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Review

Novel Perspective of Medicinal Mushroom Cultivations: A Review Case for 'Magic' Mushrooms

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Abstract: Fruiting bodies, mycelia, or spores in the form of extracts or powder of various medicinal mushrooms are used to prevent, treat, or cure a range of ailments and balance a healthy diet. Medicinal mushrooms are found in several genera of fungi and their fruit bodies, cultured mycelia, and cultured broth contains phytochemical constituents such as triterpenes, lectins, steroids, phenols, polyphenols, lactones, statins, alkaloids, and antibiotics. Edible mushrooms are considered functional foods that can be used as supplements for complementary and alternative medicines where the markets are growing rapidly. Several species of edible mushrooms possess therapeutic potential and functional characteristics. The psilocybin-containing types, sometimes known as magic mushrooms, have been utilized for generations by indigenous communities due to their hallucinogenic, medicinal, and mind-manifestation properties. Recent clinical research also convinces that these psychedelics have the potential to treat addiction, depression, anxiety, and other mental health concerns. This has escalated the demand for the natural products derived from the mushrooms of these sources, yet the agronomic aspect and biotechnology approaches to produce the active ingredients are not collectively documented. The objectives of this review article are to examine the general type and variation of therapeutic mushrooms, especially those belonging to the *Psilocybe*. The biotechnology approach for cultivation and the production of secondary metabolites is also appraised. The ultimate purposes are to provide guidance for farmers and companies to pursue sustainable ways to produce natural products for the development of functional food and pharmaceuticals and to support the alteration of the stigmatic drug concerns around psychedelic mushrooms.

Keywords: biotechnology; mycology; psilocybin; psychiatric disorders; psychedelic mushrooms

1. Introduction

As ascomycetes or basidiomycetes, mushrooms are filamentous fungi at the fruiting body stage of reproduction, nourishing themselves by symbiosis, parasitism, saprotrophism, or combinations of those. They have long been utilized as both food and medicine

and are a crucial component of the human diet. Nowadays, edible mushrooms are considered functional foods which are available as supplements for complementary and alternative medicine [1,2]. The market for dietary supplements alone is expanding substantially and is now worth more than 18 billion US dollars per year, and mushrooms are playing a crucial role in this industry [3]. Numerous mushroom genera are well known for their medicinal properties. Ancient Chinese culture and the majority of Asian nations held the belief that medicinal mushrooms might prolong life and make people more vibrant [2,4]. Generally, edible mushrooms are good sources of phenolic compounds, polysaccharides such as soluble β-glucans, glucuronoxylomannan (GXM), sacchachitin, tyrosinase, and other enzymes as well as terpenoids. The complex mixture of these phytochemicals illustrates potential biological activities such as anticancer, antioxidant, antimicrobial, antiviral, antiaging, hepatic protective, hypoglycemic, and hypocholesterolemic along with the cosmeceutical potent including activation of epidermal growth factor, anti-allergic, anti-inflammatory activities, stimulation of collagen activity, inhibition of autoimmune vitiligo, and treatment of acne [2,3]. The psychedelic types, such as those of the *Psilocybe* species, usually contain alkaloids, psilocybin, and psilocin, together with other pharmacologically active substances such as indoles, phenyl- ethylamines, and baeocystin [5,6]. These psilocybin-containing mushrooms, often known as magic mushrooms, have been used for centuries by various indigenous cultures for their holy, therapeutic, and mind-manifestation hallucinogenic powers [7]. Recent clinical study data suggest that these psychedelics have the potential for treating individuals with addiction, depression, anxiety, and other mental health issues [8]. The total number of described fungi of all kinds is roughly around 100,000 species, while mushrooms constitute approximately 14,000 species [9,10]. *Lentinus*, *Auricularia*, *Pleurotus*, *Hericium*, *Grifola*, *Flammulina*, and *Tremella* are among the edible classes of mushrooms containing bioactive ingredients thereby illustrating therapeutic potential. Other species include *Ganoderma* and *Trametes*, which are distinguished by their coarser, harder texture and bitter flavor, and are only used for medicines [11]. Additionally, the polyphyletic species of *Conocybe* Fayod, *Galerina* Earle, *Gymnopilus* P. Karst., *Inocybe* (Fr.) Fr., *Panaeolus* (Fr.) Quél., *Pholiotina* Fayod, Pluteus Fr., and *Psilocybe* (Fr.) Kumm have been shown to produce psilocybin and psilocin. This genus is estimated to contain over 300 species globally, from these only 14 species have been validated as hallucinogenic species [8]. Most hallucinogenic *Psilocybe* spp. is usually found in humid environments, while some, such as *P. cubensis* (Earle) Singer, are commercially cultivated, especially in Europe [5]. Diversity studies of the *Psilocybe* are considered rare. In Thailand, only nine species have been documented, while their psychoactive components have not been evaluated [12].

Considering the growing demand for medicinal mushrooms, commercial cultivation has broadly become popular. However, for conventional cultivation, the spent substrate and methane output have raised serious environmental concerns. It was estimated that as high as 5 kg of spent mushroom substrate was generated for every 1 kg of fresh mushroom production and the yield of methane production is convincedly higher than dairy manure alone [13]. In modern efforts, numerous biotechnological approaches are used for the cultivation and production of the active ingredients including chemical synthesis of the active ingredients, tissue culturing, enzymatic biosynthesis, and cell culture using biotechnologically modified genetic model organisms [3,8]. While attention is overwhelming regarding the therapeutic use of medicinal mushrooms, there is not much detailed information regarding the cultivation and alternative production of active ingredients gathered for psychedelic mushrooms. The objectives of this review are to review the general type and variety of therapeutic *Psilocybe* and to explore cultivation and biotechnological options for the production of the active metabolites. The potential benefit of this review is to provide a single outlet for farmers and industries to pursue a sustainable way for the cultivation of food and medicine. Moreover, by reducing methane production, it could immediately slow potent greenhouse gas emissions that have an impact on global warming.

