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Review Article

Extraction, structure and bioactivity of *Tremella Fuciformis* polysaccharides: A review

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Abstract: *Tremella fuciformis* polysaccharides (TFP) are a kind of bioactive macromolecules isolated from fruit bodies, mycelium or fermentation broth of *Tremella fuciformis*. In recent years, TFP has unique biological activity, which creates new possibilities for its application in nutrition and functional food industry, and attracts widespread attention. By summarizing and comparing the research on TFP in recent years, this paper reviews the methods of isolation, purification and structural characterization of TFP, the interaction of TFP with other macromolecules to affect its antioxidant and hypoglycemic biological activity *in vivo* and *in vitro*, and the effect of TFP on intestinal flora and short chain fatty acids production. It is hoped that this paper can provide some theoretical basis and Enlightenment on the study of the biological activity and mechanism of TFP.

Keywords: *Tremella*; polysaccharides; biological activity; intestinal flora

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1 Introduction

For centuries, fungi of the phylum Strettaceae and Cysticercus have been widely used worldwide as food and medicine with ascomycete, mycelium and spore forms[1]. To date, about 20,000 species of fungi have been identified, of which about 2,000 are reported to be edible[2]. *Tremella fuciformis* Berk, a valuable medicinal fungus, also known as snow fungus and white fungus, and is the substrate of *Tremella fuciformis* Berk, a fungus of the phylum *Tremella fuciformis*, which is known as the "crown of fungi" because of its richness in protein, carbohydrates, vitamins and amino acids. Among the many nutritional substances of *Tremella fuciformis*, its polysaccharide is the most popular research direction at present. *Tremella fuciformis* polysaccharide (TFP), a non-starch polysaccharide, is widely found in the fruiting body, mycelium, fermentation broth and cell wall[3]. Studies have shown that the main chain of TFP may consist of xylose, mannose, and glucuronic acid connected by α-(1,3)-glycosidic bonds, and the side chains consist of galactose, arabinose, and a small amount of fucose[4], but the polysaccharide composition of *Tremella fuciformis* from different sources and origins may also vary somewhat. In recent years, numerous studies have shown that TFP have various health-promoting effects, including immunoregulatory and antitumor[5,6], neuroprotective[7], antioxidant and anti-inflammatory effects[8,9], hypoglycemic and lipid-lowing activities[10], and regulation of intestinal flora as prebiotics[11,12].

At present, the research on TFP is mainly focused on two aspects. On the one hand, the extraction and purification methods are improved and optimized to obtain the yield and purity of TFP[13]. On the other hand, the biological activity and pharmacological effects of TFP are studied[14-16], including the development of functional foods and drugs and clinical application research[17-19]. However, the advanced structure of TFP and the conformational mechanism between chemical structure and biological activity are still unclear. At present, most of the reviews on TFP have reviewed its acquisition and biological activity, and few have reviewed its specific mechanism of excellent performance in many aspects. Therefore, based on the extraction, separation and purification of TFP, this paper elaborates its physicochemical and structural characteristics in detail, discusses the interaction between TFP and various macromolecules, the excellent performance of TFP in antioxidant, hypoglycemic and regulating intestinal health, in order to provide a scientific basis for the follow-up study of TFP and its derivatives in many aspects.

2 *Tremella fuciformis* polysaccharides: extraction, separation and purification

2.1 Extraction of *Tremella fuciformis* polysaccharide

TFP is an important active component in *Tremella fuciformis* with a variety of heteropolysaccharides extracted and purified from fruiting bodies and deep fermentation spore fluid[20]. According to Fig.1, the first step of extraction of TFP is to grind dry fruites or mycelium into powder, and then place the powder in organic solvents such as ethanol or acetone to remove lipids or phenols and improve the yield of polysaccharides[21]. After

