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Mushrooms as Medicinal and Therapeutic Agents

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Abstract

Mushrooms constitute a broad group of macrofungi, distributed all over the world, and serves as a reliable source of nutrients and medicine. While the importance of mushroom as single cell protein is well characterized, its potentiality in medical application is much less addressed and characterized. Mushrooms harbor several bioactive compounds of pharmacological significance like β-glucans, terpenes, steroids, proteins and peptides which exhibit antimicrobial, antiviral, anticancer, anti-angiogenic, anti-neurodegenerative, antioxidant, anti-thrombotic, anti-inflammatory, hepatoprotective, immunomodulatory and hypoglycemic properties. *Agaricus blazei*, *Ganoderma*, *Auricularia*, *Lentinus*, *Flammulina*, *Grifola*, *Trametes* (*Coriolus*), *Tremella* and *Pleurotus* are some of the mushrooms which have been used in medicines. However, there are yet unidentified and uncharacterized mushrooms available in nature and large scale exploitation of mushrooms to resolve clinical symptoms will depend on more research in identifying novel compounds and conducting extensive clinical trials in human subjects.

Keywords: Mushrooms, Therapeutics, Clinical symptoms, Medicine, Ultrasound extraction.

Introduction

The term mushroom in a broader sense refers to a group of macrofungi belonging to several orders like Ascomycetes or Basidiomycetes, thriving in a wide range of habitats like moist wood, organic matter and humid-rich soil or decomposed animal waste. Almost 2000, out of 70,000 fungal species known all over the world are edible mushrooms (Woldegiorgis et al. 2015). Over time immemorial, they are regarded as the major source of nutrient and medicine, with lots of health benefits. The concept of using fungus in medicine officially appeared first in Traditional Chinese Medicine and can be dated back to several thousand years ago. In the midst of the 20th century, some early researches were conducted on *Boletus edulis* to verify the antitumor activity of medicinal mushrooms (Rosecke et al. 2000). Mushrooms have been found to contain sufficient levels of water (90%), carbohydrates (1-55%), proteins (2-40%) with eight important amino acids, lipids (2-8%) with polyunsaturated

fatty acids and small amounts of saturated fatty acids, fibers (3-32%), ash (8-10%), volatile oils, and several antioxidants like phenolics, carotenoids, flavonoids and vitamins like B1, B2, B3, C and ergosterol. Several biologically active compounds, viz., β-glucans, terpenes and steroids are found to accumulate in mushrooms, whose function depends on the type of mushroom, developmental stage and growing conditions (Sanchez 2017). The most significant medicinal effect of mushrooms and their metabolites is their antitumor property. Prevention of life threatening diseases like hypercholesterolemia, cardiovascular disease, cerebral stroke, hypertension and atherosclerosis is possible due to the presence of high fiber content, microelements, proteins and low calorie content. The compounds extracted from mushrooms possess antimicrobial, antiviral, anticancer, anti-angiogenic, anti-neurodegenerative, antioxidant, anti-thrombotic, anti-inflammatory, hepatoprotective, immunomodulatory and hypoglycemic properties. They can reduce the blood cholesterol and blood glucose levels (Wasser and Weis 1999). Traditionally used mushrooms like *Agaricus blazei*, *Ganoderma*, *Auricularia*, *Lentinus*, *Flammulina*, *Grifola*, *Trametes* (*Coriolus*) and *Tremella* are reported to exhibit significant medicinal properties. *Pleurotus* spp. deserves special mention in this connection with high medicinal use and cultivated throughout the world because of simple and low cost production and high biological efficiency (Wasser 2002). In spite of such immense utility, mushroom consumption is mostly restricted within ethnic groups or rural population who are more acquainted with individual mushrooms and their utilities. Moreover, adequate research on mushrooms as potential source of medicines is largely ignored.

