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Review Article

Preparation and biological activity of polysaccharide metal ion complex and feasibility analysis of *Tremella fuciformis* polysaccharide with metal ions

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Abstract: Currently, the synthesis of polysaccharide metal ion complex is predominantly categorized into three approaches: chemical synthesis, physical synthesis and biosynthesis method. According to research, polysaccharide metal ion complexes usually exhibit superior biological activities than metal ions or polysaccharides alone, including antioxidant, hypoglycemic, hypolipidemic, immune regulation, anti-tumor, anti-inflammatory and antibacterial activities. In this paper, the preparation process, biological activity and structural characteristics of polysaccharide metal ion complexes were reviewed, aiming to provide references for the development of new therapeutic drugs and adjuvants. And the complexation of *Tremella fuciformis* polysaccharides and metal ions was prospected.

Keywords: polysaccharide metal ion complex; preparation; bioactivities; structure; *Tremella fuciformis* polysaccharide

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1 Introduction

Trace elements such as iron, copper, zinc, selenium, chromium, etc. exert a crucial role in the operation of various biochemical processes in the body[1,2]. They constitute indispensable substances for immune regulation, cell metabolism, energy metabolism and other physiological activities, and are essential components for many hormones and enzymes[3-6].

Iron is indispensable for the basic metabolic processes of cells and organisms[7]. It predominantly exists in the body in the form of functional iron and stored iron, and has the functions of transporting oxygen and nutrients, and enhancing immunization[8,9]. Copper is merely concentrated in the liver, brain, kidneys, and hair[10]. In the body, copper combines with the catalytic proteins of metalloenzymes to participate in a series of physiological activities, such as antioxidation, cellular respiration, metabolism, etc.[11-13], and can also maintain the normal hematopoietic function of the body, the health of the central nervous system, and the health of the central nervous system[14]. Zinc has three important functions: catalysis, structure and regulation. It combined with enzyme plays a role in regulating enzyme catalysis, promoting interactions between proteins, and regulating gene expression[15]. Selenium, an essential micronutriant, is mainly present in the form of protein complexes[16]. There are 25 selenoproteins that have been identified in the human body, which can engage in the body's anti-oxidation, regulation of redox reactions, and a variety of specific metabolic pathways[17]. Chromium is of great significance to the body's metabolism of sugars, lipids and proteins. It also has physiological functions such as repairing and activating islet cells, regulating blood glucose, reducing blood lipids and preventing cardiovascular diseases. The deficiency of human trace elements will affect almost all components of the innate immune response[18], and affect the heart blood vessels, musculoskeletal, hematopoietic and nervous system[19,20].

Polymeric carbohydrates composed of at least 10 monosaccharides linked by glycosidic bonds are called polysaccharides[21]. As a natural polymer compound, polysaccharides are prevalently present in the animals, plants and microorganisms[22]. Owing to its unique biological functions, such as anti-oxidation[22], blood glucose lowering[23], anti-tumor[24-26], anticoagulant[27-29], immune regulation[30], and intestinal homeostasis enhanment[31,32], it has been widely utilized in food, medical, cosmetics and other fields. In addition, the polysaccharide of non-toxic, easy degradation and good biological compatibility also interested researchers[33]. In recent years, a considerable number of studies have explored whether chemical modification of polysaccharides can produce new biological activities or enhance the activity of polysaccharides. For example, when *Daucus carota* polysaccharide was phosphorylated, its antioxidant activity was enhanced[34]. The anti-oxidative and anti-inflammatory effects of *Pholiota nameko* polysaccharides were

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significantly strengthened after phosphorylation[35]. Complexation and chemical modification of polysaccharides with metal ions are similar.

Since trace elements and polysaccharides possess beneficial biological functions for human health, and the majority of the polysaccharide molecules contain active groups such as hydroxyl, amino and negative oxygen groups, they are prone to form complexes with various metal ions through chemical and physical adsorption[36,37]. Li *et al.*[38] have investigated the simultaneous thermal analysis of *Ganoderma lucidum* polysaccharide (GLP) and GLP-Cr (III) complex by chemical synthesis method and discovered that the GLP-Cr (III) complex had superior thermal stability than GLP. It has been reported that the biological activity of Se-containing polysaccharides is generally higher than that of common polysaccharides[39]. Therefore, it is rational to think that the combined use of trace elements and polysaccharides can exert more excellent biological effects.

Tremella, a renowned edible fungus, belongs to the order Silverear and the family *Tremella*[40]. In recent decades, many researchers have disclosed that *Tremella fuciformis* has antioxidant[41,42], immune regulation, anti-aging, lipid-lowering[43] and hypoglycemic effects[44]. *Tremella* polysaccharide, as the main active component of *Tremella tremella*, has garnered extensive attention in the fields of medicine and food because of its non-toxic and wide range of biological activities[45]. Studies have shown that both metal ions and polysaccharides have unique physical and chemical properties and have many benefits to human health. Additionally, the combination of metal ions and polysaccharides will increase or enhance their physiological activities while retaining certain biological activities of polysaccharides. In recent years, people have used polysaccharides from tea, angelica, astragalus, and other polysaccharides to prepare polysaccharide-iron (III) complexes. However, the current research on the iron (III) complex of *Tremella fuciformis* polysaccharide is still limited.

This article presents an overview of the complexation methods of polysaccharides and metal ions, the structure identification and physiological activities of the complexed polysaccharides, and summarizes the pros and cons of the complexation methods. The researches on the complexation of *Tremella* polysaccharides with metal ions are relatively scarce, and the complexation method involved in this article can provide a theoretical foundation for it.

2 Preparation of polysaccharide metal ion complex

The complexation of active polysaccharides pertains to the complex reaction between polysaccharides and metals or certain non-metal ions to form complexes. At present, complex mainly employs chemical synthesis method, physical synthesis method and biosynthesis method.