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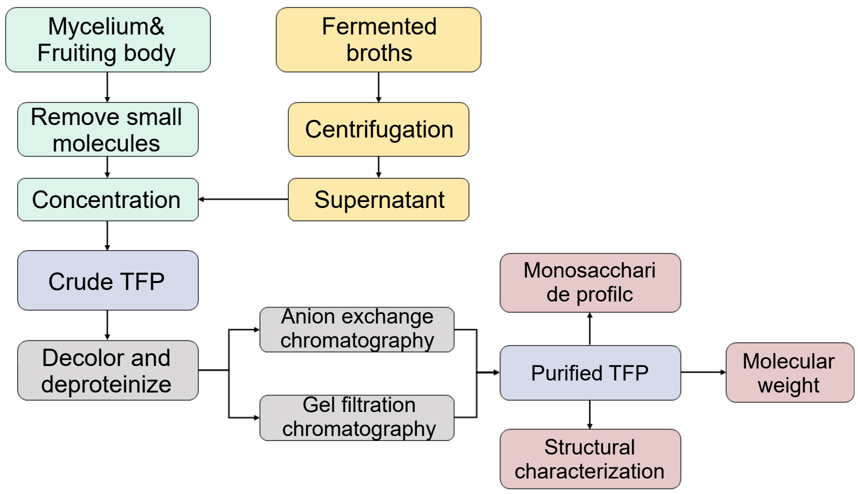

Figure 1 Extraction, purification and structural characterization of *Tremella fuciformis* polysaccharide.

pretreatment, TFP was extracted by hot water, acid or alkaline aqueous solution, among which hot water extraction was the most widely used polysaccharide separation agent. Finally, the extract was neutralized and precipitated with methanol, ethanol or acetone, centrifuged and dried to obtain crude polysaccharide[22].

Studies have shown that extraction affects the yield, chemical structure, quality and biological activity of polysaccharides[23]. Currently, innovative technologies have been used in *Tremella fuciformis* polysaccharides extraction in order to improve yield and extraction productivity. These technologies include microwave-assisted extraction[24], ultrasound-assisted extraction[25], enzyme-assisted extraction[26], high-pressure-assisted extraction[27], and subcritical pressurized water extraction[28]. Technologies used define the physicochemical properties and bioactive potential of TFP, thus the selected extraction method and its extraction parameters including solvent type, solid-liquid ratio, pH value, temperature and time, should be considered during extraction[29]. These methods may accelerate cell wall decomposition, and also enhance the polysaccharide dissolution and diffusion into the extraction solvent, so as to effectively improve the extraction rate. Box-behnken design or response surface method is usually used to optimize extraction conditions.

2.2 Separation and purification of *Tremella fuciformis* polysaccharide

Generally, it is difficult to accurately characterize the structure and conformation of TFP because of the interference of inorganic salts, proteins, monosaccharides, amino acids and other related molecules. Sevag method is the most common chemical method for decolorization and deproteinization for crude polysaccharide[30]. Subsequently, polysaccharide from *Tremella fuciformis* can be separated by anion exchange chromatography (DEAE Sepharose Fast Flow) according to its different ionic properties[31]. According to different molecular weights, gel filtration chromatography (Sepharose Cl-4B) can be performed[32] to purify TFP (As shown in Fig.1). Finally, pure polysaccharides are obtained by concentration, dialysis and freeze drying.

In the process of separation and purification of TFP, many technical means are used to obtain TFP. At present, most of the separation methods of TFP are limited to laboratory scale or prone to organic solvent residue, which may affect its biological activity evaluation and future application. Therefore, it is a hot topic to find green operation and efficient technical methods for the separation of TFP. For instance, Zhang *et al.*[33] used polyethylene glycol (PEG) combined with ultrasonic-assisted extraction to separate TFP. The yield and purity of polysaccharide are higher than those of traditional ethanol precipitation method, and most of the PEG can be recovered, which is a relatively green method. Zou *et al.*[34] used ultrasound-assisted extraction, DEAE-Sepharose and Sephadex G-100 column chromatography to separate and purify TFP. The yield of polysaccharides was higher than that of traditional hot water extraction, and the obtained polysaccharides had stronger Fe^{2+} chelating activity and superoxide anion radical scavenging activity. This indicates that the polysaccharides extracted by ultrasonic wave have high antioxidant activity. In conclusion, the use of green and efficient separation and purification methods not only helps to increase the yield of polysaccharides, but also can obtain TFP with better biological activity to a certain extent.

3 Polysaccharide physiochemical and structural features

The analysis of the structural characteristics of TFP mainly focuses on monosaccharide composition, molecular weight, type of glycoside bond and conformation of molecular chain. The main analytical methods used to characterize TFP include scanning electron microscopy (SEM), atomic force microscopy (AFM), nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), gas chromatography-mass spectrometry (GC-MS), methylation analysis, high performance liquid chromatography (HPLC), high performance size exclusion chromatography (HPSEC), high performance gel permeation chromatography (HPGPC) and gel permeation chromatography (GPC), etc.

