due to gyromitra ingestion, administration of pyridoxine (B6) could be at 25 mg/kg IV can be given as treatment or as prophylactic for seizure control, or in some cases, benzodiazepines could be an alternative [21, 97] In case of patients ingesting amatoxin, consideration of the administration of N-acetylcysteine (NAC), silibinin, and penicillin can be used for treatment intervention. Clinical toxicologists and other health practitioners are advised to evaluate and manage patients in consultation with the local poison control (toxicovigilance center) or toxicology resource. Complications of ingestion depend on the toxin ingested and may range from dehydration in benign cases to renal failure, liver failure, and death in severe toxicities [89, 91]. Most mushroom poisonings result in mild to moderate gastrointestinal manifestations which include nausea, vomiting, and diarrhea. Other varieties of disorders that may lead to organ failure and even death her been reported and therefore it is important for foragers to know that there are many differing mushroom species with potential morphological similarities; very challenging in particular for those who are new in the mushroom collection as a new hobby. An understanding of local edible and toxic mushroom species is the key for amateur foragers, especially as the onset of just mild nausea will require evaluation as this could be an early manifestation of severe illness [3, 11].

5.5 Stages of amanita poisoning

Amatoxin poisoning and stages of pathology have four phases as described.

Phase 1: The latency or lag period that may occur within 10–12 hours after ingestion, with the toxins absorbed via the digestive system and subject to the assault of the kidneys and liver.

Phase 2: Gastrointestinal phase. This is the onset of symptoms like severe abdominal pains, nausea, vomiting, diarrhea, delirium, hallucinations, hypoglycemia, and life-threatening dehydration.

Phase 3: Manifestation of severe gastrointestinal complications, a brief remission of symptoms after 3–4 days. The onset of jaundice, renal failures, toxic hepatitis, liver enlargement, liver hemorrhage.

Phase 4: Manifestation of lethality. Death can occur within 6–8 days after ingestion as a result of liver and kidney failure, followed by cardiac dysfunction.

The main challenge for the treatment of mushroom poison is the fact that there is no known antidote. Therefore, an immediate evacuation of gastrointestinal tract fluids, hemodialysis, slurry of activated charcoal, supportive measures, and if all else

fails, administering a liver transplant can be timely [41, 50]. The use of thioctic acid in glucose delivered intravenously has been recommended by some experts. Bastien treatment like the use of vitamin C, nifuroxazide and dihydrostreptomycin, fluids, electrolytes, and penicillin are also applicable [89].

5.6 Chemical test for mushroom toxicity

The Meixner mushroom toxicity test can be used to determine whether a particular mushroom contains amatoxins. The stalk or cap is crushed to a piece of newsprint or other crude paper containing lignin. This crushed mass is allowed to dry and a small drop of concentrated hydrochloric acid is added. The presence of a blue color appearing in 5–10 minutes is an indication that amatoxins are present. This procedure involves an acid-catalyzed reaction of the lignin in the paper with the alpha amatoxin as the main structure as is well illustrated in **Figure 12** showing the structure of alpha amanita [5, 37, 40].

5.7 Orellanine poisoning and symptoms

Orellanine poisoning symptoms are similar to poisoning induced by amatoxins. However, muscular pain, excessive thirst, and painful urination may occur after 36 hours and could be delayed as long as 1–2 weeks after ingestion [86]. Orellanine invades and destroys the kidney tubules and in extremely severe cases, the treatment may require blood dialysis or kidney transplant. Lethalities in some cases have been

