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Review

Classification, structure and mechanism of antiviral polysaccharides derived from edible and medicinal fungus

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ABSTRACT

The deficiency of chemical-synthesized antiviral drugs when applied in clinical therapy, such as drug resistance, and the lack of effective antiviral drugs to treat some newly emerging virus infections, such as COVID-19, promote the demand of novelty and safety anti-virus drug candidate from natural functional ingredient. Numerous studies have shown that some polysaccharides sourcing from edible and medicinal fungus (EMFs) exert direct or indirect anti-viral capacities. However, the internal connection of fungus type, polysaccharides structural characteristics, action mechanism was still unclear. Herein, our review focus on the two aspects, on the one hand, we discussed the type of anti-viral EMFs and the structural characteristics of polysaccharides to clarify the structure-activity relationship, on the other hand, the directly or indirectly antiviral mechanism of EMFs polysaccharides, including virus function suppression, immune-modulatory activity, anti-inflammatory activity, regulation of population balance of gut microbiota have been concluded to provide a comprehensive theory basis for better clinical utilization of EMFs polysaccharides as anti-viral agents.

Contents

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1. Introduction

Virus is a filterable vector and is sub-microscopic, with most animal viruses physically ranging in size from 20 to 200 nm in diameter [1]. As is well-known, about 60% of epidemic infectious diseases are caused by viruses and viral infections have always been a worldwide problem that jeopardizes human health. The current common antiviral drugs on the market are mainly the following: 3CLpro inhibitors (generated immature or weakly infectious virus by inhibiting 3CLpro activity), such as lopinavir/ritonavir [2–5], and darunavir/cobicistat [6–8]; RdRp inhibitors, (inhibited viral nucleic acid synthesis by intervening), such as remdesivir [9–11], favipiravir [12,13], and ribavirin [14,15]; Arbidol (blocking virus entry by interfering with clathrin) [16–18] and ribavirin combined with PegIFN-α2a [19–22], glucocorticoid [23–25], chloroquine and hydroxychloroquine [9,26–28], camostat mesylate [29] and nitazoxanide [30–32]. However, the use of these drugs is frequently restricted as a result of toxic side-effects (such as headache, nausea, vomiting, decreased appetite, skin rash, fever, fatigue, osteoporosis, metabolic disorders, heart damage, leukocyte reduction leading to reversible anemia and so on), weak oral bioavailability and the occurrence of drug resistance [9,15,33,34].

Coronavirus disease 2019 (COVID-19) caused by a new emerging coronavirus, has been pronounced as a Public Health Emergency of International Concern (PHEIC) by WHO [35]. By early October 2020, more than 36,382,001 patients had been diagnosed with the disease worldwide, with 1,056,131 deaths. The number of infected and dead people is still increasing rapidly every day. However, according to the data collected by the National Health Commission of the People's Republic of China, clinical practice in common antiviral drugs such as oseltamivir, arbidol, and lopinavir/Ritonavir failed to cure these patients of this epidemic. Until now, no specific therapeutic strategies or medicine has been developed to cure the new emerging virus yet. Hence, screening possible anti-viral drug candidate attract more and more attentions.

Traditional Chinese medicine has been used in the prevention, treatment, and rehabilitation of virus for a long history and plays a critical role in the batting of COVID-19 [36]. It is worth noting that the main components of the "Lung Cleansing and Detoxifying Decoction" widely used in the prevention and treatment of COVID-19 includes edible and medicinal fungus (EMFs) (*Poria cocos*, *Polyporus umbellatus*) [36]. EMFs commonly known as mushrooms, are large fungi that can be employed to food and medicine and have fleshy, gelatinous, woody and leathery proton entities. In China, mushrooms that occur in wood are called "fungus" and "mushroom", while those that emerge from soil are called "蕈". In Japan, the two terms "蕈 and fungus" are combined as a synonym for mushroom. More than 2000 species of EMFs have been identified to date [37]. EMFs as a branch of traditional Chinese herbal medicine, also played a vital role in the prevention and control of virus for a long history, such as, this COVID-19 outbreak [36]. As early as the Eastern Han Dynasty (25–220 CE) period of Chinese history, the classic Chinese medicine book "*Shennong's Herbal Classic* (*Shennong baicao jing*)" contains records on the treatment of plagues with edible and medicinal fungus, such as *Ganoderma lucidum* (Lingzhi), *Polyporus umbellatus* (Zhu ling) and *Omphalia lapidescens* (Lei wan). In addition, the classic book of Chinese medicine "*Compendium of Materia Medica* (*Bencao gangmu*)" also contains records of the treatment of plague with edible and medicinal fungus. With in-depth research, the efficacy of EMFs polysaccharides in suppressing viruses has attracted the attention of many scholars (Fig. 1). Although the direct antiviral edible fungus polysaccharides were previously summarized by He et al. [38]. Here we add recent studies on the direct or indirect antiviral activity of medicinal fungus polysaccharides and more comprehensively summarize the structure, mechanism, and structure-activity relationships of EMFs polysaccharides with antiviral effects from a classification perspective so that people can be better utilization of them.

