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BIOACTIVE METABOLITES WITH PHARMACOLOGICAL POTENTIAL FROM MEDICINAL MUSHROOMS

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ABSTRACT

Medicinal mushrooms comprise powerful tools for new pharmaceutical products. Traditional folk medicine and ethnomycolgy contains many natural compounds are the important source of bioactive compounds. Many basidiomycetes mushrooms contain biologically active polysaccharides, triterpenoids, lignins, sterols in fruit bodies, cultured mycelium and culture broth. It is also understood that the mushroom may be a potential source of therapeutically useful compounds. The current review states the various mushrooms and their bioactive metabolites with some pharmacological potential which could be the potential source of medicinal compounds in future.

Keywords: Medicinal mushrooms, pharmacological potential, nutraceuticals, bioactive metabolites

INTRODUCTION

The fungi are commercial used in pharmaceutical industry, textile industry, detergent industry, food and feed industry, paper and pulp industry and beverage industry. Greek and Roman authors mentioned mushrooms as food and medicines. But still human being has been using fungi in their day to day life and the historical records showed that they were use fungifor making wines, cheese, bread etc. The medicinal mushroom, Shiitake (*Lentinula edodes*) has been cultivated and used for its medicinal effect **[1]**. Medicinal musrooms like *Ganoderma lucidum* (Ling

zhiin Chinese), reveals its ancient use and comprise untapped source of new pharmaceutical products **[2]**. Fleshy mushrooms have been used as nutritional foods throughout the world by people **[3]**.

As mushrooms and their compound isolated from extracts have promising health promoting benefits and consequently, became essential components in many traditional Chinese medicines. More than 300species of mushrooms that is widely known to possess various therapeutic potential **[4]**.

REVIEW AND DISCUSSION

BIOACTIVE METABOLITES OF MEDICINAL MUSHROOMS

There are variety of pharmaceutical substances with potent and unique health-enhancing properties were isolated recently from medicinal mushrooms **[5]**. Mushrooms are functional food and are a source of biologically valuable components that offer great therapeutic potential for the prevention and control of several diseases. Higher basidiomycete contains the wide ranges of chemical substances which have been described and their medicinal properties evaluated.

Polysaccharides are the best known and most potent bioactive compounds in mushrooms with antitumor and immune modulating properties **[2, 5, 6]**. Three polysaccharide based carcinostatic (immuno therapeutic) agents viz., Lentinan, Kerstin and Schizophyllan have already been commercialized from mushrooms namely, *Lentinus edodes*, *Coriolus versicolor* and *Schizophyllum commune* respectively. These are used currently in the treatment of cancer of the digestive organs, lungs, breast, stomach and cervical cancers **[7]**. Numbers of promising candidate still are to be worked out for the potential polysaccharide source and their biological activities. Further, there is an urgent need to study the downstream mechanism of action at molecular level that occur in specific immune modulation such as receptors and the various events triggered by the binding of these polysaccharides to the target cells **[7]**.

Lentinan is a β-D-glucan, shown by electrophoresis and ultra-centrifugation, as well as by other chemical techniques and instrumental analysis and isolated from the mushroom *Lentinus edodes* (≡ *Lentinula edodes*). Wasser and Weis studied the extraction, structure and activities of lentinan in details **[1, 5]**. Several species belonging to the polyporaceae are also studied as multipurpose medicines that are not only carcinostatic but also anti-inflammatory,

antiviral (against AIDS), hypoglycemic and anti-thrombotic **[7]**.

The major groups of polysaccharides are glucans with different types of glycosidic linkages, viz., 1-3, 1-6 β-glucan and α-glucan. β-glucans are the polysaccharides which yields D-glucose on acid hydrolysis **[6]**. Variation also observed in chemical conformation, the structure of schizophyllan (β-D-glucan) has a triple strand right winding, whereas the acidic glucoronoxylomannan from *Tremella fuciformis* shows left handed three-fold helical back bone **[2]**.

In addition to the heteropolysaccharides, proteoglycans i.e., protein polysaccharide complex have also been reported from various mushrooms. These types of complexes are reported to possess more bioactivity than polysaccharide. Here in the backbone of polysaccharide is attached with side chains of peptides as in case of Ganoderan B and C **[8, 9]**. Wasser has reported various polysaccharides and their structures from different mushrooms having antitumor and immunostimulant activity **[2]**.

