



Review

Structure, bioactivities and applications of the polysaccharides from *Tremella fuciformis* mushroom: A review



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ABSTRACT

Tremella fuciformis is an important edible mushroom that has been widely cultivated and used as food and medicinal ingredient in traditional Chinese medicine. In the past decades, many researchers have reported that *T. fuciformis* polysaccharides (TPS) possess various bioactivities, including anti-tumor, immunomodulatory, anti-oxidation, anti-aging, repairing brain memory impairment, anti-inflammatory, hypoglycemic and hypocholesterolemic. The structural characteristic of TPS has also been extensively investigated using advanced modern analytical technologies such as NMR, GC-MS, LC-MS and FT-IR to dissect the structure-activity relationship (SAR) of the TPS biomacromolecule. This article reviews the recent progress in the extraction, purification, structural characterization and applications of TPS.

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1. Introduction

Tremella fuciformis belongs to the order *Tremellales* and the family *Tremellaceae* [1]. It has many common names, such as snow fungus,

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snow ear, silver ear fungus, white jelly mushroom and white auricularia. It is a widespread fungus and can easily be found on the dead branches of broadleaf trees in the tropical areas [2]. Although it was first found in Brazil, it has developed as one of the most popular cultivated fungi species in China and other countries in Asia [3]. The fruiting bodies of *T. fuciformis* are gelatinous with white or light yellow color. They are clustered by a number of flat flaky or corrugated leaflets, or clustered by limbs or brainlike [4].

Nutritionally, *T. fuciformis* is low in energy and lipid, but rich in protein, polysaccharides and dietary fiber. It contains a variety of minerals, trace elements and vitamins. It is a popular food and herbal medicine ingredient, widely used as a tonic in Asian countries [5]. Recently studies reported that *T. fuciformis* polyphenol has high antioxidant activity [6]. Natural polysaccharides derived from *T. fuciformis* are viewed as ideal ingredients for healthy foods and pharmaceuticals [7]. The polysaccharides obtained from *T. fuciformis* (TPS) have been regarded as the major active component related to the nutritional and human's health [8]. TPS has many bioactivities such as improving immunity, lowering blood sugar, lowering blood fat, anti-aging, anti-ulcer, anti-thrombosis, and anti-mutagenicity.

While there are many research articles on mushrooms, there are few reviews on TPS. This article reviews the extraction, isolation, purification, structure characterization, biological activities and applications of TPS.

2. Extraction and purification

In the past most studies have focused on the extraction of polysaccharides from the fruiting body and mycelium. Extraction and purification should rely on authentic source material to verify the structure and characterization of polysaccharides [9]. Extraction is a key step for obtaining polysaccharides and can impact polysaccharide yield, quality, chemical structure, and biological activities [10]. The generally adopted polysaccharide extraction method is to stir the pulverized fruiting bodies in hot water for several hours. This extraction method is easy to carry out, but requires a long extraction time, large volumes of solvents and elevated temperatures. A response surface optimization was taken to increase polysaccharide extraction rate and yield. Factors including temperature, material-liquid ratio, extraction time, extraction medium, ultrasonic power, microwave irradiation were examined in this study. There are several ways to extract polysaccharides (Table 1). After the extraction method is selected, the supernatant is collected by centrifugation or filtration, and the residue is generally extracted three-times. The extraction can then be concentrated to a quarter of the original volume [11], and then precipitated with three volumes anhydrous ethanol for 24 h at 4 °C. The precipitate is collected by centrifugation and then freeze-dried [12] or low temperature dried [13] to obtain crude polysaccharide.

Purification of crude TPS polysaccharide often relies on ion-exchange chromatography to separate neutral polysaccharides and acid polysaccharides and is eluted with water and a gradient of different concentrations of NaCl. The principle of separation is related to the balance between ion exchange and molecular weight effects. In addition,

gel filtration chromatography can separate polysaccharides according to their molecular weight. A higher molecular weight is beneficial for faster separation by column chromatography [16].