2. Types and structural characteristics of EMFs antiviral polysaccharides

Ever since polysaccharides were first found to have bioactivities and applied to clinical practice, many scholars have devoted research to polysaccharides from different sources. Also, exploration of EMFs polysaccharides and the development of related medicines has always been the research of hot topics. To date, the China Food and Drug Administration (CFDA) has approved some patent drugs, such as *Coriolus versicolor* polysaccharides capsules, *Poria cocos* polysaccharides oral liquid, *Polyporus umbellatus* polysaccharides capsules, *Lentinula edodes* polysaccharide injection, *Lentinula edodes* polysaccharides medicinal tablet and *Lentinula edodes* polysaccharides capsules (Table S1) which can be applied for the treatment of chronic hepatitis, and as adjuvant drugs help to regulate the immune system and to enhance the efficacy and thereby reducing the side effects of chemotherapeutic agents.

The classification of Table 1 is shown by the mushroom taxonomy "Subphylum, Class, Order, Family, Genus, Species" and alphabetical order according to Colored illustrations of mushrooms of China. So as Table S2. Specifically, it generally divides into two subphylum (*Ascomycotina* and *Basidiomycotina*). The reported antiviral EMFs and its polysaccharides over the past decade and a piece of comprehensive information (classification, molecular weight, monosaccharide composition, and antiviral-biological activity) have been shown in Fig. 2 and listed in Table 1, and the structures of common EMFs polysaccharides with direct or indirect antiviral effects was shown in Fig. 3. Based on the available references, most of the antiviral EMFs polysaccharides source from *Basidiomycotina Heterobasidiomycete* EMFs, such as *Holobasidiomycetidae Aphyllophorale* (*Cantharellaceae*, *Ganodermataceae*, *Hericiaceae*, *Polyporaceae*, *Steccherinaceae etc.*) EMFs, and *Phragmobasidiomycetidae Auriculariales* (*Auriculariaceae*), *Tremellaceae* (*Tremellaceae*) EMFs. The number of *Hymenomycetes Gasteromycetidae* and *Holobasidiomycetidae* antiviral EMFs polysaccharides occupied second, specifically such as *Phallales* (*Phallaceae*), *Agricales* (*Agaricaceae*, *Bolbitiaceae*, *Boletaceae*, *Pleurotaceae*, *Pluteaceae*, *Russulaceae*, and *Tricholomataceae*) EMFs polysaccharides. Additionally, there is part of *Ascomycotina Discomycetes* and *Pyrenomycetes* EMFs polysaccharides with directly or indirectly antiviral activity, such as *Pezizales* (*Morchellaceae*), *Clavicipitales* (*Clavicipitaceae*), *Sphaeriales* (*Hypocreaceae*) and *Xylariales* (*Xylariaceae*) EMFs polysaccharides. Interestingly, only 15 EMFs polysaccharides (*Cordyceps militaris*, *Ganoderma lucidum*, *Hericium erinaceus*, *Fomitiporia punctate*, *Grifola frondosa*, *Inonotus obliquus*, *Auricularia auricular*, *Tremella*, *Agaricus blazei*, *Lentinus edodes*, *Pleurotus abalonus*, *Pleurotus ostreatus*, *Pleurotus pulmonarius*, *Pleurotus tuber-regium*, and *Flammulina velutipes*) could directly exhibit anti-virus effect but others just have antiviral effects through indirect antiviral-biological activity such as improving immunity, eliminating inflammation, and regulating intestinal function.

