Polysaccharides from fungi: A review on their extraction, purification, structural features, and biological activities

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A B S T R A C T

Fungi, as the unique natural resource, are rich in polysaccharides, proteins, fats, vitamins, and other components. Therefore, they have good medical and nutritional values. Polysaccharides are considered one of the most important bioactive components in fungi. Increasing researches have confirmed that fungal polysaccharides have various biological activities, such as antioxidant, immunomodulatory, anti-tumor, hepatoprotective, anti-aging, anti-inflammatory, and radioprotective activities. Consequently, the research progresses and future prospects of fungal polysaccharides must be systematically reviewed to promote their better understanding. This paper reviewed the extraction, purification, structure, biological activity, and underlying molecular mechanisms of fungal polysaccharides. Moreover, the structure–activity relationships of fungal polysaccharides were emphasized and discussed. This review can provide scientific basis for the research and industrial utilization of fungal polysaccharides.

1. Introduction

Among the 15,000 species of macrofungi distributed throughout the world, particularly in many countries of the northern temperate zone, including China, Japan, and Korea, and more than 2000 species are edible. Notably, the usage of fungi for a dietary supplement or a herbal medicine has a long history in China. More than 1000 kinds of edible fungi have been recorded in China (Shao, Si, Zhang, Tu, & Zhang, 2020). The long tradition of edible and medicinal fungi has attracted the attention of researchers at home and abroad. The global trade of edible fungi reached US $35 billion in 2015 and is expected to reach US $60 billion by 2023 (Yang, Tb, Hpdb, Li, & Zl, 2019). The scientific research reports on edible fungi are increasing year by year. The edible parts of fungi with delicious taste and rich nutrition are generally the fruiting bodies of higher fungi (Miao et al., 2021). Additionally, fungi are rich in polysaccharides, proteins, fats, vitamins, and other active components (Lu, Perera, & Hemar, 2012; Neil & Rowan, 2003). In recent years, several bioactive components of fungi have attracted increasing attention with the rise of the concept of healthy diet. Polysaccharides, as one of the most important active components in fungi, are long-chain

carbohydrates formed by complex polymerization of various neutral sugars or uronic acids through glycosidic bonds (Liang, Zhang, Wang, Ren, & Gao, 2021; Vu, Beeson, Phillips, Cate, & Marletta, 2013; Xin, Beeson, Phillips, Marletta, & Cate, 2012). At present, fungal polysaccharides, as a natural active ingredients, have been extensively used in cosmetic, food, and health product industries (Li et al., 2020; Zhao, Lv, & Lu, 2019). In addition, previous scientific studies have introduced numerous discoveries, indicating that fungal polysaccharides have various biological activities, such as, immunomodulatory, antioxidant, anti-tumor, hepatoprotective, anti-inflammatory, anti-aging, hypolipidemic, and radioprotective activities (Fan et al., 2014; Hoang, Kim, Lee, You, & Lee, 2015; Wang et al., 2021a; Yang, Jia, Meng, Wu, & Mei, 2006; Zhang, Zhou, Wang, Zhou, & Xie, 2021). Moreover, the extraction and purification methods, structural characteristics, and chemical modification of fungal polysaccharides have been widely studied, and a certain research foundation has been achieved (Ahmad, 2021; Jiang, Li, Cui, Dong, & Du, 2021; Wang, Li, Hu, Gong, & Zhao, 2021b).

The physicochemical properties (solubility, viscosity, and structure) of polysaccharides affect their biological activities to a certain extent (Sow, Toh, Wong, & Yang, 2019; Sow, Tan, & Yang, 2019; Yang, Gao, &

Yang, 2020). High viscosity has become a major problem in the research of various fields of polysaccharides, and the difficulty of production greatly increases their cost, resulting in the challenging large-scale application of polysaccharides (Colletti, Delgado, Cabezas, Wagner, & Porfiri, 2020; Urshev, Dimitrov, Fatchikova, Petrova, & Ishlimova, 2008). In addition, the literature about the exact structural information and potential molecular mechanisms of fungal polysaccharides is limited. According to existing literature, fungal polysaccharides can be used as functional active ingredients and therapeutic agents for disease

prevention and treatment. Hence, a systematic review of research advances and future prospects of fungal polysaccharides is very necessary for facilitating their better understanding. In this paper, the studies on the extraction and purification methods, structure, and biological activities of fungal polysaccharides in recent years were summarized (Fig. 1), and the research progress and future development trend were described in detail. This review may provide some valuable insights for further researches regarding fungal polysaccharides.
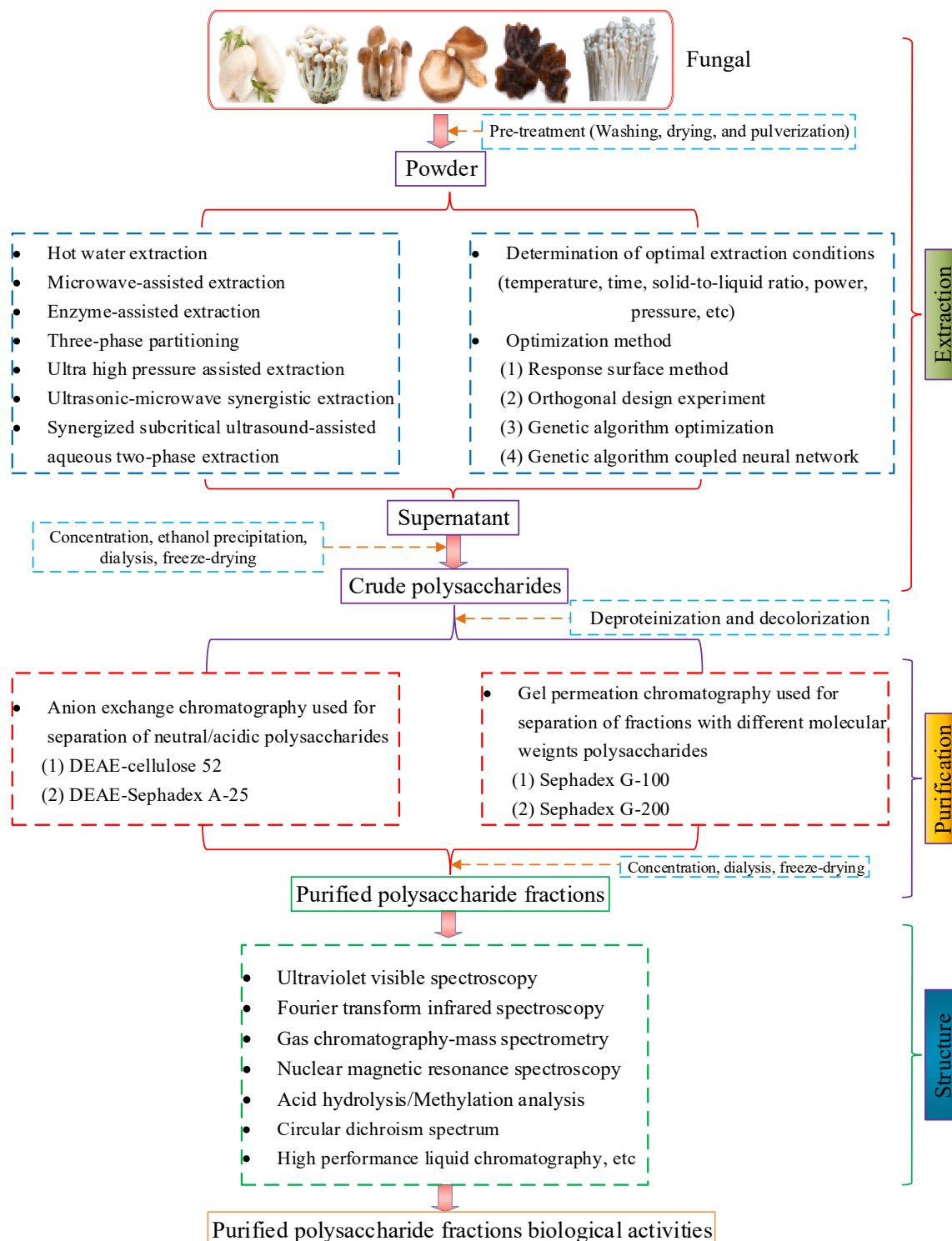

Fig. 1. Currently methods of extraction, purification, structural characteristics of fungi polysaccharides and their biological activities.

