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Mushroom Polysaccharides: a Potent Immune-Modulator

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Abstract: From ancient times, mushrooms are being used as nutraceuticals, food supplements, and dietary fibers for their high nutritional value. Modern medicinal researches have depicted immune-modulating effects of wild edible mushrooms. Among several metabolites of mushroom origin, polysaccharides are known to have the most potential immune-modulatory functions on both innate and adaptive immune systems. Mushroom polysaccharides (MPs) are the diverse groups of macromolecules which show considerable variability in their physicochemical properties. These variations in properties are considered as determining factors of the immune-stimulation activities. In this present review, a broad outline of different MPs and their purification, the relationship between physical properties and bioactivity, immune cell receptors, and impact on both innate and adaptive immune systems is enlightened.

Keywords: Cancer adjuvants; dectin-1; immuno-stimulant; polysaccharides receptors.

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1. Introduction

With the escalating progression of civilization, mushrooms gained values as immune-modulatory, medicinal and pharmaceutical reinforcement agent, based on the long history of its usage as culinary purposes. Mushrooms are the macrofungi having fleshy spore-bearing fruiting bodies (epigeous or hypogeous) and distinctly conspicuous to the naked eyes [1, 2]. From ancient times mushrooms and their extracts are being used for improving general health and also for the treatment of other diseases in some Asian countries like China and Japan [3]. China is recognized as the first country to initiate the cultivation of mushrooms all over the world and also secured the first position in mushrooms yielding through the cultivation process. However, the cultivation of mushrooms in India is a new incident, and it was more likely to start in India from the middle of the 19th century. It has been reported earlier that over 1,40,000 mushrooms species are known to occur worldwide, 10% of which are known to us among which 2000 species are edible, and approximately 650 species are known for their medicinal and pharmaceutical uses [4, 5].

Classic and synthetic drugs are used to treat certain viral pathogens and diseases. Several antibiotics and antiviral drugs are available in the market, but often they are nonfunctional, ineffective in patients due to pathogen resistance, and also cause side effects [6]. During the exploration of potential alternatives, active medicinal compounds obtained from any biological sources are found as non-hazardous and safest. Among them, mushrooms are

always a great deal of interest in the food and biopharmaceutical industry because of their high nutritional values and for a wide range of bioactive compounds [7]. Dry matter of mushrooms contains approximately 10%-40% of protein, 2%-8% of fat, 3%-28% of carbohydrate, 3%-32% of fiber. Apart from these, a number of bioactive mushroom metabolites like lectins, terpenoid, peptide, glycoproteins play an important role in modulation and boosting up the components of the immune system [8, 9]. Several scientific studies and clinical application suggested that mushrooms can act as anti-cancer, anti-inflammatory, anti-microbial, anti-allergic, anti-diabetic immune-modulatory agents since they are rich in bioactive metabolites and other phytochemicals [10-12]. Due to such immense medicinal and nutritional benefits, FDA has dignified mushrooms as proper healthy food [13].

Nowadays, mushrooms derived polysaccharides gained a remarkable interest for their immune-modulatory and anti-cancerous properties. In modern medicinal research and pharmaceutical industries, immune-modulators are the main focusing agents [14]. These agents are falls under 2 groups: immune-suppressants (that can able to inhibit and lowers body's immune responses) and immune-stimulants (that can be able to stimulate the immune system by activation of components immune cells like macrophages, natural killer cells, dendritic cells, etc.) [15]. There are several ways by which the human immune system modulates their functions; it may be by endogenous bioactive compounds or by the use of food supplements [16]. Several mushrooms derived polysaccharides have been isolated, which can modulate both innate and adaptive human immune system and can protect from certain autoimmune diseases by interacting with immune cells like NK cells, macrophages, lymphocytes, dendritic cells through cytokine productions [17-22]. For example, polysaccharides like lentinan, polysaccharide peptide (PSP), Schizophyllan, polysaccharide K (Kerstin) are used in cancer immunotherapy [23, 24]. Most of the mushrooms polysaccharides are glucans, and they show a highly complex structure, where β -D-glucans are linked with various types of monosaccharide units with the help of glycosidic bonds. Besides this, other different glycosidic linkages may also found to occur, such as (1 \rightarrow 3), (1 \rightarrow 6)- β -glucans, and (1 \rightarrow 3)- α -glucans. The immune-modulatory properties of mushroom polysaccharides are depended on their branching pattern, side-chain modification, high molecular weight, and the ability to interact with different receptors such as dectin-1 [25]. Several scientific investigations have revealed that glucans, mannans, galactans, and fructans, are some other well studied MPs having potential immune-stimulatory activities [26].