In Tables 1 and S2, most of the polysaccharides are heteropolysaccharides consisting of 2 or more kinds of monosaccharides like glucose (Glc), xylose (Xyl), rhamnose (Rha), mannose (Man), fucose (Fuc), fructose (Fru), galactose (Gal), arabinose (Ara), ribose (Rib), glucuronic acid (GlcA), and galacturonic acid (GalA). It is worth noting that *Morchella conica* polysaccharides (MCP) and *Agaricus bisporus*

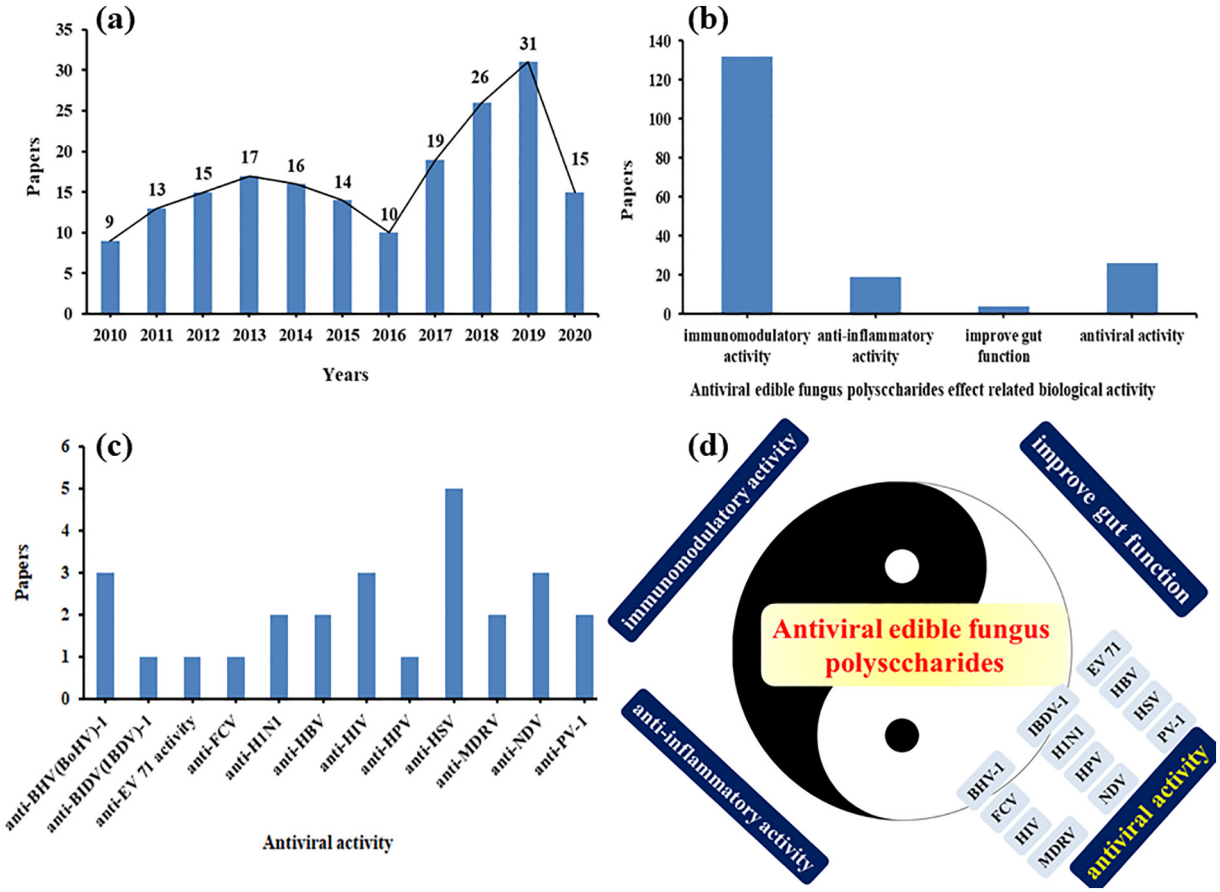

Fig. 1. Statistical analysis of the literature on the antiviral activity of edible and medicinal fungus polysaccharides. (a) Antiviral polysaccharides derived from EMFs related papers published between 2000– 2020 (based on Web of Science). (b) Antiviral EMFs polysaccharides effect related biological activity papers. (c) The categories of antiviral EMFs polysaccharides. (d) Antiviral EMFs polysaccharides investigate the relationship among immunomodulatory activity, anti-inflammatory activity, improve gut function, and antiviral activity.
Abbreviations: BHV (BoHV)-1: Bovine herpesvirus 1; BIDV (IBDV)-1: Infections bursal disease virus 1; EV 71: Human enterovirus 71; FCV: Feline calicivirus; H1N1: Influenza A virus; HBV: Viral hepatitis type B; HIV: Human immunodeficiency virus; HPV: Human papillomavirus; HSV: Herpes simplex virus; MDRV: Muscovy duck reovirus; NDV: Newcastle disease virus; PV-1: Poliovirus 1).

polysaccharides (TJ3) consist only of Man. At the meantime, their polysaccharide structure is made up of Man repeating units linked by α (1 → 6) glycosidic bonds. *Sarcodon aspratus* polysaccharides (HBP) consist only of Glc, and backbone of (1 → 6)-β-D-Glc*p*, which occasionally branched at *O*-3 position on along the backbone and substituted by the side chains that consisting of (1 → 3)-β-D-Glc*p*, (1 → 4) linked-β-D-Glc*p* and non-reducing end β-D-Glc*p*. *Volvariella volvacea* polysaccharides (VGPI-a, PS) consist only of Glc, and backbone of (1 → 4)-D-Glc*p* with the substitution at C-6 with 1-D-Glc*p* residue. These EMFs polysaccharides composed of a single monosaccharide do not appear to have a paradigm that can be systematically summarized in their structure. However, there are many studies on EMPs polysaccharides that do not characterize the composition of monosaccharides and molecular weight but only explain the biological activity. Next, we will try to summarize the structure-activity relationships of these EMFs polysaccharides from the perspective of the same classification.