2. Extraction and purification methods of fungal polysaccharides

With the development of extraction and purification technology, the nutritional and medical values of fungal polysaccharides have increasing attracted attention. All kinds of traditional and potential extraction methods have already been established and proposed (Golbargi, Gharibzahedi, Zoghi, Mohammadi, & Hashemifesharaki, 2021; Luan, Ji, Peng, Liu, & Zeng, 2021; Ma, Wang, & Zhang, 2008; Xu, Zhang, & Jiang, 2016). Table 1 summarizes the different extraction methods and the corresponding fungal polysaccharides yield. According to the distribution and cell localization of fungal polysaccharides, and they are mainly divided into intracellular and extracellular polysaccharides (Du, Yang, Bian, & Xu, 2017; Zhang et al., 2012). Notably, the crude extracellular polysaccharides can be directly extracted from fungal fermentation medium by ethanol precipitation methods (Miao et al., 2020; Zhao et al., 2015). As for intracellular fungal polysaccharides, they are mainly from fruiting bodies or mycelium of fungi by different extraction methods (Ba et al., 2020; Do, Lai, Stephenson, & Tran, 2021; Moradi & Kalanpour, 2019; Zhang et al., 2020a). Before extracting intracellular fungal polysaccharides, raw materials undergo a series of pretreatment, including washing, drying, crushing, and degreasing. Currently, hot water extraction (HWE) has become one of the most commonly used extraction method because of its convenient operation, simple equipment, and easy to implement (Udchumpisai & Bangyeekhun, 2019; Zhong & Wang, 2010). In addition, dilute alkali method, as another traditional extraction method, can enhance the extraction efficiency and reduce the separation time of acidic fungal polysaccharides (Teng, Qin, Shi, Zhang, & Ren, 2020). Nevertheless, The addition of dilute alkali solution is easy to cause the structural damage of fungal

Table 1
Extraction and purification methods, biological activities and mechanism of fungal polysaccharides.

Source	Extraction methods	Yield%	Purification methods	Biological activities	Mechanism	References
Lentinus edodes	EAE	15.65	DEAE, Sephadex-100	Antitumor	Inhibition of HeLa cell proliferation	Cogdill et al., 2018
Agaricus bisporus	EAE	–	–	Antioxidant Anti-aging	Scavenging DPPH and OH radicals Increasing antioxidant enzymes, reducing lipid peroxidation and releasing lipid metabolism	Li et al., 2018b
Agaricus bisporus	EAE	6.87	DEAE-52, Sephadex G-100	Antioxidant	Scavenging DPPH and OH radicals	Yin et al., 2015
Lentinus velutinus	HWE	0.025	DEAE, Sephadex G-100	Antitumor	Specific cytotoxicity to cancer cells (HeLa and HepG2 cells)	Udchumpisai & Bangyeekhun, 2019
Pleurotus ostreatus	HWE	–	DEAE, Sepharose CL-6B	Antioxidant	–	Xia et al., 2011
Pleurotus djamor	HWE	–	–	Antioxidant	–	Maity et al., 2021
Ganoderma capense	HWE	–	DEAE, Sepharose CL-6B, Sephadex G-75	Antioxidant, anti-inflammatory, anti-tumor	–	Lu et al., 2012
Cordyceps minlitaris	HWE	–	Sephadex G-75	Antioxidant	–	Hou et al., 2008
Flammulina velutipes	HWE	–	DEAE-52, Sephadex G-100	Antioxidant	–	Gao et al., 2019
Auricularia auricula	HWE	–	–	Regulating immune	Promoting macrophage activation	Bao et al., 2020
Pleurotus eryngii	HWE	10.69 ± 0.31	Ultrafiltration	Antitumor	Activating mitochondrial apoptosis pathway	Ma et al., 2016
Gray oyster mushroom	SE	–	Column chromatography	Regulating immune	Enhancing the killing activity of neutrophils against Candida albicans	Decha et al., 2018
Flammulina velutipes	MAE	–	–	Antioxidant	–	Liu et al., 2016a
Flammulina velutipes	UAE	20.52	–	Antioxidant	–	Yu et al., 2017
Tricholoma mongolicum Imai.	UMSE	35.41 ± 0.62	DEAE-52, Sephadex G-100	Antioxidant	–	You et al., 2014a
Inonotus obliquus	TPP	–	–	Antioxidant	Strong free radical scavenging ability	Liu et al., 2019
Phellinus linteus	ATPS	–	–	Antioxidant	Scavenging free radicals	Wu et al., 2021
Mushroom	SEM	31.14	–	Antioxidant	–	Chikari et al., 2020
Cordyceps gunnii mycelia	HWE, MAE, UAE, EAE	–	Sephadex G-100	Antitumor	–	Wang & Li, 2019
Boletus edulis	CCPUE	8.21	DEAE-52, Sephadex G-75	Antioxidant	–	You et al., 2014
Mushroom	–	–	–	Antibacterial	–	Mai et al., 2017
Agaricus bisporus	–	–	DEAE-52, Sephadex G-200	Regulating immunity	–	Liu et al., 2020
Spent *Lentinus edodes* substrate	–	–	Sephadex G-150	Antioxidant	–	Zhu et al., 2018
Cordyceps militaris	–	–	Macroporous resins NKA-9	Antioxidant	–	Zhu et al., 2012
Mushroom *Lepista nuda*	–	70.60	Macroporous resin D301, DEAE Cellulose-52, Sephadex G-150	Antioxidant	Scavenging DPPH and O^{2-} radicals	Shu et al., 2019
Auricularia auricula-judae Quel	–	–	–	Hypoglycemic	Reducing plasma and urinary glucose levels	Liang et al., 2018
Auricularia auricular	–	–	–	Hypoglycemic	Promoting glucose metabolism to greatly reduce blood glucose levels	Chen et al., 2018

Note: HWE: Hot water extraction; UAE: Ultrasound assisted extraction; MAE: Microwave assisted extraction; EAE: Enzyme assisted extraction; UHPAE: Ultra-high pressure assisted extraction; UMSE: Ultrasonic-microwave synergistic extraction; ATPS: Aqueous two-phase system; UMSE: Ultrasonic-microwave synergistic extraction; SSUAATPE: Synergized subcritical ultrasound-assisted aqueous two-phase extraction; PCUAE: Pulsed counter-current ultrasound-assisted extraction; TPP: Three-phase partitioning; SE: Solvent extraction.

polysaccharides. To sum up, although the traditional extraction methods have certain advantages, these methods have significant disadvantages, such as long time-consuming, low efficiency, and large solvent consumption and high temperature (Lazaridou, Chornick, Biliaderis, & Izydorczyk, 2008; Zhou, Liu, Xue, & Zhang, 2014). Hence, the application of these methods are limited.

To solve the limitations of traditional solvent extraction, some advanced and effective extraction methods were developed based on the principle of enhancing cell wall decomposition without destroying the structure of fungal polysaccharides. Especially, ultrasound assisted extraction (UAE), microwave assisted extraction (MAE), enzyme assisted extraction (EAE), and ultra-high pressure assisted extraction (UHPAE) methods have been widely used in the extraction of fungal polysaccharides (Imbs, Skriptsova, & Zvyagintseva, 2015; Shang et al., 2019; Wang et al., 2016). UAE utilizes the cavitation effect and strong shear forces produced by ultrasound to enhance the extraction ability and shorten the extraction time of natural polysaccharides (Zhu, Yu, Ge, Li, & Ouyang, 2020), and this method has some advantages, such as high fast and extraction efficiency, no damage to the target component, and environment friendly. MAE is to enhance the extraction of natural polysaccharides by destroying plant cell walls, reducing mass transfer resistance, and improving diffusion coefficient (Wang, Niu, Mai, Shi, & Liu, 2020). However, UAE and MAE methods can lead to the structural destruction of fungal polysaccharides, which are mainly attributed to local excessive vibration and local high temperature of the extract, respectively. EAE and UHPAE methods are widely employed to improve the extractability of natural polysaccharides via degrading of plant cell walls and large osmotic pressure difference (Bai et al., 2016; Gcab et al., 2019). However, the above two extraction technologies need to strictly control the extraction conditions. In addition, the extraction parameters (solid-to-liquid ratio, ultrasonic/microwave power, extraction temperature/time, and pressure) are optimized by using response surface analysis, orthogonal test, genetic algorithm, and genetic algorithm coupled neural network (Dulla, Krasileva, & Lindow, 2010; Sengar, Rawson, Muthiah, & Kalakandan, 2020; Shu, Zhang, Jia, Ren, & Wang, 2019). Besides, EAE method has attracted increasing attention because of its high efficiency and environmental protection. It is worth noting that controlling the levels of extraction temperature, pH, extraction time, enzyme dosage, and other factors is key to ensure EAE (Yin, You, & Jiang, 2011; You, Yin, & Zhao, 2013).

