Medicinal mushrooms: Towards a new horizon

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ABSTRACT

The arising awareness about functional food has created a boom in this new millennium. Mushrooms are widely consumed by the people due to their nutritive and medicinal properties. Belonging to taxonomic category of basidiomycetes or ascomycetes, these mushrooms possess antioxidant and antimicrobial properties. They are also one of the richest source of anticancer and immunomodulating agents. Thus these novel myochemicals from these mushrooms are the wave of future.

Key words: Anticancer,antimicrobials, antioxidants, immunomodulators, mushrooms, myochemicals

INTRODUCTION

The concept of "functional food" has been raised from the knowledge of a relationship between diet and disease and thus it has led to the development of a new scientific discipline, which is termed as "functional food science."[1] A food could be accounted as "functional" if it contains food component that affects any identified body function in a positive manner, and could be available in different forms or under different names viz. dietary supplements, medicinal foods, vita foods, phytochemicals, and myochemicals and also pharmafood, which could be used specifically to improve the health.[2]

Among the developed nations, there are many causes of death or disability that include heart diseases, diabetes, obesity. and cancer, which could be attributed to diet.[3] Scientific evidences justify the fact that diet influences the health as well as controls and modulates many functions of body and thus plays an important role in the maintenance of good health; this homeostasis produced. therefore, decreases the chances of many chronic diseases.[4] Millennia are evident that mushrooms have been extensively used by human for consumption, which is due to their flavor and medicinal properties. Widely sold as nutritional agents, these mushrooms are helpful to human health.[5,6] These mushrooms are extensively known for their immunomodulatory, hepatoprotective, antinoceceptive, antidiabetic, antiviral, and antimicrobial properties.[7,8]

"Mushroom" is not a taxonomic category. Chang *et al*. defined the mushrooms as "a macro fungus with distinctive fruiting bodies that could be hypogeous or epigeous, large enough to be seen by naked eyes and to be picked by hands."[9] From taxonomic view, mainly basidiomycetes and some species of ascomycetes belong to category of mushrooms. Mushrooms constitute 22,000 known species. They are widely available on earth and about 10% of them are explored. It is an estimate that there are about 140,000 species of mushroom present on earth.Among the unexplored and unexamined mushrooms, if the proportion of useful mushroom is 5%, it suggests that 7000 undiscovered species would possibly provide benefit to mankind.[10] Several thousand years ago, it was recognized that many edible and some nonedible, nonconsumable mushrooms could have valuable health benefits. The edible class of mushrooms that shows potential medicinal and functional properties includes *Lentinus*, *Auricularia*. *Hericium*, *Grifola*, *Flammulina*, *Pleurotus*, *and Tremella*. The other species known only for their medicinal properties include *Ganoderma*, *Trametes*, etc. As they are coarse, harder in texture, and are bitter in taste.[11,12] Mushrooms are found to be good source of vitamins especially thiamine [B_1], riboflavin [B_2] niacin, biotin, and ascorbic acid (vitamin C). Vitamin A and D are rarely found but certain species contain detectable amount of vitamin D when exposed to UV light. Crude fat content of mushroom consists of lipids viz. mono, di, and triglycerides, sterols, phospholipids.[13]

In the present era, medicinal mushrooms are being focused for discovering such compounds that could modulate the response of immune cells. Thus by doing so, they might be useful for stimulating and enhancing the biological response of immune system. And therefore they could be utilized for the treatment of tumor and other immunodeficiency status along as a combination with antibiotics as well as vaccine adjuvant.[14] In case of immunosuppressive activity, they might be used in autoimmune diseases.[15]

As stated earlier, being fungi, mushrooms contain a variety of

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constituents that have plethora of activities including antioxidant activity, antiinfective activity, anticancer activity, as well as modulation of immune system.