In *Ascomycotina Discomycetes Pezizales Morchellaceae* EMPs polysaccharides, Mw is substantially in the range in the range of 6.9–192 kDa [39,40,97–105]. Based on Tables 1 and S2, there is no directly antiviral ability in *Morchellaceae* polysaccharides, and more is the ability to increase the immunity of indirect anti-virus. Besides that, there are some anti-inflammatory polysaccharides in *Morehella esculenta*, such as EMP-1, SEMP-1, PEMP, Ac-PMEP1-3 [97,99], which may be related to the sulfate and acetylation of morel polysaccharides.

In *Ascomycotina Pyrenomycetes Clavicipitales Clavicipitaceae* EMPs polysaccharides, Mw is approximately in the range of 20.2–853.8 kDa [41,43,44,106–118]; expect a special high-molecular-weight (47,960 kDa) polysaccharide from *Cordyceps militaris*, CMP-III, and predicted structural feature is 1 → 4)-α-D-Glc*p*-(1→, →4,6)-α-D-Man*p*-(1→, α-D-Man*p*-(→1 and →2,6)-α-D-Gal*p*-(1→ [42]. In addition to the anti-NDV and anti-H1N1 activity of *Cordyceps militaris* polysaccharides [111,117] (CMP40, 50, and APS respectively). Unfortunately, no research has been done to analyze the structure of these three polysaccharides. Other *Clavicipitaceae* polysaccharides are indirectly anti-virus by improving immunity. In *Basidiomycotina Heterobasidiomycetes Holobasidiomycetidae Aphyllophorales*, there are few antiviral-biological activity studies on the *Cantharellaceae* polysaccharides (Tables 1 and S2), and most of these polysaccharides could improve the immune function, to achieve an indirect anti-virus effect, but their molecular weights vary enormously [46–49,119]. The smallest molecular weight is WCCP-N-b isolated and purified from *Cantharellus cibarius*, only 18 kDa, and a linear methylated galactan which was composed of α-(1 → 6)-α-D-Gal*p*. CC-1 also isolated from *Cantharellus cibarius* has the highest molecular weight of 61,056 kDa, and the backbone composed of (1 → 4)-β-D-Glc*p* which branched at *O*-6 and the branches were mainly composed of 6 → 1)-α-D-Xyl*p*. *Ganodermataceae* (*Ganoderma atrum*, *Ganoderma lucidum*, and *Ganoderma sinense*) is a kind of rare EMFs, in recent years, many scholars on the composition and function of its polysaccharides (Tables 1 and S2). As a result of the difference between the different varieties, their Mw (from 8 to 1860) also makes a significant difference [50–59,65,120–130]. Among these polysaccharides from *Ganodermataceae*, except for APBP (*Ganoderma lucidum*), which has anti-HSV properties [130], but the precise structure of the polysaccharide is unclear. Other polysaccharides reach indirectly