Chemicals and compounds of medicinal importance

Glucan polysaccharides are isolated from the mycelia and fruiting bodies of different mushrooms like *Pleurotus ostreatus* (pleuran), *Schizophyllum commune* (schizophyllan), *Lentinula edodes* (lentinan), *Ganoderma lucidum* (ganoderan A and B), as well as from *Agaricus blazei*, *Caripia montagnei*, *Lactarius rufus* and *Pholiota nameko*. Such polysaccharides activate macrophages, thereby enhancing immunity and exhibit anticancer, antioxidant, anti-inflammatory, antidiabetic and immunomodulatory activities. Oxygen-derived free radicals like superoxide and hydroxyl radicals, hydrogen peroxide, etc., are constantly generated within the human body during oxidative metabolism and energy production, leading to the formation of reactive oxygen species (ROS) within the system. This leads to inevitable oxidative stress that causes cellular damages, tissue injuries and different clinical disorders like rheumatoid arthritis, ischemia, acute hypertension, myocardial infarcation and diabetes mellitus (Friedman 2016). Dietary intake of antioxidants like phenolics can help overcome these abnormalities. The phenolic compounds like oxidized polyphenols, phenolic acids, flavonoids, hydroxybenzoic acid, hydroxycinnamic acids, tannins and stilbenes are capable of scavenging free radicals. Mushrooms like *Hericium erinaceus* (hericenones), *Craterellus cornucopioides* (polyphenol and myricetin), *Albatrellus ovinus* (grifolin and grifolin derivatives) and *Agaricus bisporus* (pyrogallol) provide a

valuable source of such phenolics. Agaritine and its derivatives which chemically belong to hydrazines are the main aromatic compounds of *A. bisporus*, etc. Agaritine was found to contribute to the formation of toxic aryl diazonium ions. Gamma glutaminyl 4 hydroxybenzene is the principal phenolic compound present in mushrooms (Palacios et al. 2011). Terpenoids are another group of metabolites which act as anticancer, antioxidant and anti-inflammatory agents. Triterpenes like lucidenic acids, ganoderic acids, and lanostane-type triterpenic acids are obtained from *G. lucidum*, while *Inonotus obliquus* is the source of various sterols and triterpenes like trametenolic acid, inotodiol, ergosterol, and ergosterol peroxide (Ruan and Popovich 2012). Several proteins and peptides like ribosome-inactivating proteins (RiP), lectins, laccases and other immunodialatory proteins isolated from mushrooms have clinical significances, viz., *P. ostreatus* (pleurostrin, antifungal peptide), *Agrocybe cylindracea* (agrocybin, antifungal peptide), *Russula paludosa* (SU2, antiviral peptide), *Cordyceps sinensis* and *Cordyceps militaris* (cordymin peptide, anti-inflammatory). By chemical nature, cordycepin is 30-deoxyadenosine, a purine alkaloid and cordycepic acid is D-mannitol, both found in *C. sinensis*. *C. militaris* contains cordycepin, adenosine, polysaccharide, mannitol, trehalose, polyunsaturated fatty acids, δ-tocopherol, p-hydroxybenzoic acid, and β-(1→3)-D-glucan. The components like deoxynucleosides, produced by *C. sinensis*, such as the compounds 2′, 3′ deoxyadenosine which is marketed under the trade name ‘Didanosine’ in the USA, is used as a medication for the treatment of acquired immune deficiency syndrome (AIDS). Similarly, quinic acid derived from cordycepin (3′ deoxyadenosine) is found to have antiviral and antibacterial properties (Wang et al. 2007).

Extraction of medicinal components

Ultrasound extraction in the releasing of full spectrum of bioactive compounds from mushrooms within a comparatively short time is the most common and convenient technique. Compression and expansion cycles are formed in the extract when intense ultrasound waves, also called acoustic cavitation, are applied. Growing vacuum bubbles so formed reach a stage where they collapse violently, being unable to absorb further energy. During this phenomenon, termed bubble implosion, extreme conditions like high temperature, pressure gradient and shearing forces are generated locally which break apart the mushroom cells releasing the polysaccharides, terpenes, phenolics, etc. into the solvent. Cavitation is the term given to the formation, growth and collapse of the vacuum bubbles. Ultrasonic extraction can be performed in several solvents like methanol, ethanol, isopropanol, glycerine, water, water/ethanol mixture, etc.

Therapeutic applications of mushrooms

As antimicrobial agent

Chloroform, petroleum ether and acetone extracts from *Osmoporus odoratus* that can act against *Sterptococcus pyogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*,

Escherichia coli and *Bacillus subtilis*, are strong antibacterial agents. The methanolic / ethanolic / acetone / aqueous extracts of other mushrooms like *G. lucidum* and *Phellinus* can also act against pathogens like *B. subtilis, E. coli, Salmonella typhi*, etc, the latter mushroom also act against fungal pathogens like

Aspergillus niger, Penicillium spp, Aspergillus fumigatus, Aspergillus niger, Mucor indicus and *Aspergillus flavus* (Ramesh and Pattar 2010).