A large number of studies have investigated several bioactive polysaccharides from different mushrooms over the years, which have potent antitumor and immune-stimulatory functions. In this present review, we will discuss the details structures of different mushrooms polysaccharides and their bioactivity with immune-modulatory mechanisms.

2. Bioactive Mushroom's Polysaccharides (MP)-an Overview

Among all the bioactive compounds, polysaccharides are the most potent, well studied, and widely distributed compounds responsible for the bioactivities of some mushrooms species. Mushroom polysaccharides are a structurally diverse group of a macromolecule with a common β -linked glucose backbone [27]. Glucans are very common polysaccharides present in the fungal cell wall, mainly in the form of cellulose and reported as one of the potent antitumor polysaccharides [28, 29]. However, for chitin and chitosan (a deacetylated form of chitin), no such activities were reported [30]. Among several polysaccharides, β -glucans are

the well studied bioactive component that can enhance the immune system by various strategies such as activation of macrophages [31, 32].

Polysaccharides can be divided into two distinct groups, homopolysaccharides, contains only one kind of monosaccharide unit (homo PSs), and heteropolysaccharides, contains different types of monosaccharide units (hetero PSs), and they may possess different homo or hetero linkage position in accordance to their configuration [33]. Hetero PSs have various types of glycosidic linkages on the basis of their sequence of monosaccharide units, which gives the structural variability of MPs [34]. Lentinan, a β -1,3-D-glucan with triple-helical conformation, was the first MP isolated from *Lentinus edodes* (shiitake) in Japan having immune-modulating and anti-cancer activity [35]. Besides this, several other MPs like ganoderan from *Ganoderma lucidum*, calocyban from *Calocybe indica*, pleuran from *Pleurotus* species, were reported as representatives of β -D-glucans with glycosidic linkages at different position and can be distinguished with different molecular weight and branching pattern [36].

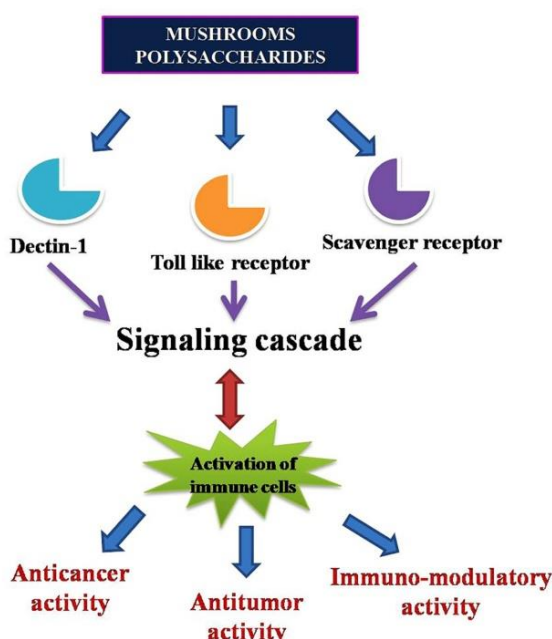


Figure 1. Concept of biological activities of mushrooms polysaccharides.

