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Bioactive Mushroom Polysaccharides: Immunoceuticals to Anticancer Agents

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Abstract

Medicinal and edible mushrooms have been widely used for centuries as nutraceuticals to improve health and to treat numerous diseases. Several species of mushrooms such as *Lentinula edodes*, *Schizophyllum commune*, *Ganoderma lucidum* and *Coriolus versicolor* have been used as immunostimulators and anticancer agents. Mushroom polysaccharides, as the main active ingredient in the mushroom, belong to a special group of immunoceuticals that inhibit cancer cells by activating host immune system. These special properties along with minimal side effects make mushroom polysaccharides as ideal candidates for developing novel anticancer therapies. This review highlights the current status of research in the area of mushroom polysaccharides, focusing on their structure-function relationship and mechanism of biological activities, as well as the potential of using these biopolymers as therapeutic agents.

Keywords: Mushroom polysaccharides; Immunoceuticals; Nutraceuticals; Structural feather

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Introduction

Mushrooms have long history of traditional use for improving general health and for the treatment of various ailments [1]. Their application as nutraceuticals is also well-known [2]. Literature reports that there are over 12,000 wild species of mushrooms worldwide and about 2000 species are edible [3]. A couple of hundreds of wild species are used for medicinal purposes [2,3].

A large number of scientific studies indicate that edible and medicinal mushrooms are rich in a variety of nutraceutical compounds such as polysaccharides, dietary fibres, terpenes, peptides, glycoproteins, mineral elements, unsaturated fatty acids, as well as antioxidants like phenolic compounds, and vitamins [2,4-7]. The presence of these compounds makes mushrooms display significant biological activities against various pathological conditions or diseases including cancer [2-8].

During the past several years, significant progress has been made in understanding mushroom polysaccharides, including their chemical structures and bioactivities, such as antioxidant, immunostimulatory and anti-proliferative properties and their use as immuno-chemotherapeutic agents [9-13]. For example, lentinan derived from *Lentinula edodes* [14-16], Polysaccharide Krestin (PSK) derived from *Coriolus versicolor* [17,18], Polysaccharopeptide (PSP) isolated from *Coriolus versicolor* [19], and schizophyllan from *Schizophyllum commune* have been shown with certain anticancer applications [13,15]. These mushroom polysaccharides are mainly developed and used as anticancer agents in Japan, China and other Asian countries following favourable clinical trial results [12,13]. This review highlights bioactivities of mushroom polysaccharides, their structure-activity relationship and the possible mechanisms of action, as well as their potential as immunoceuticals and anti-cancer agents.

Literature Review

Bioactive polysaccharides isolated from medicinal/edible mushrooms

Large numbers of polysaccharides have been reported that display immuno-stimulatory and anti-tumour activities [9,11-13,20-22]. These include plant, fungal, yeast and algal polysaccharides [9,21]. Some of the potent immunostimulatory and anti-tumour polysaccharides and their sources are highlighted below.

Polysaccharide-Krestin (PSK) and polysaccharopeptide (PSP) are

the well-known polysaccharides isolated from *Coriolus versicolor*, and both are currently used as immuno-chemotherapeutic agents for the treatment of cancer [12,13,19]. PSK was first isolated in Japan [19]. *In vivo* studies have shown that PSK enhanced the cytotoxicity of chemotherapeutic drugs [23,24], such as trastuzumab, and significantly suppressed tumour growth through its immunostimulatory activity [25,26]. PSK also showed direct anti-tumour effects by inhibiting the proliferation of various tumour cells via the arrest of cell cycle and the induction of apoptosis [26,27]. PSP is another important polysaccharide isolated from *C. versicolor* in China, and was developed as an anticancer agent after extensive studies [19]. It has been demonstrated that PSP inhibited tumour cell proliferation through immunostimulatory activity [28]. PSP in combination with certain S-phase targeted chemotherapeutics, such as doxorubicin, etoposide, camptothecin and cyclophosphamide can enhance cytotoxicity against human cancer cells [26,29]. In addition, PSP has been shown with chemopreventive effect on prostate cancer by targeting prostate cancer stem cell-like populations [30]. Clinical studies have demonstrated that PSP combining with chemotherapeutic agents reduced the chemotherapy-induced side effects and increased the survival rates and quality of life of cancer patients [19,26,28].

Lentinan is derived from a commonly used food mushroom *Lentinula edodes* (Berk) Pegler (*Polyporaceae*) and has been used clinically as anti-tumour polysaccharide for the treatment of gastric cancer in Japan [13,15,16]. Clinical studies demonstrate that lentinan used in immuno-chemotherapy in combination with chemotherapeutic agents (e.g. oral fluoropyrimidine) significantly prolonged the survival of patients with advanced gastric cancer, as compared to chemotherapy alone [16]. In addition, *in vivo* studies demonstrated that lentinan enhanced the anti-tumour ability of trastuzumab, and significantly suppressed tumour growth [16,31].