3.1 Average molecular weight

The average molecular weight of TFP is closely related to the source of TFP and the way of extraction and purification. Different sources and purification methods will lead to different polysaccharide yield. Methods for the determination of average molecular weight of TFP include HPLC, HPGPC, etc. Yang *et al.*[31] purified three components, namely FTP-1, FTP-2 and FTP-3, from the fermentation broth of TFP fermented from GCMCC5.39, among which FTP-1 and FTP-2 are the main components of TFP. Their average molecular weights (Mw) are

25.722 kDa and 177.263 kDa, respectively. Ge *et al.*[35] isolated two polysaccharide from *Tremella fuciformis* fermentation broth, one of which was small-molecule weight polysaccharide TFPA with Mw of 0.225 kDa. The other was TFPB with a Mw of 1.14 kDa. Yuan *et al.*[36] isolated two peaks from *Tremella fuciformis* crude polysaccharide by column chromatography. One was a small-molecule polysaccharide and the other was a large-molecule polysaccharide TFP1 with a molecular weight of 5,800 kDa. The results showed that TFP1 had uniform composition. Zhu *et al.*[37] determined the molecular weight of polysaccharide extracted by atmospheric hot water extraction and pressurized hot water extraction with flaky tremella as raw material. The molecular weight of polysaccharide was 0.163×10^3 to 16.992×10^3 kDa and 0.072×10^3 to 3.271×10^3 kDa, respectively. In conclusion, combined with Table 1, it is shown that the molecular weight of polysaccharide from fruity body of *Tremella fuciformis* is much higher than that of polysaccharide from liquid fermentation.

3.2 Monosaccharide composition

Due to the use of different raw materials, extraction methods and purification processes, the monosaccharide composition and molar ratio of TFP are different, but in general, current studies show that TFP is composed of caramel, galactose, xylose, mannose, glucose and glucuronic acid in different molar ratios. Yang *et al.*[31] determined monosaccharide composition and molar ratio of TFP fermented from GCMCC5.39 by high performance anion-exchange pulsed ampere chromatography (HPAEC-PAD). The monosaccharide composition of FTPs-1 and FTPs-2 were consistent, but the monosaccharide ratio was slightly different. However, FTPs-2 had higher levels of galactose and glucose, indicating that FTPs-2 was weakly acidic polysaccharide. Ge *et al.*[35] detected the monosaccharide composition of TFPB obtained from TFP fermentation broth by HPLC, and the results showed that TFPB was mainly composed of mannose, glucuronic acid, glucose, galactose, xylose and rhamnose, with molar ratios of 3.5: 1.2: 2: 6: 1.4: 3, respectively. Yuan *et al.*[36] detected the monosaccharide composition of TFP1 obtained from fresh white fungus by HPIC, and the results showed that TFP1 was composed of mannitose, xylose, caramel, glucose and glucuronic acid, with molar ratios of 1.91: 0.1: 2.49: 6.23: 0.95, respectively. Shi *et al.*[40] continuously extracted TFP from fruiting body of *Tremella fuciformis* by four methods to obtain its monosaccharide composition of fucose, galactose, glucose, xylose, and mannose, respectively. Xu *et al.*[41] used the SHISIDO C_{18} column (Agilent 1200) to analyze the monosaccharide composition of TFP extracted from the fruited body. The main monosaccharide part of TFP consisted of mannose, followed by glucuronic acid, xylose, caramel, glucose, galactose, arabinose, rhamnose and ribose. In conclusion, the monosaccharide composition of polysaccharide from fermented *Tremella fuciformis* is different from that from fruiting body.

3.3 Chemical structure

Except for molecular weight and monosaccharide components, little structural or conformational information on TFP is available. The primary structure of TFP was reported as a linear backbone of *α*-1, 3-linked *D*-mannan residues with side chains that contain glucosyl, mannosyl, fucosyl, xylosyl, and glucuronic acid substituents, commonly linked to the main chain with *α*-1, 2 bonds[42]. Yui *et al.*[43] investigated the backbone conformation of TFP as left-handed and three-fold helical symmetry by means of the X-ray diffraction and the computational model technique and found the primary structure of extracted and purified TFP 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. A study on pure TFP with neuroprotective effect, a fraction termed TL04 with a 2,033 kDa molecular weight was obtained. The backbone of TL04 is composed of (1→2)- and (1→4) linked mannose and (1→3) linked glucans[7].

