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The Anti-Diabetic Potential Of Mushrooms: A Review

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Abstract

Diabetes is emerging as a pandemic, so it is essential to find new nutraceuticals or drugs to treat or prevent it. Some mushrooms appear to be effective in controlling blood glucose levels and correcting diabetes problems without any negative side effects. Mushrooms with immune-modulating polysaccharides are used in limited areas as palatable food or health-promoting dietary supplements or medicine. However, to date, scientific or clinical research on mushrooms has not been sufficient to allow them to be used as recognized medicines or nutraceuticals worldwide. These functional fungi may have a greater impact on the prevention and treatment of diabetes. Therefore, further studies are needed to identify their active compounds for improving diabetes drugs or nutraceuticals. This review focuses on prospective mushrooms that have demonstrated anti-diabetic effects in clinical or experimental studies and prevent or slow the progression of diabetes mellitus

Keywords: Biological activities; Fungi; Medicinal mushrooms; Secondary metabolites

Introduction

Many researchers are interested in the use of microbial secondary metabolites normally, and mushroom metabolites in particular in various fields of biotechnology, due to the bioactive properties of these metabolites, which have led to their use in pharmaceutical, industrial, and agricultural fields. Diabetes is a serious health problem that predisposes to noticeably increase. Despite numerous prevention strategies and a range of drugs, the treatment of diabetes remains largely unsatisfactory (1). Diabetes is one of the prominent public health problems at present. Lifestyle changes directly relate to this problem (2). Most of the chronic complications of diabetes are micro- and macrovascular diseases resulting from established hyperglycemic conditions. After the failure of the first-choice therapy, which is based on dietary modification and exercise, conventional treatment using anti-hyperglycemic substances with different mechanisms of action is used for type II diabetes in modern medicine (3). Abou Zaid et al. (2017) and Elkhateeb et al (2021a) defined the mushrooms as macro-fungi with prominent fruiting bodies that may be hypogeous or epigeous, large enough to be seen with naked eyes and to be picked by hand (4-5). Mushrooms were valued as palatable foods and as medicinal substances. Mushrooms are also considered functional foods for their bioactive compounds that have multiple beneficial effects on human health

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(6). Diabetes mellitus is a metabolic disorder shown by high blood glucose levels. It is indicated by insulin insufficiency, receptor, or dysfunction that causes increased blood glucose levels and metabolic problems. Polysaccharides, proteins, fibers, and many other biomolecules isolated from mushrooms have been exhibited to be beneficial in the treatment of diabetes as biological anti-hyperglycemic drugs (7). Studies have shown that mushrooms display anti-diabetic properties, including antioxidant, blood glucose level reduction, insulin secretion through glucose stimulation, digestive enzymes, and inhibitory effects on tyrosine kinase (8-16). Mushrooms in the phyla *Ascomycota* and *Basidiomycota* are much admired for their nutritional value and pharmacological properties. In traditional medicine, they have long been used to maintain health, and prevent and treat various human diseases. Many studies have documented the beneficial effects of medicinal mushrooms in the treatment of diabetes (17-21). However, scientific evidence is insufficient to conclude the effectiveness of individual medicinal mushrooms. Mushrooms belong to the genera *Ganoderma* (*G. lucidum*), *Auricularia* (*A. auricula-judae*), *Inonotus* (*I. obliquus*), *Morchella* (*M. conica*), *Coprinus* (*C. comatus*), *Tremella* (*T. fuciformis*), *Laetiporus* (*L. sulphurous*), *Lentinula* (*L. edodes*), *Agaricus* (*A. blazei*), *Lignosus* (*L. rhinocerotis*), *Grifola frondosa* and *Phellinus* (*P. linteus*, *P. ribis, P. rimosus* and *P. igniarius*) have shown considerable hypoglycemic effect in experimental diabetic models (3, 6, 20, 22). This review focuses on mushrooms' antidiabetic effects and potential mechanisms of action in both in vitro and in vivo studies. Prospects in this field of research and limitations that may affect the development of potential drugs in mushrooms are also being considered.