The chemical synthesis method features simple operation steps, facile control of the reaction, a green production process, low cost, suitable for industrial production (Fig.1). But it need to pay attention on difficult preparation, unstable, easy to hydrolysis, easy to produce poisonous gas, complex preparation technology and so on. Additionally, physical synthesis has the advantages of simple process, high efficiency, low cost, and no use of toxic reagents, etc. Nevertheless, the physical synthesis method has more stringent requirements for the necessary equipment and higher energy consumption. Moreover, the product of biosynthesis possesses relatively stable activity, difficult to decompose, low toxicity, and short growth cycle, but its cost is high. The fermentation system is relatively complicated, the product separation is difficult, and there are also shortcomings such as long growth cycle of the strain.

Many studies have shown that active polysaccharide metal ion complexes can not only retain the biological activity of the polysaccharide itself, but even give it new functions. In addition, the complexed metal is more easily absorbed by organisms. The complexation of active polysaccharides and metal ions has become a kind of modification method, and received much attention in the field of polysaccharide modification.

2.1 Chemical synthesis method

The complexation of polysaccharides and metal ions is

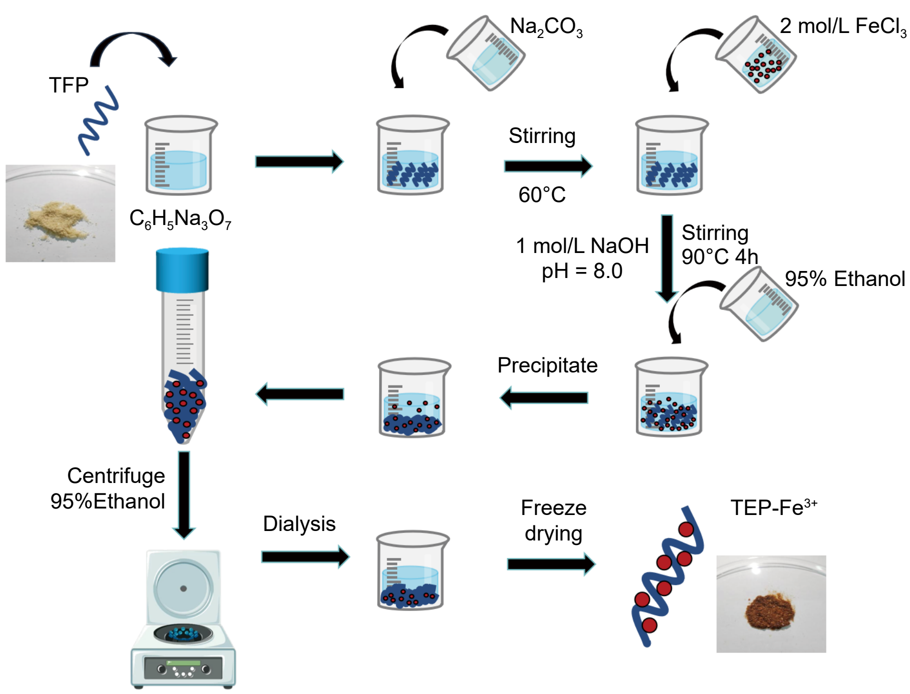

Figure 1 *Tremella fuciformis* polysaccharides (TFP)-Fe^{3+} was fabricated through chemical synthesis.

primarily carried out via chemical synthesis, namely, under the action of complex catalysts. During the preparation process, factors such as pH, reaction temperature, catalyst, the amount of metal ions added, the type and purity of polysaccharide, etc. exert an influence on the preparation of polysaccharide metal ion complex.

These synthetic polysaccharide metal ion complexes typically possess an extremely high content of metal ions, but their toxicity cannot be disregarded. The United States Poison Control Center had reported the toxicity of exposure to polysaccharide-iron complex. This study indicated that a small number of cases exhibited mild gastrointestinal and central nervous system toxicity[46]. In this review, the preparation of polysaccharide metal ions through chemical synthesis is presented in the Table 1.

The aforesaid studies suggest that polysaccharide and metal ions can be effectively combined through chemical synthesis. The combination of polysaccharide with metal ions does not cause the loss of its antioxidant activity, hypoglycemic activity, and other biological activities, while its biological activity remains largely unaltered or even slightly enhanced. Based on this finding, it is hypothesized that the compound can exert its antioxidant and hypoglycemic effects upon entering the human body. The chemical synthesis method is the most prevalently adopted complexing approach, featuring straightforward operation procedures, easy reaction control, and low production cost.

2.2 Biosynthesis method

Studies have demonstrated that microorganisms, including fungi and certain algae, can effectively absorb trace amounts from the culture element[62,63]. Among them, edible fungi are frequently employed by researchers to prepare polysaccharide metal ion complexes due to their a series of biological activity such as anti-oxidation, anti-cancer, immune function enhancement, hypoglycemic, and hypolipidemic effects[64].

The method can be illustrated as follows: The acid solution of metal ions is incorporated into the microbial culture medium for fermentation to obtain the fermentation broth. After the fermentation broth is centrifuged, 95% ethanol is added to the supernatant, and ultimately the product is left to stand, centrifuged, washed, and freeze-dried. The biosynthetic products of polysaccharide metal ions are summarized as follows (Table 2).

The aforementioned studies indicate that polysaccharides and metal ions can be successfully complexed through biosynthesis. The biological activity of polysaccharides remains unaltered after complexation with metal ions. The biosynthesis approach employs microorganisms such as fungi and certain algae to effectively absorb metal ions in the medium, and the operational procedures are straightforward and more environmentally friendly.

2.3 Physical method

The physical method involves complexing the polysaccharide with metal ions through specific approaches without the use of a catalyst. Table 3 presents the complexes acquired through physical means. Although the method steps are straightforward, the requirements for the instrument and environment are higher, which has not aroused the research interest of researchers.

When preparing polysaccharide metal ion complex, appropriate methods should be adopted to synthesize the complex in line with the actual conditions of the polysaccharide properties, operation procedures, and cost. The properties of complex prepared through different methods may be different, and the quality control of the complex products ought to be investigated.