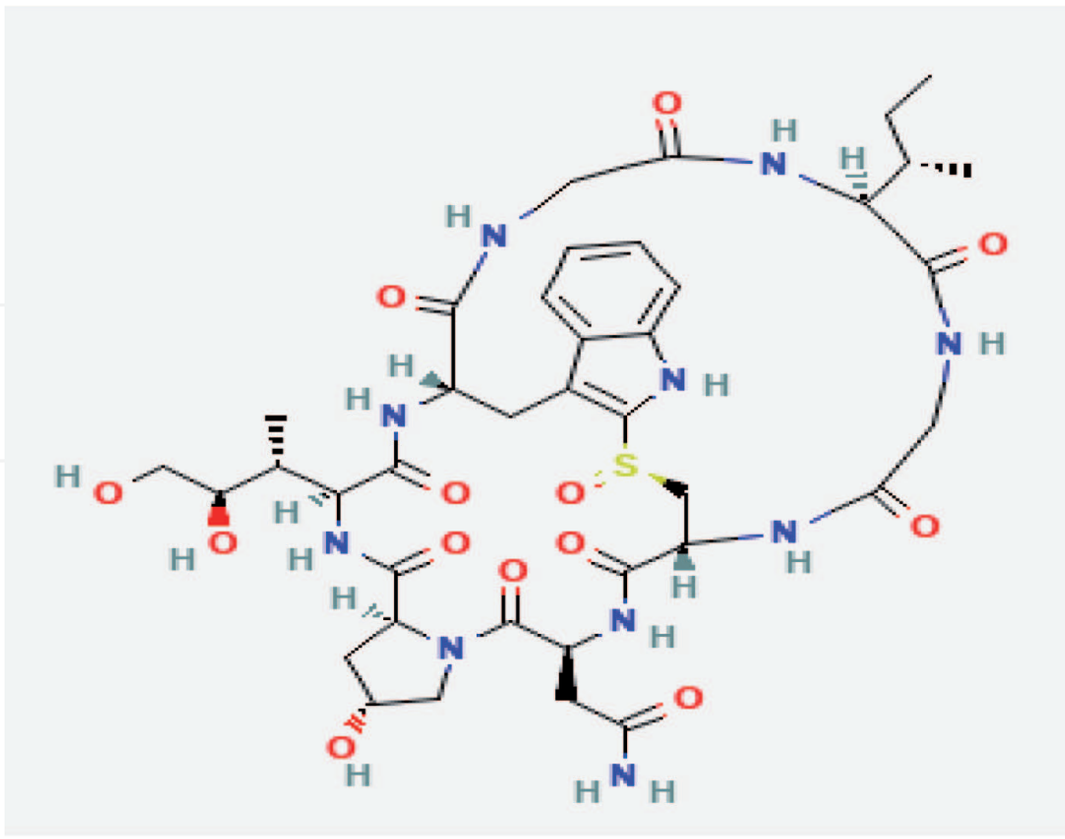

Figure 12.
Alpha amanitin (alpha-amanitin, 4-(2-mercapto-L-tryptophan)-(compound).

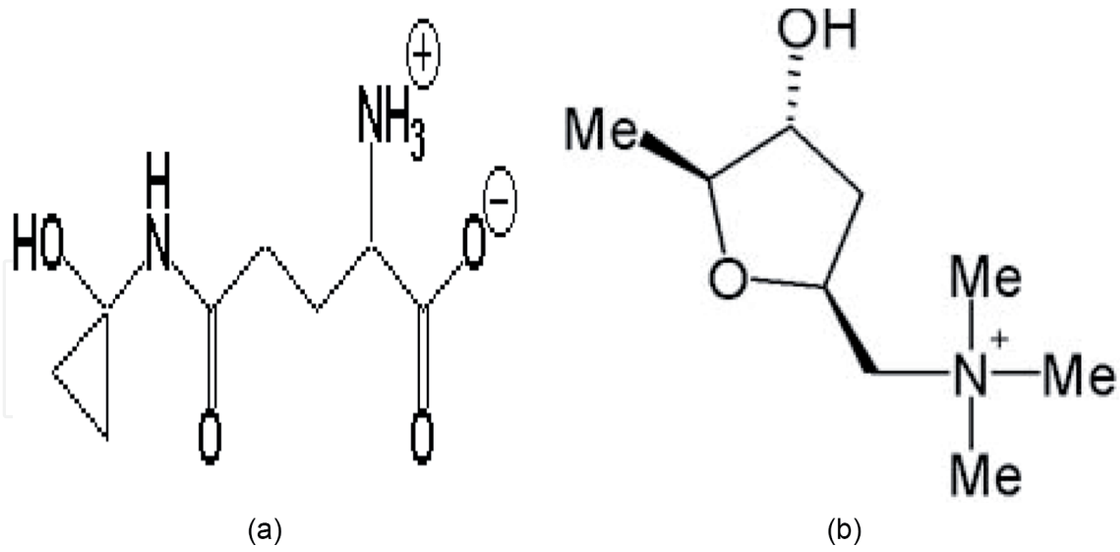

Figure 13
(a) A coprine (antabuse-like-disulfiram-like poisoning). *(b) Muscarine (me = methyl group –CH).*