Antioxidant activity

Oxygen by the virtue of its oxidation properties plays a pivotal role in biological system that include nutrient utilization, transport of electrons for production of ATP, and removal of xenobiotics.[16] Oxygen gets converted into reactive form, for instance, superoxide radical [O_2^-], hydroxyl radical [·OH], and H_2O_2 that have the DNA nicking property, which could also harm essential enzymes and structural proteins and may lead to autooxidation or lipid peroxidation.[17,18] Mushrooms have been found to contain antioxidant substance that could prevent the destructive oxidative process within the organism.

Phellinus rimosus

The species is mostly confined to plains and tropical forest.[19] In Chinese medicine, the hot water extracts of fruiting body *of Phellinus* spp. have been reported to be used to cure many ailments and it is believed to refresh human body and promotes longevity.[20] Various extracts of *Phellinus* spp. are found to scavenge O_2^-, ·OH, and nitric oxide radicals generated from free radicals when studied *in vitro*.[21-23]

Ganoderma

Ganoderma lucidum and other related species describe their longest historical usage. Near about 4000 years ago due to their medicinal properties,[24] *Ganoderma* spp. is to be famous tonic and found an important place in Chinese medicine due to its beneficial effects to all viscera and nontoxic nature [Figure 1].[25]

Phenolics and other phytoconstituents found in *Ganoderma* efficiently scavenged the O_2^-, ·OH radical generated experimentally during *in vitro* studies and thus are found to have antioxidant and chelating activity along with reducing power and chelating abilities.[26]

Agaricus bisporus

Commonly known as button mushroom or table mushroom, *A. bisporus* is cultivated edible basidiomycetes found extensively in Europe and North America.It is perhaps one of the most cultivated species of mushroom across the world. Boiled as well as raw extract of *A. bisporus*, due to virtue of some antioxidants in it, effectively inhibited the oxidative crisis in *in vitro* experiments [Figure 2].[27]

Pleurotus species

Oyster mushroom/*Pleurotus* spp is an edible and extensively grown mushroom.[28] Some species of *Pleurotus* are found to contain antioxidants, antiinflammatory, and antitumor compounds.[29,30] Methanolic extract from fruiting body of *P. florida* are found to have ·OH radical scavenging activity and lipid peroxidation inhibiting activities [Figure 3].[29]

Mushrooms with antioxidant activities are summarized in Table 1

Figure 1: *Ganoderma lucidum*

Figure 2: *Agaricus bisporus*

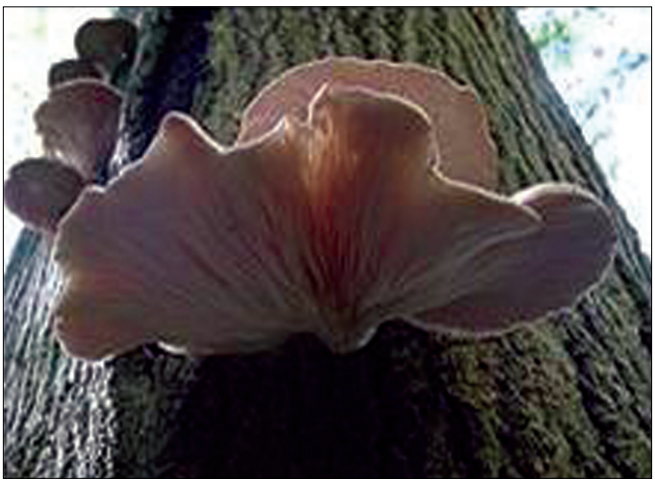

Figure 3: *Pleurotus ostreatus*

Antimicrobial activity

Up till date, multiple drug resistance in human pathogenic microorganism has developed, which might be due to the use of commercial antimicrobial drugs that are used to treat infection.

This has lead to search of a new antimicrobial agent.[34] The mycelia and fruiting body extracts of various array of mushroom have been accounted for antimicrobial activity against a wide range of infectious microorganisms.[35,36]

In order to endure in their natural milieu, mushroom needs antibacterial and antifungal compounds. A number of antimicrobial agents with less or more activities might be isolated from the mushrooms, which may prove themselves to be beneficial to human health.[37] Some mushrooms with antimicrobial activities are discussed next.