3 Structure identification of active polysaccharide metal ion complex

The characterization not only can determine the structure of the product, but also determine whether polysaccharide and metal

Table 1 Preparation of polysaccharide metal ion complex compound by chemical synthesis method

Name	Metal ion content	Bioactivity	References
Pyracantha fortuneana polysaccharide-iron complex (PPI)	30.76%	Showed potent effects on the scavenging of ABTS free radicals and superoxide anions and induced apoptosis and alter gene expression in Skov3 cells.	[47]
Glehniae Radix polysaccharide-iron complex (GLP80-Fe)	15.61 ± 0.04%	Showed potent effects on scavenging of DPPH and hydroxyl radicals.	[48]
Flammulina velutipes polysaccharide-iron complex (FVP-Fe (III))	11.70%	Exhibited strong antioxidant activity.	[49]
Garlic polysaccharide-Fe (III) complex (FePS)	9.20%	Showed potent antioxidant activities and obvious synergistic antioxidant effect.	[50]
Co-cultured *Lepista sordida* and *Pholiota nameko* polysaccharide-iron (CP-1-Fe and CP-3-Fe)	2.63 ± 0.03% 2.49 ± 0.15%	Exhibited stronger -OH and O^{2-} scavenging activity than the CP.	[51]
Rosa roxburghii Tratt fruit polysaccharide-iron (III) complex (RTFP-iron (III))	16.17%	Showed excellent antioxidant activity on scavenging of DPPH, ABTS and hydroxyl radicals and good digestion properties.	[52]
Poria cocos polysaccharide iron (III) complex (PCP1C-iron (III))	28.14 %	Demonstrated antioxidant and antianemia effects.	[53]
Prunella vulgaris polysaccharide-zinc complex (P1-Zn)	27.00 ± 2.4 mg/g	Demonstrated antiproliferative effect on HepG2 human hepatocellular carcinoma cells.	[54]
Flammulina velutipes polysaccharide-iron complex (FVP1-Fe (III))	16.79 ± 3.15%	Regulated gut microbiota dysbiosis in iron deficiency rats.	[55]
Momordica charantia L. polysaccharide chromium (III) complex	14.68 ± 0.35%	Ameliorated carbohydrate metabolism and lipid metabolism.	[56]
Selenium-containing derivatives of *Cordyceps militaris* polysaccharide	16.30-576.40 μg/g	Showed greater DPPH, superoxide anions and hydroxyl radical scavenging ability.	[57]
Anemarrhena asphodeloides polysaccharide-zinc complex (AAP-Zn)	0.20%	Modification with $ZnCl_2$ enhanced the immunomodulatory effect of AAP70-1.	[58]
Selenium-*Euryale ferox* Salisb. polysaccharide (Se-ESPS)	2.915 ± 0.03 mg/g	Exhibited strong antioxidant activity to eliminate DPPH, ABTS, -OH, and increasing reduction ability.	[59]
Coriolus versicolor selenium polysaccharides (Se-YZP-1a)	173.80 μg/g	Exhibited antitumor activity.	[60]
Polysaccharide-iron(III) complex	28.40%	Assist the treatment of iron deficiency anemia.	[61]

Table 2 Preparation of polysaccharide metal ion complex compound by biosynthesis method

Name	Metal ion content	Bioactivity	References
Se-enriched *Lentinus edodes* Se-polysaccharides (Se-P-LE)	29.51 ± 0.23 μg/100g	Showed good antioxidant ability and anti-inflammatory ability.	[65]
Grifola frondosa SH-05 intracellular Zinc Polysaccharides (IZPS)	16.50 ± 0.03 mg/g	Showed superior scavenging activities of the hydroxyl radicals, DPPH, and anti-aging effect.	[66]
Pholiota nameko SW-02 mycelia zinc polysaccharide (MZPS)	16.68 ± 0.73 mg/g	MZPS could improve blood lipid levels , liver lipid levels and antioxidant status.	[67]
Sweet corncob polysaccharide-chromium complex (SCP80-Cr)	/	Showed better hypoglycemic and antioxidant activity *in vitro*.	[68]
Pleurotus cornucopiae SS-03 intracellular zinc polysaccharides	/	Showed certain scavenging effects on superoxide anion and DPPH radicals and upregulated the activities of antioxidant enzymes.	[69]
Rehmanniae Radix Praeparata polysaccharide iron (III) complex	/	antioxidant properties and treating iron deficiency anemia (IDA).	[70]
Cordyceps militaris polysaccharide-iron (III) (CPS-iron)	2.73%	Exhibited strong antioxidant activity.	[71]

Table 3 Preparation of polysaccharide metal ion complex compound by physical method

Name	Metal ion content	Preparation method	References
Bacterial exopolysaccharide iron	/	Simulated biomineralization.	[72]
Lentinula edodes polysaccharide-calcium complex	/	Hydrothermal synthesis method.	[73]

ions are successfully complexed under certain conditions. Common means of the characterization are summarized in this paper (Fig.2).

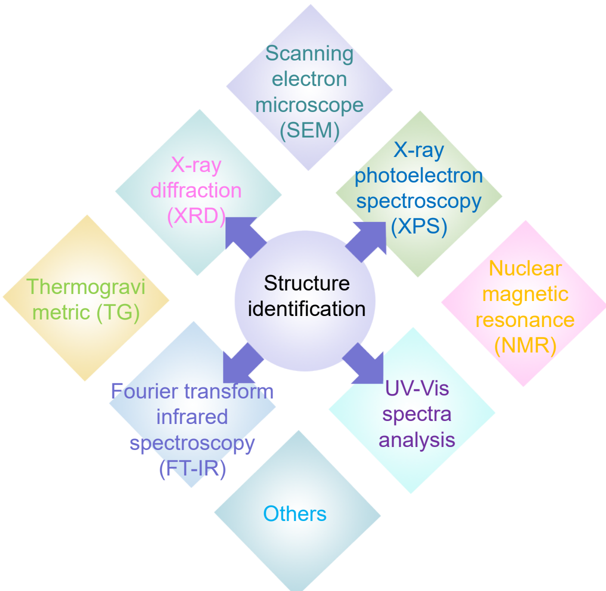

Figure 2 Structural identification method.