2. Medicinal Mushrooms

Nowadays, mushrooms are regarded as functional foods for their promising therapeutic capabilities with a global production of production over 30 million tons [2,3,14]. *A. bisporus*, the white button mushroom, *Lentinula edodes*, *Pleurotus* spp., *Auricularia auricula*, *Flammulina velutipes*, and *Volvariella volvaceaea* made up 87% of the total production of cultivated edible and/or medicinal mushrooms. This volume is estimated to be worth over 20 billion US dollars, particularly in the functional food industries as sources of proteins, chitin (dietary fiber), vitamins, and minerals [14]. The edible mushrooms are also cholesterol-free, low in total fat but high in unsaturated fatty acids with distinctive aromas and flavors. By the definition, medicinal mushrooms are dried fruit bodies, mycelia, or spores that are available in the forms of extracts or powder for use in preventing, treating, or curing a variety of illnesses as well as balancing a good diet. They are also referred to as "fungal medications" or "mushroom drugs" [14]. The primary phytochemical components of medicinal mushrooms are polysaccharides, particularly β-glucans, and polysaccharide–protein complexes, which are renowned for their anticancer and immunostimulatory properties. In addition, various kinds of biologically active high-molecular-weight and low-molecular-weight compounds (triterpenes, lectins, steroids, phenols, polyphenols, lactones, statins, alkaloids, and antibiotics) have been found particularly in the fruit bodies, cultured mycelia, and cultured broth [3,14,15]. These mushroom drugs have been also known for a decade as biological anti-hyperglycemic agents which are medicinally proven to treat diabetes and its complications including hypercholesterolemia and hyperglycemia [16]. Table 1 illustrates the active phytochemical constituents of MMs and their medicinal uses.

Table 1. The bioactive constituents of some medicinal mushrooms.

Mushrooms	Uses	Bioactive Constituents	References
White button mushroom (*Agaricus bisporus*), Almond mushroom (*A. subrufescens*), Caterpillar fungus (*Cordyceps sinensis*), Shaggy ink cap (*Coprinus comatus*), Lingzhi (*Ganoderma lucidum*), White rot fungus/Chaga (*Inonotus obliquus*), *Phellinus linteus*, Oyster mushroom (*Pleurotus* spp.), *Poria cocos*, and *Sparassis crispa*	Possessed hypoglycemic effects on reducing blood glucose levels and antidiabetic effects.	Dietary fiber along with the polyphenols, vitamin C, and ergothioneine, as well as proteins, and polysaccharides (β-Glucans and oligosaccharides).	[16–19]
Almond mushroom	Induced apoptosis of intestinal cancers.	Soluble fibers serve as a desirable food source for bacteria that generate short-chain fatty acids such as butyrate, which may be able to stimulate apoptosis of cancers in human intestinal.	[20]
Lingzhi	Effective for treatment of gastric cancer.	Treatment of a gastric cancer cell line with methanolic extract resulted in an increase in cellular autophagy and the production of autophagosomes (AGS).	[21,22]
Himematsutake (*A. blazei*)	Traditional medicine from Japan and used for treatments of diabetes, hyperlipidemia, arteriosclerosis, and chronic hepatitis. In animal study, it increased proliferation of monocyte and promoted destruction of cells with DNA alterations that correlate with the development of cancer.	The immune system is modulated by bioactive β-glucans in supplemental diets and is rendered more effective with regard to phagocytic activity.	[20]

Table 1. *Cont.*

Mushrooms	Uses	Bioactive Constituents	References
Trametes versicolor	The medicinal mushroom frequently used in traditional Chinese medicine for its antiviral, antitumor, and immunomodulatory effects.	The polysaccharide Krestin (PSK) is commercially available for use in cancer immunotherapy.	[23]
Flammulina velutipes, *Pholiota* spp., Lingzhi and straw mushroom (*Volvariella volvacea*)	The immunomodulatory proteins had been isolated from the fruiting body and cultured mycelia of the mushrooms.	Lectins can bind to cell surface carbohydrates, agglutinate cells, and inhibit cancer cell growth.	[24–26]
Chaga (*Inonotus obliquus*)	A fungal parasite, grows on birch trees in colder northern climates with anticancer properties.	Betulin or betulinic acid isolate illustrates platelet adhesion and aggregation plays an important role in the pathogenesis of thrombosis, particularly arteriothrombosis.	[27]
Cordyceps spp.	The mushrooms are used in Traditional Chinese medicine due to their various therapeutic properties including immunoregulative, anticancer, antibacterial, and antifungal activities.	Cordycepin, ophicordin, polysaccharides, and L-tryptophan are bioactive constituents isolated from the Cordyceps such as *C. militaris*, also known as north *Cordyceps*.	[28,29]

Among those used in therapeutic, magic mushrooms, are thought to have been used throughout centuries by numerous ancient cultures for their hallucinogenic, spiritual, and medicinal properties due to the active psilocybin present [7]. After Albert Hofmann identified, structurally characterized, and synthesized the alkaloids psilocybin and psilocin in 1958, psychoactive mushroom species in the genus *Psilocybe* gained prominence in medicine [5]. It was suggested that using these psychedelics illustrated beneficial effects, including decreased anxiety and depression as well as improvements in mood and behavior [30]. The typical psilocybin dosage needed to induce hallucinogenic effects is 4–10 mg or roughly 1–3 g of dry or 10–50 g of fresh magic mushrooms [6]. Additionally, magic mushrooms generally contain other pharmacologically active substances such indoles, phenylethylamines, and baeocystin with antioxidant and anti-inflammatory properties [6,7].