Gill mushrooms (Agaricus and Coprinus)

The genus *Agaricus* is the most cultivated edible mushroom in the world (Figure 1). It contains bioactive compounds that may have valuable effects on patients with diabetes mellitus (23-25). *Agaricus bisporus* (white button mushroom) contains high amounts of dietary fibers and antioxidants, including vitamin C, D, and B12; folates; and polyphenols which may have beneficial effects on cardiovascular and diabetic diseases (24). Ekowati et al. (2018) determined the effects of *A. bisporus* administration on the blood glucose, and malondyaldehyd levels as well as superoxide dismutase activity of alloxan-induced diabetic rats and showed that *A. bisporus* extract could lower blood glucose levels and malondyaldehyde and also increase superoxide dismutase (26). *A. bisporus* extract can be used as an alternative natural anti-diabetic agent and can be applied easily and on a more controlled industrial scale in the community (26). Abou Zaid et al. (2017) concluded that, *A. bisporus* has an anti-diabetic effect against streptozotocin-induced pancreatic islet damage (4). In addition, repair/regeneration of β-cells in the islets of Langerhans and induce insulin synthesis and secretion. The therapeutic effects of *A. bisporus* are dependent on its anti-oxidant properties and improving the action of the anti-oxidant system against the oxidative stress of Streptozotocin and its harmful effect.

Coprinus is also called shaggy mane, shaggy ink cap, chicken drumstick mushroom, or lawyer's wig. In Asian countries, *Coprinus comatus* is approved as an edible mushroom and is often cultivated for consumption, while in many other countries, although it is widespread, it is not recognized and not used (Figure 1). Various studies have shown many biological activities of *C. comatus*, including anti-diabetic, anti-cancer, anti-oxidant hepatoprotective, anti-inflammatory, anti-obesity, anti-bacterial, anti-androgenic, anti-fungal, anti-nematode, and anti-viral (15). *C. comatus* is a nutritious and delicious edible mushroom that is also highly valuble due to its physiological benefits. It has been reported to have anti-diabetes, anti-tumor, and anti-mutagen properties and to protect the liver from damage (27-30). Also, Ding et al. (2010) reported that, *C. comatus* declined blood glucose levels and enhanced glucose tolerance in normal mice due to a diet containing 33.3%

(w/w) dried fruiting bodies of *C. comatus,* and it had a slowly developed, mild hypoglycaemic condition on normal mice (27).

Ganoderma is a fungus that causes a wood rot infection through tree injuries. It strikes large roots and the base of the trunk but can expand several feet. *Ganoderma* is a rot fungus widely distributed in Asian countries, and many species are used as tonics to increase longevity and health (31) as illustrated at Figure 2. *G. lucidum* extracts have been identified as a possible supplemental treatment for diabetes. Polysaccharides, proteins, proteoglycans, and triterpenoids of *G. lucidum* have been shown hypoglycemic effects (32-33). *G. lucidum* polysaccharides have been shown hypoglycemic activity by decreasing plasma sugar levels and increasing plasma insulin levels in mice. Protein tyrosine phosphatase 1B is a good therapeutic target in diabetes, and *G. lucidum* proteoglycan can hinder this enzyme *in vitro*. Also, *G. lucidum* triterpenoids have exhibited an inhibitory effect on aldose reductase and α-glucosidase, which can suppress postprandial hyperglycemia (34). Jung et al. (2005) reported that, the bioactive polysaccharide components of *G. applanatum* are responsible for anti-diabetic properties (35).