Earlier reports have suggested that homo PSs, especially β -D-glucan are the only MPs with bioactive properties, but later studies revealed that heteroPSs are also capable of showing bioactivity. HeteroPSs are more complex than β -D-glucose since they possess more variability in their monosaccharide composition, linkage, and branching patterns, and some of these molecules show natural methylation [37, 38]. Glucose, galactose, fructose, fucose, arabinose, xylose, mannitol, trehalose are some very common monosaccharides components detected from MPs [39]. Mushroom polysaccharides extracted from *Agaricus bisporus* have a direct action against breast cancer. Along with this recently, researchers have found a proteoglycan from *A. blazei* having tremendous immune-modulatory activities and can act as therapeutic agents against certain immune-deficient diseases by the regulation of dendritic cells [40].

The overall concept about the immune-modulatory, antitumor and anti-cancer activities (Figure 1) of these MPs are due to their diverse structural conformation, variability in monosaccharide composition and ability to interact with several polysaccharide receptors present on the cell surface (dectin-1, toll-like receptors) which ultimately activate different immune cells like cytotoxic macrophages, natural killer cells, dendritic cells, cytokines [41].

However, more studies are needed in the future to understand the relationship between structural conformation and the corresponding immune function mechanism of these MPs.

3. Production/Purification of Mushrooms Polysaccharides

Several medicinally important food supplements and nutraceuticals obtained from MPs are now available in the market, but it was still unknown about the fact that how to extract these polysaccharides from fruiting bodies or other parts of the mushrooms. Mizuno et al. were able to give a reliable approach to the extraction and purification of MPs from fruiting bodies in Japan [42, 43]. The overall procedure is an ethanol (80%) extraction, which eliminates low molecular weight polysaccharides followed by three successive water extractions in addition to ammonium oxalate and NaOH. Polysaccharides extracted from this procedure are further purified by using a few combinations of techniques such as acidic precipitation, ethanol concentration, fractional precipitation with gel filtration, ion-exchange chromatography, and affinity chromatography. Neutral polysaccharides can be separated from acidic ones by the help of ion-exchange chromatography through DEAE cellulose columns, α and β -glucans are then purified from high molecular weight neutral polysaccharides through gel filtration chromatography [43, 44]. The general extraction procedure of the mushrooms polysaccharides presented schematically in Figure 2.

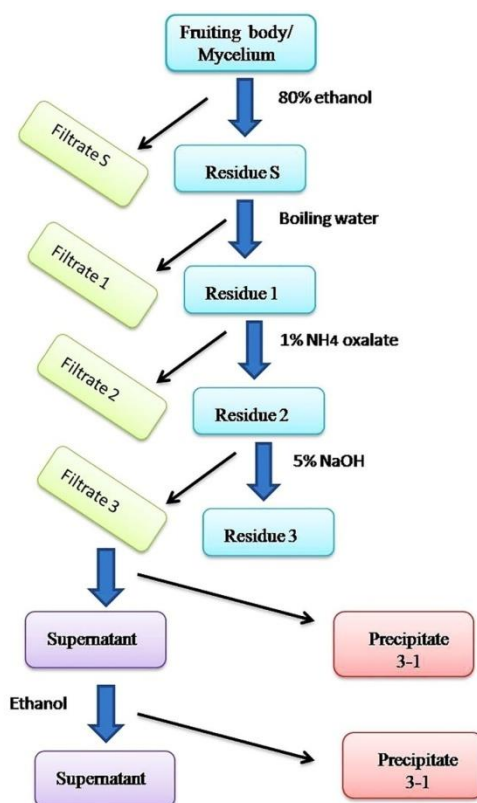


Figure 2. Schematic representation showing purification of polysaccharides from mushrooms.

The production of pleuran, a polysaccharide from *Pleurotus ostreatus* can be made by using submerged and solid-state fermentation. Extracellularly produced polysaccharides of *P. ostreatus* can be extracted by direct precipitation method followed by using cold ethanol and lyophilization. The endopolysaccharides are extracted using the general method of extraction by using hot water, ethanol, and ultracentrifugation [15]. A large number of scientific

investigations have revealed several potential bioactive MPs, their source, and immunomodulatory mechanisms, which are outlined in Table 1.