Table 1: Polysaccharides from different mushrooms and their biological activities [10]

Mushroom	Compound name	Activity
Calvatia gigantean	Calvacin	Antitumor
Schizophyllum communae	Schizophyllan	Antitumor
Lentinus edodes	Lentinan	Antitumor, anti-cancer, immunostimulating, antiviral
	KS-2 (glycoprotein)	Antitumor, interferon induction, cytocidal
	LAP	Immunoactivation, Antitumor
	LEM, EP3	Immunoactivation, Antitumor
Tremetes versicolor	PSK, Krestin, CPS	Immunostimulating, Antiviral, Antitumor, antigenotoxic
Innonotus obliqus	Befungin	Antitumor
Agaricus blazei	ATOM. AB-FP	Antitumor
Auricularia auricular	—	Antitumor
Pestalotia species	—	Antitumor
Volvariella volvaceae	—	Antitumor
Phellinus linteus	glucans	Antitumor, Immune modulation
Falmmulina veluticeps	EA-6, Proflamin	Antitumor, Immunostimulating
Dictyophora indusiata	T-4-N, T-5-N	Weak antitumor
Grifiola frondosus	—	Antitumor, Immunostimulating
Tremella fusiformis *T. messenterica*	— GXM	Antidiabetic —
Cordyceps sp.	CS F30, CI-P and CI-A	Anticancer, Hypoglycemic, Immunostimulating

The triterpenes are called as Ganoderic acids, Lucidenic acid etc., which are the acid type of triterpene whereas the triterpene alcohols are called as Ganoderiol or Lucidumol etc. **[11]**.

Proteins have been isolated and analyzed from various species of *Ganoderma*. Many

bioactive proteins have also been isolated from different medicinal mushrooms, e.g. LZ –8 (Ling Zhi –8), which is an immunomodulatory protein isolated from the mycelia of *Ganoderma lucidum*. The complete amino acid sequence of this protein has also been carried out [12]. Similarly, another immunomodulatory protein has been isolated from *Ganoderma tsugae*; (Fungal immunomodulatory protein) Fip –gts **[13]**. Other Fips have been isolated form *Flamulina veltipes* (Fip –fve) and *Volvariella volvacea* (Fip –vvo), **[13]**. Apart from these, proteins with relatively low sugar content (lectin) have been isolated from the mycelia of *Ganoderma lucidum* (GLL –M) and from fruit body (GLL -F) **[14, 15]**.

Germanium in organic form is found in many plants and fungi. The organic form is known to possess anticancer and immune enhancer / stimulator it induces interferon and activates macrophages, also enhances the natural killer cell activity **[16]**. Patocka highlighted the importance of the germanium from *Ganoderma lucidum*, and also supported the above mentioned biological activities of germanium.*Cordyceps sinensis* show antitumor activity **[17]**. Ergo peroxide was found to be greater inhibitor to the proliferation of K562, Jurkat, WM – 1341, HL – 60 and RPMI – 8226 tumor cell lines **[18]**. The ergo peroxide from *Meripilus giganteus* was identified as immunosuppressive component **[19]**.

The physiologically active substances of *Ganoderma*spp. are water-soluble polysaccharides and alcohol-soluble triterpenoids. The dietary supplements from *Ganoderma*are valued for their immunomodulating, anticancer, antiviral properties. Most bioactive β-D-glucan and schizophyllan from split gill effective against cervical cancer **[20]**.

Coprinus comatus and *Phellinus linteus*arerich in trace elements like vanadium, chromium, zinc, magnesium, copper, iron, and nickel on glycemic response and enhanced the expression of co-stimulatory molecules **[21, 22]**. Antimicrobial activity of puffball (*Boviste llaradicata*) was carried out by Ye et al, the different extracts and fermentation broth of puffball was investigated by LC–MS and semi-preparative chromatograph **[23]**. This Puff balls contains bioactive constituents which showed inhibition of the enzyme α-amylase and the *in vivo* antidiabetic activity exhibited by *Calvatia gigantean* **[24]**.

SUBMERGED CULTURE OF MUSHROOMS

Polysaccharides are the best known and most potent bioactive compounds in mushrooms

with medicinal properties against various diseases **[2, 5, 6]**. Exopolysaccharides (EPS) from microorganisms have been extensively studied due to the wide range of applications in various fields, including the food, pharmaceutical and cosmetics industries and their medicinal properties. Many investigators use submerged culture for the production of mycelial biomass and bioactive polysaccharides which possess polysaccharides produced by fungi possess biological and pharmacological activities. Khdari *et al.,* **[25]** investigated the pharmacological importance of *Phellinus torulosus*, *Fomes fomentarius*, *Trametes versicolor*, *Pisolithus albus*, and *Fomitopsis pinicola* **[25]**.