G. annulare and allied species

Applanoxidic acid isolated from *G. annulare* [Fr.] Glibn show weak antifungal activity against trichophyton mentagrophytes.[38] Steroidal compounds like 5aergosta-7,22-dien-3b-ol or 5,8 epidioxy-5a,8a-ergosta 6,22- dien 3b ol isolated from *G applanatum* [Pers.] Pat., proved to be weakly active against a number of Gram-positive and Gram-negative microorganisms.[39]

Lentinula edodes

It contains oxalic acid, which is responsible for antimicrobial effect against *Staphylococcus aureus* and other bacteria. Ethanolic extract from the mycelium of *Lentinula edodes* also possess antiprotozoal activity against *Paramecium caudatum* [Figure 4].[40]

A. bisporus

A. bisporus show potential activity against gram positive bacteria and to a lesser extent gram negative bacterium, due to narrow spectrum of activity, it is also effective against *Bacillus subtilis*.[27]

Some antifungal proteins,[41] lectins,[42] ribonucleases,[43] and laccases[44] of mushroom origin are known to inhibit HIV 1 reverse transcriptase [Table 2].

Anticancer activity

National Cancer Institute (NCI US) recently has emphasized upon natural products like plants, marine organisms, and microorganisms as source of new drug discovery. In the year 1956, NCI started screening of some plant drugs for studying anticancer activity. Today currently available and therapeutic useful anticancer drugs are natural products from plants and their derivatives. Mushrooms comprise a vast and yet largely untapped source of powerful new pharmaceutical products. They are the unlimited source of polysaccharides which possess anticancer and immunostimulating properties. The polysaccharides found in mushroom do not directly attack cancer cells but produce antitumor effects by activating different immune response in host. The antitumor actions of these polysaccharides require a T-cell component and their activity is mediated through thymus-dependent immune mechanism. This application depends on biological properties as well as biotechnological availability.[53,54] Some mushrooms with potential anticancer activity are discussed next.

Table 1: Antioxidant properties of some mushrooms

Biological source	Activities
Agaricus bisporus[27]	Effective scavenger of ABTS +
Ganoderma lucidum[31,32]	Effective scavenger of $O_2^{-}\cdot$ and ·OH radicals
Pleurotus florida[29]	·OH radical scavenging and lipid peroxidation inhibiting activities
Phellinus rimosus[22,23]	Effective scavenger of $O_2^{-}\cdot$ and ·OH
Leucopaxillus giganteus[33]	Effective scavenger of O_2^{-}

Figure 4: *Lentinula edodes*

Table 2: Role and therapeutic activities of myochemicals from mushrooms

Biological source	Activity	Constituent
Leucopaxillus giganteu[33]	Antibiotic	Clitocybin
Agaricus bisporus[27]	Antibiotic	-
Phellinus linteus[45,47]	Potent protein glycation inhibitor	Interfungins A,
Phellinus linteus[46]	Potential antitumor agent in breast and bladder cancers	Hispolon
Ganoderma lucidum[95]	Hypoglycemic activity	Ganoderans A and B
Phellinus linteus[48]	Antiarthritic activity	Proteoglycan
Ganoderma lucidum[49-51]	Antifungal	Ganodermin
	Cholesterol synthesis inhibitors	Ganoderic acid
	Txa-2 inhibitor	Ganoderic acid
Piptoporus betulinus Lu[52]	Antibiotic	Piptamine

Phellinus linetus

P. linetus is a basidiomycetes fungus that is found mainly in America, Africa, and Asia and has been recognized as medicinal mushrooms.[55] The biological active component isolated from *P. linetus* are polysaccharides,[56], acidic proteoheteroglycans with mixed α, β linkage, and a [1-6] - branched type [1-3]-glycan.[57] These complex polysaccharides have been detected in a variety of different mushroom species and linked to the immunostimulatory and antitumor activities.[54] Inhibition of invasive melanoma B 16 cells through downregulation of m-RNA level of urokinase plasminogen activator [μPA] and by the inhibition of pulmonary metastasis in mice.[58]

