Active Ingredients and Medicinal Properties of Medicinal Mushrooms

Subjects: Mycology

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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.

Keywords: mycology ; psilocybin ; psychiatric disorders ; psychedelic mushrooms

1. Medicinal Mushrooms

Nowadays, mushrooms are regarded as functional foods for their promising therapeutic capabilities with a global production of production over 30 million tons [1][2][3]. *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 [3]. 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” [3]. 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 [2][3][4]. 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 [5]. **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).	[5][6][7][8]
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.	[9]
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).	[10][11]
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.	[9]
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.	[12]
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.	[13][14][15]

Mushrooms	Uses	Bioactive Constituents	References
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.	[16]
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*.	[17][18]

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 [19]. 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 [20]. It was suggested that using these psychedelics illustrated beneficial effects, including decreased anxiety and depression as well as improvements in mood and behavior [21]. 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 [22]. Additionally, magic mushrooms generally contain other pharmacologically active substances such indoles, phenylethylamines, and baeocystin with antioxidant and anti-inflammatory properties [19][22].

2. 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 [23][24]. 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*) [25]. 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 [26]. 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 [27]. 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 [25]. 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 [28]. 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) [29]. 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 [30]. 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 [31].

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 [32]. 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 [33] (**Figure 1**). The *Psilocybe* often has a sticky cap when wet and dark to purplish-black spores with a dark purple-brown spore print [34]. 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 [20]. 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 [35]. *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 [20]. 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 [36].

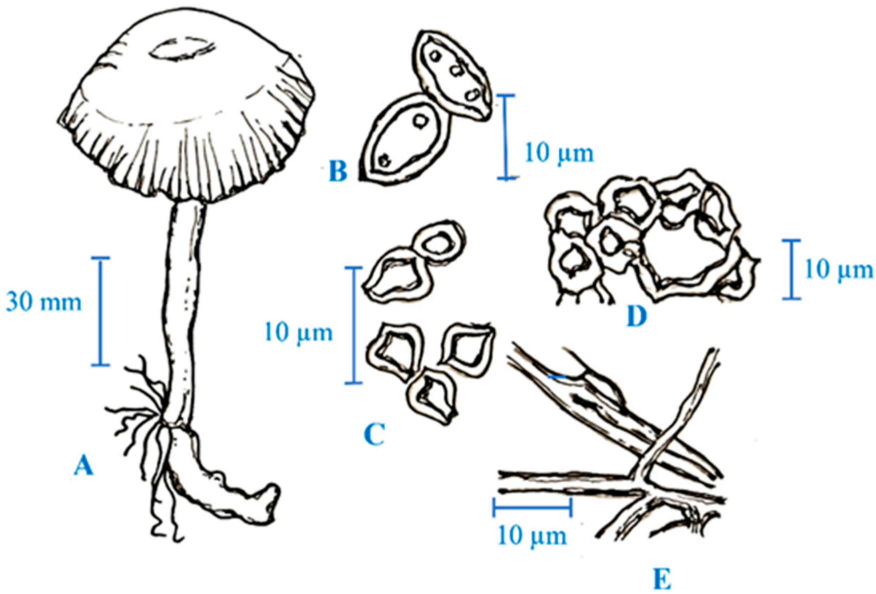

Figure 1. (**A**) *Psilocybe subaeruginosa*; (**B**) basidiospores; (**C**) subrhomboid basidiospores; (**D**) radial pileus trama; (**E**) setoid hyphae.

Globally, there are up to 29 species of *Panaeolus*, with *P. papilionaceus* being the most widely recognized [37]. 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**) [38]. The most conspicuous characteristic is the gills that mottled with shades of grey and black when young, and later become completely black [39]. There are spores with an apical germ pore and a cellular pileipellis that are resistant to high sulphuric acid [32][40]. The *Panaeolus* are coprophilic and are frequently found in animal droppings such as horses, cows, buffalo, and elephants [32][40][41].

