Chapter

Mushroom Polysaccharides: Chemistry and Anticancer Potentials

Moyen Uddin Pk, Rumana Pervin, Jabin Jahan, Rabiul Islam Talukder, Sourav Ahmed and Matiar Rahman

Abstract

Mushrooms have been used as a common folk medicine due to their effective bioactive compounds including polysaccharides. It is known that the glucans are the main bioactive mushroom polysaccharides. This review study explains the method of isolation, structural characterization, and antitumor activities of mushroom polysaccharides. In many laboratories, these trials are still underway, and the function of polysaccharides as an antitumor agent is particularly under intense discussion. This review aims to summarize the accessible data and reflect this study area's current status with a perspective to future direction.

Keywords: polysaccharides, edible mushrooms, immunomodulation, glucans, tumoricidal

1. Introduction

Polysaccharides obtained from mushrooms have played a significant role as food and medicinal agent in the therapy of cancer in Asian nations such as China and Japan [1]. The consumption of fresh or dried mushroom powder in pre- and postmenopausal females might prevent breast cancer [2]. Mushrooms with distinctive fruiting bodies that have an impact on cancer curing belong to *Basidiomycetes* class and sometimes *Ascomycetes* classes. The main typical taxa are *Ganoderma lucidum*, *Lentinus edodes*, *Tremella fuciformis*, and *Pleurotus ostreatus*. For the first time in 1957, Lucas verified the bioactivity of *Basidiomycetes* mushrooms. Lucas isolated a *Boletus edulis* substance with an important inhibitory impact on tumor cells from sarcoma S-180 [2]. In 1966, Gregory conducted an extensive study, using submerged fermentation to the respective mushroom types, to isolate the active substances from fruiting bodies of mushroom species [3]. Applied to rodent animal model antitumor testing for the active agents, polysaccharides, which were isolated from 22 mushroom species, had inhibitory effects on tumor cells like sarcoma S-180, adenocarcinoma 755, and leukemia L-1210 [4].

2. Chemistry of polysaccharides

Polysaccharides are the most recognized and powerful mushroom-derived substances with antitumor and immunomodulating characteristics. Because of its

wide biological range, polysaccharide β-glucan is the most versatile metabolite. The β-glucans consist of a backbone of glucose residue associated with β-(1 to 3) glycosidic bonds, often connected by β-(1 to 6) linkages with the adjoining side-chain glucose residue [5]. It may be linear or branched to polysaccharides. Polysaccharides are split into two groups according to the number of distinct monomers: homopolysaccharides consist of only one type of monosaccharides, whereas heteropolysaccharides consists of two more types of monosaccharides [6]. Homopolysaccharides and heteropolysaccharides may have homolinkages or heterolinkages in configuration and/or position of connection. Polysaccharides with a powerful antitumor action vary significantly in their chemical structure. Antitumor activity is shown by a broad spectrum of glycans ranging from homopolymers to extremely complicated heteropolymers [7]. A broad variety of antitumor or immunostimulating polysaccharides were explored from distinct chemical structures from greater *Basidiomycetes* mushrooms, and the primary kinds are listed in **Table 1**.

Antitumor polysaccharides comprise monosaccharides like glucose, mannose, xylose, fucose, arabinose, galactose, glucuronic acid, and ribose. In few mushrooms, polysaccharides are conjugated with peptides or proteins which exhibited potent anticancer activity [8]. The origin, type, and bioactivity of the most common edible mushrooms, in Bangladesh, are given in **Table 2**. Some of them have been sold for clinical treatment in patients receiving anticancer treatment with polysaccharides and polysaccharide conjugates.

Glycans are structurally diversified. There are no unique protocols for the analysis of glycans. The primary structure of mushroom polysaccharide comprises the sequence and composition of monosaccharide, position, and configuration of monosaccharide, nature, and number of noncarbohydrate moieties.

During structure analysis, the composition of monosaccharide gives information on the molar ratio of monomers and nature and the location of glycosidic linkages,

Polysaccharides	Glycosidic linkage
Linear	
Amylose	α-(1 → 4)-Glc
Xylan	β-(1 → 4)-Xyl
β-Glucan	β-(1 → 4, 1 → 3)-Glc
Branched	
Amylopectin	α-(1 → 4, 1 → 6)-Glc
Glycogen	α-(1 → 4, 1 → 6)-Glc

Table 1.
Examples of homopolysaccharides [8].