Agaricus bisporus

The polysaccharide fraction of *A. bisporus* extract, which is commercially developed as a dietary supplement for use as an immunostimulating agent and kidney tonic, is also suggested as an anticancer compound due to its immune stimulating properties.[58] Button mushroom are one of the main dietary constituent that can reduce the risk of hormone-dependent breast cancer in women.[59,60] Thus they could be a good prevention strategy because they are available readily, affordable, and acceptable worldwide to people [Figure 5].[66,67]

Pleurotus species

These have high medicinal value. The compounds isolated from them have antihypertensive antihypercholestremic activity.[61-63] Methanolic extract of the fruiting bodies of *Pleurotus florida,*[29] occurring in South India showed profound antitumor activity against the Ehrlich's ascites carcinoma (EAC) cell-line induced solid tumor model in mice.

Lentinus edodes

Lentinan is the first compound isolated which has shown greater antitumor and antiproliferative effects as compared to other mushroom polysaccharides.[64,65] The purified polysaccharides from mushrooms in many xenografts have shown tumor regression. The cytostatic effect produced by lentinan is mainly due to activation of host immune response.[66] Lentinan is a pure polysaccharide composed only of atoms of carbon, oxygen, and hydrogen, the glycoprotein have also shown antitumor activity in xenograft model. Lentinan, therefore, has proved successful in prolonging the overall survival of cancer patients, mainly in patients with gastric and colorectal cancer.[67,68]

Table 3: Cytotoxic and antitumor potential of some mushrooms

Biological source	Activity/use
Pleurotus ostreatus[71,72]	Cytotoxic,apoptotic
	Antihepatoma and antisarcoma activitiy
Agaricus biosporus[73]	lower estrogen levels in the human body, reduce breast cancer susceptibility
Phellinus rimosus[74]	Cytotoxic and antitumor activities
Agaricus blazei Murrill[75]	Antitumor activity
Calvatia caelata[76]	Antiproliferative and antimitogenic activities
Hohenbuehelia serotina[77]	Antitumor activity
Inonotus obliquus[78]	Antitumor and hypoglycemic activities

Grifola frondosa

B D Glucan and glycoprotein complexes derived from this mushroom possess strong antitumor activity in xerographs.[69] More recently, a highly purified extract, β-glucan [β-1, 6 glucan branched with a β-1, 3-linkage] has become available which has considerable immunomodulating and antitumor activities in animal models, and is orally bioavailable [Figures 6-8][70] [Table 3].

Immunomodulator activity

Compounds like proteins, peptides, lipopolysaccharides, glycoproteins, and lipid derivatives, have all been classified as molecules that have potent effects on the immune system. Polysaccharides are generally T-lymphocyte-dependent antigen, which does not elicit cell-mediated immune response. Certain natural polymeric polysaccharides have recently been cited as potent immunomodulatory agents.[79]