As antioxidant

The ethanolic extract of *G. lucidum* possesses antiperoxidative capacity, whereas methanolic, ethyl acetate and aqueous extract can inhibit uncontrolled production of hydroxyl and superoxide radicals that lead to the onset of cancer, atherosclerosis and rheumatoid arthritis (Halliwell 2003).

As anti-inflammatory agent

Ethanolic extract of *Morchella esculenta* and ethyl acetate and methanolic extracts from *G. lucidum* are considered as potential anti-inflammatory agents, which have undergone trial in mice (Joseph et al. 2009).

As antitumor agents

The antitumor property of mushrooms has been tested in mice model using different tumor cell lines. The β-(1-6)-branched β-(1-3)-linked glucans, schizophyllan, lentinans and grifolan, all exhibit antitumor activity. The mushrooms important in this regard are *Grifola frondosa*, *Schizophyllum commune*, *Lentinus edodes* and *Sclerotinia sclerotiorum*. The methanolic / ethyl acetate / aqueous extract of *Pleurotus rimosus* also shows impressive result in retarding tumor development (Akihisa et al. 2007).

As medicines

A. blazei can be used against different diseases like diabetes, hyperlipidemia, chronic hepatitis and cancer. Extracts from *Pleurotus* can fight against chronic diseases like hypercholesterolemia, hypertension, etc. *G. lucidum* finds regular use in treating patients infected with human immunodeficiency virus (HIV) and AIDS (Jose et al. 2002). Specially, *P. ostreatus* contain high levels of isomers of lovastatin, which are well-known blood cholesterol reducing compounds. The presence of dietary fibers, lectins, chitin, β-glucans and polysaccharide-protein-complex (PSPC) makes these mushrooms highly effective against a host of clinical symptoms, including renal failures, gout, dropsy, jaundice, night sweating in tuberculosis and intestinal infection with worms.

Representative mushrooms and their therapeutic roles *(Table end of the paper)*

Conclusion and future perspectives

In spite of immense medicinal and therapeutic applications of mushrooms as discussed, their potentiality is still under-rated or under-estimated. Moreover, many novel mushrooms present in nature are largely unidentified, so that it is necessary to elaborately study mushroom diversity and make a reliable database. The chemical profiling of the secondary metabolites of the yet uncharacterized mushrooms and their applications against different clinical symptoms will also provide further scope of deriving novel bioactive compounds from mushrooms and exploiting them for therapeutics and medicines. Not only that, it is also vital to conduct more *in-vivo* experiments and clinical trials, rather than merely showing their effects in *in-vitro* cell lines in order to generate a broader and holistic effect on the body system as a whole. This will throw light on the complex modes of interaction, synergistic interplay of bioactive compounds with different endogenous signaling molecules within human system, and their molecular targets. The words of Hippocrates (the father of medicine) “Let food be your medicine and medicine be your food” apply very aptly for the mushrooms which have both nutritional and medicinal importance, and hence regarded as valuable assets for human welfare.

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Genus with family	Common species	Regions or habitats found	Therapeutic uses
Phellinus (Hymenochetaceae)	*P. senex, P. rimosus, P. badius, P. fastuosus, P. adamantinus, P. caryophylli* and *P. durrissimus*	Plains and tropical forests, tree trunks; common in Kerala, South India	Suppression of tumor proliferation, scavenging of ROS (Ajith and Janardhanan 2006).
Ganoderma (Polyporaceae)	*G. lucidum*	South India	Reduce hepatopathy, chronic hepatitis, nephritis, hypertension, arthritis, insomnia, bronchitis, asthma, gastric ulcer, blood pressure, blood cholesterol and blood sugar level as well as inhibition of platelet aggregation (Jones and Janardhanan 2000)
Pleurotus (Pleurotaceae)	*P. ostreatus, P. florida, P. pulmonarius*	Asia, Central Europe, South America and Africa	Hypertension, hypercholesterolemia, antitumor, antioxidant and anti-inflammatory functions (Gunde-Cimmerman 1999)
Cordyceps (Ophiocordycipitaceae)	*C. sinensis, C. militaris*	Grasslands; entomophagous fungi growing on all species of insects	Increasing utilization of oxygen and production of ATP, antioxidant and anti-ageing Stabilizing sugar metabolism in the blood; anti-diabetic (iii) Lowering the total cholesterol level and the level of triglycerides; helps in increasing the ratio of the good cholesterol (high-density lipoprotein cholesterol) to bad cholesterol (low-density lipoprotein cholesterol (iv) Improve kidney functions by elevating 17-ketosteroid and 17-hydroxycorticosteroid levels in the body