3.4 Conformation characteristics

The chain conformational characteristics of polysaccharides make profound and significant influence on the bioactivities, physicochemical properties, and potential applications[44]. Up to now, little is known about its chain conformation properties, including chain shape and flexibility[45]. Theoretically, the conformational parameter αs of 0.33, 0.5-0.6, 1.0 represents the chain shape of sphere, flexible chain and rigid rods, respectively. The exponent αη in Mark-Houwink-Kuhn-Sakurada equation of 0.22, 0.5-0.8 and 1-2, reflects the conformation of spheres, flexible chain and rigid rods, respectively. In addition, the structure-sensitive parameters ρ (ρ = Rg/Rh) of 0.78, 1.7, and 2 correspond to spheres, random coils, and rigid rods, respectively. Xu *et al.*[45] studied that the conformational properties of TFP, and further illustrated as a typical flexible chain in 0.15 mol/L NaCl (pH 7.4) solution, with persistence length of 9.20 nm and chain diameter of 0.97 nm.

3.5 Digestibility

In recent years, it has been reported that many edible fungus polysaccharides were hardly digested in saliva, stomach and intestinal tissues. However, after being transported to the colon, they could show probiotic properties by affecting the composition

Table 1 Comparison of extraction methods of *Tremella fuciformis* polysaccharide

Sources	Methods	Liquid-solid ratio	Condition	Mw (kDa)	Polysaccharide yield	References
Tremella M38 (MY)	Alkali	1:37.5 (g/mL)	20 h	1.24	-	[38]
Tremella (FB)	Hot water	1:80 (g/mL)	2 h	560	45.31%	[21]
Tremella (FB)	Microwave assisted	1:50 (g/mL)	400 W, 2 h	-	33.25%	[24]
Tremella (FB)	Ultrasonic assisted	1:90 (g/mL)	60 W, 2 min	-	12.00%	[39]
	Enzyme assisted	1:80 (g/g)	50 °C, 1 h	1.16×10^4	68.93%	
Tremella (FB)	Acid	1:80 (g/g)	95 °C, 100 min	3.55×10^3	77.99%	[26]
	Alkali	1:80 (g/g)	95 °C, 4 h	6.35×10^3	70.61%	
Tremella (FB)	High pressure & water	1:80 (g/mL)	120 °C, 40 min	-	46.25%	[27]
Tremella (FB)	Subcritical pressurized water extraction	1:30 (g/mL)	138 °C, 30 min	-	34.58%	[28]

of intestinal flora[46]. However, the metabolic pathway of TFP in the gastrointestinal tract is not completely clear. Wu *et al.*[47] have studied the digestibility of TFP by simulating *in vitro* digestion conditions. After simulated digestion, there was no significant difference in the total polysaccharide content and total uronic acid content of TFP, indicating that the chemical composition of TFP was stable under different simulated digestion conditions *in vitro*. The molecular weight and monosaccharide composition of polysaccharides after digestion determined by SEC method were similar to TFP, and the results also showed that TFP is stable after simulated digestion *in vitro*. In conclusion, TFP is stable under simulated digestion conditions, and its physical and chemical properties will not be changed. The digestion and biological distribution of TFP need to be further studied.

4 Interaction between *Tremella fuciformis* polysaccharides and macromolecules

4.1 *Tremella fuciformis* polysaccharide-protein interaction

Protein and polysaccharide are two indispensable biological macromolecules in biological system, which are of great significance to maintain food quality and play a full role in food functional characteristics. Protein has good stability and emulsification, and polysaccharide has certain viscosity and antioxidant activity. Proteins and polysaccharides can form composite aggregates through electrostatic interaction in solution. The formation of composite aggregates is affected by the types of proteins and polysaccharides, the concentration, proportion, charge density, molecular weight, pH, ionic strength, temperature and other factors[48,49]. It is found that when protein and polysaccharide form a complex, its thermal stability, emulsification, solubility and antioxidant performance are improved compared with those of monomers[50,51].