3. Medicinal Mushroom Diversity and Taxonomy Characteristics of Magic Mushrooms

As many as 10 million species of fungi are known to earth, and of these figures, around 140,000 are mushroom species, although only about 10% have been taxonomically characterized [9,11]. In an ecological sense, mushrooms can be categorized into three groups: saprophytes (saprotrophism), mycorrhiza (symbiosis), and parasites (parasitism). The majority of edible mushrooms are wood-decomposing, saprophytic fungi and the most commonly known are oyster mushrooms and Shiitake (*Lentinula edodes*) [31]. These saprophytic fungi are regarded as decomposers of our ecosystem. The filamentous mycelia form the networks that weave in and out of plant cell walls. The secreted enzymes and acids break down complex molecules into simpler forms, reintroducing minerals, carbon, hydrogen, and nitrogen to the natural surroundings [32]. The primary decomposers are often fast-growing and produce the ropey strands of mycelium that adhere and decompose plant tissue. The secondary decomposers, such as button mushrooms, rely on the broken-down substrate because they reduce the bulk and composition of the material, whereas tertiary decomposers, including *Agrocybe* spp., are typically found in decomposing greens including grass, chip wood, and garden mulch [13]. The mycorrhiza and the roots of the host plants develop a mutually beneficial interaction. Mycelium is the filament that forms the mushroom body, once forms an exterior sheath covering the roots of plants, it is called

ectomycorrhizal. The endomycorrhizal is when the fungi invade the interior root cells of the host [31]. The mycorrhizal species are also essential for the diversity of the forest and ecosystem. They are dependent on the photosynthetically fixed carbon generated by their related host trees to grow their vegetative mycelium in the soil and create fruiting bodies for sexual reproduction [33]. In turn, the fungi provide soil nutrients and improve soil fertility which is beneficial for the host plants. The commonly known gourmet mushrooms of the mycorrhizal fungi are *Tuber magnatum* Pico (Piedmont white truffle), *T. melanosporum* Vittad. (Périgord black truffle, also known as "the black diamond"), and *T. aestivum* Vittad. (Burgundy truffle) [34]. Of this interesting type, the "matsutake" refers to a family of higher fungi in the *Tricholoma* genus and *T. matsutake* is the commercially known species. They are naturally occurring mycorrhizal fungi that have symbiotic interactions with specific tree species, primarily pine and oak [35]. The parasites live off a host plant, endangering the host's health as it grows; however, it is beneficial for the creation of new habitats for many organisms. The recently recovered species, *Taxomyces andreanae*, produced taxol and related compounds when cultured in a semi-synthetic liquid medium. These compounds are proven to reduce the size of breast cancer [36].

The hallucinogenic mushrooms of the major species *Psilocybe* are typically saprophytic and found generally in the wet climate on substrates such as dirt, manure, wood, and moss [37]. They are often tiny, indistinct, brown to white fungi with caps and stems, but not always; they bruise purplish to black when the tissue is damaged or sliced due to an oxidative reaction of psilocybin [38] (Figure 1). The *Psilocybe* often has a sticky cap when wet and dark to purplish-black spores with a dark purple-brown spore print [39]. Other characteristics include a separable gelatinous pellicle, fringed whitish gill edges, and typically collyboid or mycenoid aspects. In addition to the cultivation of subtropical species such as *P. cubensis* (Earle) Singer, a variety of other naturally occurring species is prevalent across Europe [5]. It is estimated that the genus *Psilocybe* contains more than 300 species and is dispersed globally and 57 hallucinogenic *Psilocybe* species have been documented in Mexico. From these, 35 species and 9 varieties, corresponding to 14 valid species, have been reported to be used by ethnic groups and mestizos mainly in central and southern Mexico [8]. *P. semilanceata* (Fr.) Kummer contains comparatively high amounts of active ingredients including psilocybin (around 1% dry weight) and some baeocystin, which is the monomethyl analog of psilocybin. The newly identified taxon *P. germanica* sp. nov. which also illustrated high amounts of psilocybin and baeocystin was autumnal and lignicolous, growing in soils enriched with deciduous wood debris, and exhibited pronounced *bluing* behavior after being bruised or aged [5]. Five species of *Psilocybe* spp. including *P. deconicoides*, *P. cubensis*, *P. magnispora*, *P. samuiensis*, and *P. thailandensis* have been reported in Thailand with four new species of the sects; Cordisporae, Mexicanae, Stuntzae, and Zapotecorum were also added in 2010 [12].

Globally, there are up to 29 species of *Panaeolus*, with *P. papilionaceus* being the most widely recognized [40]. These little brown mushrooms (LBMs) are characterized by their tiny, grayish, brown, or black conical or bell-shaped caps, elongated thin stalks, connected gills, and dark brown to purple-brown to black spore print (Figure 2) [41]. The most conspicuous characteristic is the gills that mottled with shades of grey and black when young, and later become completely black [42]. There are spores with an apical germ pore and a cellular pileipellis that are resistant to high sulphuric acid [37,43]. The *Panaeolus* are coprophilic and are frequently found in animal droppings such as horses, cows, buffalo, and elephants [37,43,44].