			(v) Treating liver disorders including hepatitis B; increased secretion of glucokinase and hexokinase which are glucose-regulating enzymes secreted by the liver (vi) Treating cardiac arrhythmia and chronic heart failure (vii) Anticonvulsant and sedative effects,; reduce weakness and fatigue (viii) Treating asthma and bronchitis (ix) Anti-tumor, anti-inflammatory, antimicrobial, anti-influenza (Dworecka-Kaszak 2014)
Fomitopsis (Fomitopsidaceae)	*F. pinicola*	Dead wood of coniferous and broad-leaved trees, which are common throughout the temperate Northern Hemisphere.	Contains triterpenes, esters, lactones and steroids; hemostatic and anti-inflammation agents; antioxidant; antimicrobial; antitumor and anticancer property less characterized, though ergosterols and polyphenols take part (Choi et al. 2007).
Hericium (Hericiaceae)	*H. erinaceus*	Saprotroph or a weak parasite found on oak and beech trees in Europe, North America, Japan, Russia, and China	Erinacines derived from the mycelium or hericenones derived from the fruiting bodies; neuroprotective properties; salutary influence on the digestive organs, including stomach, liver, intestine and colon; inhibit the growth of *Helicobacter pylori*, the bacterium causing gastritis and ulcer; anti-carcinogenic used in gastrointestinal cancers due to the presence of polysaccharides, lipids, terpenoids (including unique erinacines), and even proteins; anti-metastatic activity due to suppression of matrix metalloproteinases 2 and 9, ERK and JNK kinase activation; pro-apoptotic activities;

			immune-stimulatory activities; antioxidant potential; inhibition of angiogenesis (Thongbai et al. 2015).
Inonotus (Hymenochaetaceae)	*I. obliquus*	Grows as parasite on the trunks of living birch trees in the colder northern climates	Unique lanostan-type triterpenoids, inonotodiol and inonotsuoxides with anti-carcinogenic effects, capable of reducing tumor growth by induction of apoptosis; low molecular weight polyphenolic compounds with topoisomerase II inhibiting activity, leading to growth reduction in colon carcinoma cells; Chaga-derived polyphenol, 3,4-dihydroxybenzalacetone, capable of inhibiting the NF-κB activation and NF-κB-dependent gene expression in cancer cells, followed by suppression of synthesis of TNF-induced and NF-κB-dependent proliferative; anti-apoptotic and pro-metastatic gene products; polysaccharides with anti-metastatic activities, blocking the expression and activity of matrix metalloproteinases 2 and 9, via suppression of MAPKs, PI3K/AKT, and NF-κB signaling pathways (Lee et al. 2014).
Trametes (Polyporaceae)	*T. versicolor*	Tree trunks throughout the world in many diverse climates, including North America	Carbohydrates and proteoglycans with immune-modulatory potential; β-glucan-based polysaccharopeptide fraction (PSP) activates cells of the immune system, boosts production of cytokines and chemokines, such as TNFα, interleukins (IL-1β and IL-6), histamine, and prostaglandin E; stimulates dendritic and T-cell infiltration into tumors and reduces the harmful side effects of

			chemotherapy; the polysaccharide fraction known as Krestin (PSK) mostly used as an adjuvant for cancer (breast cancer, prostate cancer and hepatocellular carcinoma) immunotherapy (Standish et al. 2008).
Agaricus (*Agaricaceae*)	*A. bisporus*	Native to grasslands in Europe and North America, thrive in humic‐rich environments	Immunomodulation; decrease in total cholesterol, triglycerides and low-density lipoprotein; treating breast cancer by decreasing aromatase enzyme and estrogen biosynthesis; anticholesteterolemic and antiglycemic; anti-inflammatory; maturation of bone marrow-derived dendritic cells; source of antibiotics since it contains benzoquinones; skin disorders; antimicrobial against bacterial and fungal pathogens (Bozena et al. 2017)