3. Structure features

3.1. Natural structure

Purified polysaccharides can be analyzed using high performance liquid chromatography (HPLC) to determine its molecular weight. Subsequent analysis with ultraviolet spectroscopy (UV), infrared spectroscopy (IR), gas chromatography (GC), mass spectrometry (MS), and nuclear magnetic resonance (NMR) can be used to determine the structure of the polysaccharide [17]. The primary structure of polysaccharides is defined by the placement of the monosaccharide residues, the position and chirality of glycosidic linkages, and the sequence of monosaccharide residues. These three factors result in the high potential structural variability of polysaccharides [18]. In 1995, Yui et al. found the primary structure of extracted and purified TPS was α -D-mannose in the main (or backbone) chain, and β -D-xylose, β -D-gluconic acid and β -D-xylobiose linked to the C-2 of the main chain mannose. The chain has a left-handed triple helix symmetrical structure comprised of 6 mannose residues. These residues and the three side-chain groups form a repeating unit along the central axis of 2.42 nm [19]. In 2016, A TPS, referred to as TL04, was purified by Jin and colleagues. And they found that the backbone of TL04 is composed of (1 \rightarrow 2)- and (1 \rightarrow 4)-linked-mannose and (1 \rightarrow 3)-linked-glucans [20]. There are fewer studies on primary repeating unit structure of the polysaccharide, but the most papers on TPS showed only monosaccharide composition and the molecular weight (Table 2).

3.2. Chemical modification of structure

After recognizing the structure of natural polysaccharides, it was established that the effective chemical modification of this natural structure could improve the biological activities and some key parameters, including solubility, bioavailability, and pharmacokinetics [29]. Chemical modification can control the final structure of polysaccharides, thus, it can also control the specific biological functions. The chemical modification of polysaccharide structure mainly utilizes the polysaccharide's reactive groups, such as hydroxyl, carboxyl and amino groups, to chemically introduce new functional groups. Chemical modification of polysaccharides includes acetylation, carboxymethylation, sulfation, phosphorylation, alkylation and selenization [30]. The most common chemical modification of TPS is sulfation, which was used to enhance its biological activities and water solubility [31]. For example, on chemical modification, TPS not only retains its original biological activities of enhanced humoral immunity and cellular immunity, but these activities are significantly improved [32]. Functional substances, such as catechin grafted to TPS, afford a catechin-TPS conjugate with enhanced biological activity. The antioxidant activity of catechin-TPS is 41.67% higher than TPS [33].

Table 1
Summary of the process of TPS extraction and purification.

Extraction solvent	Extraction	Extraction rate (%)
Water	Microwave-assisted extraction: liquid-solid ratio was 20:1, extraction time was 60 s, microwave output power was 750 W [2].	69.07
	Enzymatic extraction: the amount of pectinase enzyme was 0.7%, optimum temperature was 50 °C, the enzymolysis time was 50 min, the extraction time was 60 min, and liquid-solid ratio was 60:1 [13].	Unknown
	Sonication-assisted extraction: sonication intensity was 6 W/cm ² , temperature was 85 °C, ratio of liquid to solid was 46:1, sonication time was 2 h [14].	8.95
Alkaline	The NaOH concentration was 0.7 M, the liquid-solid ratio was 90:1, and the extraction time was 3 h [15].	10.49
Organic solvents	The PEG-based extraction and ultrafiltration separation: 10.0 g of pretreated <i>T. fuciformis</i> spores powder was mixed with 300 ml of PEG aqueous solution and ultrasonic assisted extraction [1].	Unknown

Table 2
Studies on the monosaccharide composition and molar weight of polysaccharides purified from *T. fuciformis*.