According to the research of Chen *et al.*[52], it can be concluded that the effect of low-density lipoprotein (LDL)/TFP ratio (LDL/TFP) on the structure such as the ratio of R_g (radius of gyration) to R_h (hydrodynamic radius) and molecular weight of the complex depends on the method of preparing the LDL-TFP complex. In the electrostatic method, when LDL/TFP is 1: 1 (*w*/*w*), the RG (the ratio of R_g to R_h) and Mw of LDL-TFP were the largest. In the covalent method, RG and Mw of LDL-TFP complex were obtained in the ratio of LDL/TFP of 1: 4. The LDL-TFP composite has a spherical structure, the LDL-TFP composite has a rod structure, and the LDL-TFP has the strongest oxidation protection ability. The results showed that the spherical structure and LDL modified by phospholipase A2 were beneficial to the antioxidant activity of LDL-TFP complex.

TFP improves the stability of high concentration whey protein isolate (WPI) solution by forming an orderly electrostatic complex with WPI. In addition, the digestion rate of WPI adds with TFP in simulated gastric juice is significantly lower than that of WPI alone. The decrease of the digestibility of TFP-WPI solution indicates that the beverage products containing TFP-WPI may reduce the gastric emptying time, thus increasing the sense of satiety and promoting the production of high protein beverages[53].

In conclusion, the interactions between protein and polysaccharide molecules include covalent interaction, electrostatic interaction, hydrophobic interaction, hydrogen bond, van der Waals force and spatial repulsion[54]. Understanding the interaction mechanism of protein and polysaccharide under different conditions, exploring their complex aggregation behavior, and constructing multi-scale protein polysaccharide complexes with specific structure and function have broad application prospects in food, medicine and other fields.

4.2 *Tremella fuciformis* polysaccharide-polyphenol interaction

Polyphenols include flavonoids, phenolic acids, tannins and lignans. They have antioxidant, UV protective and antibacterial properties, of which flavonoids and phenolic acids are the most commonly studied. Polysaccharide polyphenol complexes and adducts have been extensively studied at the molecular level and in various food systems because they show to affect the sensory and phenolic related nutritional properties of food and beverages, as well as the processing of plant-based materials. These complexes also isolate phenolic compounds throughout the digestive tract, thereby reducing their bioavailability and potential biological activity.

Curcumin (cur) is a natural dietary polyphenol extracted from the root of *Curcuma longa*, which has potential biological activities such as anticancer, antioxidant, anti-inflammatory, antibacterial and neuroprotective effects[55]. Zhang *et al.*[56] prepared novel curcumin-loaded gliadin/TFP nanoparticles (cur-Gli/TFP NPs) loaded with TFP by anti solvent method. It is found that different Gli/TFP mass ratios and pH values had a great impact on the formation of Gli/TFP NPs, and TFP has a positive effect on improving the stability and redispersibility of cur-Gli/TFP NPs. In conclusion, TFP can improve the stability and bioavailability of curcumin in Gli nanoparticles.

4.3 Interaction between *Tremella fuciformis* polysaccharides and other macromolecular substances

TFP and chitosan can also be assembled to form nanostructures, such as nanofilms and nanoparticles, which were further applied in food packaging and drug carriers[57], indicating TFP to be a sustainable and bioactive ingredient for the development of new functional food and pharmaceutical product.

TFP could be also assembled with carboxymethyl cellulose (CMC) and nonionic surfactant-Decyl *D*-glucopyranoside (C10APG) to form a novel pH/temperature responsive micelle-laden hydrogel, further applied to control the release of bioactive ingredients[58].

5 Antioxidant activity

The world's population is aging, so people are increasingly concerned about physiological and health needs and the increase in the cost of health care systems. Aging is usually defined as the cumulative changes of various pathologies that increase the risk of disease and death. Aging leads to a significant decline in immune function (immune aging), such as decreased proliferation of circulating T cells and pro-inflammatory cytokines interleukin-6 (IL-6), cytokines interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) production and decreased NK cell activity[59]. As shown in Fig. 2, superoxide anion ($\bullet O_2^-$) enters and leaves cells through NADPH oxidases (NOX) and CLC voltage-gated chloride (Cl^-) channel-3 (CLC-3), and hydrogen peroxide (H_2O_2) enters and leaves cells through aquaporin (AQP). TFP can increase the levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in organs, reduce malondialdehyde (MDA), p21 protein and