Based on a thorough review of previous literature, it was found that fungal polysaccharides could normally be extracted by HWE method under the following conditions: Extraction time of 2–4 h, extraction temperature of 60–100 °C, solid-to-liquid ratio of 1:50–1:100 g/mL (Cai, Lin, Luo, Liang, & Sun, 2015; Hajji, Falcimaigne-Gordin, Ksouda, Merlier, & Nasri, 2021; Wang et al., 2017; Wu et al., 2010a). Udchumpisai and Bangyeekhun (2019), Guo, Zhao, Zhen, Mahfuz, and Zhang (2019), Bao, Yao, Zhang, and Lin (2020), and Ma et al. (2016a) prepared an antitumor, antioxidant, immunoactive polysaccharides, and a non-toxic polysaccharides by using HWE method, respectively. Yu et al. (2017) separated a polysaccharides from *Flammulina velutipes* with antioxidant activity by UAE under optimized extraction conditions as follows: Ultrasound power of 380 W, extraction time of 25 min, and material granularity of 400-mesh, and the yield of polysaccharide was 20.52 %. Al-Dhabi and Ponmurugan (2020) found that the optimal extraction process to achieve the highest yield of polysaccharides (4.71 ± 0.02)% was obtained at the microwave power of 515 W, extraction time of 3.1 min, liquid-to-solid ratio of 15 mL/g, and pH of 3.2. Ryu, Kim, and Lee (2009), Tang, Huang, Lin, Yin, and Cui (2021), and Yin, You, and Zhou (2015) extracted an anti-proliferative, anti-aging, and antioxidant polysaccharides by EAE method, respectively. Gao, Lin, Zeng, and Brennan (2017) extracted a polysaccharides with antioxidant activity using UHPAE and obtained the optimized extraction process parameters as follows: Treatment time of 17 min, pressure of 460 MPa, and liquid-to-solid ratio of 15 mL/g as well as the yield of polysaccharides of 12.01 %. Moreover, some new technologies with development potential have

become promising substitutes for the traditional extraction methods of fungal polysaccharides, such as ultrasonic-microwave synergistic extraction (UMSE) (You, Yin, Zhang, & Jiang, 2014), three-phase partitioning (TPP) (Liu et al., 2019), aqueous two-phase system (ATPS) (Wu et al., 2021), synergized subcritical ultrasound-assisted aqueous two-phase extraction (SSUAATPE) (Chikari, Han, Wang, & Wenmei, 2020), and pulsed counter-current ultrasound-assisted extraction (PCUAE) (You, Yin, & Ji, 2014). Currently, the combination of various extraction technologies is used for the extraction of polysaccharides to achieve their efficient extraction and separation. Then, the crude polysaccharides extracts are dialyzed, precipitated, and freeze-dried to obtain crude fungal polysaccharides.

Due to the limitations of extraction methods, the crude polysaccharides contain various impurities, such as pigment, protein, monosaccharide, and other substances. Hence, the isolation and purification of crude fungal polysaccharides are extremely important to obtain homogenous polysaccharide fractions, identify structural features, and determine biological activities. As we all know, all kinds of purification methods are usually used to further purify crude polysaccharides (Table 1) (Praveen, Parvathy, Balasubramanian, & Jayabalan, 2019; Tang, Liu, Yin, & Nie, 2020). Traditionally, the crude fungal polysaccharides are deproteinized and decolorized using the Sevage method and hydrogen peroxide treatment method, respectively (Lu, Lee, & Yang, 2022; Yin et al., 2015). Subsequently, the crude fungal polysaccharides are further purified via different column chromatography (Ji et al., 2019; Sun et al., 2020). Generally, separation of neutral or acidic polysaccharides are usually carried out by ion exchange chromatography. The chromatographic medium mainly includes DEAE-cellulose 52 and DEAE-Sephadex A-25. For gel filtration chromatography, Sephadex G-100 or Sephadex G-200 are usually used as chromatographic medium to separate polysaccharides with different molecular weights (Li et al., 2018a; Zhang, Zhang, Tang, & Mao, 2020b). Then, the purified fractions from fungal polysaccharides are prepared by concentration, dialysis, and freeze-drying. Finally, the phenol–sulfuric method and Bradford's method are used to measure the contents of polysaccharides and protein in the purified fractions, respectively. The schematic diagram of extraction and purification process of fungal polysaccharides is presented in Fig. 1.

3. Structural characteristics of fungal polysaccharides

Natural fungal polysaccharides, as high molecular polymers isolated from fungi, have complex and diverse structures. To better understand fungal polysaccharides, it is necessary to describe their structural characteristics in detail, including molecular weight (Mw), monosaccharide composition (MC), monosaccharide sequence, configuration, type of glycosidic bonds, and spatial conformation. Currently, a series of advanced analytical technologies, namely, Fourier transform infrared spectroscopy (FT–IR), nuclear magnetic resonance (NMR), high performance liquid chromatography (HPLC), gas chromatography mass spectrography (GC–MS), and other methods, are used to determine the fundamental structural characteristics of fungal polysaccharides (Ferreira, Passos, Madureira, Vilanova, & Coimbra, 2015; Huang, Theng, Yang, & Yang, 2021b; Jin, Zhao, Huang, Xu, & Shang, 2012; Mohan et al., 2020; Ren et al., 2021). Table 2 summarizes the existing information on the basic structural characteristics of fungal polysaccharides.

3.1. Monosaccharide composition (MC)

As we all know, polysaccharides are composed of various monosaccharides connected by glycosidic bonds. The MC of fungal polysaccharides is measured by acid hydrolysis and derivatization, and then through gas chromatography (GC) and HPLC analysis (Liu, Tang, Yin, Nie, & Xie, 2021; Xie, Zou, Xie, Wu, & Wang, 2021). It is observed that fungal polysaccharides are mainly consisted of galactose (Gal), glucose (Glc), and mannose (Man) with in different molar ratios (Liu et al., 2019;

Table 2
Structural characterization methods and structural characteristics of fungal polysaccharides.

Source	Compund name	M_w/ kDa	Monosaccharide composition	Analysis Technique	Chemical structure	References
Lentinus edodes	LEP-1, LEP-2	–	–	GC, FT–IR	–	Cogdill et al., 2018
Agaricus bisporus	EnAPS-1, EnAPS-2, EnAPS-3	–	–	–	–	Li et al., 2018b
Agaricus bisporus	ABP-1	–	Glc, Gal, Man, Xyl	–	–	Yin et al., 2015
Lentinus velutinus	LVP	336	Glc	FT–IR	–	Udchumpisai & Bangyeekhun, 2019
Pleurotus ostreatus	POPPS-a	33	Ara:Man:Gal:Glc:GalA = 1:0.9:1.7:5:0.6	HPGPC, GC	–	Xia et al., 2011
Pleurotus djamor	–	161	Glc:Gal = 3:1	NMR	–	Maity et al., 2021
Ganoderma capense	GCP50-1	50	–	GC–MS, FT–IR, NMR	GCP50-1 was an α-D-glucan with the main backbone chain of (1 → 4)-α-D-glucopyranosyl residue interspersed with (1 → 4, 6)-α-D-glucopyranosyl residue	Lu et al., 2012
Cordyceps minlitaris	CMP-1, CMP-2	–	–	–	–	Hou et al., 2008
Flammulina velutipes	FVSP-1, FVSP-2, FVSP-3	–	–	–	–	Gao et al., 2017
Auricularia auricula	AAP	23.51	Man:Rha:GlcA:Glc:Gal: Ara:Fuc = 5.02:0.9:0.12:4.48:0.37:1.0:0.36	–	AAP mainly consisted of 1,4-linked-Glcp, 1,4,6-linked-Glcp, terminal Glcp, 1,4-linked-Manp, 1,2,6-linked-Manp, and terminal Arap	Bao et al., 2020
Pleurotus eryngii	CPPS-1, CPPS-2	–	–	–	–	Ma et al., 2016
Gray oyster mushroom	SG1-1	–	–	FT–IR	containing β-(1 → 3) glucan and mannan	Decha et al., 2018
Flammulina velutipes	FVRP-1 FVRP-2 FVRP-3	29.93 62.29 36.31	Gal Glc Glc	–	α-type glycosidic linkage β-type glycosidic linkages β-type glycosidic linkages	Liu et al., 2016a
Flammulina velutipes	–	–	–	–	–	Yu et al., 2017
Tricholoma mongolicum Imai.	TMIP-1, TMIP-2, TMIP-3, TMIP-4	–	–	FT–IR	–	You et al., 2014a
Inonotus obliquus	IOPS	40	Gal:Glc:Xyl:Man = 2.0:3.5:1.0:1.5	–	–	Liu et al., 2019
Phellinus linteus	PLPS	15.2	–	–	–	Wu et al., 2021
Mushroom	LEP	–	Man, Glc, Ara, Xyl, Gal	FT–IR	–	Chikari et al., 2020
Cordyceps gunnii mycelia	CPS	–	–	–	–	Wang & Li, 2019
Boletus edulis	BEP-1 BEP-II BEP-III	10.278 23.761 42.736	Xyl, Man, Gal, Glc	–	–	You et al., 2014
Mushroom	PL1, PL2	–	Glc:Rha:Man = 1:3.13:1.16	FT–IR	–	Mai et al., 2017
Agaricus bisporus	ABP-Ia	784	Rib:Rha: Ara:Xyl: Man:Glc: Gal = 2.08:4.61:2.45:22.25:36.45:89.22:1.55	UV, GC–MS, FT–IR, AFM	ABP Ia was an α-pyran polysaccharide composed of 1 → 2 and 1 → 4 glycosidic bonds, a possible 1 → 3 glycosidic bond	Liu et al., 2020
Spent *Lentinus edodes* substrate	SLSP-F	16.77	–	FT–IR, NMR	PSP has both α and β glycosidic bonds and massive acetyl groups, which is different from LP-F mainly composed of 1, 3 linked α-D-Manp residue with some acetyl groups	Zhu et al., 2018
Cordyceps militaris	–	–	–	–	–	Zhu et al., 2012
Mushroom *Lepista nuda*	LNP-1 LNP-2	11.703 13.369	Man, Glc, Gal, Xyl, Ara, Fuc Man, Glc, Gal, Ara, Fuc	–	–	Shu et al., 2019

Xia, Fan, Zhu, & Tong, 2011; Yin et al., 2015). In addition, other monosaccharides, such as arabinose (Ara), xylose (xyl), fucose (Fuc), Ribose (Rib), and rhamnose (Rha) are also detected in fungal polysaccharides (Maity et al., 2021; Shu et al., 2019; You et al., 2014). Table 2 lists the detailed data of MC of fungal polysaccharides. Moreover, the MC of the prepared fungal polysaccharides was significantly different, which was mainly due to the different raw materials, and extraction and purification methods.