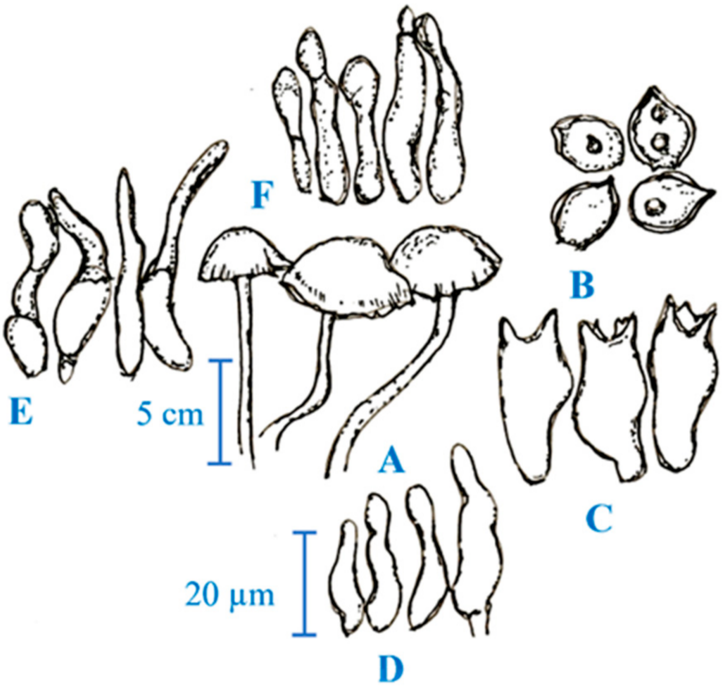

Figure 2. *Panaeolus paplilionaceus* var. parvisporus. (**A**) Carpophore; (**B**) basidiospores; (**C**) basidia; (**D**) caulocysitidia; (**E**) pileocysitidia; (**F**) cheilocysitidia.

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. [42]. 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**) [43]. 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 [44]. 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 [45][46][47].

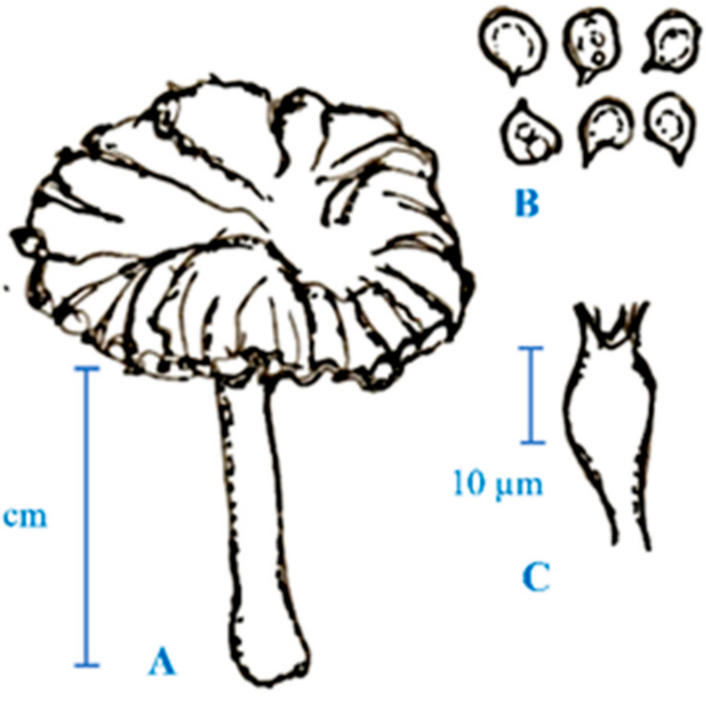

Figure 3. *Pluteus parvicarpus*. (**A**) Carpophore; (**B**) basidiospores; (**C**) basidium.

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 [48][49]. 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 [48][49].