3.1 Fourier transform infrared spectroscopy (FT-IR) analysis

By utilizing the infrared spectra of the polysaccharide and polysaccharide metal ion complex and comparing the alterations in the maps, it can be determined whether the complexation was successful. Chen *et al.*[74] found that zinc may bind to -OH and -COOH in *Crassostrea hongkongensis* polysaccharides through infrared spectrum analysis. Xiu *et al.*[68] synthesized sweet corncob polysaccharide iron (III) complexes and analyzed it by infrared spectroscopy. The results indicated that 900 cm^{-1} and 695 cm^{-1} are the fingerprint peaks of β-FeOOH, indicating that complex had a β-FeOOH structure. The broad and intense peak of *Fritillaria ussuriensis* polysaccharide-zinc (FUP-Zn) complex prepared by Zhang *et al.*[75] at 3428 cm^{-1}, this was attributed to the fact that FUP molecules easily form intramolecular or intermolecular hydrogen bonds, resulting in O-H stretching vibrations. When zinc was combined with FUP, the absorption peak becomes sharp and intense, which was consistent with the previous report of Wang *et al.*[76]. Sun *et al.*[77] conducted infrared spectroscopy analysis on *Cordyceps gunnii* Se-polysaccharides, and a strong absorption peak appeared at 920 cm^{-1}, which pertained to the stretching vibration of C-O-Se. The band of 1,150-1,028 cm^{-1} signified that the sugar had a pyran structure. The 852 cm^{-1} band demonstrated the presence of α-type glycosidic bonds, indicating that SeCPS II was a pyranose. Infrared spectroscopy serves as a common approach for characterizing polysaccharides and can also be employed for comparison. The infrared spectra of polysaccharides and polysaccharide metal ion complexes can be evaluated based on the wavelength range of absorption peaks.

3.2 Thermogravimetric (TG) analysis

Thermogravimetric analysis is a straightforward and effective approach for probing the thermostability of polysaccharides and polysaccharide metal ion complexes. Liu *et al.*[61] characterized the structure of *Auricularia auricula* potentially polysaccharide (AAPS)-iron (III). The analysis indicated that AAPS and its iron complexes exhibited similar weight loss tendencies and significant differences in residual mass after decomposition. This may be attributed to the fact that the iron ions cannot be decomposed during the heating process, which further explains the occurrence of the coordination reaction. Jing *et al.*[48] demonstrated that the stability of *Glehniae Radix* polysaccharide-iron complex (GLP80-Fe) was higher than that of GLP80, according to the TG curves. The exothermic peaks of GLP80 and GLP80-Fe are obviously different, and the exothermic peak of GLP80 becomes broad and obtuse, showing the characteristics of amorphous structure. Peng *et al.*[78] reported that the weight of the Vaccinium bracteatum thunb leaves polysaccharide-iron (III) complex (VBTLP-2b-iron (III)) did not change when the temperature was below 150 °C, and the weight loss rate of the VBTLP-2b-iron (III) complex was slightly lower than that of the VBTLP-2b in the range of 0-700 °C. The results showed that the thermal stability of the complex was superior than that of the polysaccharide. Thermogravimetric analysis can not only determine the thermal stability of polysaccharides and their metal ion complexes based on the weight loss trend, but also indirectly validate the successful coordination of polysaccharides and metal ion complexes.

3.3 X-ray diffraction (XRD)

X-ray diffraction serves as an effective approach for identifying the crystalline phase of the substance, analyzeing the microstructure of the polysaccharide, and verifying the success of metal ion complexation with the polysaccharide. Oshtrakh *et al.*[79] employed extensive X-ray absorption fine structure analysis to hypothesize that the iron on the surface of the iron core of the polysaccharide iron complex was linked to the hydroxyl group on the polysaccharide to form a complex. Wang *et al.*[52] synthesized *Rosa roxburghii* Tratt fruit polysaccharide-iron (III) complex (RTFP-iron (III)) and analyzed it using XRD. The results indicated that RTFP exhibited a characteristic peak at 2θ=20.8°, while complex, the band around 20° nearly vanished, and there are strong diffraction bands around 35° and 63°, which could be attributed to iron (III), and was different from the previously reported Garlic polysaccharide-Fe (III) complex[50] which was similar with the characteristic peaks of the map. Li *et al.*[38] performed XRD analysis on Ganoderma lucidum polysaccharide-chromium (III) complex (GLP-Cr (III)). GLP presented broad and sharp peaks from 5° to 50°. The mapping framework of the complex was similar to that of GLP. The significant difference was that there existed a series of faint diffraction peaks, indicating that the crystallinity of GLP vanished after chelating with Cr (III). Thus, X-ray diffraction can be employed to determine whether polysaccharide and metal ions are successfully complexed based on the characteristic peaks of the material.

3.4 Scanning electron microscope (SEM)

SEM can mirror the alterations in the surface morphology of polysaccharides and their complexes, which can serve as a foundation for determining the success of complexation. Zhang *et al.*[75] employed scanning electron microscopy to investigate *Fritillaria ussuriensis* polysaccharide-zinc complex (FUP-Zn). The SEM image outcomes demonstrated that the surface of FUP was rough, porous, and had evident cracks. The surface of FUP-Zn exhibited a porous structure with reduced pores. The disparity in the surface structure of the two indicates the achievement of the chemical modification. Lu *et al.*[80] observed *Astragalus membranaceus* polysaccharide (APS)-iron (III) complex under 3,000 times magnification through scanning electron microscopy as a sheet, featuring a flat and smooth surface, and APS particles in a relatively regular round shape. Thus, SEM can determine whether polysaccharide and metal ions are successfully complexed by observing the apparent morphological changes before and after complexation.

3.5 X-ray photoelectron spectroscopy (XPS)

XPS can be employed to ascertain the elemental composition of the polysaccharide metal ion complex and determine whether iron exists within in the complex. Xiu *et al.*[68] affirmed that Fe (III) was successfully combined with sweet corncob polysaccharide based on XPS full-scan spectrum, and the introduction of iron ions did not disrupt the fundamental framework of polysaccharides. Zhang *et al.*[81] verified through XPS analysis that selenium had been successfully incorporated into the polymer chain of *Eriobotrya japonica* 90-1. Wang *et al.*[52] carried out XPS spectral analysis of *Rosa roxburghii* Tratt fruit polysacchride (RTFP) and its complex, and discovered that a strong iron element was detected in the complex, but not in the polysaccharide, indicating that the polysaccharide was successfully combined with iron under feasible circumstances. Therefore, XPS can ascertain whether the complex is successfully formed by determining the elemental composition of the sugar metal ion complex.

