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A comprehensive review on the pharmaceutical applications of mushrooms

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Abstract

In spite of the several technological advancements human still face the basic problems like poor health and lack of proper medication. So, there is an urgency to address this problem. Mushrooms are well known herbal drug which can solve this problem of health and medicinal needs of human being. Mushrooms are ubiquitous in nature and are well known functional food in terms of nutrition and medicine. They have played a prominent role in traditional and folk medicine. Mushroom genera such as *Auricularia, Flammulina, Ganoderma, Grifolia, Lentinus, Trametes, Pleurotus, Schizophyllum* and *Tremella* were demonstrated to possess significant medicinal property which is the outcome of traditional medicine system. Although mushrooms have long been used by various cultures, only recently, modern science rediscovered what the ancients knew long ago that mushrooms can be deep reservoirs of powerful medicines. Considering the above facts in view, this review provides comprehensive information on the pharamaceutical applications of mushrooms in the current scenario.

Keywords: Mushrooms, nutrition, medicine, pharmaceuticals and herbal drug.

1 Introduction

Mushrooms manage to grow in darkness and dampness in highly competitive environment and protect themselves from the attack of microbes and other agents by developing natural protective substances within them. Because of which they are a known to be the source of many biologically active compounds (Isabel et al.). There are approximately two hundred species of mushrooms that have been found to inhibit the growth of different types of tumors [1]. They possess effective substances for antifungal, anti-inflammatory, antitumor, antiviral, antibacterial, hepatoprotective, antidiabetic, hypolipedemic, antithrombotic and hypotensive activities. Furthermore, the significant pharmacological effects and physiological properties of mushrooms are bioregulation (immune enhancement), maintenance of homeostasis, regulation of biorhythm, prevention, cure of various diseases and improvement from life threatening diseases such as cancer, cerebral stroke and heart diseases. Mushrooms contain biologically active polysacchrides in fruit bodies, cultured mycelium and cultured broth. They represent an unlimited source of antitumor or immunostimulant polysaccharides. The bioactive polysaccharides isolated from mushroom are either water-soluble β-D-glucans, β-D-glucans with heterosaccharide chains of xylose, mannose, galactose, or uronic acid, or β-D-glucan-protein complexes or proteoglycans [2,3]. Polysaccharides contain anticancer effects can vary greatly in chemical composition, configuration, and physical properties. Polysaccharides isolated from different species, and even from different strains of the same species, can have unique structures [4]. For example, PSK and PSP are isolated from different strains of *Trametes versicolor*, these compounds contain different peptide molecules bound to same polysaccharides. The potentialities of anticancer polysaccharides are based on their molecular weight, degree of branching, and solubility in water. Some common anticancer polysaccharides isolated and have been subject to early clinical trials are lentinan (*Lentinus edodes*), schizophyllan (*Schizophyllum commune*), PSK and PSP (*Trametes versicolor*), and Grifron-D (*Grifola frondosa*) [5]. The mushrooms like *Grifola frondosa*, *Pleurotus eryngii*, *Lyophyllum shimeji* and *Flammulina velutipes* are edible and are found to possess medicinally active compounds with potential benefit to health. The species like *Ganoderma lucidum*, *Trametes viscolor*, and *Inonotus obliquus* are very bitter or hard to eat and used in the form of extract or powder. Among the edible mushroom species, *Agaricus* are produced in larger rate, and from the non-edible medicinal species, *Ganoderma* are produced more. Several mushroom species belonging to the Polyporaceae family are now being regarded as the next major producers of possible valuable medicines [6]. *Ganoderma lucidum*, *Ganoderma tsugae* and *Coriolus versicolor* are three important species of medicinal mushrooms which are commonly used in Taiwan. They are commercially available and are used as pharmaceuticals and also as a healthy diet. These mushrooms were found to be medically active in several therapeutic effects such as antitumor, immunomodulating and chronic bronchitis with high antioxidant activity, reducing power, scavenging and chelating ability.