Schizophyllan (SPG) is a mushroom polysaccharide isolated from *Schizophyllum commune* Fr (Schizophyllaceae), which has also been clinically used for the treatment of cancer in Japan [26,32]. Komatsu et al. discovered SPG and demonstrated that it displayed host-mediated anti-tumour activity against Sarcoma 180 [33]. SPG was shown to stimulate immune system and activate NK cells, spleen cells, lymphoid cells as well as bone marrow cells and enhance the production of anti-tumour/immunostimulatory cytokines such as interleukines 1, 2 and 3 [32,34]. Clinical studies indicated that SPG used in immuno-chemotherapy in combination with chemotherapeutic agents (tegafur or mitomycin and 5-fluorouracil) significantly prolonged the survival of patients with stage II cervical cancer, compared to chemotherapy without SPG [32].

Ganoderma lucidum (*Ganodermataceae*) is an important medicinal mushroom which is traditionally used for the treatment of various conditions, including heart disease, hypertension, hepatitis, diabetes, neurasthenia and cancer in China and other countries [35]. Mushrooms belonging to *Ganodermataceae* family contain a number of bioactive polysaccharides [35,36]. Studies found that a majority of bioactive polysaccharides isolated from Ganoderma species consist of β-(1→3)-D-glucans with β-(1→6)-D-glucopyranosyl branches [35]. Recent studies on the polysaccharides isolated from *Amauroderma rugosum* (*Ganodermataceae*) produced two immunostmulatory β-glucans for the first time in the Authors' laboratory [37]. These two novel polysaccharides have β-D-(1→3)-glucan backbone with β-D-(1→6) branched structures and displayed significant immunostimulatory and antioxidant properties [37].

Structure-function relationship and mechanism of biological activity of mushroom polysaccharides

Mushroom polysaccharides (PS) include both α- and β-glucans, however, β-glucans are the most studied [21,38]. The structure function relationship of these polysaccharides is discussed in this section.

Structural features of polysaccharides responsible for their bioactivity: Structure-activity studies of polysaccharides have revealed that the following structural features are important for activation of immune system [21,22,38-40].

The polysaccharide conformation (such as glycosidic linkage and helical structure) is one of the major factors influencing their biological activities. For example, (i) Glucans with (1→3)-β-linkages in the main chain is an important structural feature for immunostimulatory and anticancer activities [21,38,40,41]. However, β-glucans with (1→3) linkage and with mixed (1→4) linkage are non-active/less active [39] (ii) Triple helical conformation of (1→3)-β-glucans that can be recognised by glucan receptors has been shown to correlate with their immunostimulatory activity [21,28,38,40,42].

The degree of branching (DB) is another factor that significantly influences the immunostimulatory activities of polysaccharides [21,28,38]. For example, β-(1→3)-glucans with high degree of (1→6) branching (DB≈0.33) displayed higher immunostimulatory and anticancer activities as compared with less branched or linear β-(1→3)-glucans [21,38]. It should be noted that, β-(1→3)-glucans with higher DB allows the formation of tighter triple helical structure that is important structural feature for their immunostimulatory activities [21].

β-(1→3)-glucans conjugated with a peptide/protein are known to enhance immunostimulatory activity [22].

Polysaccharides with higher molecular weight displayed higher immunostimulatory activities [28,38].

Studies on α-(1→4)-D-glucans with similar conformations and molecular weights demonstrated that the lower degree of branching was preferred structural feature for their immunostimulatory activity which is the major difference between α- and β-glucans [21,43].

Mechanism of bioactivity of polysaccharides: Recent studies have demonstrated that polysaccharides possess one or several 'active sites' that interact with pattern-recognition receptors (PRR) in immune cells and activate the immune response [38]. A brief description of molecular mechanisms that are

responsible for the immunostimulatory properties of mushroom *polysaccharides* are summarised below.

The most common immune receptors that recognise bioactive polysaccharides are: Dectin-1 (glucan receptor), Mannose receptor (MR), complement receptor-3 (CR-3), Toll-like receptor (TLR) and scavenger receptor (SR) [21,28,38,39]. Dectine-1, a type II transmembrane receptor, is highly specific receptor for (1→3)-β-D-glucans with (1→6) branching [21,39,44]. The carbohydrate recognition domain (CRD) of dectin-1consists of the amino acid sequence Tryptophan (Trp 221) -Isoleucine (Ile 222) -Histidine (His 223) that can interact with (1→3)-β-D-glucans and activate immune cells [39,44]. Furthermore, β-(1→3)-glucans can bind with several other immune receptors and activate signalling pathways to promote immune response. For instance, PSK can bind with Toll-like receptor (e.g. TLR-2), activate innate as well as adaptive immune response to produce natural killer (NK) cells, lymphokine-activated killer (LAK) cells and tumour antigen-specific cytotoxic T lymphocytes (CTLs) [25,38,45].