Table 1. Different mushroom polysaccharides, their source, and probable mechanism as immune-modulator.

| Scientific name | Common name | Bioactive polysaccharides | Parts used | Immune-modulatory Mechanism | Reference |
|-------------------------------|------------------------------------|---|--|--|-----------|
| <i>Lentinus edodes</i> | Shiitake | Lentinan | Fruiting body | By enhancing cytokine production | [37, 45] |
| <i>Ganoderma lucidum</i> | Reishi | Ganoderan | Fruiting body, culture broth | By regulating NF- κ B signaling pathway | [46, 47] |
| <i>Pleurotus ostreatus</i> | Oyster mushroom | Pleuran | Fruiting body, culture broth | Induce gene expression of cytokines | [48, 49] |
| <i>Grifola frondosa</i> | Maitake | Grifolan | Fruiting body, culture broth | Through macrophage activation | [50, 51] |
| <i>Cordyceps sinensis</i> | Caterpillar fungus | Cordyglucan | Fruiting body, culture broth, mycelium | Induce IL-5 production to suppress IL-4 and IL-17 | [52] |
| <i>Morchella esculenta</i> | Sponge morel | Galactomannan | Fruiting body | Activates macrophages | [53] |
| <i>Scizophyllum commune</i> | Split gill mushroom | schizophyllan | Whole mushroom, fruiting body | Activate T-cells and increase the production of interleukins | [38, 54] |
| <i>Polystictus versicolor</i> | Turkey tail | Krestin, polysaccharide peptide (PSP) polysaccharide K (PSK), | Fruiting body, culture broth, mycelium | Induced genes that code cytokines production and stimulates T-cell activation | [55, 56] |
| <i>Agaricus blazei</i> | Almond mushroom | Glycoprotein, β -1,3-glucan | Fruiting body, culture broth | Induction of TNF and IL-8 production | [57, 58] |
| <i>Inonotus obliquus</i> | Chaga | β -D-glucan | Fruiting body, mycelium | Induce the expression of TNF- α and IL-6 in macrophages | [59] |
| <i>Hericium arinaceus</i> | Pom mushroom, monkey head mushroom | Heteroglycan peptide, heteroglycan | Fruiting body, the culture broth | Regulate the expression of TNF- α and IL-12 also induce NO production | [60] |
| <i>Phellinus linteus</i> | Black hoof mushroom | Glucan | Fruiting body | Block production of TNF- α , IL-4 production, activates murine B cells | [61] |
| <i>Xylaria nigripes</i> | Dead man's fingers | B-glucan | Whole mushroom | Inhibits IFN- γ , NO, TNF- α , IL-6 production | [62] |
| <i>Sarcodon aspratus</i> | Black tiger paw | Fucogalactan | Fruiting body | Regulate release of TNF- α and NO in macrophages | [63] |
| <i>Flammulina velutipes</i> | Golden needle mushroom | Homogeneous heteropolysaccharide | Fruiting body | Increases proliferation of mouse spleen lymphocytes and antibody levels such as IgM and IgG | [64] |
| <i>Pleurotus eryngii</i> | King trumpet mushroom | 3-O-methylated heterogalactan | Fruiting body | Activates murine macrophage cells via toll-like receptor-2 pathway and stimulates the secretion of cytokines and other immune mediators. | [65] |

4. Factors Determining Immune-Stimulatory Activities of Mushrooms Polysaccharides

A detailed study over the past several years on the structure-activity of mushrooms polysaccharides has revealed the correlation between structural variability and bioactivity. MPs are characterized by highly diversified macromolecules. They show diversity and variability in their molecular weight, helical conformation, branching patterns, sugar composition, chemical

modification, and other physical properties, which significantly affects their immune-stimulatory actions [66, 67].