3.2. Molecular weight (Mw)

Mw is considered to be a critical parameter for the chemical properties of polysaccharides (Udchumpisai & Bangyeekhun, 2019; Xia et al., 2011). Besides, biological activities are closely related to the molecular weight of polysaccharides. Nowadays, the analyses of osmotic pressure and sedimentation, HPLC, and high pressure gel permeation chromatography (HPGPC) were usually used for the molecular weights of polysaccharides (Li, Yan, Hua, & Zhang, 2013; Maity et al., 2021). In

particular, HPLC is the most commonly used technique for determining the Mw of polysaccharides. In addition, HPLC combined with DLLs is recognized as the most effective method to determine the Mw of polysaccharides exacts (Liu et al., 2016, 2019). It was observed that the Mw distribution of fungal polysaccharides ranged from 10.278 kDa to 784 kDa based on previous reports (Table 2) (Liu et al., 2016a; Shu et al., 2019; You et al., 2014; Zhu et al., 2018). The great difference in the Mw of fungal polysaccharides may be mainly attribute to different materials and experimental methods.

3.3. Chemical structure

Nowadays, numerous techniques (FT–IR, GC–MS, and NMR) are used to determine the structural characteristics of fungal polysaccharides (Zhu et al., 2018). Notably, the MC, glycosidic bond position and configuration, ring structure type, polysaccharide branch chain position, and proportion can be obtained by NMR (Jin et al., 2012). According to the latest report, increasing researchers have prepared a large number of natural fungal polysaccharides and their derivatives. Nevertheless, the published reports on the structure of fungal polysaccharides are still limited due to the limitations of identification methods and techniques. Nevertheless, the current data on the proposed structure of fungal polysaccharides are reviewed as follows (Table 2). A large number of literature have proved that the most of isolated fungal polysaccharides are heteropolysaccharides. Li et al. (2013) extracted polysaccharides from *Ganoderma capense* by HWE, and then isolated and purified the crude polysaccharides through different column chromatography techniques to obtain a novel water-soluble polysaccharides (GCP50-1) with Mw of 1.5×10^4 Da. Subsequently, its structure was further characterized via GC–MS, FT–IR, and NMR. It was observed that GCP50-1 was an α-D-glucan with the main backbone chain of (1 → 4)-α-D-glucopyranosyl residue. Bao et al. (2020) extracted *Auricularia auricula* polysaccharides (AAPs) by HWE and purified them to obtain three fractions (AAP-I, AAP-II, and AAP-III). AAP-I and AAP-II belonged to the glycoproteins, and only AAP-III belonged to a homogeneous pure polysaccharides. Besides, the structural characteristics of AAP-III was evaluated by FT–IR and methylation analysis. These results indicated that AAP-II with the Mw of 23.51 kDa was consisted of mannose (5.02 %), rhamnose (0.9 %), gluconic acid (0.12 %), glucose (4.48 %), galactose (0.37 %), arabinose (1.0 %), and fucose (0.36 %). In addition, AAP-III was mainly composed of 1,4-linked-Glcp. Moreover, Zeng, Zeng, Gao, Jia, and Chen (2012) prepared *Auricularia auricula* polysaccharides with antioxidant activity (AAP) and characterized its structure through acid hydrolysis and GC–MS. It was observed that AAP contained glucose (37.53 %), galactose (1 %), mannose (4.32 %), arabinose (0.93 %), and rhamnose (0.91 %). Furthermore, AAP was mainly consisted of (1 → 3)-linked glucose. Decha et al. (2018) extracted and purified by different extraction methods and purification techniques to obtain the homogeneous polysaccharides fraction (SG1-1). The results suggested that SG1-1 contained β-(1 → 3) glucan and mannan. Liu et al. (2016a) prepared *Flammulina velutipes* residue polysaccharides (FVRP) by MAE and then purified them via different column chromatography techniques to obtain three homogeneous polysaccharides fractions. Moreover, three polysaccharides fractions were characterized through different methods. Results implied that three polysaccharides fractions mainly contained glucose and three fractions were an α-type, β-type, and β-type glycosidic linkages, respectively, suggesting that FVRP are more suitable to be used as functional factors in food, drugs, and cosmetic fields. Liu et al. (2020) extracted *Agaricus bisporus* polysaccharides (ABP) using HWE and purified them by DEAE-52 and Sephadex G-200 column chromatography to obtain the homogeneous fraction (ABP Ia) with the Mw of 784 k$_D$. Subsequently, the structural characteristics of ABP Ia were determined by GC–MS and FT–IR. Results showed that ABP Ia contained ribose (2.08 %), rhamnose (4.61 %), arabinose (2.45 %), xylose (22.25 %), mannose (36.45 %), glucose (89.22 %), and galactose (1.55 %). In addition, ABP Ia was an α-pyran polysaccharide composed of 1 → 2 and 1 → 4 glycosidic bonds, as well as a possible 1 → 3 glycosidic bond. Notably, there are significant differences in the chemical structure of fungal polysaccharides products owing to the different raw materials and preparation methods. In addition, the previously reported literature on the chemical structure of fungal polysaccharides has been summarized in Table 2.

4. Biological activities of fungal polysaccharides

As a popular active component of medicinal and edible fungi, fungal polysaccharides have significant pharmacological activity and health care effect (Li et al., 2021; Maity et al., 2021). Recently, with the in-depth study of fungal polysaccharides, researchers have obtained a comprehensive understanding of their biological activities (Ferreira et al., 2015; Mohan et al., 2020; Ran, Yang, Chen, & Yang, 2022). The biological activities of fungal polysaccharides mainly include immuno-modulatory, antioxidant, anti-tumor, hepatoprotective, and other activities (Fig. 2). The biological activities of fungal polysaccharides are closely related to their structural characteristics (Chen, Zhang, Zong, Li, & Jin, 2020a; Mohan et al., 2020). Hence, clarifying the relationship between the structure and efficacy of fungal polysaccharides is significant to improving the performance of fungal polysaccharides and developing future drugs. However, the current reports on the relationship between fungal polysaccharides structure and biological activities are limited, and no consensus has been established due to the complex structure of fungal polysaccharides. Therefore, we can only review it on the basis of existing research reports.