Grifola frondosa (Maitake), belonging to phylum: *Basidiomycota*, class: *Agaricomycetes*, order: *Polyporales*, and family: *Meripilaceae* (Figure 2) has been verified to possess substances with anti-diabetic activity. When 1 g/d of powdered fruit body of maitake was administered orally to a genetically diabetic mouse (KK-Ay), a decrease in blood glucose was observed, in contrast to the control group. In addition, plasma insulin and triglyceride levels showed a similar change to blood glucose levels when maitake was administrated (36). *Grifola frondosa*, a high-value medicinal mushroom, is popularly consumed as traditional medicine and health food in China and Japan. It is an herbal medicine traditionally used to treat inflammation, cancer and diabetes (37). Kou et al. (2019) also indicated that *G. frondosa* polysaccharides exhibited hypoglycemic activities against diabetic rats (38).

In the last decade, several investigations have documented the biological activities of *Inonotus obliquus* fruiting bodies, such as anti-cancer, anti-oxidation, anti-inflammatory, anti-diabetic and immune-enhancing activities (4, 39-40) (Figure 2). The medicinal benefits of *I. obliquus*, known as 'Chaga' have recently been demonstrated with strong anti-cancer, anti-oxidation, anti-inflammatory and anti-diabetic effects (13). Etracts of Chaga (*I. obliquus*) act as an anti-diabetic by lowering blood glucose levels. Polysaccharides are one of the main components of Chaga extracts, are able to inhibit alpha-glucosidase, an enzyme that hydrolyzes carbohydrates. Thus, Chaga extracts act as a hypoglycemic agent by slowing glucose uptake in the digestive tract, thereby preventing hyperglycemia (41-42). Sun et al. (2008) and Thomas et al. (2020) reported that polysaccharides of *I. obliquus* are capable of lowering the level of glucose triglycerides, fatty acids, and cholesterol levels in the blood (43, 13). *Laetiporus sulphurous* species commonly known as sulfur shelf, sulfur polypore, or chicken of the woods. It is an edible wood-rotting basidiomycete fungus belonging to the family *Polyporaceae* (Figure 2). It is widespread in Europe, Asia, and North America. This fungus is commonly found on hardwoods or conifers. *L. sulphureus* can be easily recognized by its striking yellowish or orange-coloured shelf-like fruit bodies. It is also easily recognized in forests and urban areas due to its impressive size (up to 40 cm wide) and brilliant bright sulfur yellow to orange coloured porous basidiocarps. *L. sulphureus* species is rich in several bioactive compounds such as polysaccharides, triterpenes, laetiporic acids, lectins, α-glucans, and phenolic compounds. Unlike other polypores, *L. sulphureus* has a long consumption history, especially in Thailand, North America and Japan. Additionally, this fungus has long been used in Asian herbal medicine and is also known as a source of anti-diabetic, anti-oxidant, anti-tumor, anti-viral,

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anti-inflammatory, anti-coagulant, anti-bacterial and other properties (15, 44).

The mushroom *Lignosus rhinocerotis*, belonging to phylum: *Basidiomycota*, class: *Agaricomycetes*, order: *Polyporales*; and family: *Polyporaceae,* which is native to tropical regions such as Malaysia, Indonesia, and the Philippines (Figure 2), contains a very large amount of potential anti-oxidants and anti-diabetic agents. Biological compounds present in the freeze-dried *L. rhinocerotis* powder have been found to exhibit anti-diabetic properties by significantly reducing elevated blood glucose concentrations to a normal range (Nyam et al. 2017, Ganesan & Xu 2019). *Phellinus* mushroom, known as "Sanghuang" in China, is a valuable functional mushroom that has been considered a food source for centuries in several East Asian countries, including China, Korea, and Japan (Figure 2). *P. baumii* has a wide range of biological activities, such as blood lipid-lowering, anti-tumor, anti-influenza, anti-oxidation abilities, and blood sugar regulation (45). Earlier studies have revealed that extracts and some phenolic compounds from the wild *Phellinus* show a hypoglycemic effect. Phenolic compounds isolated from the fruit body of wild *Phellinus* have been shown to exhibit a hypoglycemic effect; they consist of hispidin, chlorophellins C, gilvsins A, B, C, D, 7,8-dihydroxycoumarin, 3,4-dihydroxybenzalacetone, 7,3′-dihydroxy-5′-methoxyiso-flavone, and inoscavin C (46-47).