Molecular weight: Mushroom polysaccharides generally with high molecular weight (500-2000 kDa) appear to be more biologically active in comparison to low molecular weight polysaccharides. [43, 68]. For instance, when four fractions of Polysaccharide K (PSK), each having different molecular masses were extracted from turkey tail mushrooms, the high molecular mass fraction showed the greater immune-modulatory effects [69]. A β -glucan was reported from *Grifola frondosa* with high molecular mass (<800 kDa) known to have antitumor and immune-modulatory activity [70]. This study has revealed the fact that for immune-stimulatory activities, high molecular weight polysaccharides are the most appropriate macromolecules. However, there are some low molecular weight polysaccharides, which also showed significant bioactivity. For example, certain low molecular weight polysaccharides fractionated from *Schizophyllum* and *Lentinus* species exhibited anti-cancer and immune-modulatory potency [71].

Monosaccharides composition: The relationship between the polysaccharides composition and bioactivity has gained attention during the past decade. Polysaccharides composed of monosaccharide residues such as Mannose, Rhamnose, and Fucose are known to have better bioactivity [72]. The Immune response activity of *Tremella mesenterica* is responsible for Mannose rich exopolysaccharides [73]. Rhamnose rich exopolysaccharides from *Lactobacillus rhamnosus* shows potential pharmaceuticals activities [74]. Many polysaccharides contain Mannose as their monosaccharides component, which gives protection against some virulent pathogens. Human cells also have Mannose receptors, which can induce cytokines production and confer immune responses [75]. Some of the bioactive MPs and their functional monosaccharide components with immune-stimulatory activities are presented in Table 2.

Table 2. Mushrooms polysaccharides with different active monosaccharides component and their biological activities.

| Mushroom name | Active monosaccharide component | Biological activity | Reference |
|-----------------------------|---------------------------------|--------------------------------|-----------|
| <i>Ganoderma lucidum</i> | Rhamnose | Immune-modulatory, anti-cancer | [76] |
| <i>Sarcodon aspratus</i> | Mannose, Rhamnose | Immune-modulatory | [77] |
| <i>Inonotus obliquus</i> | Mannose, Rhamnose, Xylose | Cytokines induction | [78] |
| <i>Tremella mesenterica</i> | Man | Cytokine stimulation | [73, 75] |
| <i>Agrocybe cylindracea</i> | Glucose, Galactose | Antioxidant activity | [79] |

Solubility: The solubility of mushrooms polysaccharides depends on some physical properties like structural configuration, the complexity of side chains, degree of polymerization, and physical organization [80]. When a branched insoluble (1→3) β -D-glucan was fractionated from *Auricularia auricular-judae*, it did not exhibit any bioactivity later it was chemically modified and made water-soluble, and then it was found to be a potential antitumor agent [81, 82].

Branching configuration: The degree of branching is another significant attribute of certain MPs to determine the immune-modulatory functions. Most of the immune-modulatory MPs contain linear 1,3 β -D-glucans configuration in their main chains with a very small number of short branched chains. β -glucans that possess linear structures with short or no side branches show greater antitumor activities. The degree of branching for Lentinan, Schizophyllan, and polysaccharide K (PSK) is 40% (2/5), 33% (1/3), and 20% (1/5)

respectively but they exhibit more or less same bioactivity even though having differences in their degree of branching (DB). The optimal DB for a bioactive MP is between 20% to 33% [36, 83]. Debranching of MPs can sometimes increase their bioactivity extensively; for example, pachyman, a branched polysaccharide from *Poria cocos* showed no or very little bioactivity, but when it made debranched pachyman, by using hydrolysis and periodate oxidation it exhibited antitumor and great medicinal and pharmaceutical activities [84]. Debranched Lentinan also showed potential antitumor and immune-stimulatory activities [85].