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Pleurotus species are excellently edible, nutritious and widely cultivated mushroom in the world. It has high medicinal value and is found to possess significant antioxidant, anti- inflammatory and antitumor activities. The fruiting bodies of *Pleurotus florida*, *Pleurotus pulmonaris* shows profound antitumor activity [7]. Compounds extracted from these mushrooms shows activity against chronic diseases such as hypertension and hypercholesterolemia. Many basidiomycetous mushrooms are unlimited source of therapeutically useful biologically active compounds. Most of the bioactive compounds have unique structures in different species. This includes low-molecular-weight compounds (LMW, e.g. quinones, cerebrosides, isoflavones, catechols, amines, triacylglycerols, sesquiterpenes, steroids, organic germanium and selenium) and high-molecular-weight compounds (HMW, e.g. homo and heteropolysaccharides, glycoproteins, glycopeptides, proteins, RNA protein complexes) with potential antitumor and immunostimulating properties. Along with polysaccharides, several proteins are also found in mushrooms that have been described as having antitumor activity, like flammulin from *Flammulina velutipes*, protein LZ8 from *Ganoderma lucidum*, clitocypin from *Clitocybe nebularis* and lectins from different species.

According to the recent estimate the number of fungi on earth range from 500,000 to 10 million species and the total number of all kinds of described fungi is 100,000 species. This data is obtained by summing the numbers of species in each genus given in the last edition of the Dictionary of the Fungi and also includes all organisms traditionally studied by mycologists: slime molds, chromistan fungi, chytridiaceous fungi, lichen-forming fungi, filamentous fungi, molds, and yeasts. Among these, mushrooms alone comprise 14,000 species but the number of mushroom species on earth is currently estimated as 150,000, which is perhaps only 10% (approximately 15,000 named species) of documented species or can go as high as 22,000 [8,9]. There are approximately 700 species of higher basidiomycetes that have been found to possess significant pharmacological activities, in which most of the scientific studies were carried out in Japan, China, Korea and USA. Medicinal mushrooms can be equally compared with medicinal plants and are defined as macroscopic fungi especially higher Basidiomycetes, which are used in the form of extracts or powder for elimination, mitigation, healing of diseases and also as complete nutritional supplement. In European Union directive 2004/24/EC fungi is also included in the definition of herbal substances. Herbal medicinal products are defined as "Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations." Herbal substances are defined as "All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Therefore, in the sense of the European Medical Agency (EMA), "mushroom pharmaceuticals" are considered as "herbal preparations" [10]. Almost 126 medicinal properties are thought to be produced by medicinal mushrooms and fungi including antitumor, immunomodulating, antioxidant, radical scavenging, cardiovascular, antihypercholesterolemia, antiviral, antibacterial, antiparasitic, antifungal, detoxification, hepatoprotective and antidiabetic effects. These medicinal properties are attributed to the bioactive components of medicinal mushrooms. The bioactive components include polysaccharides, phenolics, terpenoids etc. mostly the activity is rendered by low molecular weight compounds rather than high molecular weight compounds. The compounds from medicinal mushrooms can be divided into low molecular weight compound and high molecular weight compound which are given in the flow chart below.