No.	Name	Monosaccharide composition	M.W. (Da)	Reference
1	T3a-1	Unknown	5.5×10^5	[21]
2	T3a-2	Unknown	4.2×10^5	[21]
3	T3a-3	Unknown	5.5×10^4	[21]
4	T3a-4	Unknown	4.8×10^4	[21]
5	T2a	Unknown	4.1×10^5	[22]
6	T2b	Unknown	2.5×10^5	[22]
7	T2c	Unknown	3.4×10^4	[22]
8	T2d	Unknown	2.0×10^4	[22]
9	SAE-1	Unknown	9.85×10^4	[14]
10	SAE-2	Unknown	6.64×10^4	[14]
11	TWE-1	Unknown	4.75×10^5	[14]
12	TWE-2	Unknown	2.81×10^5	[14]
13	A-BTF	Unknown	6.7×10^4	[23]
14	PTF-M38	Xyl, Man, Glc, Gal in a ratio of 1.00:1.47:0.48:0.34	1.24×10^3	[24]
15	PTF-Y3	Xyl, Man, Glc in a ratio of 1.00:1.65:4.06	1.08×10^3	[24]
16	PTF-Y8	Xyl, Man, Glc in a ratio of 1.00:1.21:0.44	1.19×10^3	[24]
17	T-19	Xyl, Man, Fuc, GlcA in a ratio of 1.00:2.10:0.45:0.80	Unknown	[25]
18	T-7	Xyl, Man, Fuc, GlcA in a ratio of 1.00:3.48:0.11:1.31	Unknown	[25]
19	TAPA1	Man, Xyl in a ratio of 5.00:4.00	1.35×10^6	[26]
20	Unknown	Xyl, Man, Gal, Glc in a ratio of 2.00:4.00:5.00:3.50	8×10^3	[28]
21	TP	Glc, Xyl, Man, Gal, Fuc in a ratio of 0.3:1.00:1.59:0.01:0.85	3.43×10^6	[29]
22	TPS	Rha, Xyl, Man, Glc in ratio of 1.13:1.00:4.70:0.81	Unknown	[8]

4. Bioactivities

4.1. Antitumor and immunomodulatory

In recent years, studies on the mechanism of polysaccharides have shown that polysaccharides have an immunosuppressive activity protecting against tumor growth. TPS exerts anti-tumor activity by promoting the host's natural immune defenses. These polysaccharides can modulate the body's immune functions by regulating immune organs, immune cells and immune molecules, and their immune activity without significant side effects [34]. TPS also has the effect of regulating body immunity and inhibiting tumor growth. Its inhibitory effect on tumors is achieved through the intermediate host effect, that is, by enhancing the body's immune function to a tumor. TPS can inhibit the growth of Hep G22 cells and at concentrations of 50 mg/ml, the antitumor activity can reach 92% [12]. TPS can reduce side effects during treatment of tumors and can enable patients to rebuild their own immune system improving their cancer resistance [35].

Polysaccharides mainly play an immune function through macrophages, and macrophages can respond to infections, tumors and inflammation. Macrophages directly kill pathogens through phagocytosis and present antigens to elicit an immune response [36]. Macrophages produce a large number of biologically active molecules, including nitric oxide (NO), reactive oxygen species (ROS), and cytokines including tumor necrosis factor TNF- α , interleukin (IL)-1 α , IL-1 β , for defense of IL-6, IL-10 [37]. TPS can reverse the effect of proliferation and polarization of CD4⁺ T cells in *Pseudomonas aeruginosa* infected scald mice, resulting in a decline in the level of IL-10 [38]. TPS can inhibit modulate cyclophosphamide-induced mouse leukopenia. Leukocytes increase in a dose-dependent fashion [39]. Cyclophosphamide significantly reduces the mRNA expression of IL-1 β , IL-4 and IL-12 in liver and spleen, and significantly increases the expression of TGF- β in liver and spleen. CY significantly reduces serum immune organ index and serum cytokine levels (IL-2, IL-12, INF- γ , and Ig G) and increases serum TGF- β levels. These results suggest that low-dose TPS has no obvious effect, high-dose TPS can effectively protect the immunity index [40].

4.2. Anti-oxidation and anti-aging

The worldwide population is aging so that increasing attention is being paid to physiological and health needs and to the increased costs in the health care system. The dream of fending off old age is as old as human civilization, so it is important to take interventional measures care in aging and to delay age-related diseases [41]. Aging is often defined as a cumulative change in diverse pathologies that increase the risk of disease and death [42]. Aging leads to a marked decline in immune function (immunosenescence), such as decreased proliferation of circulating T-cells, increased production of pro-inflammatory IL-6, IL-1 β , TNF- α , and diminished NK cell activities [43]. Overexpression of SOD can increase the lifespan of fruit flies [44]. TPS can increase the levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in organs and reduce malonaldehyde (MDA), P21 protein and lipofuscin (LP) to achieve anti-oxidant and anti-aging effects [45].