A number of studies have demonstrated immunostimulatory activities and cell signal modulation capacity of polysaccharides [21,28,40,45]. Two important mechanisms have been thought to be responsible for the anticancer action of polysaccharides, namely, (i) indirect anticancer effect through the stimulation of innate as well as adaptive immune response [21,28,40,41,45], and (ii) direct cytotoxic effect where the polysaccharides can directly inhibit cancer cell growth by reducing the expression of cell cycle related proteins such as cyclin D1, cyclin E and Bcl-2 and up-regulation of p12 [40]. β-(1→3) glucans (e.g. PSK) have been shown to directly inhibit cancer cell growth by anti-angiogenesis activity [45]. This mechanism involves the inhibition of basic fibroblast growth factor (bFGF)-induced angiogenesis. It is speculated that this action is the result of direct binding of PSK with bFGF. PSK is also known to inhibit metastasis by (a) suppression of intravasation through the inhibition of tumour invasion, (b) suppression of tumour cell migration after extravasation by the inhibition of tumour cell motility and (c) by direct suppression of matrix metalloproteinase (MMP) [45].

Nutraceutical/Immunoceutical potential of mushroom polysaccharides: Glucans, mannans, galactans and fructans are widely studied immunostimualtory/anticancer polysaccharides [21]. Amongst them, glucans are most promising immunostimulatory/anticancer polysaccharides [9,12-13,21,28,38]. They are D-glucose based polymers joined mostly by β-glycosidic linkages and in some instances by α-linkages [21,22]. While β-glucans are the most studied active immunostimulators, α-glucans were considered to be non-active until recent years [22,38]. Recent studies demonstrate that α-glucans with (1→4) and (1→6) glycosidic linkages display immunostimulatory activity [21,22,43,45].

Discussion

As discussed before, polysaccharides act as immunostimulatory agents by their interaction with various receptors on immune cells [21,37]. Most mushroom β-glucans display extremely significant immunostimulatory activities that range from high nutraceutical to pharmaceutical levels [2,8,10,37]. Some of the β-glucans derived from mushrooms are currently in use for immuno-chemotherapy to treat cancer [12,13,26]. As highlighted in section 2, immuno-chemotherapy using mushroom polysaccharides is beneficial for the survival and to improve the quality of life of cancer patients. Recent studies demonstrated that PSP is also an effective chemopreventative agent that completely inhibited the formation of prostate tumour [30]. In addition, PSP has been shown to reduce the rate of cell proliferation and to selectively induce apoptosis of cancer cells [46]. Other mushroom polysaccharides (such as PSK and Lentinan) displayed huge potential for immuno-chemtherapy [12,13,16,31]. These findings demonstrate the future prospects of mushroom polysaccharides as immunoceuticals for the prevention and treatment of various cancers. Due to the fact that polysaccharides and other constituents of mushrooms have been demonstrated to repair oxidative damage and suppress neuroinflammation, they have great potential to develop therapies for neurodegenerative conditions [47,48]. Further research involving development of formulations by combining polysaccharides that activate multiple immune pathways is important future direction for the discovery of novel immunoceuticals to treat cancer and relevant diseases.

Despite the successful use of several mushroom polysaccharides in Asia for several years, they are not widely used in Western countries [4]. Further detailed studies to investigate therapeutic effects, of these polysaccharides and their combinations, against different type of cancers are expected to lead to the development of effective treatment strategies and result in their wider use in Western world.

Due to their well-demonstrated bioactivities and high safety profile (low toxicity), mushroom polysaccharides have a great potential as nutraceuticals as well as therapeutic agents [9,11,37]. Bioactive mushroom polysaccharides consumed in the form of isolated extracts, dietary supplements, herbal products and food will therefore provide significant health benefits [1,2,4,37,49].

Conclusion

There has been significant progress in understanding the structure and bioactivity of mushroom polysaccharides. α- and β-glucans derived from fungi and other food sources have been shown to possess effective imunostimulating activity and some display direct anticancer effect. α-glucans with suitable structural features have significant bioactivity and β-glycosidic linkage is not an explicit requirement for immune enhancing activity. The discovery that specific receptors exist for some α-glucans helped to reveal new actions of α-glucans. It is also possible that α- and β-glucans may have synergistic actions. Further study on the activities of their combinations is expected to lead to the development of novel nutraceutical and therapeutic agents for preventative as well as curative applications against various diseases including cancer.

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