3.6 Nuclear magnetic resonance (NMR)

By comparing the NMR hydrogen spectra of polysaccharides and polysaccharide-metal ion complexes, the success of complexation can be determined based on the magnetic blind area formed in the magnetic field. Through ^{1}H NMR analysis, Yuan *et al.* [82] discovered via ^{1}H NMR analysis that the characteristic peak of the polysaccharide was weakened as the spin of iron would form a specific magnetic blind area in the magnetic field. That is, the absorption peak produced by Lotus root polysaccharide (LRP) and Fe (III) vanished, indicating that LRP is bound to Fe(III) in LRPF. Li *et al.*[38] discovered that the entire signal pattern of GLP was absent in the ^{1}H NMR spectrum of GLP-Cr (III), which could be attributed to the specific covalent binding of Cr (III) and GLP. Lin *et al.*[83] analyzed the structure of *Cordyceps cicadae* exopolysaccharide (EPS) and EPS-Fe (III) using ^{1}H NMR. Compared with EPS, the spectral signal of EPS-Fe (III) is incomplete. The extensive blind area herein suggests that EPS-Fe (III) has a high spin state at the center of the oxygen-iron bond, which clearly indicates that the polysaccharide is bound to iron. Guo *et al.*[84] further compared the chemical shift of *Grifola frondosa* polysaccharide (GFP) and GFP-Cr (III) using ^{1}H NMR and verified the successful preparation of GFP-Cr (III). The above-mentioned studies suggest that hydrogen NMR spectra can reflect the successful complexation of polysaccharides and metal ions.

3.7 UV-Vis spectra analysis

The successful complexation can be determined through the absorption peaks of polysaccharide and polysaccharide metal ion complexes within different wavelength ranges in the ultraviolet spectrum. Yuan *et al.*[82] discovered by ultraviolet spectroscopy that in contrast to LRP, LRPF exhibited a distinct absorption peak at 210 nm, indicating that the combination of LRP with iron ions enhanced its ultraviolet absorption intensity, thereby indicating the successful construction of LRPF. Peng *et al.*[85] discovered via the UV-VIS spectra of *Flammulina velutipes* scraps polysaccharide (FVSP) and FVSP-Fe (III) that, in contrast to FVSP, the absorption of FVSP-Fe (III) was conspicuously enhanced within the range of 250-350 nm, suggesting that the Fe-O bond had been successfully formed in FVSP-Fe (III). Xiu *et al.*[68] determined by ultraviolet spectrum that the absorbance of sweet corncob polysaccharide iron (III) complex was significantly higher than that of sweet corncob polysaccharide (SCCP) within the range of 200-400 nm, which might be the outcome of the interaction between Fe (III) in sweet corncob polysaccharide and the iron (III) complex. Lin *et al.*[83] discovered that in comparison with EPS, the UV absorption of EPS-Fe (III) was significantly enhanced within the range of 250-350 nm, which was associated with the charge transfer of oxygen to the metal. Thus, UV analysis affirmed the successful complexation of EPS with Fe (III). The aforementioned studies suggest that UV-VIS absorption spectra can verify whether polysaccharides and metal ions are successfully complexed.

3.8 Others

Additionally, particle size distribution, monosaccharide composition analysis, Circular Dichroism (CD) spectra analysis, and Energy Dispersive X-Ray Spectroscopy (EDX) analysis can be used to directly or indirectly estimate the successful complexation of polysaccharides with metal ions. For instance, Zhang *et al.*[53] determined the particle size distribution of PCP1C and PCP1C-Fe (III) complex, in combination with SEM-EDS analysis. The results indicated that, compared with PCP1C, the particle size of the PCP1C-Fe (III) complex was significantly increased. The study conducted by Zhang *et al.*[86] demonstrated that Pumpkin Peel Polysaccharide (PPP) and PPP-Cr (III) consisted of the same type of monosaccharide, yet the proportion differed. The incorporation of Cr^{3+} into PPP would induce certain alterations in the monosaccharide composition of pumpkin peel polysaccharides. Yuan *et al.*[82] discovered via circular dichroic chromatography that the signal curve of LRP was relatively smooth. Once LRP was complexed with iron ions, distinct absorption peaks emerged at 192 nm and 194 nm. The outcomes demonstrated that metal ions altered the original molecular configuration of the polysaccharide and verified the successful complexation of the polysaccharide with metal ions. Majeedet *et al.*[87] confirmed through EDX analysis that the EDX spectrum of *Tamarix* seed polysaccharides and copper nanocomposites contained a certain quantity of copper. The above mentioned characterization approach is not merely a common method for identifying polysaccharides, but also can directly or indirectly indicate whether polysaccharides have been successfully complexed with metal ions.

4 Bioactivities of the polysaccharide metal ion complex

In recent years, an increasing number of studies have been carried out regarding polysaccharide metal complexes and their associated activities. Compared with traditional small-molecule metal complexes, macromolecular polysaccharide metal complexes exhibit higher safety and water solubility. And the synergistic interaction between polysaccharides and metal ions can potentiate the biological activity of polysaccharides. In this paper, the bioactivities of polysaccharide metal complexes were summarized (Fig.3). And biological activities and structure before and after the complexation of polysaccharides and metal ions were shown in Table 4.