Currently, *P. cyanescens* is the most well-known psychoactive representative and contains high levels of psilocybin, that are even higher than those found in the *Psilocybe* spp. [45]. The Pluteus are small, brown- or white-capped mushrooms (1 to 15 cm in diameter) that begin conical or convex and flatten to a classic mushroom form, with many caps having a prominent central umbo (Figure 3) [46]. The genus is distinguished by free lamellae and lack of annulus and volva. The spherical ellipsoid spores are smooth that create a pink spore print, with the presence of pleurocystidia and an inverted hymenophoral trama [47].

Psilocybin (<~0.25%) has been detected in the dried fruiting bodies of *P. salicinus* (Pers.: Fr.) Kumm. and *P. nigroviridis* Babos but these species were rare and grew on decaying plant material such as wood chips [48–50].

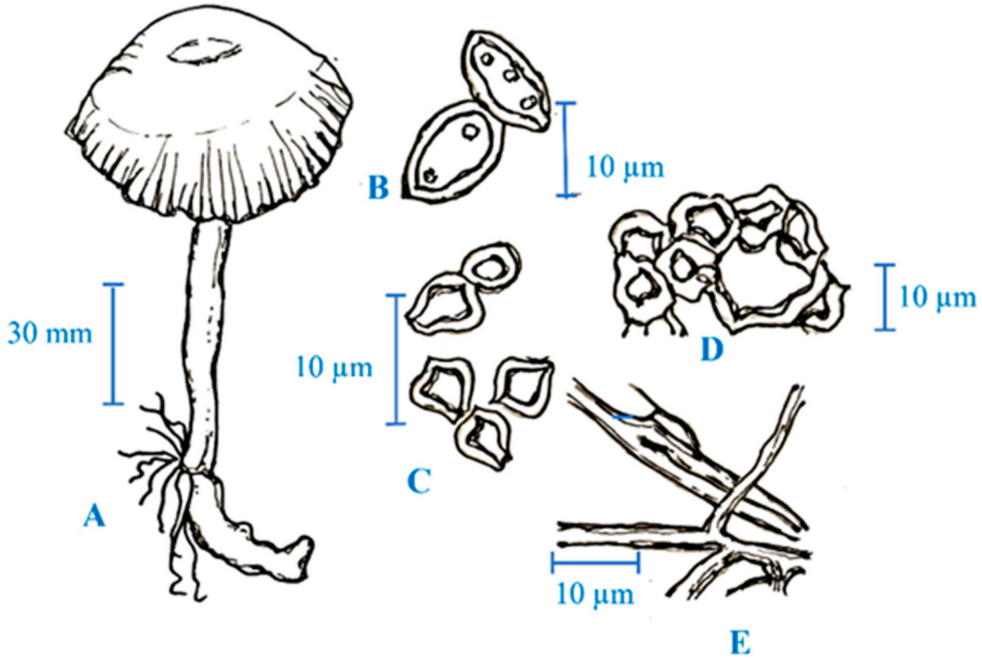

Figure 1. (**A**) *Psilocybe subaeruginosa*; (**B**) basidiospores; (**C**) subrhomboid basidiospores; (**D**) radial pileus trama; (**E**) setoid hyphae.

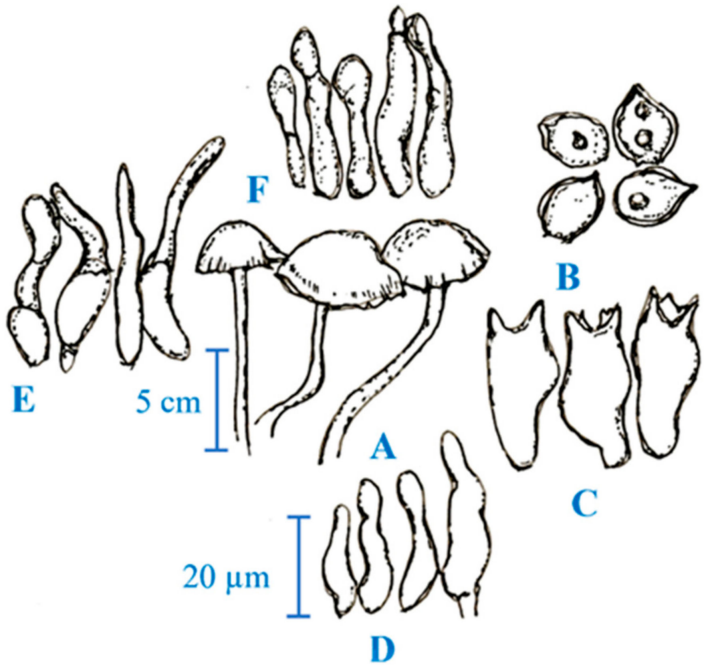

Figure 2. *Panaeolus paplilionaceus* var. parvisporus. (**A**) Carpophore; (**B**) basidiospores; (**C**) basidia; (**D**) caulocysitidia; (**E**) pileocysitidia; (**F**) cheilocysitidia.

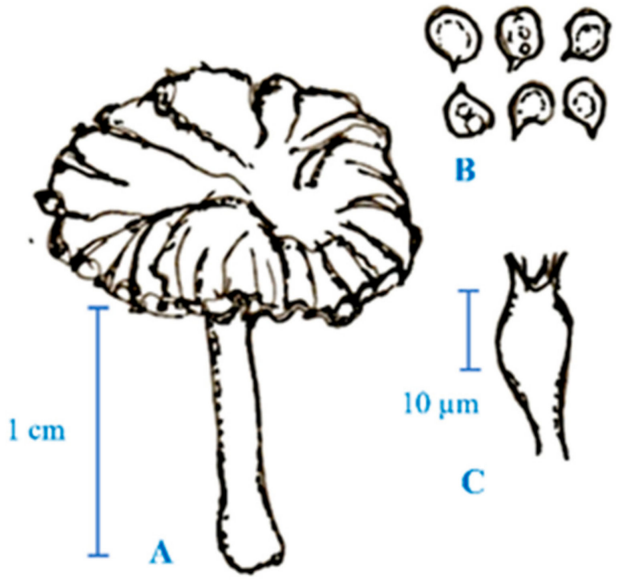

Figure 3. *Pluteus parvicarpus*. (**A**) Carpophore; (**B**) basidiospores; (**C**) basidium.