Free radicals produced during the metabolism of oxygen play an important role in the homeostasis of organisms. If excess free radicals are produced they will result in damage to cells and lead to a series of diseases such as cognitive disorders, cancer, and Parkinson's disease [46]. Ultraviolet radiation can also lead to excessive production of free radicals. Overproduction of ROS, including superoxide anion ($\bullet\text{O}_2^-$), hydroxyl radical ($\bullet\text{OH}$) and hydrogen peroxide (H_2O_2), in the epidermis destroys the steady-state balance of antioxidant defense systems causing oxidative stress leading to DNA damage, activation of signalling pathways related to cell (or tissue) growth, differentiation, senescence, and connective tissue alterations [47]. TPS has demonstrated anti-oxidant activities, not only can reduce hydroxyl radical and superoxide radical, but also enhance reducing power [48]. Wen and colleagues reported that TPS can remove 87% and 80% of superoxide and hydroxyl radicals, respectively, by reducing ROS caused by UV irradiation [28]. Hydrogen peroxide induces oxidative stress and apoptosis in skin fibroblasts in a concentration-dependent manner. Hydrogen peroxide decreased human skin fibroblast viability with a concurrent increase in ROS generation and cell apoptosis. TPS pretreatment reduced oxidative stress and cell apoptosis in hydrogen peroxide-treated skin fibroblasts. Furthermore, TPS additionally protected fibroblasts through the upregulation of SIRT1 expression, and this was abrogated by the SIRT1 inhibitor niacinamide. SIRT1 (Sirtuin1: a nicotinamide-adenine dinucleotide-

dependent class III protein deacetylase belonging to the silent information regulator 2 gene family) levels were significantly increased when the skin cells were treated with TPS. TPS at concentrations ranging 100 to 200 $\mu\text{g/ml}$ resulted in excellent anti-aging and cell protective effects [49]. SIRT1 inhibitor niacinamide reversed the protective effect of TPS.

4.3. Repair brain memory impairment

There are many factors that cause damage to memory functions in humans and animals. As we know in Alzheimer's disease (AD) patients, AD can cause dysfunction within the nerves and neurons, eventually leading to cell death. In consequence, people suffer from AD and show memory degradation [50]. In 2007, Ju and colleagues demonstrated that TPS can promote synaptic outgrowth in PC12 cells. And it can be used as a preventive agent for degenerative diseases [51]. In 2012, A model for rats learning and memory deficits induced by trimethyltin was explored to investigate the protective effects of TPS on learning and memory-deficient neurons. Treatment with TPS significantly increased neurite outgrowth on PC12 cells in a dose-dependent manner, increasing glucose metabolism in the brain. Compared to the control group, the number of CREB neurons increased by 134%, avoiding a decrease of cholinergic neurons, and the time spent by the rats around the water maze platform was significantly reduced [52].

4.4. Anti-inflammatory activity

As early as 1997, one paper has shown that TPS induce the production of interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF) in human monocytes [53]. In 2016, the anti-inflammatory effect of *T. fuciformis* extract in RAW 264.7 cells was confirmed, and LPS induced iNOS/NO, COX-2/PGE 2 production was effectively inhibited [54]. In 2018, Ruan and colleagues found that after treatment of RAW 264.7 cells with LPS, up-regulation of miR-15 and then up-regulation of NF- κ B activation in cells. When TPS was used to treat RAW 264.7 cells, the phenomenon was reversed. When the concentration of TPS reached 200 $\mu\text{g/ml}$, the expression levels of TNF- α and IL-6 in RAW 264.7 cells decreased in a TPS concentration-dependent manner [55]. Furthermore, people found that LPS inhibited SIRT1 protein expression in A549 lung cancer cells, but TPS could increase SIRT1 protein expression and subsequently inhibit LPS-induced apoptosis and autophagy in A549 lung cancer cells. SIRT1 protein expression was examined to understand the anti-inflammatory role of TPS in LPS infection in lung cancer [56].

4.5. Hypoglycemic and hypocholesterolemic activities

TPS exhibited a significant dose-dependent hypoglycemic activity in normal mice and also showed a significant activity in streptozotocin-induced diabetic mice, by intraperitoneal administration [57]. The hypoglycemic activities of exopolysaccharides (EPS) produced by submerged mycelial culture of *T. fuciformis* in mice was investigated. The result suggested that EPS exhibited considerable hypoglycemic effects and improved insulin sensitivity by regulating PPAR- γ -mediated lipid metabolism [58].