4.1 Antioxidant activity

Numerous researchers have demonstrated that polysaccharides can be employed as novel antioxidants. Likewise, polysaccharides also possess antioxidant activity upon complexation with metal ions, and certain complexes even exhibit higher antioxidant activity than polysaccharides[33]. Zhang *et al.*[56] demonstrated that *Fructus mori* L. polysaccharide-iron (III) chelate can scavenge -OH and inhibit the production of malondialdehyde in the liver homogenates of experimental mice. Liu *et al.*[90] investigated the mechanism of porcine circovirus type 2 (PCV2) replication promotion induced by oxidative stress. The findings indicated that selenizing *astragalus* polysaccharide (sAPS) inhibits autophagy by activating PI3K/AKT, and significantly reduces PCV2 induced by oxidative stress. Lian *et al.*[91] utilized *Glycyrrhiza uralensis* polysaccharide (GUP) as the raw material to prepare SeGUP through the HNO_3-Na_2SeO_3 method. Antioxidant tests revealed that complex displayed stronger antioxidant activity than GUP. The results demonstrated that the antioxidant activity of polysaccharides was enhanced after Se modification. Wang and Li[76] manifested that zinc-*Hohenbuehelia serotina* polysaccharides (HSP) complex had significant scavenging ability on -OH, ABTS and O^{2-} *in vitro* based on the results of antioxidant activity. Qiu *et al.*[92] employed the HNO_3-Na_2SeO_3 method to modify *Lycium barbarum* polysaccharide (LBP) to obtain Selenizing *Lycium barbarum* polysaccharide. Through antioxidant experiments, it was demonstrated that Se-LBP can exert better antioxidant

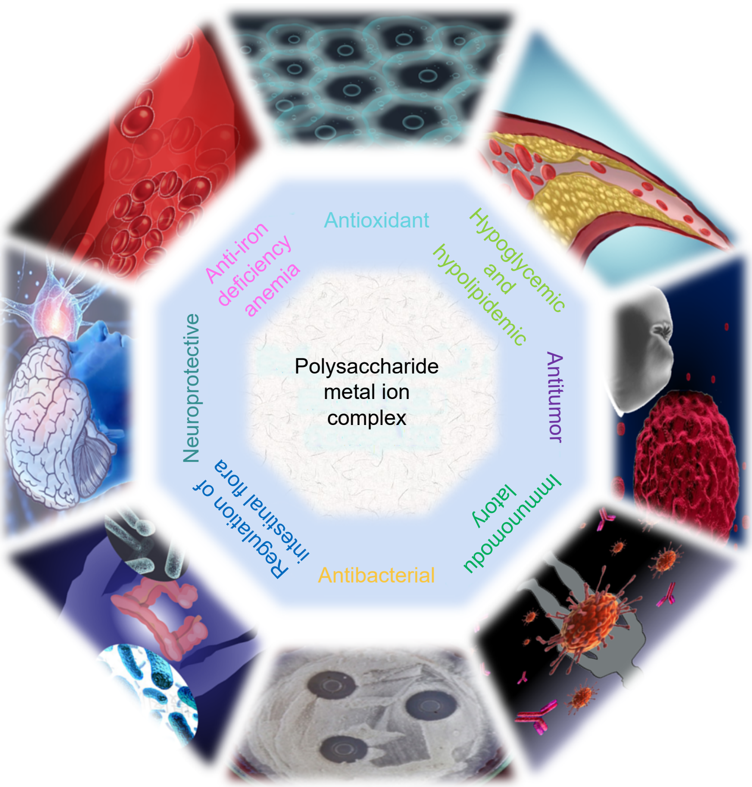

Figure 3 Bioactivities of the polysaccharide metal ion complex.

Table 4 Comparison of biological activities and structure of polysaccharide before and after complexation with metal ions

Before	After	Alteration of bioactivity/structure	References
Polysaccharide from *Flammulina velutipes* scraps (FVSP)	Polysaccharide-iron (III) from *Flammulina velutipes* scraps /FVSP-iron (III)	Showed better thermal stability and stronger antioxidant activities.	[85]
Pumpkin Peel Polysaccharide (PPP)	Pumpkin Peel Polysaccharide-Chromium(III) Complex /PPP-Cr(III)	Showed more higher α-glucosidase inhibitory activity.	[86]
Grifola frondosa polysaccharide (GFP)	*Grifola frondosa* polysaccharide-iron (III) complex/(GFP-iron)	The lymphocytes proliferation of GFP-iron (III) complex was increased by 61.68%.	[88]
Poria cocos polysaccharide (PCP1C)	*Poria cocos* polysaccharide iron (III) complex/ PCP1C-iron (III)	Exhibits stronger DPPH scavenging activity and hydroxyl radical scavenging capacity.	[53]
Sweet corncob polysaccharide complexes (SCCP)	Sweet corncob Polysaccharide Iron (III) Complexes /SCCP-Fe	Exhibits stronger antioxidant, α-glucosidase and α-amylase inhibitory capabilities *in vitro*.	[68]
Sweet corncob polysaccharide/SCP	Sweet corncob polysaccharide-chromium (III) complex /SCP-Cr(III)	Possesses a more significant hypoglycemic potential.	[89]
Poria cocos polysaccharide (PCP1C)	*Poria cocos* polysaccharide iron (III) complex/ PCP1C- Fe (III)	The particle size of the PCP1C-Fe (III) complex was significantly augmented.	[53]

activity. The aforementioned studies indicated that the antioxidant activity of polysaccharide remained largely unaltered upon complexation with metal ions, and certain complexes even exhibited higher antioxidant activity than polysaccharide.

4.2 Hypoglycemic and hypolipidemic activity

The antioxidant activity of the combination of metal ions and polysaccharides is manifested in its anti-hyperlipidemic and anti-diabetic activities. Zhang *et al.*[93] synthesized and identified a novel *Sophora* polysaccharide-Chromium (III) complex (MCPIIaC) and evaluated its anti-diabetic effect and hypoglycemic mechanism in streptozotocin (STZ)-induced diabetic (DM) mice. After 4 weeks of MCPIIaC treatment, fasting blood glucose levels and body weight were significantly reduced in STZ-induced DM mice. The results demonstrated that MCPIIaC had the ability of lower blood glucose and increase insulin level. Wang *et al.*[94] discovered that *Inonotus obliquus* polysaccharides-chromium (III) complex could effectively lower blood glucose and plasma insulin levels in type 2 diabetic (T2DM) mice. Zeng *et al.*[95] investigated the hypoglycemic and lipid-lowering effects of lotus leaf selenium (Se)-polysaccharide (LLP) in gestational diabetes mellitus (GDM) rats. The results indicated that LLP could reduce the blood glucose level and improve the lipid level of GDM rats compared with GDM rats. Yuan *et al.*[96] utilized STZ-induced diabetic rats as experimental subjects to test the anti-diabetic effect of selenylation sweet potato polysaccharide (Se-SWP). The results revealed that Se-SWP could restore blood glucose and insulin levels in the diabetic rats. Surhio *et al.*[97] used the HNO_3-Na_2SeO_3 method to prepare selenium modified exopolysaccharide of *Lachnum* sp (SeLEP-1b). Experiments confirmed that oral administration LEP-1b could significantly reduce lipids of serum and liver in hyperlipidemia mice, the atherosclerosis index, increase the activity of antioxidant enzymes, improve the pathological state of liver tissue, and possess good lipid-lowering and liver-protecting activities. Guo *et al.*[98] prepared the *G. frondosa* polysaccharide-chromium (III) complex under the optimal condition with approximately 1.0% chromium content, this complex exhibited significant hypoglycemic and lipid-lowering activities in both high-fat diet and STZ-induced diabetic mice. The aforementioned studies demonstrated that metal ions in combination with polysaccharides still exhibited remarkable hypoglycemic and hypolipidemic activities.