Gymnopilus contains over 200 species worldwide and is characterized by dry, medium to large fruiting bodies that range in color from rusty orange to yellow with well-developed veils (Figure 4). The spore is verrucose to rugulose ornamentation but lacks germinal pores of the basidiospores, and no germ pore or dextrinoid walls, while spore prints are rusty brown in color [51,52]. So far, 16 species have been found to contain psilocybin and psilocin are commonly found including *G. cyanopalmicola*, *G. palmicola*, *G. igniculus*, *G. validipes*, *G. aeruginosus*, *G. braendlei*, *G. intermedius*, *G. lateritius*, *G. liquiritiae*, *G. luteoviridis*, *G. luteus*, *G. purpuratus*, *G. sapineus*, *G. spectabilis*, *G. subpurpuratus*, *G. validipes*, and *G. viridans*. *Gymnopilus* can grow on wood or grassy areas with decomposing wood [51,52].

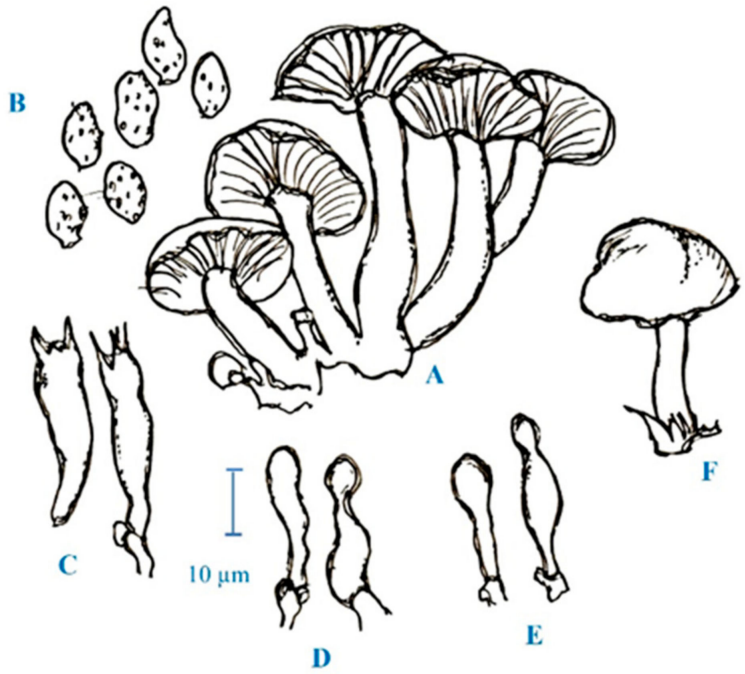

Figure 4. *Gymnopilus spectabilis*. (**A**,**F**) Carpophore; (**B**) spores; (**C**) basidia; (**D**) pleurocystidia; (**E**) cheilocystidia.

4. Active Ingredients and Medicinal Properties

Mushrooms are abundant in protein, as well as essential amino acids and carbohydrates. They also contain bioactive peptides, such as lectins, fungal immunomodulatory proteins, ribosome-inactivating proteins, and laccases [2]. Besides their low-fat content, they are also rich in many essential unsaturated fatty acids including linoleic and oleic acids that are vitally important for the proper functioning of the human body [1,53]. The medicinal ones contain bioactive, low-molecular-weight metabolites which are produced in response to stress that help in its survival by signaling and defense but are generally not required by the fungi for their normal growth and reproduction. These metabolites possess medicinal properties, particularly in the prevention and control of several diseases such as antitumor, immunomodulating, and chronic bronchitis [4]. The most significant secondary metabolite in medicinal mushrooms is a polysaccharide, which is a member of the 1,3-β-glucans family and exhibits antitumor properties by enhancing and inhibiting the cellular immune pathway through the activating macrophages [1]. It illustrates antioxidant, anticancer, antidiabetic, anti-inflammatory, antimicrobial, antiobesity, and immunomodulatory properties [54–56]. The total phenolic content of the medicinal mushrooms is about 6.0 mg while the flavonoid content can be found as high as 3.0 mg per gram of dried matter in which homogentisic acid, benzoic acid (protocatechuic, 4-OH-benzoic, vanillic, salicylic) and cinnamic acid derivatives (caffeic, p-coumaric, ferulic, as well as myricetin and catechin), were among the principal components [57,58]. These compounds have been demonstrated to have antioxidant potentials through different pathways, including the inactivation of metals, acting as oxygen scavengers, or inhibiting free radicals. Many terpenes and terpenoids (terpenes with the addition of functional groups, usually oxygen-containing) can be isolated from the medicinal mushrooms which are responsible for their antioxidant, anticancer, anti-inflammatory activities, and immunomodulatory [59].

Psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) and psilocin are indole alkaloids that were discovered in many fungi species, mostly in the *Psilocybe* [60]. Psilocybin is biosynthesized from 4-hydroxy-L-tryptophan with the presence of decarboxylase PsiD, the kinase PsiK, and the methyltransferase PsiM. The prodrug psilocybin is rapidly dephosphorylated to psilocin in the intestinal mucosa by alkaline phosphatase and nonspecific esterase, therefore the equimolar dose of psilocin is 1.4 moL of psilocybin [61]. Figure 5 illustrates the chemical structures of these indole alkaloids. After ingestion, about 50% of the total volume of psilocin is absorbed from the digestive tract of the animal [62,63]. The psilocin binds to 5-hydroxytryptamine (5-HT2A, 5-HT2C, 5-HT1A, 5-HT1B, and 5-HT1D) receptors, which are structurally similar to the neurotransmitter serotonin (5-hydroxytryptamine), interrupting serotonergic neurotransmission and having physiological effects [64]. The general activity of psilocybin by resting-state functional magnetic resonance imaging demonstrating psilocybin administration to alter acutely brain network activity, including the decrease in connectivity within the default mode network, the system of brain regions that interact strongly with one another thereby supporting the treatments of the diseases relating human central nervous system [65]. Psilocybin use is regarded as being fairly safe due to its minimal physiological toxicity and limited potential for misuse, as shown by the low levels of nonhuman animal drug self-administration [66,67]. Recently therapeutic studies on psilocybin for mood and anxiety disorders, especially in the context of cancer-related psychiatric distress, have gained abundant attention [60]. It was also shown that a high psilocybin dose of around 0.4 mg/kg resulted in numerous improved clinical outcomes over anxiety-related disorders in relation to a life-threatening cancer diagnosis [68]. In recent modest, open-label pilot research, the impact of psilocybin on severe depression was also investigated outside the context of cancer. The research found that the patients showed reduction in depression severity at 1 week that was sustained in the majority for 3 months after administration of 10–25 mg of philocybin [69]. Other studies also conducted on Obsessive–Compulsive Disorder (OCD) and cluster headaches also found positive symptom reduction after treatments with the psilocybin [70,71].

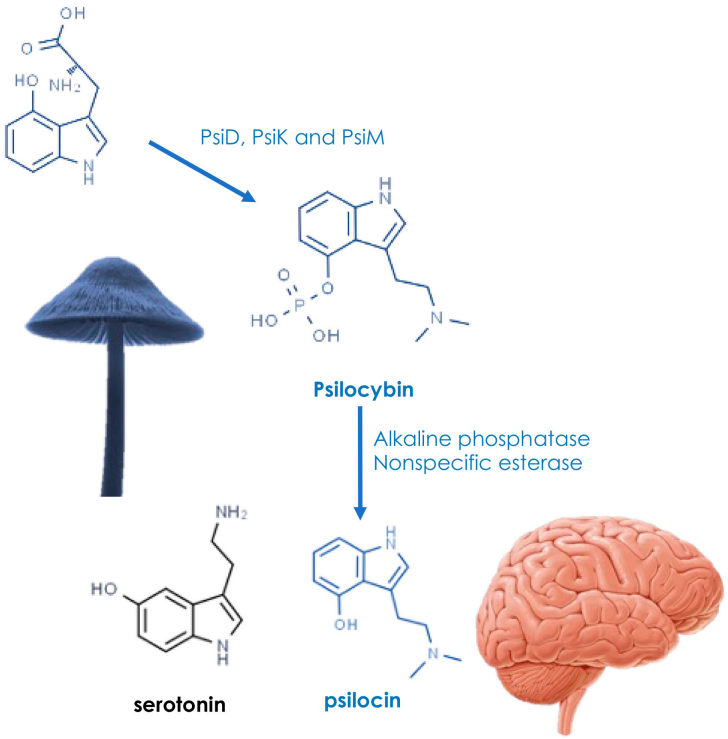

Figure 5. Chemical structures and biosynthesis pathway of the indole alkaloids in magic mushrooms.

The chemical synthesis of psilocin and psilocybin originally employed dibenzylphosphoryl chloride. This reagent was hazardous and unstable, therefore later was substituted by tetrabenzylpyrophosphate [72,73]. A far more efficient synthesis employing direct phosphorylation of psilocin with phosphorous oxychloride, thereby avoiding the necessity for the tetrabenzylpyrophosphate as the phosphorylating reagent and the following hydrogenation step, yields high-quality pure psilocybin [73]. Psilocybin was synthesized enzymatically from the 4-hydroxy-L-tryptophan substrate involving a step-economic route of the PsiD/PsiK/PsiM reaction. This was also claimed as the foundation for the biotechnological production of psilocybin [61,74].

5. Traditional Cultivation

Mushrooms are vegetatively reproduced and so maintain a single clone. Mycelium may be preserved for an extended period of time, and its genetic and biochemical integrity can be evaluated after storage for a long period [14]. Unlike plants with photosynthesis apparatus, most of the medicinal types are basidiomycetes with a saprobic lifestyle. Instead, they rely on organic matter produced by nearby green plants, including organic substances found in crop waste known as substrate [13,15]. They may indeed be cultivated using a number of techniques. Some techniques are extraordinarily simple and require minimal or no technological skill. Others, such as sterile tissue culture, are considerably more technically demanding [36]. The primary decomposing mushrooms can be cultivated using various types of lignocellulosic materials including straws, cotton seed hulls, corn cobs, peanut shells, coffee pulp, and leaf compost [75–77]. Mycelial culture is favored practically because spores are difficult to handle, and their genetic traits may differ from those of the parent. The intended mushroom must colonize the substrate prior to other fungi or bacteria. In order to do this, a sterile substrate is infected with the mycelium of the fungi known as spawn that has been pre-grown and is devoid of contaminants [78,79]. During the vegetative growth phase, the mycelia grow profusely reaching the maturity phase. After which, the mycelial growth at the tips should be slowed down to induce the reproductive (fruiting) growth phase. At this point, the umbrella-like body is seen (Figure 6). The substrates used to cultivate medicinal mushrooms must be abundant in vital

nutrients that the mushrooms can easily access and free of toxins that hinder their growth. Practically, the substrates should contain solid matters such as a mixture of fine and coarse sawdust to ensure good aeration, 75–80%, supplemented with wheat bran (coarse), 20% gypsum (calcium sulfate), 1% with sucrose, 1% [36,80]. Moisture content (60–65%), pH (5.5–6.0), and adequate gas interaction between the substrate and the environment are also essential factors during cultivation [15].