Mushrooms	Polysaccharide source	Type	Bioactivity
Ganoderma lucidum [9]	Fruiting bodies	Heteroglycan Glycopeptide	Antitumor Antioxidative Immunomodulating
Lentinus edodes [10]	Fruiting bodies	Glucan	Antitumor Immunomodulating
Pleurotus tuber-regium [11]	Fruiting bodies Mycelium	B-D-glucan	Anticancer Hepatoprotective

Table 2.
Common edible mushrooms in Bangladesh.

Methods	Structural features
GLC-FID, GLC-MS, HPLC	Monosaccharide compositions
IR, NMR	Glycosidic bonds, configuration
NMR	Sequence analysis

Table 3.
Common methods for primary structure analysis of polysaccharide [12].

detection, and quantification of monomers. In **Table 3**, we represented the analytical methods that are used to analyze the primary structures of polysaccharides.

3. Purification of polysaccharides

Mushroom polysaccharide consists of two main polysaccharide kinds as the structural elements of the fungal cell wall. The celluloses and matrix-like glycoprotein are a rigid cellulose fibrilla, α-glucan or β-glucan. The selection of mushroom polysaccharides is usually based on the cell wall structure. A reliable procedure has been developed for successful polysaccharide mining of either cultivar mycelia or fruit body [13]. The process of extraction usually involves 80% ethanol to remove low molecular substances from the pest material and 3–5 repeated water extractions (100°C, 2–4 h). Alternatively, 5% sodium hydroxide (80°C, 6 h) or 2% ammonium oxalate (100°C, 6 h) is used. Using a mixture of methods such as ethanol precipitation, fractional precipitation, acidic precipitation with acetic acid, ion-exchange chromatography, gel filtration, and chromatography of affinity, extracted polysaccharides can be further purified. The precipitation of ethanol excludes polysaccharides from the impurities. Acidic and neutral polysaccharides can be separated on a DEAE-cellulose column by anion-exchange chromatography. First, a suitable running buffer elucidates the neutral polysaccharide in the blend; then the acid polysaccharide is eluted at a greater salt concentration [14]. Using gel filtration and affinity chromatography, neutral polysaccharides can be further divided into α-glucans (adsorbed fraction) and β-glucans (non-adsorbed fraction). Affinity chromatography is a selective adsorption method and the subsequent regeneration from an immobilized ligand of a compound. This method now enables some carbohydrates to be extremely specific and efficiently purified [15]. Previous studies have indicated that the mushroom sample fractionation for polysaccharides usually began with the extraction of warm water. Pk et al. described the isolation and characterization and anticancer effect of antioxidant polysaccharide from *Pleurotus ostreatus* [16].

4. Anticancer role

4.1 *Pleurotus ostreatus*

Pleurotus ostreatus protein extracts demonstrated therapeutic effectiveness against human colorectal adenocarcinoma cells and cells of human monocytic leukemia [17]. Cao et al. investigated that the colony-forming potential of the BGC-823 cells was significantly reduced, after *Pleurotus ostreatus* polytherapy [18]. Ivette González-Palma et al. (2016) studied the antioxidant properties of fungi *Pleurotus ostreatus* obtained from a local farm in Thailand [19]. Studies of histopathology confirmed the hepatoprotective effect of *P. ostreatus* extract. Such findings suggest that a *P. ostreatus* extract can significantly reduce hepatotoxicity [20]. Vamanu isolated exopolysaccharides and internal polysaccharides from *Pleurotus ostreatus*

and investigated in vitro antioxidant activity revealed strong antioxidant ability, which was demonstrated by the EC50 value for DPPH, ABTS scavenging activity, energy reduction, and iron-chelating operation [21]. **Figure 1** shows the concentration effects of polysaccharides from *Pleurotus ostreatus*.