4.3 Antitumor activity

The anti-tumor activity of the combination of metal ions and polysaccharides encompasses multiple mechanisms, such as induction of apoptosis and cell cycle arrest. Li *et al.*[54] discovered that Zinc polysaccharide of *Pleurotus ostreatus* can effectively inhibit the morphological alteration, chromatin agglutination and G0/G1 cell cycle arrest of HepG2 cells, and exhibited an effective anti-tumor effect. *Codonopsis pilosula* polysaccharide-iron synthesized by Feng and Zhang[99] exerted a strong inhibitory effect on the growth of A2780 cells and possesses potential anti-tumor activity. Yuan *et al.*[100] prepared *Pyracantha fortuneana* Se-containing polysaccharides containing 3.7 μg/g selenium, this polysaccharides blocked G2 phase cells by suppressing CDC25C-CyclinB1/CDC2 pathway, thereby inhibiting the proliferation of human breast cancer cells, and presenting as a potential anti-tumor drug. Mao *et al.*[101] demonstrated that Se-enriched *Grifola frondosa* selenium-polysaccharide could significantly inhibit the reproduction of Heps tumor in tumor-bearing mice, and it exerted anti-tumor effect by improving immune function. Liu *et al.*[102] separated and purified three components of selenized *Cordyceps militaris* polysaccharides (SeCPS) by ultrafiltration. The results showed that SeCPS-Ⅱ had the strongest anti-tumor effect on two tumor cell lines *in vitro*. Liao *et al.*[103] first reported that selenium-modified ginseng polysaccharide (sGP) could induce apoptosis of HL-60 cells and produce anticancer effects. The experimental results showed that in HL-60 cells, sGP apoptosis is associated with loss of mitochondrial membrane potential, the release of cytochrome c from the mitochondria to the cytosol, the activation of caspase-3 and caspase-9, a rise of Bax/Bcl-2 ratio, as well as the cleaved of the poly ADP-ribose polymerase in HL-60 cells. He *et al.*[104] investigated the inhibitory effect of selenium-containing tea polysaccharides (Se-GTPs) on human MCF-7 breast cancer cells. Se-GTPs can induce G2/M phase arrest and apoptosis of MCF-7 cells, with an IC_{50} of 140.1 μg/mL, and may be utilized as a potential novel dietary preparation for the chemoprevention of human breast cancer. Hence, the combination of metal ions and polysaccharides still exhibits anti-tumor activities, such as inducing apoptosis and arresting the cell cycle.

4.4 Immunomodulatory activity

The binding of metal ions to polysaccharides exhibits immunomodulatory activity. The immunomodulatory mechanisms include regulating cytokines and signaling pathway regulators, enhancing immune function by reducing oxidative stress damage to the body, regulating intestinal flora, and regulating the immune system[25]. Haibo *et al.*[105] assessed the immune enhancement effect of selenizing *Chuanminshen violaceum* polysaccharides (sCVPS) using experiment. The results demonstrated that selenization of sCVPS could enhance the immune activity *in vitro* and *in vivo*, and sCVPS could be used as a new adjuvant for vaccine design. Jia *et al.*[106] indicated that with the escalation of the concentration of *Astragalus membranaceus* polysaccharide-iron (III) complex (APS-iron (III)), the stimulation index increased. When the concentration of APS-iron (III) was 50 μg/mL, lymphocyte proliferation increased by 35.7% compared with APS. The *Ulva Pertusa* polysaccharide iron complex (UPP-iron (III)) prepared by Gao *et al.*[107] was investigated on the immunomodulatory activity in a mouse immune deficiency model. The results showed that the UPP-iron (III) could promote the proliferation of lymphocytes and enhance the activity of macrophages in mice. UPP-iron (III) has the potential to be an immune-enhancing functional food. The aforementioned studies suggest that the combination of metal ions and polysaccharides possesses immunomodulatory activity.

4.5 Antibacterial activity

Some metal itself possess antibacterial properties, polysaccharide and its combination also exhibit antibacterial activity. The *Flammulina velutipes* polysaccharide-Fe prepared by Dong *et al.*[108] possessed significant antibacterial activity. Marine red microalga produce spikes polysaccharide-Cu complexes had antimicrobial activity[109]. Zhang *et al.*[66] used *Staphylococcus aureus*, *Escherichia coli*, and *Listeria monocytogenes* to investigate the antibacterial activity by determining the sterilization zone. The results manifested that the intracellular zinc polysaccharide (IZPS) of *Grifola frondosa* SH-05 strain had potential antibacterial activity. Lü *et al.*[110] had revealed that degraded polysaccharide selenide (Se-LEP) had a strong inhibitory effect on *Escherichia coli* and plant pathogenic fungi. Thus, the metal ions still maintain their antibacterial attributes even after complexation with polysaccharide.