In the previous studies by Yang et al. (2020), and Jang et al. (2010), the fruit body of wild *P. baumii* has been reported to alleviate diabetes, and antioxidants are beneficial to diabetes by protecting the β-cell from damage due to oxidative stress (46, 48). The cultivated *P. baumii* fruit body was extracted with 80% ethanol extracts, and different fractions were obtained using petroleum ether, ethyl acetate (EtOAc), n-butanol (n-BuOH), and water. The results revealed that the ethyl acetate fraction showed the highest inhibitory effect on α-glucosidase activity, which was higher than the positive control. It was composed mainly of phenolic compounds with a purity of 79.45% and characterized by liquid chromatography-mass spectrometry as osmudacetone, hispidin, davallialactone, 2,5-bis(4,7-dihydroxy-8-methyl-2-oxo-2H-chromen-3-yl) cyclohexa-2,5-diene-1,4-dione, hypholomin B, and inoscavin A. Furthermore, the ethyl acetate fraction increased the glucose consumption of insulin-resistant HepG2 cells. The ethyl acetate fraction also demonstrated antioxidant activities by scavenging1,1-diphenyl-2-picrylhydrazyl,2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic) diammonium salt, and hydroxyl radicals. The ethyl acetate fraction of the cultivated *P. baumii* fruit body had significant anti-diabetic effects, probably due to the high content of selective phenolic compounds. Thus, the cultivated fruit body of *P. baumii* can be a sustainable source for the treatment of diabetes (48).

Jelly mushrooms (*Auricularia and Tremella*)

Auricularia auricula-judae or commonly known Judas's ear or the jelly ear fungus, is an edible mushroom characterized by its brownish, ear-like jelly shape. *A. auricula-judae* fruit body consists of a high content of carbohydrates, protein, and minerals such as calcium, phosphorous, potassium, and iron. *Auricularia* species are widely investigated due to medicinal biological activities exerted by their extracted compounds (20). Fruit bodies of *A. auricula-judae* grow on wood and are commonly used as food and as anti-diabetic, anti-hypertensive, anti-inflammatory, immunomodulatory, anti-cancer, and anti-microbial drugs in many Asian countries (Figure 3). *A. auricula-judae* has been commercialized in industry and represents a promising source for new chemical compounds with different biological functions (13, 20). *Tremella* is a genus of fungi belonging to Division; Basidiomycota, Class; Tremellomycetes, Order; Tremellales, Family; Tremellaceae. Basidiocarps are gelatinous and described as jelly fungi (Figure 3). *Tremella* species grow mainly on wood rotting. Some species of *Tremella* parasitize the fruiting bodies of their hosts (fun-

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gal hosts) and are sometimes attached to the host's hyphae, and others to wood mycelium. *Tremella* species occur worldwide as a group. Currently, more than 100 species of *Tremella* are identified worldwide. *Tremella fuciformis*, and *Tremella aurantialba* are cultivated commercially for food and medicinal purposes (4). Exo-polysaccharides from *T. fuciformis* may be beneficial for the fight against type 1 diabetes mellitus. When the blood glucose level is higher than exo-polysaccharides from *T. fuciformis* the lowering effect is not fast and the function is not satisfactory (49). Kiho et al. (2001) reported that continuous oral administration of a solution of acidic polysaccharide (TAP) (0.5 g/l) and TAP-H solution (degradation products of TAP) (1.5 g/l) reduced plasma glucose levels in diabetes and that demonstrated by using KK-Ay mice (non-insulin dependent diabetes) (50). TAP and TAP-H significantly reduced insulin, total cholesterol, and triglyceride levels in the blood of the mice. In fecal excretion, TAP and TAP-H significantly increased the total bile acid, while the cholesterol content of both groups was lower than the control. In addition, TAP and TAP-H significantly reduced the plasma lipoperoxide level. A study shows that TAP and TAP-H have an anti-diabetic effect in a diabetes model mouse (50).