The antimicrobial activity of *P. ostreatus* extracts was determined by the disc diffusion method for Gram-negative bacteria and Gram-positive bacteria. The acetone extracts had antimicrobial activity against only *B. subtilis* and *E. coli*, while the other extracts inhibited the growth of most oral bacteria, indicating a significant growth inhibition of *S. sanguinis* [22].

4.2 *Ganoderma lucidum*

G. lucidum polysaccharides perform anticancer action, by inhibiting the development and growth of the tumors [23], by increasing the immune function of patients, and by different mechanisms, such as anti-proliferating, anti-metastatic [24], antioxidant, and immunomodular [25] (**Figure 2**).

GLP shows activity against cancer by inducing immune responses and directly cytotoxic effects on tumor cells. GLP blocked the proliferation of mouse melanoma cells (B16F10) and human bladder cancer cells (HUC-PC and MTC-11). Several studies have found the mechanism of GLP anticancer role [26].

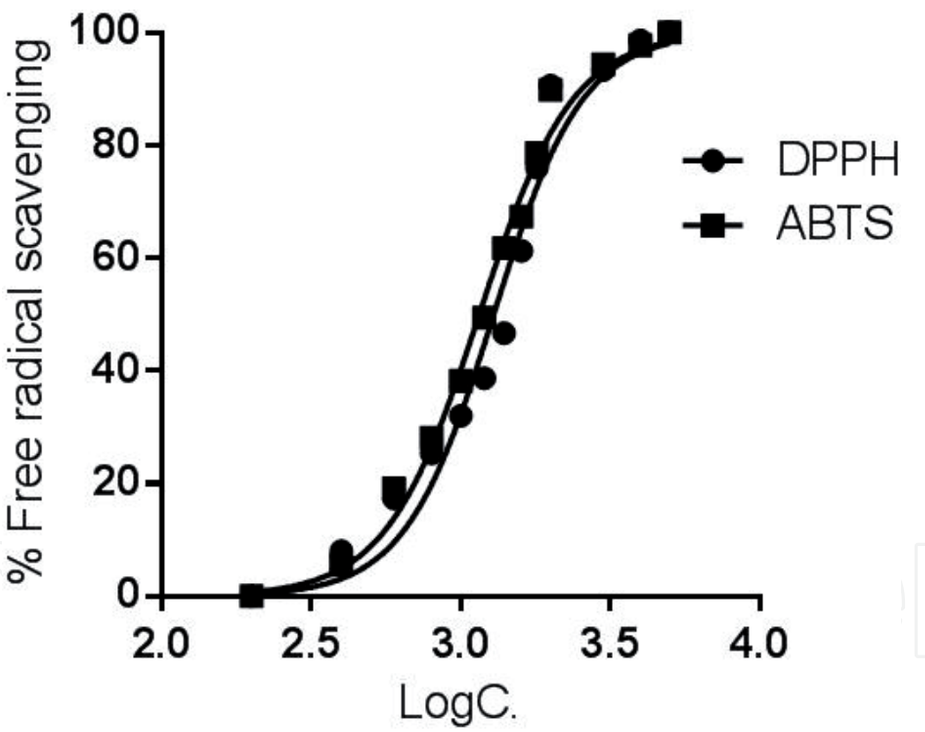

Figure 1.
The effects of POP on DPPH and ABTS radical scavenging.

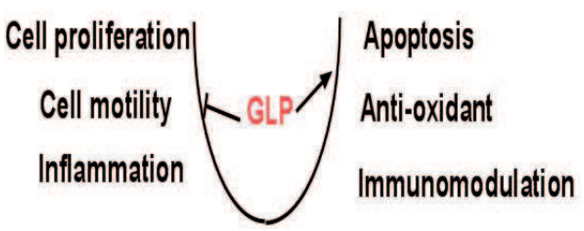

Figure 2.
Ganoderma lucidum *polysaccharides (GLP) results associated with cancer. Arrows are activation, but bars are inhibition.*