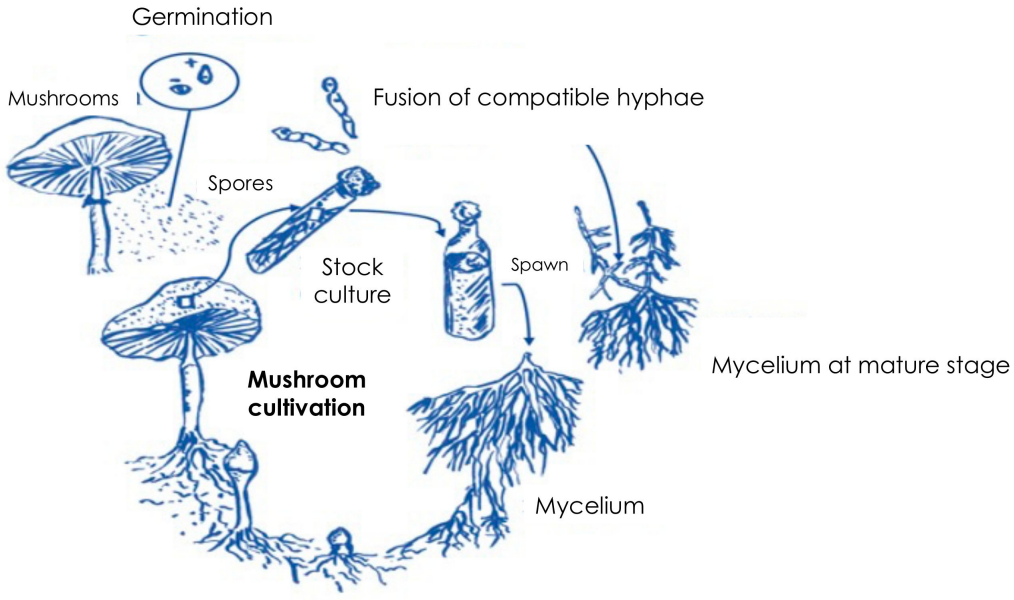

Figure 6. Lifecycle of mushroom and spawn cultivation.

Log and stump cultures are suitable for *Grifola frondose* (Mitake) and *Garnoderma lucidum* (Reishi), *Phellinus linteus* and Shiitake [36,81,82]. Two crops of mushrooms are produced annually during this process, which lasts for several years until the log literally collapses as a result of wood deterioration. Although this outdoor cultivation process yields high-quality mushrooms, it is not ecologically suitable for widespread production [80]. In addition, before the wild mushroom season, when the air fills with spores of wild mushrooms, the stump should be inoculated. The wild spores could become the natural competitors to the mushrooms. The composition of the wood should be considered. In general practice, the C/N ratio in the substrate should be between 25 and 60:1 during the vegetative growth stage and between 40 and 73:1 during the reproductive stage [15]. *Agaricus* spp. such as common button mushrooms and *P. ostreatus* are secondary decomposers growing on composted biomaterials such as cattle manure, broiler chicken litter, and a mixture of straw substrate [83,84]. The type of substrate used also influences mushroom production and the quantity of the metabolites, and it depends largely on the ability of the fungi to secrete enzymes needed for the digestion of lignocellulosic substrates such as ligninase, laccase, manganese peroxidase, cellulase, xylanase, and tannase and the cost [85]. In addition, P, K, and Mg, as well as trace elements such as Fe, Se, Zn, Mn, Cu, and Mo are vitally important for growth and development [86]. The lignocellulosic materials are, however, a weak source of these mineral content and to increase the efficiency of mushroom yield, organic and mineral additives should be added. A cultivation study of *Pleurotus* species using the substrates with supplemented nutrients found that growth of mycelium *P. sajor-caju* was sustained in the presence of N obtained from yeast extract, casein, and glycine [87]. The growth of mycelium and the increase in the biomass of the fruiting body of *P. ostreatus* correspond to the presence of ammonium supplementation [88].

In the laboratory, mycelium culture has been successfully achieved for *Psilocybe* spp. found in Thailand such as *P. samuiensis*, *P. tampanensis* Guzmán and Pollock and of *P. semilanceata* (Fr.: Sacc.) Kumm. [89]. The newly found species of *P. samuiensis* illus-

trated high concentrations of psilocybin and psilocin in the fruit bodies. In another study, the mycelium of *P. Mexicana* obtained from the spore print was also used as stock culture in different grain mediums. The induced sclerotia contained a significant amount of psilocybin (~0.60%) [90]. A mixture of sand and compost was found to be the suitable substrate to promote mycelium growth with the optimum temperature between 15–24 °C during fruiting in the relative humidity of 90% of *P. barrerae*, the Mexican species found in a temperate and subtropical forest of *Pinus*, *Quercus* [91]. In one intuitive study, the muddy river soil where the mycelial of *P. ovoideocystidiata* (0.4–0.6% psilocybin) was collected, was used as the substrate in the indoor-cultivation [92]. It is advised to prevent natural light from entering the harvesting chamber because the level of psychotropic substances and, consequently, the psychoactivity of *P. cubensis* appear to be influenced by light conditions [93].