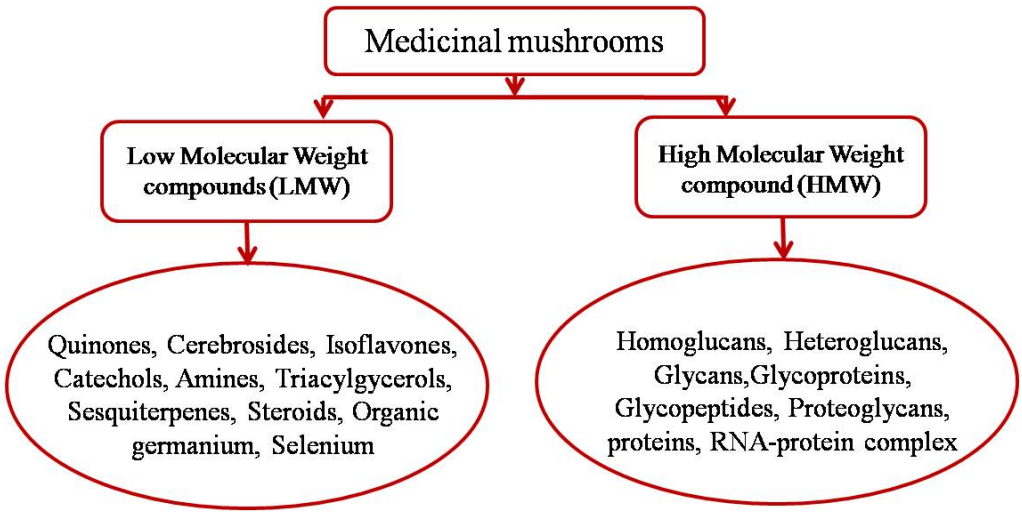

Figure 1: Bioactive compounds from medicinal mushrooms.

2. Antimicrobial extracts from medicinal mushrooms

2.1. Antibacterial compounds from mushrooms

The recent studies of over 200 mushroom species, revealed that more than 75% of screened polypores showed strong antimicrobial activity [11]. These activities are shown by both low molecular weight compounds and high molecular weight compounds. Defensive compounds from fungi can be extracted and used against microbial pathogens like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas areuginosa* and so on. Antimicrobial drugs have a long history of medicinal use, like the dry polypore, *Fomes fomentarius*, was used in the 18th and 19th centuries in dressings and bandages to stop the flow of blood and to prevent infections (Roussel et al., 2002). The antimcrobial potential of mushroom species depends on origin of samples, type of extracts obtained, analysis applied, bacterial and fungal species investigated etc. [12]. A large group of antimicrobial secondary metabolites isolated from mushrooms includes a cyclodepsipeptide, beauvericin produced by the bright yellow polypore *Laetiporous sulphureus*, oospolactone from *Gleophyllum sepiarium,* ganomycin from *Ganoderma pfeifferi,* hirsutic acid and complicatic acid were isolated from *Stereum complicatum,* frustulosin and frustulosinol isolated from *Stereum frustulosum*, ramariolides A-D isolated from the fruiting bodies of the coral mushroom *Ramaria cystidiophora* shows in vitro antimicrobial activity against *Mycobacterium smegmatis* and *M. tuberculosis* [13].

The *Armillaria mellea*, which produces antibiotic, melleolides, unusual sesquiterpene ester [14,15], showed high antibacterial activities against *Staphylococcus aureus, Bacillus cereus* and *B. subtilis*. Armillaric acid, isolated from this mushroom inhibits Gram-positive bacteria and yeast [16]. Some of the tested Ascomycetes, *Morchella esculenta* and *Tirmania pinoyi*, also reported to have excellent antibacterial activity. Mushroom extracts, especially obtained from *Lentinus edodes* and *Phellinus linteus*, have been reported as effective even towards the highly resistant bacteria like MRSA [17]. The ethyl acetate extract of *Lentinus edodes* showed inhibitory activity against *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. Chloroform extract of *Lentinus edodes* was very sensitive to *Streptococcus pyogenes* while aqueous extract have good activity against MRSA [18]. Antimicrobial activity of methanolic extract of three *Agaricus* species was published by Ozturk *et al.* [19], which shows inhibitory activity against six species of Gram-positive bacteria, seven species of Gram-negative bacteria. Similary, *Agaricus campestris* from India showed antimicrobial activity against seven bacterial species. Methanolic and ethanolic extracts of *A. bisporus, A. bitorquis, A. campestris* and *A. macrosporus* showed antibacterial potential [20]. Methanolic extract of *G. lucidum* shows activity against *S. aureus*, *B. cereus*, *M. flavus*, *Listeria monocytogenes*, *E coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*. Antimicrobial activities of *Ganoderma lucidum*, *G. praelongum* and *G. resinaceum* were evaluated against 30 strains of clinical isolates of methicillin-resistant and sensitive *Staphylococcus aureus*. Coprinol, a new antibacterial cuparane type terpenoid is extracted from cultures of a *Coprinus* sp. exhibited activity against multidrug-resistant Gram-positive bacteria [21]. Crude extracts of *Ganoderma* species, such as *Ganoderma lucidum* (Reishi mushrooms), *Ganoderma pfeifferi* and *Ganoderma resinaceum*, revealed selective activity against Gram-positive strains like *Bacillus subtilis, Staphylococcus aureus* and *Micrococcus flavus* [22].