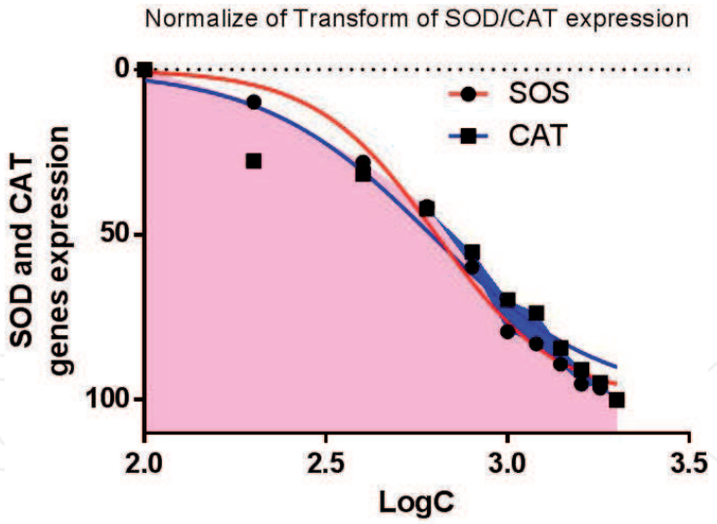

Figure 3.
Tentative relationship between SOD and CAT expressions and Ganoderma lucidum.

Mechanism 1: GLP downregulation of cyclin D1 in human ovarian OVCAR-3 cells is associated with growth inhibition and cell cycle arrest [27].

Mechanism 2: The anticancer activity of GLP includes both phosphoinositide 3-kinase (PI3K)/AKT/mammalian rapamycin (mTOR) and MAPK signaling pathways [28].

Mechanism 3: GLP decreases the expression of certain signaling molecules at gene and protein levels in the PI3K/AKT/mTOR and MAPK pathways [29].

It has been shown that many plants contain high levels of natural antioxidants that can scavenge free radicals [30]. In addition, this property may well decrease the level of DNA damage caused by oxidative stress and thus partially account for chemopreventive mechanisms that are attributed to antioxidants derived from plants [31]. Both the extracts of triterpene and polysaccharide have an antioxidant effect on pyrogallol-induced membrane oxidation and lipid peroxidation mediated by Fe(II)-ascorbic acid [32]. The findings of this study showed that GL extracts displayed dose-dependent antioxidant activity by increasing the expression of SOD and catalase [33]. **Figure 3** shows the expression patterns of SOD and CAT genes.

4.3 *Lentinus edodes*

As edible and medicinal tools, *Lentinus edodes* are appreciated. The most active antitumor and immunomodulatory agents in *Lentinus edodes* have been found to be polysaccharides. Lentinan is an isolated component of highly distilled polysaccharide from *Lentinus edodes* (shiitake). It is known as a β-glucan in terms of its chemical composition. The main chain consists of glucose units bound by β-(1–3) glycosidic bonds, while β-(1–6) glycosidic bonds link side chains with the main chain [13]. It is an authorized anticancer drug that is widely used in Japan. It is commonly used in cancer therapy in combination with other traditional pharmaceutical drugs, e.g., against cancer of the bowel, liver, stomach, ovary, and lung. It increases the efficacy of treatment and therefore the survival of patients [34].

5. Chemical structure

The chemical structure of lentinan has a main chain consisting of β-D-(1 → 3)-linked D-glucopyranosyl residues with two (1 → 6)-β-glucoside branches

for every five D-glucose residues, and the side chains of lentinan consist of β-D-(1,6)-linked and β-D-(1 → 3)-linked glucose residues [35] (**Figure 4**).