Other mushrooms (*Morchella, Cordyceps*)

Ascomycetes inhabit a wide range of ecological niches, perform vital ecosystem roles, particularly in carbon cycling and serve as symbiotic partners with several tree species. Most ascomycetes are usually associated with plants as pathogens or decomposers. Ascomycetes mushrooms are known for their use as a source of food and therapeutic bioactive compounds, such as *Morchella. Morchella* is one of the most economically beneficial and edible wild mushrooms (Figure 4). It has several common names, such as guchi, morel, yellow morel, sponge morel, common morel, true morel, morel mushroom and so on. *Morchella* has nutritional and medicinal values due to its unique bioactive compounds, such as fibers, vitamins, polysaccharides, proteins, and trace elements (4, 51). *Morchella conica* is an edible mushroom that exhibits anti-diabetic properties. It showed controlled hyperglycemic index is an alteration of PTP1B protein indication in the liver and pancreas. *Morchella conica* is a potential source of treatment for diabetes mellitus, involved in reducing elevated blood glucose levels during diabetes, which is further studied with oral hypoglycemic therapy (52).

Elkhateeb et al. (2019) documented that, the polysaccharides of *Cordyceps sinensis* and *Cordyceps militaris* (insect pathogen mushrooms), represent the major existing compounds and exhibit anti-diabetic, anti-oxidant, anti-inflammatory, anti-cancer, anti-microbial activities (6). *Cordyceps sinensis* and *C. militaris* extracts are safe pharmacological agents with good anti-diabetic and anti-nephropathic properties and have great potential as a new source of diabetes treatment (53) (Figure 4). *Cordyceps militaris* extracts revealed a considerable decline in blood glucose levels by enabling glucose metabolism and strongly suppressed total cholesterol and triglycerides concentration in serum. Extracts of *C. militaris* exhibit anti-oxidative activity, as evidenced by normalized levels of superoxide dismutase and glutathione peroxidase. Inhibitory effects on blood urea nitrogen, creatinine, uric acid, and protein demonstrated the protection of *C. militaris* extracts against diabetic nephropathy (54-55).

Prospects of developing medicinal mushrooms for clinical trials in patients with diabetes

Currently, the enormous potential of mushrooms for treating diabetes has been studied. However, there are many unknowns and limitations in the application of fungal bioactive compounds in diabetic patients. Currently, most studies focus on polysaccharide-enriched fractions or crude mushroom extract. A relatively limited number of studies have also been conducted on several species of mushrooms that are used as medicines for patients with type 2 diabetes. Therefore, further studies are needed

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to investigate the treatment of type 2 diabetes and the pure compounds and their therapeutic potential in diabetic patients by mushroom (56).

Conclusion

Medicinal mushrooms represented by *Ganoderma applanatum* and *Ganoderma lucidum Cordyceps sinensis* and *Cordyceps militaris, Auricularia auricula-judae, Inonotus obliquus*, *Morchella, Coprinus, Laetiporus, Tremella, Agaricus, Phellinus, Grifola frondosa* and *Lignosus rhinocerotis* have been recommended as a source of natural biologically active compounds and have been targeted as potential hypoglycemic and anti-diabetic agents since ancient times. Polysaccharides, proteins, dietary fibers, and other bioactive compounds isolated from edible mushrooms have been shown to lower blood sugar levels in both in vivo and in vitro models. Currently, significant studies have been conducted to investigate the mechanisms of hypoglicemic activities of mushrooms, and a large number of triterpenes and polysaccharides have been extracted from them. However, it is important to isolate and identify bioactive compounds with anti-diabetic potential from multiple mushroom species. Future investigations and further research are needed for bio prospect new medicinal and edible mushrooms for anti-diabetic efficacy and subsequent isolation of active biomolecules.

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