The intake of *T. fuciformis* powder can reduce the serum cholesterol and LDL cholesterol levels of the experimental group by 19% and 31%, respectively, and the serum triacylglycerol level of the animal is also significantly reduced. Excretion of neutral cholesterol and bile acid in rat feces with *T. fuciformis* powder increased by 51 and 36%, respectively [59].

4.6. Biological activity of chemical modified *T. fuciformis* polysaccharides

The carboxymethylation modification of alkaline *T. fuciformis* polysaccharides resulted in CATPS. The water solubility and biological activity of CATPS also increased as the degree of substitution increased and the CATPS also show good antioxidant activity and moisture retention. The abilities of scavenging radical and holding water are very important

to keep the skin younger [60]. Homogenous TPS was phosphorylated to obtain phosphated polysaccharides. Phosphated-TPS can antagonize the decrease of number of white blood cells and increase the DNA content in bone marrow in mice, thereby reducing the hematopoietic damage caused by cytarabine and cyclophosphamide. Using the chlorosulfonic acid-pyridine method, four sulfated TPS derivatives were obtained, sTPS tp, sTPS 70c, sCPPS tp, and sCPPS 50c. Their biological activities were tested *in vitro* on spleen lymphocyte proliferation and *in vivo* experiments on Serum HI antibody, peripheral lymphocyte proliferation in chickens. The results show that sulfated-TPS enhanced humoral and cellular immunity [31].

4.7. Other activities

A TPS, referred to as EPS, was isolated from *T. fuciformis* which is not cytotoxic to mouse skin fibroblasts (NIH/3T3) and has a survival rate of more than 100% using the MTT assay [61]. TPS also have the effect of treating radiation damage in mice. It was found that mice were irradiated with 8 Gy gamma-irradiation and dealt with mice at 72 mg/kg and 54 mg/kg of TPS, the daily survival rate reached 50%. In contrast, control mice died after 21 days under the same conditions. The corresponding endogenous spleen colonies and increased the number of nucleated cells in bone marrow, indicating that TPS can effectively prevent chromosomal toxicity in mice. IL-1 was firstly proven to have the strongest anti-radiation damage effect. Pretreatment of mice with TPS can promote the secretion of IL-1, IL-6 and TNF [62,63].

5. Applications

Despite the promotion of healthy diets and the need to reduce the high-fat foods, which can cause cardiovascular disease, there has also been a surprising increase in demand for high-fat foods. For example, soldiers in the military often need calories quickly when they are on mission. Moisture and fat can be lost in storage and cooking. TPS has been added to the raw pork, reducing the loss of moisture and fat content by 5% [8]. In cooked pork patties, the moisture content of patties increased with the addition of *T. fuciformis*. Compared with control sample, the patties with *T. fuciformis* had significant higher cooking yield [64].

A novel peripheral nerve conduit containing the negatively charged TPS has been prepared. TPS modification enhanced the expression of neurotrophic genes *in vitro* in C6 glioma cells. Functional restoration of animals receiving TPS-fixed catheters was superior to functional recovery of animals receiving bare catheters over an 8 month period. In the TPS-fixed catheter group, the degree of functional recovery after 8 months reached approximately 90% [65].

T. fuciformis has also been used as an electrode material for supercapacitors. A high specific surface area (SSA) is important for electrode materials such as activated carbon. *T. fuciformis* has been carbonized and then reacted with KOH to obtain advanced activated carbon electrode materials. This material displays high specific capacitances of 71 Fg^{-1} at 1 Ag^{-1} in 6 M KOH and 60 Fg^{-1} at 0.5 Ag^{-1} in 1 M Na_2SO_4 , respectively, and excellent cycling durability of 99% and 94% capacitance retention at 5 Ag^{-1} after 10,000 cycles [66].

6. Conclusions and future prospects

TPS have been studied worldwide, but most applications are in the basic research stage. Although there are many reports on the functional properties of TPS, there are relatively few studies on its specific mechanism of action. The study of TPS structural properties has mainly focused on its molecular weight, monosaccharide composition, side chain position and how these relate to its physiological functions. However, the uses of specific TPS structures in pharmacological studies are rare. Therefore, it is necessary to focus future research on the mechanism of the polysaccharides of *T. fuciformis*, and provide theoretical guidance for the development of TPS in food, cosmetics, medicines, and health

care products. While TPS has been used in some fields, it is important to explore the application of TPS in many other areas.

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