2.2. Antifungal compounds from mushrooms

Pathogenic fungi cause infectious diseases to humans, animals, crops, and other living organisms. The main pathogens responsible for fungal infections are yeasts, moulds and dermatomycetes. In agriculture, fungal invasion brings about serious reduction in the quality and yield of crops and cause enormous economic losses. The species from genera *Penicillium*, *Aspergillus* and *Fusarium* are among the best known and widely studied moulds that mostly contaminate agricultural products and produce mycotoxins. The compounds of different biogenetic origins have been isolated from Basidiomycota and were found to have antifungal activity. Extract of *Cordyceps militaris* showed very good antifungal activity against *Penicillium ochrochloron*, *P. funiculosum* and *Trichoderma viride*. Another bioactive compound from *C. militaris* is cordymin. This peptide was studied for its antifungal properties and found to inhibit mycelial growth of *Bipolaris maydis*, *Mycosphaerella arachidicola*, *Rhizoctonia solani* and *Candida albicans* [23]. Eryngin, an antifungal peptide isolated from *Pleurotus eryngii* fruiting bodies, also gave activity against *F.oxysporum* and *M. arachidicola*. Another peptide, pleurostrin, isolated from *Pleurotus ostreatus* showed antifungal activity against *F. oxysporum*, *M. arachidicola* and *P. piricola* [24]. Agrocybin, an antifungal peptide isolated from *Agrocybe cylindracea* showed activity against *M. arachidicola* [25]. Phenolic acids and related compounds such as phydroxybenzoic and cinnamic acids identified in *Ganoderma lucidum* also revealed activity against different fungi species,such as *Aspergillus fumigatus, A. versicolor, A. ochraceus, A.niger, Trichoderma viride, Penicillium funiculosum, P. ochrochloron* and *P. verrucosum*. The mentioned compounds gave higher activity than antimycotics [26].

2.3. Antiviral activity of Mushrooms

Like bacterial diseases, viral diseases cannot be treated by common antibiotics rather it needs specific drugs. Both the whole extracts of mushrooms and also isolated compounds shows antiviral properties. They can act directly and also indirectly. Direct effects are by inhibition of viral enzymes, synthesis of viral nucleic acids or adsorption and uptake of viruses into mammalian cells. These effects are exhibited especially by smaller molecules. Indirect antiviral effects are the result of the immunostimulating activity of polysaccharides or other complex molecules [27]. The polysaccharides like PSK and PSP from *Trametes versicolor*, commonly known as turkey tail, was found to have an antiviral effect on human

immunodeficiency virus (HIV) *in vitro* [28]. Water-soluble preparations from carpophores of *Ganoderma applanatum* have potent antiviral activity against vesicular stomatitis virus Indiana serotype VSV (IND) [29]. Aqueous extracts from four polypores, *Fomitella supina*, *Phellinus rhabarbarinus*, *Trichaptum perrottotti* and *Trametes cubensis* have strong anti-HIV-1 activity without toxicity toward lymphocytic cells. It was demonstrated that the active compounds of these extracts act by a mechanism of direct virion inactivation and inhibition of syncytium formation in an in vitro culture system [30]. Water-soluble lignins isolated from the sclerotia of the polypore *Inonotus obliquus*, commonly known as "Chaga", inhibited HIV. Two phenolic compounds, hispolon and hispidin, isolated from the basidiocarps of *Inonotus hispidus* showed considerable antiviral activity against influenza viruses type A and B [31].