6. In Vitro Cultivation and Synthesis of the Active Metabolites from Medicinal Mushrooms

Nowadays, several mushroom products of medicinal interest are available in the markets in the forms of powders, pulverized preparations and extracts of the fruiting body, biomass, and dried substrate either naturally or laboratory grown, or submerged liquid culture grown in a fermentation tank or bioreactor [3]. The batch solid substrate fermentation process using the polypropylene bag (bioreactor) can be viewed as a rapid, dynamic operation for cultivation [80]. The dynamic system within this bioreactor comprises three phases namely a solid phase involving a lignocellulosic substrate, an aqueous phase when the solid surface appears in various states of sorption, and a gaseous phase continuous with the external environment. These stages involve the growth of the inoculum and morphological development of the mushrooms. The submerged technique involves growing organisms in a liquid medium where nutrients are dissolved, and oxygen supply is increased by agitation. This method can improve oxygen transfer and culture homogeneity while maintaining physical (temperature, aeration, and agitation), chemical (pH and medium composition), and biological (inoculum, morphology, and rheology) factors [94,95]. The submerged cultivations of *P. cubensis* and *P. baeocystis* have been around for several decades and it was found that the mycelium and sclerotia contain substantial degrees of psilocybin and psilocin [96]. Based upon these techniques, a grow-kit containing spores of hallucinogenic mushrooms in plastic containers has recently become available throughout Europe. It is composed of a perlite layer with water which maintains the humidity in the box and a layer of mycelium inoculum. Lastly, a thin vermiculite layer is laid to protect the mycelium from dehydration [91].

In addition, the active metabolites from these species can be produced in various ways. As mentioned, the psilocybin is synthesized enzymatically by a one-pot PsiD/PsiK/PsiM reaction using the 4-hydroxy-L-tryptophan [61,74], while PcPsiM is essential for recognition and catalytic conversion of the phosphate group. It was found that 15 moL of this substrate was able to produce 3.9 moL of psilocybin. A modular biosynthetic production platform to optimize and improve pathway performance using multiple genetic optimization techniques in *Escherichia coli* was recently developed. This resulted in a 32-fold improvement in psilocybin titer. The genetically superior strain was also used in a fed-batch fermentation process with 4-hydroxyindole as substrate and consequently could produce 1.16 g/L of psilocybin [97]. Similarly, high-level de novo production psilocybin was biosynthesized from 4-hydroxylated substrates in Saccharomyces cerevisiae by the implementation of the biosynthetic pathway from *P. cubensis* with the expression of a novel cytochrome P450 reductase [98]. In mass production, psilocin was also produced through phenethylamine, tryptamine, or lysergamide scaffolding [99].

7. Future Perspective of Medicinal Mushroom Cultivation

One of the difficult and technically challenging areas of research in the field of the agri-food sector is the reduction of food loss through bio-circular approaches [100,101]. Food producers are finding ways to upcycle agricultural biomass and focus on the environmental

benefits of this practice as an advantage [102]. The ligno-cellulose wastes generated from the production of food produce a significant amount of environmental pollution. These plant biomasses can be used as the primary ingredients to prepare organic composts for edible and medicinal mushroom growing, providing good sources of biologically active compounds from the nutritive fungal biomass produced by solid substrate cultivation or submerged fermentation [103]. For culturing *P. ostreatus*, the substrate that is digested decomposed easily, such as wheat straw [104]. The high lignin content of the substrate could inhibit the growth of the mushrooms [105]. The moisture content of the substrate and aeration remarkedly influence the solid state fermentation as they are involved in ligninolytic enzyme activity and could potentially increase delignification [106]. Based upon this, it, therefore, and among all others, is of interest to the feed industry. *Pleurotus* spp. produces enzymes that preferential degradation of lignin whereby the cellulose is exposed and can be easily utilized as animal feed such as the ruminants [107]. Additionally, it is used as a bioproducer of laccase, magnesium peroxidase, and versatile peroxidase, all of which are sought after by the pulp and paper industries. These mushroom species make excellent candidates for bioremediation applications such as soil decontamination, degradation of industrial dyes, phenols, and PAHs, and wastewater treatment due to their capacity for the oxidation and decolorization of other resistant organopollutants [108].

8. Conclusions

Various types of basidiomycetes mushrooms are recognized as the sources of biologically active high-molecular-weight and low-molecular-weight compounds with various needs for medicinal applications. Among all others, psilocybin and psilocin from psychedelic mushrooms have been clinically researched for their uses in the treatment of mental health concerns. These mushrooms may be cultivated employing a variety of approaches in addition to conventional cultivation. For medicinal mushroom cultivation, the batch solid substrate fermentation technique utilizing the polypropylene bag (bioreactor) is a novel technique for rapid and dynamic operation. The magic mushrooms of *Psilocybe cubensis* and *P. baeocystis* were submerged and grown in the media and it was discovered that the mycelium and sclerotia were excellent sources of psilocybin and psilocin. Another industrial application of medicinal mushrooms is that they also contain enzymes that preferentially degrade lignin, exposing cellulose as feed for animals such as ruminants. It also bioproduces laccase, magnesium peroxidase, and versatile peroxidase for the pulp and paper industry. Due to their ability to oxidize and decolorize other strong organopollutants, mushrooms are ideal for soil decontamination and degradation of industrial pollutants. This article not only serves as guidance for farmers and agri-food manufacturers for the cultivation and production of active ingredients from medicinal fungi, but it also provides supporting evidence for the policy makers for the alteration of the stigmatic drug involving medicinal mushrooms.

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