Figure 5: *Grifola frondosa*

Figure 6: *Trametes versicolor*

Figure 7: *Schizophyllum commune*

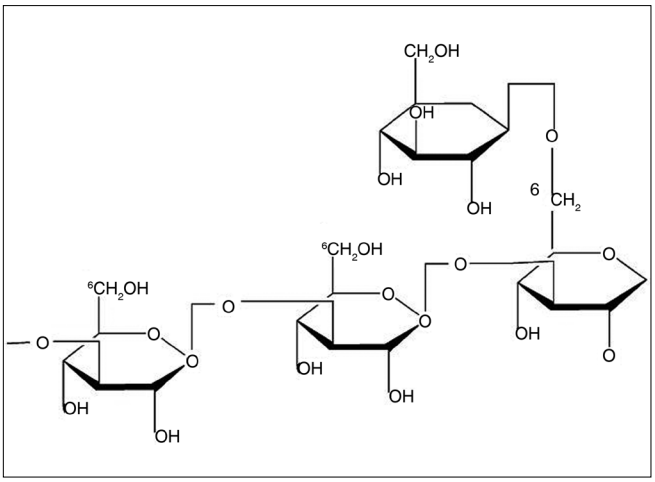

Figure 8: β *Glucan*

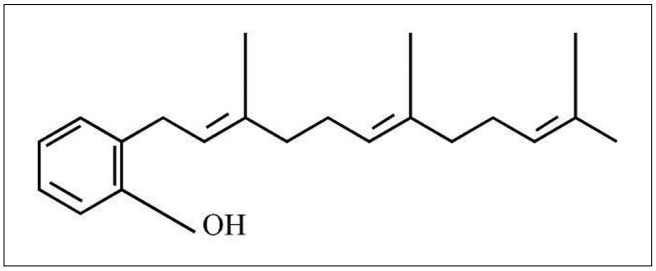

Figure 9: *Grifolin*

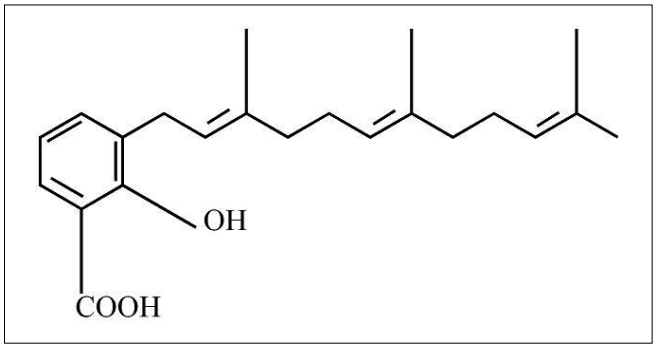

Figure 10: *Grifolic acid*

The immune system has a pivotal role in the body's defenese against infections and formation of tumors. Body's defenese against viral attack and against spontaneously arising malignant tumor cells comprises a dynamic orchestrated interplay of innate and acquired immune responses. Innate immunity that comprises macrophages, neutrophils, natural killer, and dendritic cells get regulated by cytokines and by the activation of inflammatory and acute phase responses.[80]Bioactive polysaccharides from mushrooms play a key role in immunomodulation. The ability of these bioactive polysaccharides bound protein to modulate immune cells that is contributed due to their structural diversity and variability of these macromolecules.[81]

Lentinus edodes

L. edodes is the source of two preparations with profound pharmacological effects – *L. edodes* mycelium [LEM] extract and lentinan.[82] Lentinan acts by producing its antitumor effect by activating different immune responses in the host. This immunomodulation is due to maturation, differentiation, or proliferation of cells involved in host defenese mechanisms. Therefore, Lentinan increases host resistance against various kinds of cancer and has the potential to restore the immune function of affected individuals.

Lentinan can activate NK cells *in vitro* in the same concentrations that are achieved in the blood plasma of patients treated clinically with lentinan.

NK cell activity is involved in tumor suppression and while these cells do not stimulate certain T killer cell activity, or do so only under certain conditions, they are strong T helper cell stimulants both *in vitro* and *in vivo*.

- Lentinan can inhibit prostaglandin synthesis, which can slow T cell differentiation in animals and humans, as well as inhibiting suppressor T cell activity *in vivo*.[83]
- Lentinan is also reported to increase in the activation of nonspecific inflammatory response such as acute phase protein production.[84]
- It also enhances vascular dilation and hemorrhage inducing factor *in vivo*.[85]
- It also has a role in activation and generation of helper and cytotoxic T-cells.[86]

Therefore the immunopotentiation by [1-3]-β-D-glucan of lentinan involves activation of cytotoxic macrophages, helper T-cells and NK cells, and the promotion of T cell differentiation.[87]

Ganoderma lucidum

Ganoderma lucidum has been used extensively as "mushrooms of immortality" in China and other Asian countries for 2000 years.[88] Substances with immense immunomodulating action have been isolated from this mushroom, including polysaccharides [in particular β-D-glucan], proteins [e.g., Ling Zhi 8] and triterperoids.[89]