2.4. Antihypercholesterolemia Activity

Cardiovascular disease is associated with atherosclerosis, LDL oxidation, and hypercholesterolemia, thus the regulation of the cholesterol level is important for the prevention and treatment of this disease. Mushrooms possess significant cholesterol-lowering effects like, eritadenine isolated from *Lentinula edodes* have potent hypocholesterolemic effects and are found to reduce the serum cholesterol level in mice by the acceleration of the excretion of ingested cholesterol and its metabolic decomposition [32]. Eritadenine lowers cholesterol by decreasing the ratio of phosphatidylcholine (PC) to phosphatidylethanolamine (PE) in liver microsomes and altering the composition of PC similar to soybean protein [33]. Eritadenine can also suppress the metabolism of lipids (linoleic acid) by suppressing 1,6-desaturase activity. In addition to eritadenine, nucleic acid compounds extracted from *Lentinula edodes* were also found to be inhibitors of platelet agglutination [34]. *Lentinula* mushrooms can lower both the blood pressure and the free cholesterol level in plasma and can accelerate the accumulation of lipids in the liver by removing them from circulation [35]. Lovastatin and its analogues are well-known cholesterol-lowering agents. It has also been found that the addition of 2-4% of *Pleurotus ostreatus* to a high lipid containig diet can prevent the accumulation of cholesterol and triacylglyceride in both the sera and livers of rats [36,37]. Dietary fibers (nonstarch polysaccharides, mainly β-glucans) are also an important hypocholesterolemic component in mushrooms, dietary fiber isolated from *Auricularia auricula* (Jew's ear) and *Tremella fuciformis* (white jelly-leaf) can significantly decrease the serum total cholesterol (TC) and LDL cholesterol levels. *Auricularia auricula* display anticoagulation, antiaggregatory activity in the blood platelets and can lower the total cholesterol, total triacylglyceride and lipid levels [38].

2.5. Antihyperglycemic activity

Mushrooms have the potential property of prevention of hyperglycemia because of their high dietary fiber, protein and low fat content [39]. Ganoderan A and B, glucans from *Ganoderma lucidum* fruiting bodies, coriolan, a β-glucanprotein complex from submerged grown *Trametes versicolor* biomass, Lectins isolated from mushrooms (*Agaricus campestris* and *A. bisporus*), an acidic glucuronoxylomannan from the fruiting bodies of *Tremella aurantia* exhibited hypoglycemic effects in several test systems and ameliorated the symptoms of diabetes. Dehydrotrametenolic acid, seen in polypores like *Wolfiporia cocos*, *Laricifomes officinalis* and *Laetiporus sulphureus* acts as an insulin sensitizer in glucose tolerance tests and reduces hyperglycemia in mice with non-insulin-dependent diabetes [40].

2.6. Antiallergic activity

Some of the mushroom extract can suppress the immune response. Ethanolic extracts of the edible Japanese basidiomycetes such as *Hypsizygus marmoreus*, *Flammulina velutipes*, *Pholiota nameko* and *Pleurotus eryngii* show significant antiallergic effects in mice [41]. Consuming *Tricholoma populinum* will result in the regression of severe allergic symptoms in a patient having thromboangitis obliterans and in another patient with urticaria. Compounds like hispolon and hispidin isolated from fruit bodies of *Inonotus hispidus* inhibit the chemiluminescence response of human mononuclear blood cells and the mitogen induced proliferation of spleen lymphocytes of mice [42].

2.7. Anti-inflammatory activity

Inflammation is considered to be part of the biological response to remove injury or harmful stimuli such as pathogens, damaged cells, or irritation and this is a central feature of many pathophysiological conditions such as atherosclerosis, obesity, metabolic syndrome, diabetes and even several types of cancers. But, overproduction of these inflammatory mediators can lead to different kinds of cell damage. So recently anti-inflammatory drugs (steroidal and non-steroidal) are among the most widely prescribed groups of medicines in clinical practice worldwide. Long term administration of these drugs has significant side effects on the gastrointestinal tract with numerous harmful effects such as mucosal lesions, bleeding, peptic ulcers, and intestinal perforation. Mushrooms along with other properties have also demonstrated some anti-inflammatory potential based on their ability to reduce the production of inflammatory mediators without the problem of side effects [43]. Proteoglycan from *P. linteus* show anti-inflammatory effect in the collagen-induced arthritis and in the croton oil-induced ear edema test in mice. A low molecular weight peptide, Cordymin was identified and purified from the medicinal mushrooms *Cordyceps sinensis*. This peptide significantly inhibited the infiltration of polymorphonuclear cells and IR-induced upregulation of C3 protein produced in the brain, interleukin-1β, and TNF-α, which had a neuroprotective effect on the ischemic brain, due to the inhibition of inflammation. Agrocybin