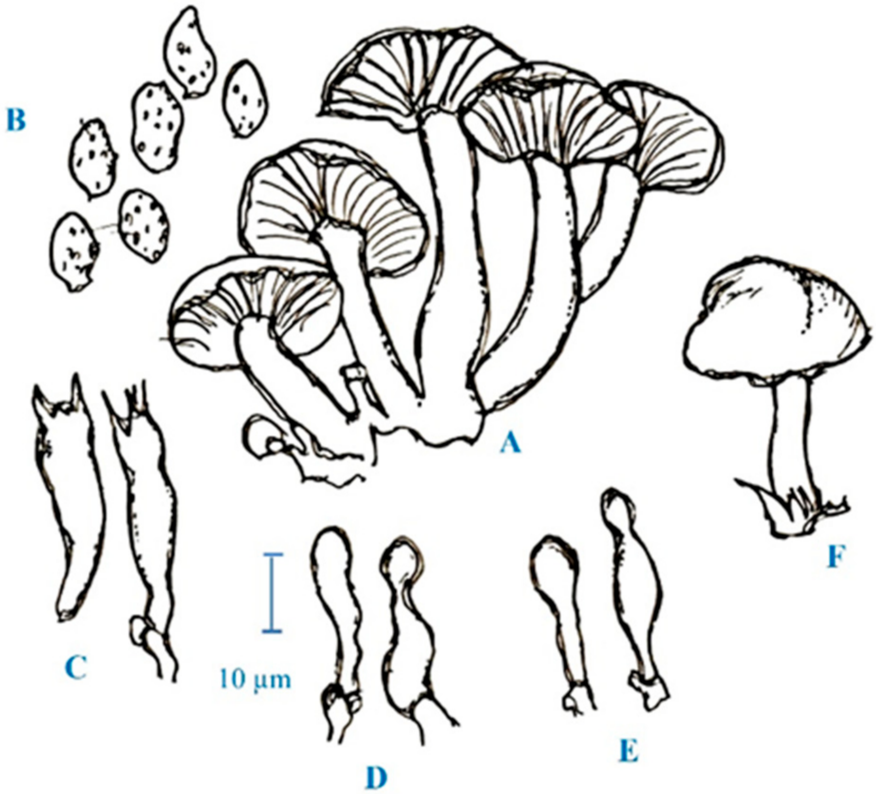

Figure 4. *Gymnopilus spectabilis.* (**A**,**F**) Carpophore; (**B**) spores; (**C**) basidia; (**D**) pleurocystidia; (**E**) cheilocystidia.

3. 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 [1]. 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 [50][51]. 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 [52]. 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 [50]. It illustrates antioxidant, anticancer, antidiabetic, anti-inflammatory, antimicrobial, antiobesity, and immunomodulatory properties [53][54][55]. 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 [56][57]. 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 [58].

Psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) and psilocin are indole alkaloids that were discovered in many fungi species, mostly in the *Psilocybe* [59]. 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 [60]. **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 [61][62]. 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 [63]. 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 [64]. 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 [65][66]. Recently therapeutic studies on psilocybin for mood and anxiety disorders, especially in the context of cancer-related psychiatric distress, have gained abundant attention [59]. 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 [67]. 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 [68]. Other studies also conducted on Obsessive–Compulsive Disorder (OCD) and cluster headaches also found positive symptom reduction after treatments with the psilocybin [69][70].

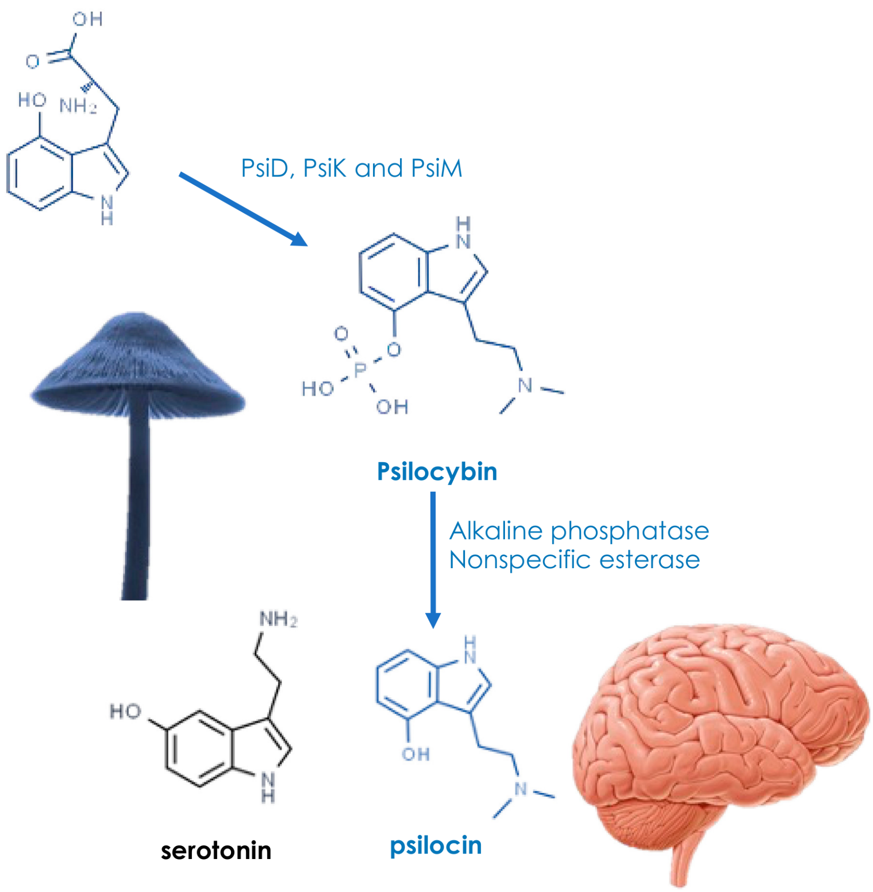

Figure 5. Chemical structures and biosynthesis pathway of the indole alkaloids in magic mushrooms.

The chemical synthesis of psilocin and psilocybin originally employed dibenzylphosphoryl chloride. This reagent was hazardous and unstable, therefore later was substituted by tetrabenzylpyrophosphate [71][72]. 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 [72]. 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 [60][73].

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