4.1. Immunoregulatory activity

Currently, fungal polysaccharides are regarded as powerful pharmacological tools, and they exhibit remarkable immunomodulatory activity by acting on immune organs or immune cells (Zhang et al., 2017; Zhao et al., 2019). A study exhibited that four extracellular polysaccharides (WPA, WPB, AP2A, and TP1A) are non-toxic to RAW264.7 cells and improved cell viability (Bao et al., 2020). In addition, four extracellular polysaccharides enhanced the immunomodulatory effect via enhancing the phagocytic activity and promoting the release of TNF-α and IL-6 from RAW264.7 cells. Liu et al. (2016b) assessed the immunomodulatory activity of *Cordyceps militaris* polysaccharides (CMPs) and observed that CMPs substantially enhanced the immune function in mice, and increased dramatically the indexes of spleen and thymus, the activity of spleen lymphocytes, the total number of leukocytes, and IgG function in mice serum. Moreover, CMPs could improve the immune function by protecting the body from oxidative stress. Chen, Liu, Deng, Shang, and Fu (2016) explored the molecular mechanism of the immunostimulatory activity of polysaccharides from *Dictyophora indusiata* in RAW264.7 cells. The results implied that polysaccharides could induce the up-regulation mRNA expression levels of IL-1β, IL-6, iNOS, and TNF-α in macrophages. Hence, polysaccharides may mediate macrophage activation through the TLR4/NF-κB signaling pathway. Zhuling polysaccharides (ZPs) act as an effective activator of B cells and dendritic cells, and it can significantly improve the lethality of natural killer cells and lymphokine activated killer cells obtained from mouse spleen (Dai et al., 2012). Chen (2010) extracted and purified *Polyporus* polysaccharides (PPs) and evaluated their immune activity. These results showed that PPs (100 μg/mL) could improve the cell-surface expression of CD86 and the production of IL-12 and IL-10. In addition, PPs treatment of murine bone-derived dendritic cells could increase the stimulation ability of T cells and reduce the phagocytotic ability. Zhang et al. (2018) obtained the two exopolysaccharides (CEPSN-1/2) and analyzed their immunomodulatory activity. Results showed that CEPSN-1/2 had a backbone chain consisted of (1 → 4)-α-D-glucan in glucopyranose type, and CEPSN-1/2 were non-toxic to RAW 264.7 cells when the concentration of CEPSN-1/2 was lower than 200 μg/mL. Furthermore, CEPSN-1/2 could enhance the release of IL-6, IL-
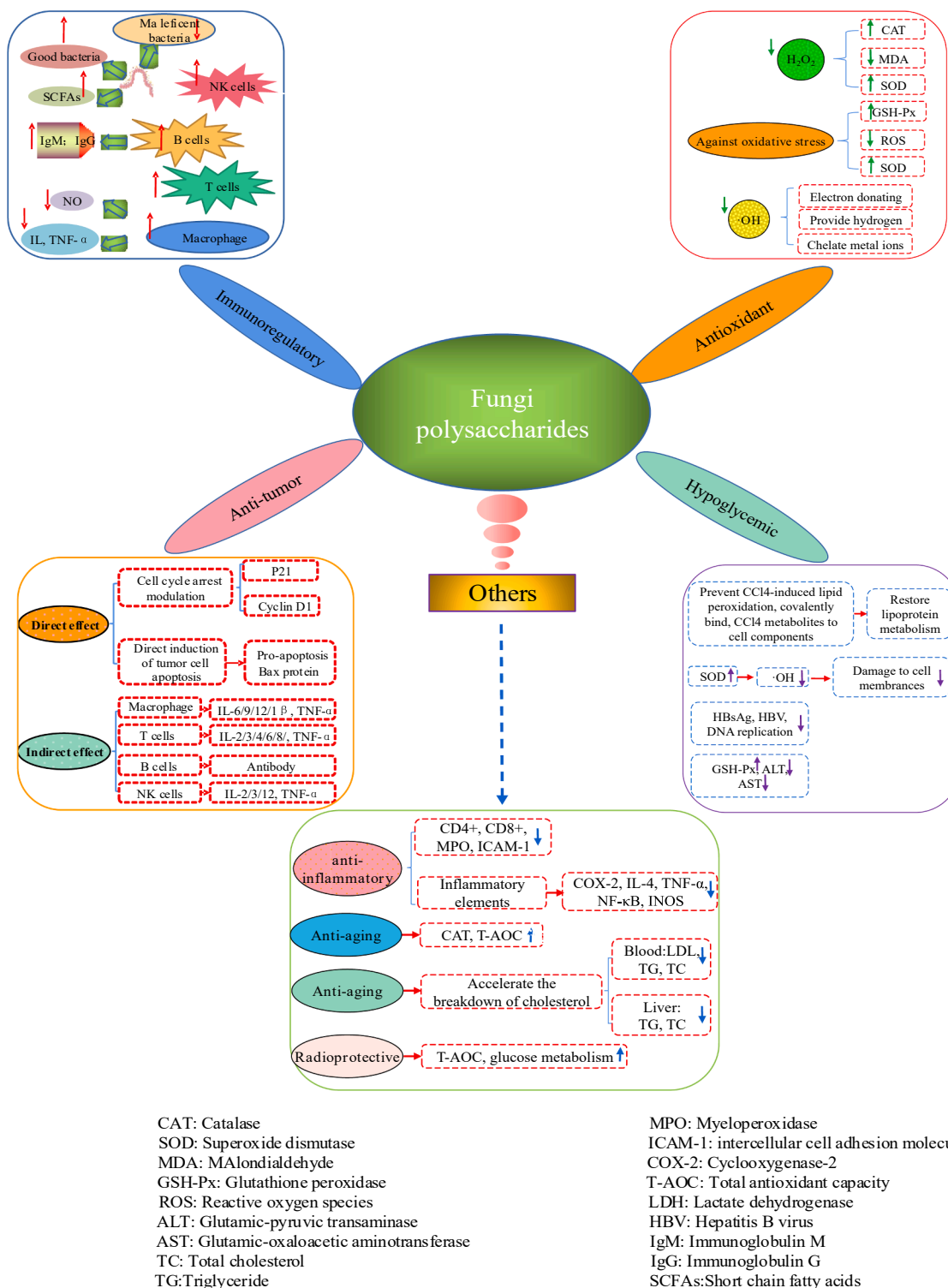
Fig. 2. The biological activities and molecular mechanisms of fungi polysaccharides.

CAT: Catalase
SOD: Superoxide dismutase
MDA: MAlondialdehyde
GSH-Px: Glutathione peroxidase
ROS: Reactive oxygen species
ALT: Glutamic-pyruvic transaminase
AST: Glutamic-oxaloacetic aminotransferase
TC: Total cholesterol
TG:Triglyceride

MPO: Myeloperoxidase
ICAM-1: intercellular cell adhesion molecule-1
COX-2: Cyclooxygenase-2
T-AOC: Total antioxidant capacity
LDH: Lactate dehydrogenase
HBV: Hepatitis B virus
IgM: Immunoglobulin M
IgG: Immunoglobulin G
SCFAs:Short chain fatty acids

10, and TNF-α. With the deepening of the study on the bioactivities of polysaccharides, except for the above direct immunomodulatory activity, fungal polysaccharides have also been found to regulate the intestinal microbiota in an indirect way to exert their immunomodulatory potentials (Cockburn & Koropatkin, 2016; Li, Zhao, & Wang, 2009). After feeding mice with polysaccharides from *Auricularia auricula*, the relative abundance of beneficial bacteria increased, whereas that of harmful bacteria decreased. In addition, polysaccharides from *Auricularia auricula* could be degraded into short-chain fatty acids to play its

immunomodulatory role through activation the MAPK signal pathway, which promoted the production of proinflammatory cytokines and maturation of T/B lymphocytes (Chen et al., 2020a).

4.2. Antioxidant activity

Oxidative stress can lead to a variety of human diseases. Therefore, it is urgent to develop efficient natural non-toxic antioxidants. Fungal polysaccharides, as a natural and low-toxicity antioxidant, play a critical

role in various diseases. Many studies have confirmed that fungal polysaccharides have remarkable antioxidant activity (Guo et al., 2019; Li et al., 2018b; Ryu et al., 2009). The antioxidant capabilities of fungal polysaccharides are usually assessed by various free radical assays, such as DPPH, OH, O^{2-}, and ABTS free-radical scavenging *in vitro*. Zhu et al. (2020) studied the *in vitro* antioxidant capability of the *Cordyceps cicadae* polysaccharides (CP) and found that CP could increase the activities of CAT and GSH-Px, and inhibit the production of MDA. Su and Li (2020) isolated and purified four polysaccharides (ACP, AAP, APP, and MFP) from *Auricularia* and investigated their antioxidant activity. The capability of APP to scavenge DPPH and OH radicals was prominently higher than that of the three polysaccharides. In addition, a remarkable positive correlation was observed between the Mw and antioxidant capacity of polysaccharides. Significantly, similar results were observed on the antioxidant activity of fungal polysaccharides (Hu, Sung, Chou, Liu, & Hsieh, 2019; Liu et al., 2016a; Zhang, Li, Xu, & Zeng, 2005). Bi, Miao, Han, Xu, and Wang (2013) studied the antioxidant activity of two polysaccharides, namely, GUMP-1-1 and GUMP-1-2 obtained from *Grifola umbellata* mycelia and found that the scavenging rates of GUMP-1-1 and GUMP-1-2 to the OH radicals were 19 % and 82 %, respectively, as well as 9 % and 82 % on the O^{2-}, respectively. Liu et al. (2016) extracted polysaccharides from *Flammulina velutipes* residue (FVRP) by MAE and further purified them via column chromatography to obtain three polysaccharide fractions (FVRP-1 with a Mw of 29.93 Da, FVRP-2 with a Mw of 62.29 Da, and FVRP-3 with a Mw of 36.31 Da) and analyzed theirs antioxidant activity *in vitro*. The results revealed that the three polysaccharides fractions presented strong antioxidant activity in the order of FVRP-2 > FVRP-3 > FVRP-1, suggesting that FVRP are suitable for functional food. These results were consistent with that reported by Yu et al. (2017). You et al. (2014) separated and purified four kinds of polysaccharides fractions (TMIP-1 ~ 4) from *Tricholoma mongolicum Imai* using UMSE, DEAE-Cellulose 52 chromatography, and Sephadex G-100 chromatography in turn. It was found that four fractions were composed of xylose, rhamnose, glucose, arabinose, and mannose, displayed strong antioxidant activity *in vitro* in the order of TMIP-4 > TMIP-3 > TMIP-1 > TMIP-2 through scavenging DPPH and OH radicals. Furthermore, the effect of fungal polysaccharides on antioxidant activity of different cells was also explored. Ma, Zhao, Yu, Ji, and Liu (2018) extracted Se-enriched *Pleurotus ostreatus* polysaccharides (Se-POP) with a Mw of 0.95×10^4 Da using HWE and analyzed their antioxidant capacity. These results showed that Se-POP consisted of arabinose (Ara), glucose (Glu), rhamnose (Rha), xylose (Xyl), galactose (Gal), and fucose (Fuc), could strongly scavenge DPPH, OH and ABTS radicals. In addition, Se-POP could dramatically inhibit H_2O_2-induced oxidative stress and the apoptosis of C_2C_{12} cells, as well as decrease intracellular ROS and free radical production. Moreover, the antioxidant activity assay *in vitro* showed that polysaccharides from yellow-strain *Flammulina velutipes* (FVYs) had a significant scavenging effect on DPPH and ABTS radicals. The half-maximal inhibitory concentration (IC_{50}) values of FVYs were 2.22 and 2.04 mg/mL for DPPH and ABTS radicals, respectively. Furthermore, FVYs substantially decreased the reactive oxygen species (ROS) content in L929 cells by 55.96 % and markedly inhibited the oxidative damage of L929 cells induced by H_2O_2 (Hu et al., 2019). In summary, the findings imply that fungal polysaccharides can be used as potential antioxidant agents. However, the potential molecular mechanism of antioxidant effect of fungal polysaccharides is unclear, and further researche is still needed.