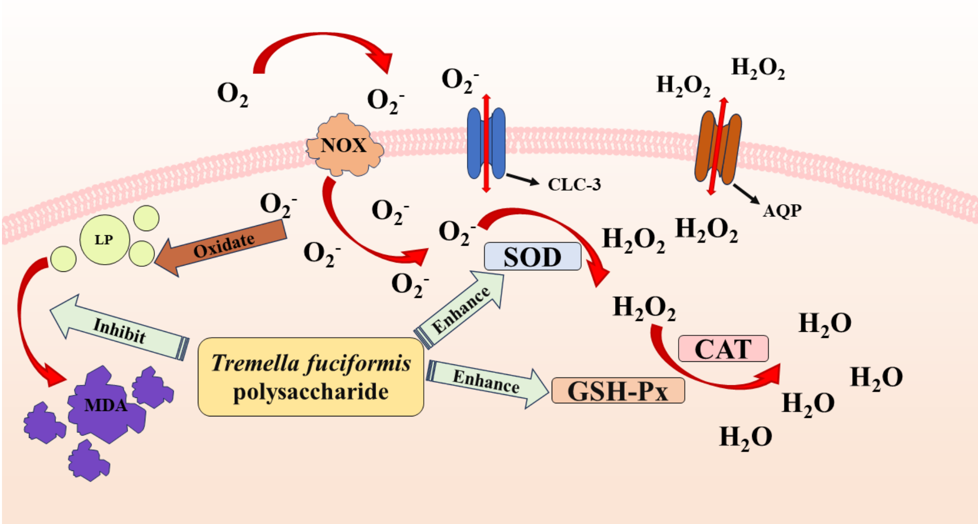

Figure 2 Antioxidant behavior of *Tremella fuciformis* polysaccharide.

lipofuscin (LP)[60]. In the end, H_2O_2 is converted into water under the action of catalase (CAT) to achieve antioxidant and anti-aging effects.

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 a series of diseases such as cognitive disorders, cancer, and Parkinson's disease[61]. Ultraviolet radiation can also lead to excessive production of free radicals. Overproduction of ROS, including $\bullet O_2^-$, hydroxyl radical ($\bullet OH$) and H_2O_2, in the epidermis destroys the steady-state balance of antioxidant defense systems, further causing oxidative stress, leading to DNA damage, activating of signaling pathways related to cell (or tissue) growth, differentiation, senescence, and connective tissue alterations[62]. TFP has demonstrated antioxidant activities, not only can reduce hydroxyl radical and superoxide radical, but also enhance reducing power[63].

In vitro studies, Shen *et al.*[64] studied the anti-aging and cytoprotective mechanisms of TFP. In their research, TFP exhibited antioxidative stress and anti-inflammatory properties in lipopolysaccharides-treated macrophages by inhibiting the miRNA-155 (miR-155) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways, suggesting that TFP may be a potential therapeutic agent for treatment of inflammation-related diseases. Furthermore, TFP 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 TFP. TFP at concentrations ranging 100 to 200 μg/mL possessed excellent anti-aging and cell protective effects.

Furthermore, TFP has been reported to protect cardiomyocytes from oxidative damage in a *D*-galactose-induced aging mouse model[65]. In the aging mouse model constructed by intraperitoneal injection of *D*-galactose, both TFP (WAK and BETA) could significantly increase the contents of hydroxyproline and hyaluronic acid in the skin, reduce the oxidative pressure of the body and the serum level of inflammatory factors, and partially reverse the abnormal changes of intestinal pH and short-chain fatty acids (SCFAs) content. Molecular weight distribution, spatial conformation and side chain functional groups are important structural characteristics that affect the activity of polysaccharides. The Mw of WSK is three times that of BETA, but there is no significant difference in the content of total sugar and uronic acid between the two. The results show that compared with WSK, BETA has a better effect on improving skin aging, reducing oxidative stress and inhibiting inflammatory response[66]. In conclusion, TFP has a good performance in anti-oxidation and has certain research value.