Helical conformation: Most of the bioactive mushroom polysaccharides possess helical structures. Antitumor and immune-modulatory polysaccharides are generally existed as triple-helical conformation, which is considered as the most stable structure of polysaccharides. In a study, when six anti-cancer mushroom polysaccharides, Schizophyllan, Lentinan, Curdlan, Scleroglucan, Cinerean, and β -D-xylan were taken for treatment of cancer, it was found that all of these MPs adopt triple-helical conformation [86]. A low molecular weight, triple-helical conformation polysaccharide from *Hericium erineceus* showed great immune-stimulatory effects by inducing NO production and expression of TNF- α , it could also activate macrophages [60]. However, single helix conformation also exhibits biological activities; a single helix β -D-glucan extracted from *Auricularia auricular* showed potential antitumor activity [87]. MPs with random coil conformation are also capable of showing significant immune-modulatory activity.

Chemical modification: In order to improve the immune-stimulatory and anti-cancer activities, chemical modifications of MPs have been incorporated. This includes hydroxylation, formylmethylation, carboxymethylation, aminoethylation. A sulfated (1 \rightarrow 3) β -D-glucan isolated from *Lentinus edodes* showed better immune-modulating, anti-cancer, antitumor activities than its native glucan [88]. Another study showed that the linear (1 \rightarrow 3) α -glucans isolated from *Amanita muscaria* and *Agrocybe cylindracea* have very little anti-cancer activity than its carboxymethylated form which showed great antitumor activity against sarcoma 180 and also immune-modulatory activity in mice [89, 90].

5. Immune Cell Receptors of Mushrooms Polysaccharides

When an infection occurs, the innate immune system is the first line of a defense system that draws barriers to the pathogens or other foreign particles and helps to slow down the infection followed by developing acquired immune responses. Phagocytes are activated in the innate immune system when a pathogen enters the host cell and eliminates the pathogens through phagocytosis [91]. Multicellular organisms recognize infectious molecules and foreign particles through pattern recognition receptors. These receptors identify pathogen-related macromolecules or foreign structures through pathogen-associated molecular patterns (PAMPs). Most of the immune-modulatory MPs are the derivatives of β -glucans, and they are considered as PAMPs [38]. Due to high molecular mass MPs cannot penetrate cells, so they need certain immune cell receptors to bind. Some of the wells studied β -glucan receptors are dectin-1, scavenger receptors, complement receptor 3, lactosylceramide, and toll-like receptors (TLR-2, TLR-4) [92].

Dectin-1 is the most studied and important fungal polysaccharide receptors. It is a type-II transmembrane receptor belongs to the C-type lectin family receptor, which comprises four component extracellular carbohydrate recognition domain, a stalk, a transmembrane region, and a short intracellular tail [93]. These receptors bind specifically (1 \rightarrow 3) β -D-glucans with

branched side chains. Dectin-1 has a variety of biological activities such as the killing of fungal cells, activation of macrophages, dendritic cells and neutrophil responses, phagocytosis, cytokines productions [94]. In a signaling pathway, dectin-1 works with TLR to generate immune responses by the increased production of cytokines such as tumor necrosis factor (TNF- α) and interleukine-2 [95].

Complement receptor-3 (CR 3) is other mushrooms β -glucan receptor, which is widely expressed by neutrophil, monocytes, natural killer cells, dendritic cells, and macrophages. CR3 is a dimer comprises two domains CD11b and CD18 [96]. CR 3 has several diverse groups of ligands and complement components, which helps other low-affinity receptors to bind with the cytoskeleton. CD11b is a lectin domain, and it has a high affinity for β -glucan. In a study, it was found that when neutrophil was added in a β -glucan solution in the presence of spleen tyrosine kinase, it showed cytotoxicity, which was mediated by CR 3 signaling pathway [97].

Scavenger receptors are expressed by myeloid and endothelial cells. It is a heterogeneous protein molecule comprises of two intracellular domains, one extracellular domain, and two transmembrane domains. It activates certain signaling pathway like mitogen-activated protein kinase (MAPK), endothelial nitric oxide synthase however there is no such reports found about the activity on fungal metabolites, more studies are needed to understand their activity on MPs [98].