4.3. Antitumor activity

The World Health Organization reported that cancer caused 8.2 million deaths every year, accounting for 13 % of the total deaths in the world (Liu, Zeng, Li, & Shi, 2016c). Although great progress has been made in the diagnosis and treatment of human malignant tumors, the long-term prognosis is still deal. Therefore, potential anti-tumor drugs with no side effects and have high efficiency must be developed. To date,

fungal polysaccharides have been confirmed to show great anti-cancer potentials, and they are considered as promising candidate drugs for cancer treatment (Cogdill, Gaudreau, Arora, Gopalakrishnan, & Wargo, 2018; Fogli et al., 2020). According to research, fungal polysaccharides and their related derivatives can be used for cancer treatment alone or in combination with other bioactive components.

Zhao et al. (2016) extracted *Lentinus edodes* polysaccharides (LEPs) using EAE, and then purified the crude LEPs to obtain two homogeneous polysaccharides fractions (LEPs-1 and LEPs-2). These results observed that LEPs-1 and LEPs-2 could markedly inhibit the proliferation of HCT-116 and HeLa cells, indicting that LEPs can be used as a potential natural anti-tumor candidate. Udchumpisai and Bangyeekhun (2019) prepared polysaccharides from the fruiting body of *Lentinus velutinus* (LVP) using ethanol precipitation method and column chromatography. The LVP with a Mw of 336 kDa consisted of only Glc units only. Moreover, LVP showed antioxidant activity and specific cytotoxicity to HeLa and HepG2 cells and changed the cancer cells morphology. Ma et al. (2016) isolated two homogeneous polysaccharides fractions (CPPS-1 and CPPS-2) via ultrafiltration method and determined their cytotoxicity and antioxidant activity. These results found that the antioxidant activity of CPPS-1 was significantly better than that of CPPS-2. Moreover, CPPS-1 could down-regulate the expression of Bcl-2 and up-regulate the expression of p53 and Bax, suggesting that the anti-tumor activity of CPPS-1 is closely related to its induction of apoptosis by activating the mitochondrial apoptosis pathway. Zhu et al. (2016) investigated the effect of different extraction methods (RWE, HWE, MAE, and CAE) on the anti-tumor activity of *Cordyceps gunnii* mycelia polysaccharides (CGMPs) found that CGMPs with molecular weights of 300–1000 kDa obtained by MAE showed the strongest anti-tumor activity, indicating that MAE is a green and efficient extraction method for improving the anti-tumor activity of CGMPs.

Furthermore, increasing studies have focused on the anti-tumor activity of fungal polysaccharides *in vivo*. Qiu et al. (2018) investigated the anti-tumor effect of FA-AAP-CDDP on cervical carcinoma cells in nude mice. The results discovered that FA-AAP-CDDP could decrease MDA production and induce more IL-2, IL-4, and interferon-γ in mice. Besides, FA-AAP-CDDP could memorably increase the protein expression of Bax and caspase-3, whereas the protein expression of Bcl-2 decreased. Similar results were reported by Wang et al. (2017). Zhang et al. (2012) evaluated the inhibitory effect of polyporus polysaccharides (PPs) on bladder cancer and determined their effect on the mRNA expression of GSTPi, NAD(P)H, and NQO1 in female Fischer-344 rats model. Theses results showed that PPs (28 mg/kg) could increase the mRNA expression of GSTPi and NQO1, implying that PPs are effective in inhibiting the occurrence of bladder cancer in female Fischer-344 rats. Especially, further studies are needed to clarify the specific mechanism of anti-tumor activity of fungal polysaccharides.

4.4. Hypoglycemic activity

With the development of social economy and the improvement of material level, diet structure and habits have undergone considerable changes, which led to an increasing trend of incidence rate of diabetes. Diabetes, as a chronic disease caused by metabolic disorders, has become widely known worldwide (Kenny & Abel, 2019). In addition, diabetes has the second highest incidence rate of cancer and cardiovascular diseases, and it has become a public health problem threatening global health (Shivaswamy, Boerner, & Larsen, 2016). At present, the main means of diabetes treatment is through oral hypoglycemic drugs and insulin injection. Nevertheless, traditional therapies are usually accompanied by a series of side effects. Therefore, Many researchers have begun to focus the developing potential, effective, low toxic, and cheap alternative drugs for diabetes. The hypoglycemic effect of fungal polysaccharides has been confirmed.

Chen et al. (2018) prepared the potential *Grifola frondosa* hetero-polysaccharide (GFP-W) with Mw of 66.1 kDa and evaluated its

antidiabetic potential. It was found that GFP-W could dramatically increase the glucose uptake of dexamethasone-induced insulin resistant HepG2 cells via enhancing the mRNA and protein of IRS1, PI3K and GLUT4, and reducing the mRNA and protein of c-JNK1. Furthermore, the antidiabetic activity of GFP-W was closely related to the remarkable changes of protein lysine acetylation, crotylation, and succinylation levels. Fu et al. (2012) extracted and purified *Acanthopanax senticosus* polysaccharides (ASPs) and determined their hypoglycemic activity, and found that ASPs could decrease the content of TC and TG. Moreover, ASPs (200 mg/kg) substantially increased the body weight and decreased the FBG levels. This study also indicated that fungal polysaccharide could replace clinical drug treatment to a certain extent, which provided an important reference for the development of new drugs. Zhu, Nie, Li, Gong, and Xie (2014) obtained new homogeneous *Ganoderma atrum* polysaccharides (GAPs-1), and diabetic mice were fed with GAPs-1 for 4 weeks. These results displayed that GAPs-1 could memorably reduce fasting blood glucose level, increase endothelium-dependent aortic relaxation, and improve the levels of PI3K, AKT, eNOS, and NO in diabetic rats compared with the control group, implying that the protective effect of GAPs-1 on endothelial dysfunction was achieved by activating the PI3K/Akt/eNOS pathway. In summary, the above results suggest that fungal polysaccharides may be good sources of dietary fiber for the treatment of diabetes.

Hu et al. (2017) established STZ-induced diabetic models in SD rats and investigated the hypoglycemic activity of *Auricularia auricular* polysaccharides (AAPs). The results discovered that AAPs (100 and 400 mg/kg) could significantly decrease blood glucose levels via improving the glucose metabolism. Moreover, the antioxidant activity of AAP was observed in diabetic rats by regulating the levels of SOD, GSH-Px, ROS, and methane two carboxylic acid. These results suggested that AAP regulated the antioxidant system and NF-κB signal pathway to maximize to the hypoglycemic effect. Lu et al. (2018) prepared the APSHs and explored their anti-diabetic effect. APSHs (150 mg/kg) markedly decreased the levels of fasting blood glucose, and increased the levels of serum TG and LDL-C, suggesting that they have a significant antidiabetic effect on experimental diabetes and potential for the treatment of diabetes. All in all, natural polysaccharides may play a hypoglycemic role through three ways, namely, glucose metabolism enzyme, controlling gluconeogenesis, and enhancing hepatic glycogen synthesis.

4.5. Other activities

Except for the above biological activities, fungal polysaccharides also showed other biological activities, including anti-inflammatory, anti-aging, hypolipidemic, and radioprotective activities. Through the in-depth study of fungal polysaccharides, we observed that fungal polysaccharides have anti-inflammatory activity. Wu, Duan, Liu, and Cen (2010b) isolated polysaccharides from Golden needle (GNP) mushroom by HPLC and then evaluated their anti-inflammatory effect. It was showed that GNP was consisted of Glu, Man, and Xyl with a molar ratio of 3.5:0.8:1.4. Furthermore, GNP dramatically reduced CD^{4+}, CD^{8+}, ICAM-1, and MPO in serum. These results indicated that GNP had strong anti-inflammatory effect on burn rats. Li et al. (2015) found that AAP administration ameliorated the LPS-induced acute lung injury in SD rats by inhibiting the levels of TNF-α, IL–6, MDA, and MPO activity and reducing the levels of MDA and lung W/D weight ratio, suggesting that fungal polysaccharides have a good protective effect on LPS-induced ALI rats. In conclusion, the above results are consistent with the previously reported literature.