Various synthetic media like mushroom complete medium, yeast malt extract and Potato malt peptone, PD broth used for submerged mycelial growth and exo-biopolymer production **[26, 27]**. The *Phellinus linteus* mushroom, optimum culture conditions for the production of mycelial growth and extracellular polysaccharides. The pH and temperature played significant role in maximum biomass production and extracellular production **[28]**.

MEDICINAL PROPERTIES OF SOME MUSHROOMS

The bioactive polysaccharides isolated from mushroom fruit-bodies, submerged cultured mycelial biomass or liquid culture broths effective against various diseases which showsimmunomodulatory, hepatoprotective, antidiabetic, arthritis, antitumor, carcinoma, Antifatigue, antistress, hypocholesteromic activities.

Phellinus rimosus showed cytotoxic and antitumor activity against the Daltons lymphoma ascites and Ehrlichs ascites carcinoma cell lines **[29]**.The cytotoxic mechanism of protein-bound polysaccharide isolated from *Phellinus linteus* which inhibited the proliferation and colony formation of human colon cancer cells **[30, 31]**. The polysaccharides from the *Phellinus gilvus* showed inhibitory effects on the benzo(a) pyrene-induced forestomach carcinogenesis in mice **[32]**. Sasaki *et al* and Chen *et al* investigated the antitumor activity of the polysaccharides from polyporaceae members like *Ganoderma applanatum* and *Phellinus linteus* **[33, 34]**. For the treatment of gestational diabetes mellitus many bioactive substances like polysaccharides, β-glucan, vanadium and other nutrients isolated from medicinal mushrooms are used which also improves immunomodulation **[35]**.

Activity of *Ganoderma lucidum* polysaccharides on immune functions with

advanced lung cancer and changes in IL-1 were correlated with those for IL-6, IFN-γ, CD3, CD8 and NK activity **[36]**.Young et al studied the immune cytokine production by endopolysaccharides and exopolysaccharides from *Lentinus Lepidus* **[37]**.

Kuo *et al* (2007) **[38]** reported the *Cordyceps sinensis* active asimmunomodulatory polysaccharides from submerged culture which enhanced the production of pro-inflammatory cytokines, TNF-α, IL-6 and IL-10 in human peripheral blood. *Cordyceps sinensis* showed hypocholesterolemic, antifatigue and antistress activity of hot water fraction by oral administration of mycelia of *cordyceps sinensis* in mice. C-peptide response observed during oral glucose tolerance test and insulin area and glucose insulin index obtained from OGTT were significantly decreased in the *Cordyceps* fermentation product **[39, 40]**.

Phellinus linteus involved in prevention and treatment of autoimmune joint inflammation such as rheumatoid arthritis. Prevention and treatment of collagen-induced arthritis in mice carried out by proteoglycans of *Phellinus linteus* showed decrease in anti-type II collagen IgG and IgG2a antibodies **[41, 42]**. Cho *et al* investigated the potential preventive effect of *Phellinus linteus* extract on the inhibition of gap junctional intercellular communication, induced by hydrogen peroxide in WB-F344 rat liver epithelial cells **[43]**.

Antioxidant activity of *Pleurotus florida*, *Pleurotus sajor-caju*, *Ganoderma lucidum* and *Phellinus rimosus*. Trolox equivalent antioxidant capacity, Ascorbic acid equivalent antioxidant capacity, DPPH and Oxygen radical absorbance capacity assay checked for antioxidant capacity. The *Pleurotus rimosus* had more ability to prevent radical scavenging activity which showed highest scavenging of ABTS (2, 2 – azobis-3-ethyl benzthiazoline-6-sulfonic acid) radical in terms of ascorbic acid equivalent **[44]**.

The pulmonary inflammation inhibits by the extract of *Phellinus gilvus* and *Phellinus baumii* in lipopolysaccharides induced rats **[45]**. Effects of *Phellinus linteus* on mast cell mediated anaphylaxis-like reaction which also showed increased level of intracellular cAMP, *Phellinus linteus* extracts inhibits the mast cell mediated anaphylaxis like reaction *in vivo* and *in vitro* murine models **[46]**. Extracts of *Phellinus linteus*, *Paecilomyces tenuipesand Cordyceps sinensis* improved the insulin secretion and insulin resistance **[47]**.

Phellinus linteus water extracts influences immune response in mitomycin-C induced

immunodeficient mice. The Plaque forming cells per 10^6 spleen cells increased and population of IFN-γ and IL-4 producing T-lymphocytes also increased **[48]**. Polysaccharides isolated from *Phellinus gilvus*effective on the healing of rat dermal wounds. *Phellinus gilvus* extract increased the rate of reepithelization is significantly higher and complete epithelization and macrophages were occurring **[49]**.