It has been shown that many mushroom β-glucans stimulate production of interferons (IFNs), interleukins (ILs), and other cytokines [34]. It is based mainly on the activation of T and B lymphocytes, macrophages, and natural killer cells [36]. Studies have found that the proliferation of mononuclear blood cells including lymphocytes, monocytes, and macrophages is induced by lentinan [37]. In addition, the production and differentiation of cells involved in the host defense mechanisms are encouraged. Lentinan can also improve immune cell reactivity and activate cytokines, hormones, and/or other biologically active substances to secrete. Lentinan increases the resistance of the body to malignant transformation by these properties [11]. Lentinan therapy has also been shown to inhibit prostaglandin synthesis, which often leads to a slowing of the differentiation of T lymphocytes and inhibition of Treg cell activities, in patients suffering from stomach cancer [38]. Increased levels of activated and cytotoxic T lymphocytes in spleen and peripheral cell mononuclear blood stimulation were also observed in generating interleukin 1α (IL-1α), IL-1β, and TNF-α [39]. Certain tumor forms have demonstrated the ability of lentinan in stimulating IL-1 release [40]. In addition to the indirect action, most polysaccharides had direct effects on cancer cells. Many researches about the tumor cell proliferation and/or apoptotic deaths in vitro and in vivo indicate that polysaccharides inhibit tumor cell growth [41]. The modulation of NF-β activity is one of the best-described mechanisms for direct anticancer action of polysaccharides derived from *Basidiomycetes*. Most types of cancer have excessive activation of NF-β. Effective NF-α encourages the development of tumors by stimulating gene transcription, inhibiting cell proliferation, or promoting angiogenesis and metastasis [42]. Polysaccharides have been proven to inhibit NF-α inhibitory phosphorylation and/or degradation [43], which prevents the transcription factor from being activated and therefore its subordinate gene expression [44]. Polysaccharides can influence cancer cells in other ways, in addition to NF-β pathway modulation. The polysaccharide protein complex derived from *Trametes versicolor* as the PSP is an

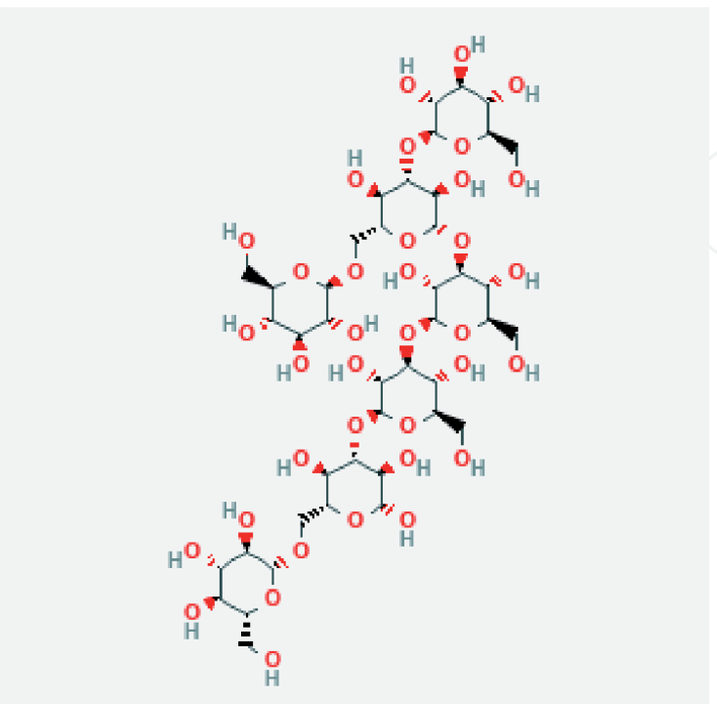

Figure 4.
Chemical structure (2D).

excellent example of this. It was shown that in the leukemia cells U-937 and in the breast cancer cells MDA-MB-231, PSP induced the arrest of cells at G1/S and G2/M restrictive points and inhibited antiapoptotic proteins that caused cell division repression and increased apoptosis [45]. In leukemia cells HL-60, however, the effect of PSP was similar by a decrease of NF-β and ERK kinase expression [46]. In oriental medicine, it is a fundamental principle to control the whole body's homeostasis and return the patient to its normal state [47].

6. Conclusions

Polysaccharides' anticancer properties depend on sugar composition [48], molecular weight [49], water solubility [1], glucose relation [25], tertiary structure [48], branching frequency and shape [41], chemical modification [40], and ligand presence [38]. Scientific approaches to mushroom compounds have allowed the isolation of many of the important active substances used in lifestyle disease prevention and treatment, including cancer. The immune system was strengthened by various polysaccharides from different mushroom varieties. Their ability to stimulate the host's immune system, rather than direct cytotoxicity, all has demonstrated strong antitumor activity. Chemotherapy or radiation therapy seem to withstand and compatible mushroom polysaccharides. Nonetheless, there are urgent needs to be studied that describe the molecular mechanism of mushroom polysaccharides such as receptors and downstream events induced by these polymers being bound to their target cells.

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