Table 4: Immunomodulators from Ganoderma lucidum

Constituents	Activity
Polysaccharides[93,94] (β-d-glucans)	Induce biological response by binding to membrane complement receptor type three (CR3, αMβ2 integrin, or CD11b/CD18) on immune effector cells such as macrophages
Triterpenoids[95] (ganoderic acid, lucidenic acid, ganodermic acids, ganoderenic acids, lucidone, ganoderal, and ganoderols)	Immunomodulating activity

A β-D-glucan [Ganoderan] and a protein-polysaccharide fraction [GLB] from *G. lucidum* are potent stimulators of mice and chicken macrophages. Ganoderan and GLB have been shown to increase the expression of MHC class II molecules on these antigen-presenting macrophages.[90] There is also evidence to suggest that extracts from *G. lucidum* can influence humoral or B-cell immunity.[91] An alkali extract from *G. lucidum* activated both the classical and alternative pathways of the complement system. This extract also activated the reticuloendothelial system and increased hemolytic plaque forming cells in the spleen of mice[92] [Table 4].

Trametes versicolor

Protein-bound polysaccharides PSK (Krestin) and PSP have been isolated from the mushroom *Trametes versicolor*. These compounds are chemically relatively similar and have a molecular mass of about 100 kDa. The polysaccharide component is made up of monosaccharide with α [1-4] and β [1-3]-glucosidic linkages and possesses immunomodulating activity [Figure 9].[96]

Schizophyllum commune

The antitumor activity of Schizophyllan is due mainly to host mediated immune responses.[97] Schizophyllan is T-cell oriented immunopotentiator and therefore requires a functional T-cell component for its biological activity and that the action of [1-3]-β-D glucans on the host's immune system might:

- increase helper T-cell production,
- increase macrophage production,
- Bring about a nonimmunological increase in the host defenese mechanisms through stimulation of acute-phase proteins and colony-stimulating factors, which in turn effects proliferation of macrophages, and lymphocytes and activation of the complement system [Figure 10].[87]

CONCLUSION

The medicinal mushrooms are intended to be used all along the globe as functional food; a wide range of purified biochemicals obtained from them could be used to benefit human health and disease management [Table 5]. In the opinion of Chang, mycelial products are the "wave of the future" because they ensure standardized quality and year around production.The mushroom genome is potentially a natural source of novel myochemicals.

Table 5: List of some edible and nonedible mushrooms and their activities

Biological source	Activity/Use
Pleurotus spp.[98]	Radical scavenger
Hygrocybe spp.[98]	Chelating effect, iron, and calcium contents
Hygrophorus spp.[98]	Iron and calcium contents
Pleurotus ostreatus[99,100]	Lowers cholesterol levels
Lentinula edodes[101,102]	Antimutagenic effects
Pleurotus ostreatus[103]	Antibacterial Activities
Grifola frondosa[104]	Anticancer and hypoglycemic effects
Sparassis crispa[105,106]	Antitumor and hematopoietic activity
	Immunomodulating activity
Hypsizigus marmoreus[107]	Antifungal and antiproliferative activities
Lactarius vellereus[108]	Antigenotoxic activity
Ganoderma lucidum[109-111]	Antiallergic
	Angiotensin
	converting enzyme inhibitors
	antioxidant and free radical scavening activity
Grifola frondosa[112]	Cyclooxygenase inhibitor
Agaricus brasiliensis[113]	Antiviral activity
Coriolus versicolor[114]	Anti HIV
Hypsizigus marmoreus[115]	Antitubercular activity
Hericium erinaceus[116]	Cognition improvement properties
Piptoporus betulinus[117]	Anti-inflammatory and antihyaluronate lyase activities
Agaricus bisporus[60]	Enhances natural killer cell activity

That's why the intelligent use of these mushrooms can boost the host defenese mechanism of populace.

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