reported, and therefore orellanine poisoning needs to be considered in cases when kidney failure occurs from an unknown cause. Toxic cyclopeptides from cortinarins may be present in some cases and could play a vital role in *Cortinarius* poisonings. There are about 800 recorded species of *Cortinarius* in North America, all of which are health risks for consumers. Mushrooms produced by members of the genus *Cortinarius* are characterized by the possession of a cobweb-like cortina that is the remnant of the partial veil covering the gills and potentially neurotoxic to the autonomic nervous system. Coprine structure of Antabuse-like disulfiram-like poisoning and muscarine are illustrated in **Figure 13a** and **b**.

5.8 Toxin found in certain species of *Coprinus*

Coprinus atramentarius also known as, *Coprinopsis atramentaria*, *Coprinus quadrifidus*, and the *Coprinopsis variegate* produce toxins that can bind to molybdenum and prevents normal acetaldehyde dehydrogenase activity, inhibiting ethanol metabolism [25]. Coprine poisoning is similar to acetaldehyde poisoning and symptoms begin 30 minutes to 1 hour after drinking alcohol when taken in 4–5 days after eating mushrooms or along with mushrooms. Symptoms include flushing of the neck and face, metallic taste in the mouth, tingling sensations in the limbs, numbness in the hands. Headache, throbbing of the neck veins, chest pains, nausea, vomiting, and sweating. Recovery from toxicity may be possible within several hours after ingestion [94].

5.9 Gastrointestinal irritants

Many varieties of undetermined toxins associated with wild mushrooms have been reported. On ingestion, the toxins may cause gastrointestinal disorders, such as nausea, vomiting, diarrhea, abdominal cramps that may occur after 30–90 minutes of ingestion. Symptoms generally may disappear spontaneously in 3–4 hours, and complete recovery can take place after 24 hours or more. Treatment strategy includes