Toll-like receptors (TLR) are certain transmembrane receptors expressed widely in the presence of microbes, fungi, and protozoa. TLR-1 binds specifically lipoglycans, TLR-4 binds bacterial lipopolysaccharides, TLR-5 binds flagellin, and as a result, phagocytosis is initiated by activation of several degrading enzymes. Polysaccharides from *Phellinus linteus* can activate TLR signaling, which helps in the maturation of dendritic cells through MAPK and p38 signaling pathway [99]. In the presence of fungal components, TLR-2 and TLR-4 can induce inflammatory mediators and trigger the expression of cytokines and chemokines. The induce production of pro-inflammatory cytokine in the yeast phagosomes by detecting fungal components was mediated by TLRs. TLR-4 can mediate the macrophage activation in the presence of a β -glucan polysaccharide isolated from *Ganoderma* species, which results in activation of NF- κ B [100, 101].

6. Response of Mushrooms Polysaccharides on Immune System

Mushrooms and their extracts are well known for their medicinal and pharmaceutical values from ancient times. The present scientific researches are now able to understand the reasons and detailed mechanisms behind the enormous biological activities of these mushrooms metabolites. In recent times different mushrooms metabolites are increasingly gaining importance in health industries due to their immune-modulating ability. β -glucans are detected as the most common MPs which are capable of exhibiting several immune responses, including induction of cytokines production, inhibition of tumor growth, and also shows anti-cancer activities. The cell surface immune cells receptors recognized these polysaccharides through pattern recognition receptors resulting in activation of macrophages, maintain the balance of the T helper cell population via cytokine production [102]. The overall host-mediated immune-modulation effects of MPs comprises both innate (macrophages, dendritic cells, natural killer cells, neutrophil) and adaptive (T cell and B cell) immune responses.

7. Effects on the Innate Immune System

Macrophages or monocytes are particularly responsible for the production of TNF- α , IL-1, IL-6, IL-10, IL-12 and also helps to maintain the balance between Th1 and Th2. Lentinan, grifolan, Schizophyllan are some of the most potent immune-modulatory MPs which can activate macrophages [17, 103]. The activated macrophages enhance the production of cytokines such as IL-1 and TNF- α , which ultimately leads to immune stimulation. TNF- α can act as both tumor-inhibiting and promoting factors and can also induce the production of some other cytokines that may play an important biological role [104]. After treating a macrophage culture with a polysaccharide isolated from the fresh fruiting body of *Ganoderma lucidum*, it showed 29 times higher levels of TNF- α and IL-1 than its untreated culture [105]. A polysaccharide fraction from *Sarcodon aspratus* exhibited immune-modulation responses by releasing TNF- α and NO in the macrophages of mice. This might also help to inhibit tumor formation and other immune-modulatory effects [99].

NK cells are the class of lymphocytes, which shows defense responses against intracellular infections by killing them. It produces cytokine IFN- γ which activates macrophages. NK cells exhibit cytotoxic activities to certain pathogens, which involves recognition and lysis of the infected cells. NK cells stimulate the immune responses by the production of IFN- γ , TNF- α , and GN-CSF. Activated dendritic cells can stimulate NK cells to produce cytokines that contribute to innate immune responses [106]. Hot water extracts of *Agaricus blazei* can induce the activity of NK cells in the spleen cells of mice besides this it can also enhance the production of cytotoxic T lymphocytes and IFN- γ [107]. A scientific study has revealed that water extracts of five medicinally important mushrooms such as *Lentinus edodes*, *Coriolus versicolor*, *Cordyceps sinensis*, *Agaricus blazei*, *Ganoderma lucidum* enhanced the NK cell activities in mice and also suppressed the growth of B-16 melanoma [108].

Dendritic cells (DCs) are the antigen-presenting cells (APC) and central component of the innate immune system, which can regulate the expression of both native T cells and B cells. They induce tumor immunity by regulating NK cell levels and also by developing cells of the adaptive immune system. Polysaccharide K (PSK) isolated from *Coriolus versicolor* can induce the maturation of DCs in human CD14 mononuclear cells. Moreover, it can reverse the immune-suppressive state of certain cancer-bearing organisms through the maturation of DCs [109]. It was reported that polysaccharide from *Ganoderma lucidum* could stimulate the maturation of DCs derived from murine bone marrow and also capable of showing significant immune-modulation responses [110]. *Phellinus linteus* and *Agaricus blazei* can produce IL-12 in DCs [17].