4.6 Other bioactivities

In addition to the above biological activities, the binding of metal ions to polysaccharides has neuroprotective, anti-iron deficiency anemia, liver protection, anti-inflammatory, regulation of intestinal flora, anti-osteoporosis, and anti-fibrotic activities. Wei *et al.*[111] confirmed the biological function of *Radix hedysar* Polysaccharide (RHP) and Se-RHP to improve oxidative stress and prevent or treat Alzheimer disease neurodegeneration through cell experiments. Ren *et al.*[112] investigated the preventive effect of selenized lentinan on chronic pancreatitis and the prebiotic-like effect of 3,5-diethoxycarbonyl-1,4-dihydrocollidine-induced mouse intestinal flora. The results showed that selenium-lentinan complex had a prebiotic-like effect, and regulated the intestinal microbiota of mice. Selenized *Ulmus pumila* L. pectic polysaccharide (Se-PPU) prepared by Lee *et al.*[113] can inhibit lipopolysaccharide-induced nitric oxide production in RAW 264.7 cells. Increasing the selenium content can enhance the anti-inflammatory properties of PPU. Therefore, Se-PPU can be used as a potential source of bioactive compounds for health care and pharmaceutical applications. Liu *et al.*[114] explored the protective effect of mycelial selenium polysaccharide (MSPS) isolated from *Hypsizigus marmoreus* SK-02 on CCl_4-induced liver injury. The results showed that MSPS can effectively remove free radicals released from the liver, indicating that MSPS can effectively protect the liver from hepatotoxic damage by mediating anti-oxidation and scavenging activities of free radicals. Gao *et al.*[115] compared the liver protective effects of selenated *Angelica* polysaccharide (sCAP) and CAP in CCl_4 induced hepatic injury mice. The results showed that selenium modification could enhance the hepatoprotective effect of *Angelica* polysaccharide. Owing to the remarkable biological activity of polysaccharide metal complexes, its application in nutritional supplements holds great promise.

5 Research progress on complexation of *Tremella fuciformis* polysaccharides with metal ions

Copper, iron, chromium, and other metal ions are regarded as crucial trace elements indispensable for the normal operation of various physiological processes. Organisms are sustained by diverse types of metal ions. Copper is among the most significant trace metals in the human body, and aside from its oxidation-reduction properties, the advancement of diseases might be influenced by copper content. Nevertheless, in extant studies, small molecular organic ligands are complexed with metal ions, which are highly toxic and insoluble in water. Such compounds exert potentially detrimental effects and irreversible toxicity on other tissues and organs of the body, thereby precluding their utilization in a broad range of applications. Hence, there is an urgent demand to develop high-quality, safe, and efficient methods for Cu delivery. Xie *et al.*[116] devised and synthesized a novel injectable gel composed of Cu ion-coordinated *Tremella fuciformis* polysaccharide (TFP-Cu) for antiosteosarcoma therapy. The findings demonstrated that this material possesses antitumor effects, the capacity to facilitate immunity and promote bone formation, and a controlled Cu^{2+} release profile in smart response to tumor microenvironment stimulation. TFP-Cu can selectively inhibit the proliferation of K7M2 tumor cells by arresting the cell cycle and promoting cell apoptosis and cuproptosis. TFP-Cu also promoted the M1 polarization of RAW264.7 cells and regulated the immune microenvironment.

Iron deficiency anemia is closely related to iron deficiency, rapid exhaustion of iron stores, or abnormal gastrointestinal absorption, and affects up to one-third of the population. Iron supplementation constitutes a key treatment for iron deficiency anemia, among which oral iron supplementation is the preferred option for patients with iron deficiency anemia. Currently, iron supplements have evolved into three generations. First-generation iron supplements encompass inorganic iron supplements, such as $FeSO_4$, which can induce significant gastrointestinal irritation in adults, including nausea, abdominal pain, diarrhea, and constipation. The second generation of iron supplements is represented by soluble small molecule organic iron salts like ferrous lactate and ferrous gluconate. Although the second generation of iron supplements has certain issues on the body with fewer side effects, it still has certain limitations, such as instability, difficulty in production and storage. At present, iron supplements have advanced to the third generation, including polypeptide iron chelates, heme iron, polysaccharide iron chelates, and other macromolecular iron complexes. The biocompatibility of polysaccharide iron chelate is similar to that of $FeSO_4$, suggesting that it has excellent bioavailability. In recent years, various polysaccharides have been utilized to prepare macromolecular iron complexes. *Tremella* polysaccharide has been identified as the main bioactive component with therapeutic effects, and it is composed of mannose, glucuronic acid, glucose, galactose, xylose, and rhamnose. In recent years, a large number of studies have confirmed the physical and physiological properties of *Tremella* polysaccharide, including its immunomodulatory, anti-tumor, anti-oxidation, anti-aging, memory enhancement, and anti-inflammatory effects. The stability of polysaccharide solutions is closely related to its potential applications in the food, cosmetic, and pharmaceutical industries. However, there are scarce reports on the complexation of *Tremella* polysaccharides with metal ions. Therefore, it can be employed as raw material of iron supplement to prepare polysaccharide iron complex. Recently, Wei *et al.*[117] investigated the the stability, release of Fe^{3+}, and biological activity of fermented *Tremella* polysaccharide after complexation with Fe^{3+}, and confirmed the successful combination of Fe^{3+} with polysaccharide through scanning electron microscopy, Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, X-ray diffraction and circular dichroism spectroscopy. The results demonstrated that the release rate of the fermented *Tremella* polysaccharide-Fe^{3+} complex in simulated gastric fluid for 0.5 h was determined to be 76% ± 2%, suggesting a favorable release profile. The results indicated that the compound exhibited good antioxidant and hypoglycemic activities *in vitro*.

Based on the previous summary, *Tremella* polysaccharides can integrate effectively with metal ions, and enhance the activity of polysaccharides to a certain degree. Meanwhile, the researchers successfully integrated *Tremella* polysaccharides with iron ions, and the complex exhibited excellent antioxidant and hypoglycemic activities *in vitro*. The results indicate that the complex possesses outstanding stability and dual functions of iron supplementation and nutrition, this complex plays a potential key role in the new iron supplement.

6 Conclusion

Currently, these artificial polysaccharide metal ion complexes exhibit a high content of metal ions and possess numerous superior properties. Therefore, they have broad application value and development potential in the fields of medicine, health care products, food, etc. However, at present the research regarding the relation between its structure-function is scarce, and there is limited research of conformation and activity of polysaccharide. Hence, it is essential to conduct in-depth studies on their biological activity and structure-activity relationship to utilize them more effectively. Moreover, the research on *Tremella fuciformis* polysaccharides is deficient at present, which can be regarded as the direction for in-depth exploration of *Tremella fuciformis* polysaccharides.

Conflicts of interest

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

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