6 Hypoglycemic activity

Diabetes mellitus (DM) is a global endocrine and metabolic disease, hyperglycemia is one of the main characteristics of DM[67]. DM can also cause liver damage or deterioration of liver function, such as non-alcoholic liver disease, steatohepatitis and cirrhosis[68]. TFP exert hypoglycemic activities; they could affect glucose-metabolizing enzyme activities, inhibit gluconeogenesis, and promote hepatic glycogen synthesis. They also appear to regulate glucose metabolic disorders and insulin resistance by promoting insulin secretion to exhibit its hypoglycemic activity[69]. Phosphatidylin-ositol-3-kinase (PI3K)/serine threonine-specific protein kinase (Akt)/glucose transporter type 4 (GLUT4) signaling pathway is one of the glucose metabolic pathways *in vivo*. Our previous studies have found that TFP (EUP-3) can activate the PI3K/Akt signaling pathway and cause glucose absorption and metabolism through GLUT4 transport, thereby improving and alleviating insulin resistance (As shown in Fig.3). In cells, phosphatidylinositol (4, 5)-bisphosphate (PIP_2) is converted to phosphatidylinositol (3, 4, 5)-trisphosphate (PIP_3) by PI3K, after this, the intracellular regulation of blood glucose *in vivo* through the glycogen synthase kinase-3 (GSK3β) and glycogen synthase (GS) pathways is carried out.

In the study of the hypoglycemic effect of TFP *in vitro*, Du *et al.*[70] found that TFP could inhibit the activities of *α*-amylase and *α*-glucosidase in pancreas, and the inhibitory effect for the former was significantly stronger than the latter. The static quenching between TFP and pancreatic *α*-amylase occurred, which changed the secondary structure of pancreatic *α*-amylase, made it more rigid, less flexible, the structure became closer, affected the formation of the active center of the enzyme, and

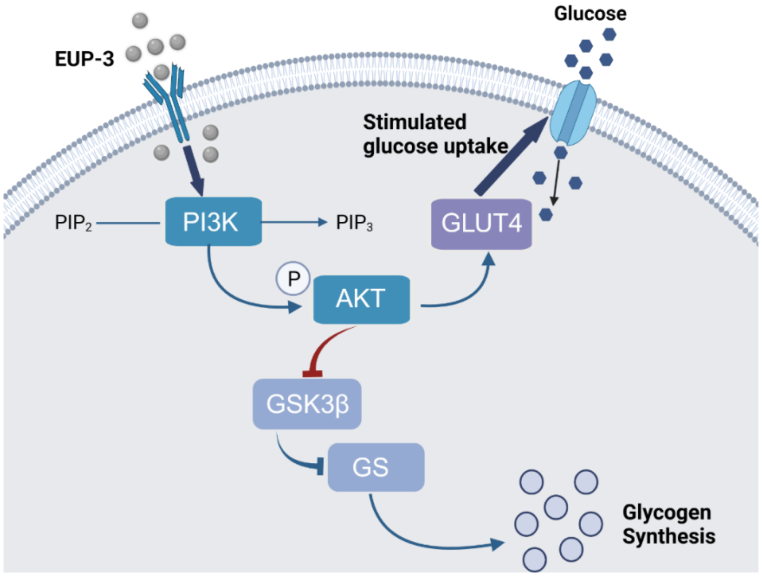

Figure 3 Mechanism of action of EUP-3 on the PI3K/Akt/GLUT4 signaling pathway.

inhibited the activity of the enzyme. However, there was a weak interaction between TFP and *α*-glucosidase, which had little effect on the secondary structure of the enzyme. These results indicated that TFP could affect starch digestion and delay glucose release by inhibiting the activity of starch digestion enzyme.

In *in vivo* studies, the hypoglycemic effect of TFP is also significant. TFP exhibited a significant dose-dependent hypoglycemic activity in normal mice and also showed a significant activity in streptozotocin-induced diabetic mice, by intraperitoneal administration[71]. The hypoglycemic activities of exopolysaccharides (EPS) produced by submerged mycelial culture of *Tremella 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[72]. Using maltodextrin (MD) and whey protein (WP) as carriers, the TFP microcapsules containing MD and WP were prepared by spray drying method. Finally, the TFP microcapsules containing lower dextrose equivalent (DE) value and higher concentration of MD had lower water adsorption and agglomeration strength. It was observed that food and water intake decreased, blood glucose and insulin levels decreased, and liver and skeletal muscle glycogen content increased. The mechanism study confirmed that TFP microcapsules improved insulin resistance by increasing glucose uptake through promoting GLUT4 translocation, and upregulating GS expression and glycogen synthesis.