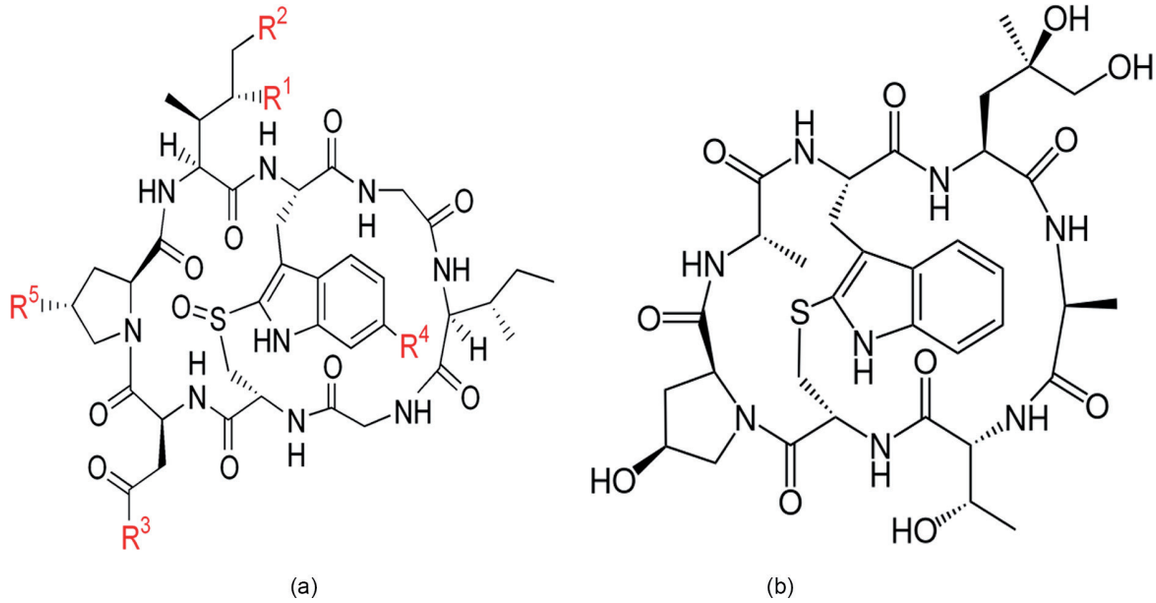

Figure 14.
Amatoxins and phallotoxins in toxic mushroom Amanita phalloides. (a) The backbone structure (black) is the same in all the amatoxins and five variable groups (red) determine the specific compound. (b) Phalliodin and Phallacidin constitute the main component structure of Phallotoxin.

emptying the stomach content, monitoring for possible dehydration, reduced blood pressure, and abnormal kidney function [17, 82].

6. Most common toxic mushrooms in Cameroon

In the forest of the Upper Nyong valley of Cameroon, some varieties of toxic mushrooms have been identified with other medicinal mushrooms. The intensive activities during the rain for mushroom harvesting come with accidental ingestion of toxic varieties, which can sometimes be fatal. Most cases of mushroom severe intoxication are linked to the dead cap mushrooms variety (*Amanita phalloides*), which is very toxic and quite common in the forests. Due to its high toxicity and common presence in our forests, *Amanita phalloides* is the most dangerous mushroom and the cause of the majority of fatal poisonings in Cameroon and the Centra African regions [14, 69]. Toxin compound amatoxins and phallotoxins are shown in **Figure 14**. A summary list of the most common toxic mushroom in Cameroon is illustrated in **Figure 15** as a guide to support mushroom foragers during field expeditions.

The list of most common toxic mushroom and edible species which they are often confused are indicated in **Figure 15**.

7. Conclusions

Mushroom is a very vital source of protein intake but some precautions should be taken for consumption and field identification of edible mushrooms. Those that cannot be identified or recognized properly should not be harvested and eaten. Cultivation of known species of mushrooms should be practiced so as to serve time

Figure 15.
The list of most common toxic mushroom and edible species which they are often confused. (a) Amanita phalloides. (b) Cortinarius orellanus. (c) Amanita verna. (d) Gyromitra esculenta. (e) Agaricus muscraris. (f) Amanita muscaria. (g) Omphalotus olearius. (h) Tricholoma pardinum. (i) Inocybe rimosa. (j) Lepiota brunneoincarnata. (k) Clitocybe dealbata. (l) Boletus satanas.

and avoid eating the poisonous ones and more advice must be taken by minors not to eat any mushrooms without showing it to parents or elderly person for proper recognition. Most mushrooms are consumed directly in different menus for healthy and medicinal purposes with contribution from their additive and synergistic effects of the bioactive compounds. The nutraceutical and therapeutic significance of mushrooms are well documented, although specific mechanisms of actions of the bioactive compounds and the many various health potentials to humans are still a subject of continuous research and intensive investigation, especially with the emergence of new technology and high throughput screening battery for new compounds, evaluation of pharmacological properties for documenting new findings of mushroom potential health benefits. The studies for the exploration of cultivated mushrooms

and isolation, chemical characterization of their secondary metabolites, and evaluation for pharmacological activities, with mechanistic based potential therapeutic evidence, is still a big challenge for researchers, and therefore mushrooms still remain an area of great research potential to generate more research interest in pharmaceutical and toxicity studies.

The complex pharmacologic and nutraceutical potential of mushrooms may be integrated not only through inhibition of certain cancer-specific processes or targeted activation of tumor-specific apoptosis, but also through indirect actions such as immunomodulation, hepatoprotection, and antioxidation. Another research dimension of mushrooms is in studying the mechanisms of action and targets of the natural products and their derivatives for different therapeutic endpoints for proof of concepts in phototherapeutics.

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Conflict of interest

The authors declare that there are no conflicts of interest between them for this manuscript.

Authors contribution

This work was carried out in collaboration among all authors. Author ETF, DJF FCN, MGA designed the study, TMV, LEA, and MEB conducted data mining and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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