Hyperlipidemia has attracted extensive attention all over the world. In addition, hyperlipidemia is closely related to the pathogenesis of various human diseases (Stewart, McCallin, Martinez, Chacko, & Yusuf, 2020). Previous reports have confirmed that natural polysaccharides in fungi could reduce blood cholesterol. Jeong et al. (2007) extracted polysaccharides by HWE and ethanol precipitation and then further purified them to obtain three kinds of polysaccharides fractions (CP, MP,

and FP). The hypolipidemic effect of three polysaccharides fractions on hyperlipidemic SD rats was explored by oral administration of 100 mg/kg polysaccharides. These results displayed that CP, MP, and FP showed cholesterol-lowering effects. The effect of FP on hyperlipidemia was significantly better than that of CP and MP. Furthermore, FP could reduce the atherogenic index, low-density lipoprotein cholesterol (L-DLC), total cholesterol (TC), and plasma triglyceride (PT). The findings were consistent with those of Chen et al. (2008). Zeng et al. (2013) prepared crude AAPs by HWE and then purified them via different chromatographic methods to obtain a homogeneous polysaccharides fraction (AAP-I). AAP-I could prominently reduce the levels of L-DLC, PT, and TC in fed Kunming mice, implying that AAP-I has a strong hypolipidemic activity and is a natural candidate drug for the development of hypolipidemic agents. At present, the reports on the lipid-lowering mechanism of fungal polysaccharides are limited, thus requiring further comprehensive research.

Numerous diseases (cardiovascular diseases, diabetes, immune system disorder, hypertension, and cancer) are closely related to senescence (Chen et al., 2020b). At present, the research on anti-aging has become the focus of global attention. Aging and its related diseases are caused by oxidative damage to cell components and tissues caused by excessive ROS in the body (Ma, Guo, Peterson, Dun, & Li, 2016b; Shields, Traa, & Raamsdonk, 2021). Hence, a large number of synthetic antioxidants are widely used to reduce the oxidative damage of free radicals. However, the increasing number of studies have confirmed that synthetic antioxidants posed a serious threat to health, such as liver injury and cancer (Poljsak, Šuput, & Milisav, 2013). Therefore, their application is limited. In view of the disadvantages of synthetic antioxidants, safe natural antioxidants must be sought to replace synthetic antioxidants. Fungal polysaccharides, as a natural antioxidants, have been extensively used in the fields of health products, drugs, and cosmetics. Li et al. (2018) extracted polysaccharides from the fruiting body of *Agaricus bisporus* by HWE and then purified them by DEAE-52 cellulose column to obtain the three main fractions, namely, AcAPS-1, AcAPS-2 and AcAPS-3, and evaluated their antioxidant and anti-aging activities. The capability of AcAPS-2 to scavenge OH (82.98 ± 4.67)% and DPPH (64.47 ± 4.05)% free radicals was significantly better than that of AcAPS-1 and AcAPS-3. Moreover, the anti-aging activity of AcAPS-2 was analyzed, and the findings revealed that it could protect the liver and kidney through enhancing serum enzyme activity, the levels of biochemical and lipid, and antioxidant status, indicating that AcAPS-2 is more suitable as a natural drug to prevent acute aging-related diseases. Besides, Yuan et al. (2019) also evaluated the antioxidant and anti-aging activities of *Flammulina velutipes* polysaccharides (FPSs) and sulfated FPSs (SFPSs) on D-galactose-induced aging mice. The results displayed that the antioxidant capacity of SFPSs was significantly better than that of FPSs. Furthermore, SFPSs had a protective effect on D-galactose-induced aging by improving antioxidant enzyme activity, reducing lipid peroxidation, and promoting inflammatory response and aging state. The above results are consistent with the previously reported findings. At present, numerous studies have focused on the anti-aging activity of fungal polysaccharides, but their mechanism remains unclear. Thus, further research is still needed to develop efficient natural anti-aging drugs.

Radiotherapy is the most commonly used clinical treatment for malignant tumors. However, unnecessary ionizing radiation may cause harmful effects on human health. Nowadays, mounting pieces of evidence have confirmed that natural polysaccharides and their derivatives confer radiation protection (Chandel, Sharma, & Rana, 2019; Yu, Fu, Guo, Lian, & Yu, 2020). Moreover, current studies have illustrated that fungal polysaccharides showed potential radioprotective activity. Bai et al. (2014) extracted and purified the acidic polysaccharides (AAP-IV) by UAE and different column chromatography techniques, and then explored their MC and radioprotective activity. It was observed that AAP-IV was consisted of Xyl (1.91 %), Man (4.67 %), Glu (9.9 %), and Gal (0.31 %). In addition, AAP-IV could markedly decrease cells

apoptosis and ROS levels induced by radiation treatment, and improve cell viability and the activity of GSH-Px. Notably, the combination of AAP-IV and GSP showed better radioprotective activity, suggesting that AAP-IV could protect against radiation injury by increasing antioxidant activity and improving immune functions. It is well known that ionizing radiation is closely related to DNA damage and cell death. Chen et al. (2019) prepared SNAAP composed of Glu (1 %) and Man (7 %), and evaluated its effects on glucose metabolic and pancreas of ^{60}Co-γ-radiated Kunming mice. These results showed that SNAAP administration could decrease radiation-induced glucose metabolism disturbance. Furthermore, relevant studies have suggested that polysaccharides from *Ganoderma lucidum* and *Hohenbuehelia serotina* showed radiation protection effects (Wang & Li, 2019; Yu et al., 2020). Overall, the findings suggested that fungal polysaccharides could be used as natural anti-radiation drug candidates. Notably, more clinical trials are demanded to verify the reliability of fungal polysaccharides as radiation protective agents.

5. Structure–activity relationships of fungal polysaccharides

The structure of polysaccharides affects their biological activities to a certain extent. polysaccharides with different biological vary greatly in structural characteristics (Huang, Mao, Li, & Yang, 2021a; Mai, Hui, Liang, Huang, & Jin, 2017; Wang, Wang, & Liu, 2019). Notably, Mw, MC, and type of glycosidic bond are key factors influencing the biological properties of polysaccharides.

Mw is an important factor affecting the biological activities of polysaccharides. Increasing numbers of research indicated that the best biological activities of polysaccharides depend on their Mw (He et al., 2018; Liang, Ni, & Han, 2018; Zhu, Sheng, Yan, Qiao, & Lv, 2012). When the molecular weight of polysaccharides is in an appropriate range, they can exert the best biological activity. With a large molecular weight, polysaccharides also exhibit a large molecular volume and increased transmembrane resistance, which are not conducive to absorption and utilization, affecting the exertion of biological activities (Yuan, He, Cui, & Takeuchi, 1998; Zhang, Sheng, Wang, Zhang, & Cheung, 2011). However, if the relative molecular weight is extremely low, polysaccharides cannot form an active structure, thus reducing their biological activities. The analysis of a large number of previously reported literature, revealed that lentinan manifested good biological activities in the molecular weights range of 4–60 KDa. These activities include antioxidant, anti-tumor activity (fibrosarcoma), anti-virus activities (Newcastle disease virus) and stimulation of cytokine expression, which may be related to the various affinities with carbohydrate receptors in immune cells (Zhang et al., 2017; Zhao, Yang, Liu, Zhao, & Wang, 2018). Moreover, Lin et al. (2004) observed that polysaccharides from *Poria cocos mycelium* showed strong anti-tumor activity only when their molecular weights was in the range of 2–40 KDa. Wang et al. (2018) simulated the gastrointestinal digestion of polysaccharides from *Inonotus obliquus in vitro* and observed that the molecular weight of digested polysaccharides decreased, but their inhibitory activity against α-glucosidase increased significantly. Their IC$_{50}$ (52.97 μg/mL) was notably lower than that of acarbose (101.12 μg/mL), implying that the digested polysaccharides showed better hypoglycemic activity.