that has been isolated from the edible mushroom *Agrocybe cylindracea* also have anti-inflammatory effects [44].

2.8. Antitumor and Immunomodulatory Activity

The conventional cancer treatment methods like chemotherapy and radiotherapy are adversely affecting the immune system of a person. Even in the presence of normal immune system cancer cells have variety of mechanisms to survive and proliferate. Here both the disease and its treatment are immunosuppressive. The use of immunostimulating agents along with conventional treatment can be effective if it is not interfering with the efficiency of conventional therapy. Immunostimulating polysaccharides are widely distributed among medicinal mushrooms with potent anticancer activity [45]. The ability of mushroom polysaccharides to enhance or suppress the host immune response depends on a number of other factors, including dosage, route of administration, timing and frequency of administration, as well as their mechanism of action [46]. Polysaccharides with potent antitumor activity have been isolated from various species of mushrooms belonging to Auriculariales, Tremellales, Polyporales, gasteromycetideae and agaricomycetideae. These antitumor substances impart there activity by activation of host immunological functions, also characterized by weak antigenicity and absence of side effects. From the fruiting body of *Lentinus edodes* a water soluble antitumor polysaccharide was isolated called "Lentinan" named after the generic name of this mushroom. Its antitumor activity is stronger than the polysaccharides from many higher plants. It is not toxic to tumor cells, but inhibits tumor growth by stimulating the immune system and also act as a host defense potentiator. Lentinan has been approved for clinical use in Japan as a pharmaceutical product since the early 1980s, and it is currently used as an adjuvant treatment for certain cancers in Japan and China [47]. Schizophyllan is from the genus *Schizophyllum* is known for its high medicinal value and aromatic taste profile and is also having immunomodulatory, antifungal, antineoplastic and antiviral activity which are higher than that of any other glucan complex carbohydrates. Schizophyllan is a neutral extracellular polysaccharide produced from *Schizophyllum commune*, it is also known as sizofiran. They have special ability to stimulate the immune system. Krestin is protein bounded polysaccharide isolated from the fruit body of *Trametes virsicolor*. Krestin shows antitumor activity against various tumors and has nonspecific immunomodulatory activity [48]. Krestin was approved for use in combination with chemotherapy to prolong survival of patients with gastric cancer or colorectal cancer and to prolong remission of patients with small-cell lung carcinoma. PSK and PSP are polysaccharides isolated from *Trametes versicolor*. PSK was first isolated in Japan in the 1960s and PSP was isolated in l983 by the Chinese. Clinical trials have proven PSK activity against a variety of solid tumors including head and neck, bowel, and lung. PSK has been used as an immunostimulant in combination with conventional chemotherapy for gastric cancer. Grifron-D is new anticancer mushroom polysaccharide extracted from *Grifola frondosa* demonstrated to have promising pre-clinical activity in cell lines and xenografts [49,50].

3 Conclusion

Mushrooms are ubiquitous in nature and are well known functional food in terms of nutrition and medicine. They have played a prominent role in traditional and folk medicine. Mushroom genera such as *Auricularia, Flammulina, Ganoderma, Grifolia, Lentinus, Trametes, Pleurotus, Schizophyllum* and *Tremella* were demonstrated to possess significant medicinal property which is the outcome of traditional medicine system. Although mushrooms have long been used by various cultures, only recently, modern science rediscovered what the ancients knew long ago that mushrooms can be deep reservoirs of powerful medicines. Hence, the complete potential of mushrooms should be exploited in future for various medical applications.

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