Anticarcinogenic activity of Phansomba (*Phellinus merrillii* and *P. fastuosus*) on SiHa cell lines, hot and cold water and ethanol extracts and were tested for cytotoxicity and cell viability. Both species inhibited the SiHa cell growth at concentration 500 µg/ml **[50]**.

MEDICINAL MUSHROOMS WITH HYPOGLYCEMIC AND ANTIDIABETIC ACTIVITY

Many investigators studied the medicinal mushrooms which contain bioactive compounds with hypoglycemic and antidiabetic properties. The exopolysaccharides from the liquid culture of medicinal mushroom *Phellinus baumii*, consist heteropolysaccharides and proteoglycans showed hypoglycemic activity on streptozotocin induced diabetic rats **[51]**. Kim *et al* reported the *Phellinus linteus* mushroom, the plasma glucose, triglycerides, cholesterol levels decreased by 49%, 32% and 28% and aspartate aminotransferase activity was significantly reduced **[52]**. Exopolysaccharides of *Phellinus baumii*produced by submerged culture its hypoglycemic activityand they were analyzed the application in proteomics for mining biomarkers of diabetes **[53]**. Cho *et al* reported the hypoglycemic effects of exopolysaccharides produced by mycelial culture of *Tremella fuciformis* (Tf) and *Phellinus baumii* (Pb) in *ob*/*ob* mice **[43]**. Extracellular polysaccharide from *Laetiporus sulphureus var. miniatus* has stimulatory effects on RINm5F cells proliferation and insulin secretion. Insulin concentration was significantly increased with increased concentration of EPS **[53]**.

Yang et al and Yamac *et al* reported exopolymer extracted from *Lentinus edodes*and *Lentinus strigosus*showed hypoglycemic effect in streptozotocin induced diabetic rats **[54, 55]**. *Pleurotus pulmonarius* extract increased the tolerance for glucose and with combination glyburide has sustained antihyperglycemic effect **[56]**. Water soluble polysaccharides from *Pleurotus citrinopileatus* glucose peptone broth by submerged fermentation and showed significantantihyperglycemic effect **[57]**. Fermented mushroom *Grifola frondosa* rich in vanadium which has potent

hypoglycemic activity in alloxan and adrenalin induced hyperglycemic mice. Vanadium at a lower dose in combination with *Grifola frondosa* induced significant decrease the blood glucose and HbA1c levels in hyperglycemic mice **[58]**.

Cordyceps militaris, *Cordyceps sinensis*, *Tricholoma mongolicum, Fomitopsis pinicola* and *Omphalia lapidescens* mushroom were studied in streptozotocin induced diabetic rats which showed a potent hypoglycemic activity **[59, 60]**. The hypoglycemic effect of aqueous crude extract of *Phellinus badius* were investigated in alloxan-induced diabetic rats **[61]**.

As plants and medicinal mushrooms contains the bioactive compound which showed antiglycemic effect. Lee *et al* studied inhibitory constituents of Aldose reductase in the fruiting body of *Phellinus linteus.* Bioactive components of Fruit body of *Phellinus linteus* was characterized and identified as hispidin, phelligridimer, davallialactone, methyldavallialactone, hypholomineB , interfungins A and inoscavin A, studied this compounds for rats lens aldose reductase inhibitory activity and Human recombinant aldose reductase inhibitory activity from this compounds davallialactone, hypholomine B and ellagic acid exhibited potent rat lens aldose reductase and human aldose reductase inhibitory activity with IC_{50} values of 0.33, 0.82, 0.63 µM and 0.56, 1.28, 1.37 µM **[62]**.

Lee et al isolated and characterized the rat lens aldose reductase inhibitory activity from the fruiting body of *Ganoderma aplanatum* **[63]**. Lee et al investigated the bioactive compounds from the *Phellinus linteus* and conducted protein glycation inhibitory activity *in-vitro* using model systems of hemoglobin-δ-gluconolactone, bovine serum albumin- methylglyoxal and N^{α}-acetyl-glycyl-lysine methyl ester-D-ribose **[62]**.

CONCLUSION

The present review focuses the potential of medicinal mushroom as hypoglycemic agent against diabetes. The present review has shown that bioactive compound like polysaccharides, β-glucan and other nutrients in mushrooms showed hypoglycemiceffect by improving immunomodulatory responses, liver and enzyme functions. Nutraceuticles and dietary sourcesareused to manage a severe diseases and metabolic disorder. Therefore, Medicinal mushroom with potent bioactive metabolites could be used widely in future research for better health benefits.

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