The monosaccharide composition of polysaccharides must be analyzed and the relationship between monosaccharide composition and polysaccharides biological activities be studied (Zhao, Kiyohara, Yamada, Takemoto, & Kawamura, 1991). The different compositions of monosaccharides in polysaccharides may lead to various biological activities. This condition is attributed to the effect of monosaccharide composition on the chain structure and higher structure of polysaccharides. The higher structure is a critical factor influencing the biological activities of polysaccharides. Numerous studies suggested that "active centers" may be formed by oligosaccharide fragments, such as uronic acid, in the structure of polysaccharides, which can substantially affect the polysaccharides activity (Yang et al., 2021). Lo, Cheng,

Chiu, Tsay, and Jen (2011) determined the relationship between the inhibition rate of 10 lentinan on lipid peroxidation and the proportion of monosaccharides by conjugated diene method. The results showed that the antioxidant activity gradually increased with increasing in the proportion of Man and Rha, whereas the antioxidant capacity decreased gradually with increasing in the ratio of Ara to Glc. In the quantitative structure–activity relationship model of antioxidant activity of polysaccharides established by Li, Nie, Wang, and Luo (2016) the contents of Ara and galacturonic acid had the most evident effect on the DPPH free-radical scavenging activity of lentinan, whereas galacturonic acid had the most remarkable effect on the hydroxyl free radical scavenging activity of lentinan.

Moreover, the type and location of glycosidic bonds are very important for the anti-tumor activity of natural polysaccharides. Previous researches have shown that the bonds in the main chain of β-(1 → 3) glucan and β-(1 → 6) branching points are important for the anti-neoplastic activity of polysaccharide-based products (Lian et al., 2018; Lu et al., 2012). Moreover, increasing pieces of evidence have indicated that appropriate chemical modification could improve the biological activities of polysaccharides by introducing functional groups such as carboxymethylation, and phosphorylation (Lu et al., 2012). The reason was that chemical modification may change the water solubility and spatial conformation of natural polysaccharides (Hou et al., 2008; Huang, Chen, Cheng, & Huang, 2020). Jia, Liu, Zou, Xu, and Zhang (2015) deconvoluted the triple helix lentinan into a single-chain state with dimethyl sulfoxide or NaOH. After adding Se nanoparticles, lentinan was reconstituted into a triple helix state and wrapped with Se nanoparticles. The generated Se/s-LNT could inhibit the proliferation of HeLa tumor cells. The smaller the nano selenium particles, the better the anti-tumor effect. The anti-tumor capability of triple-helix lentinan without Se modification was weak *in vitro*. Se/s-LNT can promote the production of ROS in HeLa tumor cells and cause tumor cell apoptosis, which may also be caused by Se/s-LNT only exerting the anti-tumor effect of Se. Wang and Zhang (2009) observed that the anti-tumor activity of lentinan with single-strand chain disappeared, whereas the introduction of sulfonic acid group could partially restore its anti-tumor activity, which might be because the charged sulfonic acid group could increase the binding between lentinan and immune cell receptor through electrostatic action to activate immune response and improve anti-tumor activity. The findings showed that chemical modification may be an effective way to improve the biological activities of polysaccharides.

All in all, previous researches have confirmed that fungal polysaccharides have various biological activities, consistent with other natural polysaccharides. The detailed structure-effect relationship will contribute to the development of potential health products and clinical drugs from fungal polysaccharides. Therefore, many studies are urgently needed to clarify the structure–activity correlation of fungal polysaccharides.

6. Concluding remarks and prospects

In the past several decades, many researchers have brought great valuable discoveries to the scientific research of fungal polysaccharides, indicating that fungal polysaccharides have considerable medical and nutritional values. Furthermore, fungal polysaccharides may serve as a potential treasure trove for pharmaceuticals, functional foods, and cosmetic additives in the future (Fig. 3). This paper mainly reviewed the research progress in the extraction, separation, purification, structural characteristics, and biological activities of fungal polysaccharides. Although considerable progress has been made in the research of fungal polysaccharides, we still need to exert continuous efforts to solve several key technical problems. Firstly, to the best of our knowledge, the current extraction and purification methods of fungal polysaccharides are inefficient, time-consuming, and complex. Feasible or effective preparation methods for industrialized large-scale extraction and purification of
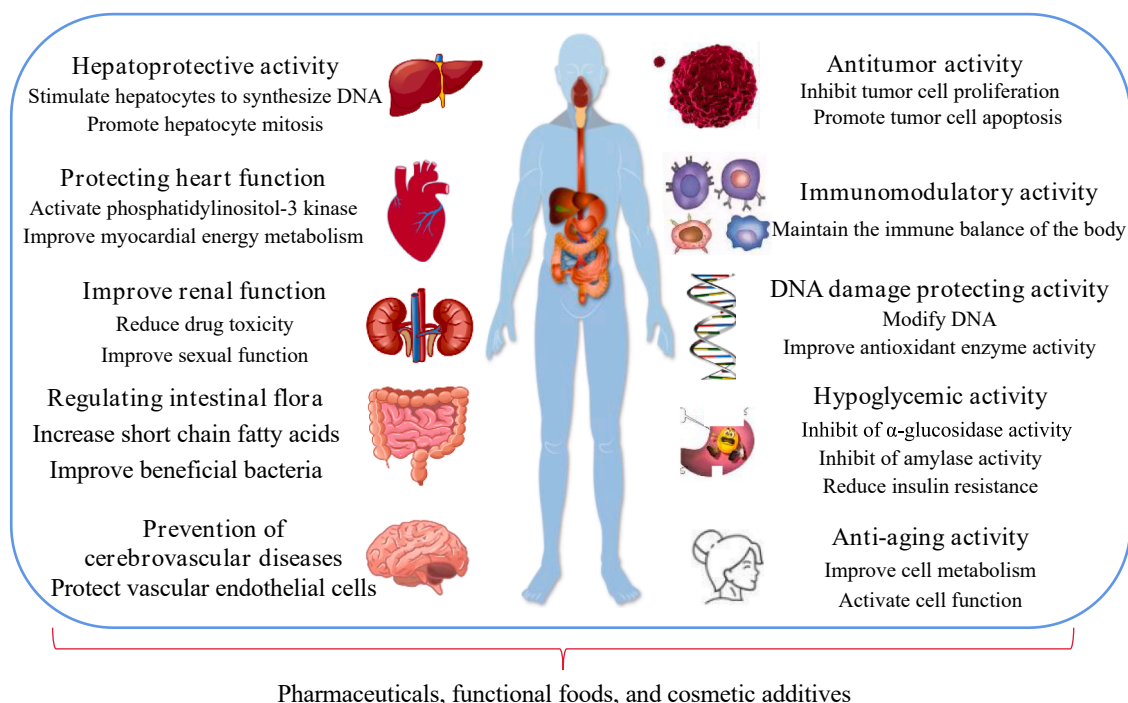
Hepatoprotective activity
Stimulate hepatocytes to synthesize DNA
Promote hepatocyte mitosis

Protecting heart function
Activate phosphatidylinositol-3 kinase
Improve myocardial energy metabolism

Improve renal function
Reduce drug toxicity
Improve sexual function

Regulating intestinal flora
Increase short chain fatty acids
Improve beneficial bacteria

Prevention of cerebrovascular diseases
Protect vascular endothelial cells

Antitumor activity
Inhibit tumor cell proliferation
Promote tumor cell apoptosis

Immunomodulatory activity
Maintain the immune balance of the body

DNA damage protecting activity
Modify DNA
Improve antioxidant enzyme activity

Hypoglycemic activity
Inhibit of α-glucosidase activity
Inhibit of amylase activity
Reduce insulin resistance

Anti-aging activity
Improve cell metabolism
Activate cell function

Pharmaceuticals, functional foods, and cosmetic additives

Fig. 3. The biological functions and future development prospects of fungi polysaccharides.

fungal polysaccharides are lacking. Hence, the combination of different extraction technologies is the most important methods to extract natural polysaccharides efficiently in the future. Moreover, the combination of ion column chromatography and gel chromatography is the most effective way to obtain natural polysaccharides fractions in the future. Secondly, great differences exist in the chemical structure and biological activities of fungal polysaccharide-based products owing to the different fungal raw materials and preparation methods. Therefore, the standardized preparation process of fungal polysaccharides must be established to ensure the consistency and repeatability of products, which are important for product quality control. Thirdly, the precise chemical structures of fungal polysaccharides are still poorly characterized. In addition, a limited number of studies reported the structure–activity relationship of fungal polysaccharides and the specific molecular mechanism of their bioactivity. More *in vivo* experiments and clinical research are need to verify the reliability of fungal polysaccharides usage. Moreover, further studies should focus on assessing the effects of fungal polysaccharides combined with other natural bioactive components to promote their clinical application.

In conclusion, previous researches have laid a solid foundation for the potential application of fungal polysaccharides in functional foods, health products, and drug therapy. Nevertheless, continuous efforts are still needed to establish preparation methods with development potential, ensure the product quality based on fungal polysaccharides, provide precise structural information, and further clarify the structure–activity relationships and potential molecular mechanisms. This review may facilitate a better understanding of fungal polysaccharides and provide new insights for further researches regarding fungal polysaccharides.

CRediT authorship contribution statement

Wenli Wang: Formal analysis, Investigation, Writing – original draft. **Jiaqi Tan:** Formal analysis, Investigation, Writing – original draft. **Lamu Nima:** Formal analysis, Investigation. **Yumei Sang:** Formal analysis, Investigation. **Xu Cai:** Formal analysis, Investigation. **Hongkun Xue:** Funding acquisition, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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