7 Effects of *Tremella fuciformis* polysaccharide on intestinal flora and bacterial metabolites

Generally, the biological activity of polysaccharides in diet is closely related to the metabolism from stomach to colon[73]. A large amount of evidence shows that due to the lack of enzymes to decompose polysaccharides in the human body. Non starch polysaccharides are usually difficult to digest in the human gastrointestinal tract, but are easy to be fermented by the colon flora in the intestine[74], producing metabolites such as short chain fatty acids (SCFAs)[75], which can not only provide energy sources and nutrients for intestinal epithelial cells, but also reduce intestinal pH and inhibit the proliferation of harmful bacteria. Therefore, the fermentation of non digestible polysaccharides by colonic flora is beneficial to human health. Many studies have shown that edible fungal polysaccharides (mainly *β*-glucan) can be degraded into oligosaccharides and monosaccharides by carbohydrate active enzymes encoded by intestinal flora, which are used by intestinal flora to further produce beneficial effects on the host[76]. However, the digestion behavior and fermentation characteristics of TFP have not been studied. Therefore, revealing the potential digestive behavior and microbial metabolic characteristics of TFP is helpful to understand the relationship between TFP, intestinal bacteria and bacterial metabolites, and to promote the design and production of TFP based functional/healthy food.

Wu *et al.*[47] showed that TFP was stable under the simulated digestion conditions, and its physicochemical properties could not be altered. Furthermore, the indigestible TFP (TFP-I) could be notably utilized by colonic microbiota in human feces at the middle fermentation stages, resulting in the regulation of its composition and abundance. Notably, TFP-I could stimulate the growth of Bacteroides, *Phascolarctobacterium*, and *Lachnoclostridium*, and promote the generation of SCFAs. The findings from the current study are beneficial to reveal the potential digestive behavior and fecal fermentation properties of TFP.

Recently, TFP (mainly 1→3-*α*-*D*-mannitol) has been shown to alleviate dextran sodium sulfate (DSS)-induced colitis in mice through regulating immune and restoring of intestinal flora and microbial metabolites[41]. The immunosuppressive mouse model was established by injecting cyclophosphamide. Cyclophosphamide can cause organ damage and intestinal flora disorder in mice, which is not conducive to the growth and development of mice. TFP can protect the intestinal flora disorder and organ damage of immunosuppressed mice, and maintain the normal growth and development of mice[77]. Fermented *Tremella*/Blueberry (FTB) treatment increased the ratio of *Proteus/Bacteroides*[78]. After FTB treatment, the flora related to the prevention of obesity (*Alveolar bacteria, Blautia, Paraspora* and *Prevotella*) increased, the pathogenic bacteria decreased, and the content of five related SCFAs (isovaleric acid, butyric acid, propionic acid, isobutyric acid and valeric acid) also increased. The abundance of intestinal flora was related to the level of short chain fatty acids. These results suggest that FTB has the potential of anti obesity in metabolically healthy obesity (MHO) rats by restoring the composition of intestinal flora affected by obesity[79].

8 Conclusion

Studies on TFP are on the rise, mainly focusing on extraction, purification and separation, structure analysis and pharmacological activities, such as hypoglycemia, liver protection, anti-oxidation, anti-tumor, immune regulation and so on. Although pharmacological activities *in vitro* have been studied in most reports, the specific mechanism of action is relatively rare. The structure, pharmacological activity and interaction with macromolecules of TFP were reviewed in this paper. TFP showed anti-oxidative stress by inhibiting miR-155 and NF-κB pathways, further up-regulating the expression of SIRT1 to achieve the purpose of anti-oxidation. TFP can affect starch digestion by inhibiting the activity of starch digestive enzymes and delay the release of glucose to reduce blood glucose. In the intestine, TFP can affect the activity of intestinal flora and has a certain role in promoting digestion and anti-obesity. The following research on TFP should be based on the excellent biological activity of TFP, explore the specific mechanism of its various activities, and reveal the intrinsic relationship between biological activity and its structure. At the same time, it can also develop the field in which TFP interacts with other molecules to affect its structure and biological activity.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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