8. Effects on Adaptive Immune System

T cells or T lymphocytes are of two types T helper cells (T_H) and cytotoxic T cells (T_C). T_H cells can interact with B cells and help them to divide and killing intracellular pathogens while T_C cells directly destroy infected host cells [111]. The activation of T cells is mediated by CD4⁺ through secretion of a certain number of cytokines, which also induce the production of innate immune cells. T_H1 contributes to cellular immunity by producing cytokines such as IFN- γ , TNF- β , and IL-2 while T_H2 contributes to humoral immunity by producing IL-4, 5, 6, 10, and 13 [99]. D-fraction from *Grifola frondosa* controls the balance of T_H1 and T_H2 and can inhibit the activation of B cells resulting in enhances cellular immunity [112]. Lentinan has

considered a T cell oriented adjuvants [113]. A glucan from *Sclerotinia sclerotiorum* can induce the response of T_H cells via the IL-12 pathway [114]. Besides MPs several fungal immune-modulatory proteins (FIP) can also induce T cell-mediated bioactivities. For example, FIP from two edible mushrooms *Volvariella volvacea* can induce the expression of both T_H1 and T_H2 specific cytokine [115].

There are many mushrooms metabolites which can activate B cells mediated immune-stimulation. A proteoglycan from *Phellinus linteus* was found to involves in this process. Three polysaccharides extracted from the fruiting body of *Ganoderma lucidum* (PL-1, PL-3, and PL-4) enhanced proliferation of B cells, PL-1 have immune-stimulatory functions [116]. A proteoglycan from *Ganoderma lucidum* was found to stimulate the activation marker of murine splenic B cells, which induced their differentiation into IgM secreting plasma cells[117, 118]. However, there are some MPs that suppress B cells' function. For instance, a polysaccharide obtained from *Ganoderma* spores inhibits the function of antibody-producing cells in mice [116]. Recently, a purified polysaccharide isolated from *Poria cocos* was tested for its adjuvant property on inactivated rabies vaccine. It was found that the polysaccharide was capable of activating both humoral and cellular immune responses in mice as well as dogs, and also it markedly induced cytokines secretion from splenocytes [119].

9. Conclusions

The immune-modulatory effects of different mushrooms polysaccharides are presented in this review. One of the main goals of the present and advance medical researches is to discover new and safe drugs with no or very negligible side effects. In the past 20 years, research on MPs has increased significantly; the most studied biological activities of these MPs are immune-modulation, anti-cancer, and tumor inhibition. Clinical studies have suggested that nutraceuticals obtained from medicinal mushrooms are considered as natural drugs with very few side effects. Mushrooms polysaccharides are the emerging new agents that could enhance immune responses. The effectiveness of a drug obtained from any natural resources solely depends on the dose, concentration, methods of purification, and duration of treatment. The medicinal properties of different mushrooms species have been determined, and it was found that there are remarkable differences in their immune-modulating properties. We have represented a different source of immune-modulatory polysaccharides from different mushrooms with their corresponding effects on the immune system. The major immune-stimulatory effects of these MPs include activation of different immune cells. Different physical properties of polysaccharides can play an important role in their bioactivity. The biochemical mechanisms of polysaccharides are still unclear; more studies are needed on different mushrooms species and their extracts to understand the detailed mechanisms of how they inhibit tumor formation and can act as adjuvants in cancer therapy. More clinical trials should be done on humans to understand the bioactivities of different polysaccharide fractions. Different investigations are still going on to improve the immune-stimulatory activities of MPs, which will also increase their clinical qualities.

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Conflicts of Interest

The authors declare no conflict of interest.

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