Table 1
The composition of monosaccharides, molecular weight, antiviral activity, and cytotoxicity of polysaccharides from the edible mushroom.

Classification	Polysaccharides name	Monosaccharide composition	MW (kDa)	Structural feature	Biological activity	Ref.
Ascomycotina Discomycetes Pezizales						
Morchellaceae						
Morchella conica	MCP	Only Man	81.2	→6)-α-D-Man*p*-(1 → 6)-[α-D-Man*p*-(1 → 6)-]$_n$-α-D-Man*p*-(1→	Immunomodulatory activity	[39]
Morehella esculenta	MIPW50-1	GlcNAc:Gal:Glc:Man = 1.00:14.95:1.53:10.51	28.5	→2,3,6)-α-D-Man*p*-(1→,→3,6)-α-D--Man*p*-(1→,→2)-α-D-Gal*p*-(1→,→6)-α-D--Man*p*-(1→, →4)-β-D-Glc*p*-(1→, →4)-α-D-Glc*p*NAc-(1→, →6)-α-D-Glc*p*-(1→, α-D-Gal*p*-(1→, α-D-Glc*p*NAc-(1 → and β-DGlc*p*-(1→	Immunomodulatory activity	[40]
Ascomycotina Pyrenomycetes Clavicipitales						
Clavicipitaceae						
Cordyceps militaris	CMP-III	Glc:Man:Gal = 8.09:1.00:0.25	47,960	1 → 4)-α-D-Glc*p*-(1→, →4,6)-α-D-Man*p*-(1→, α-D-Man*p*-(→1 and →2,6)-α-D-Gal*p*-(1→	Immunomodulatory activity	[41]
	SDQCP-1	Man:Glc:Gal = 13.3:1.0:9.7	19.3	Backbone composed of (1 → 2)-α-D-Man*p* and (1 → 4)-β-D-Glc*p* residues. Branched chains at *O*-6 position of (1 → 2)-α-D-Man*p* mainly by (1 → 2)-β-D-Gal*f* or (1 → 6)-α-D--Man*p* residues	Immunomodulatory activity	[42]
Cordyceps sinensis	UM01 PS	Glc:Man:Gal = 100:59:17	610,86,25	(1 → 6)-α-D-glucosidic linkages	Immunomodulatory activity	[43]
Hirsutella sinensis	HS002-II	Man:Rib:Rha:GlcAc:GalAc:Glu:Gal:Xyl:Ara = 6.47:2.27:1.25:0.69:0.42:65.89:16.17:2.13:4.26	44	Backbone composed of (1 → 3)-α-D-Rib (1 → 4)-α-D-Xyl and (1 → 4)-β-D-Glc, which was substituted at C-6. The two branches were mainly composed of (1 → 4)-D-Gal*p*, and terminated with D-Gal*p*	Immunomodulatory activity	[44]
Hypocreaceae						
Shiraia bambusicola	SB2-1	Glc:Gal:Man = 2.0:1.5:1.0	22.2	The Man core was composed of (1 → 2)-Man*p* as the main chain. Glucose with (1 → 4)-D-Glc*p*, (1 → 2)-D-Glc*p* and (1 → 6)-D-Glc*p* at different degrees of polymerization were linked at C-6 and C-3 of the (1 → 2)-Man*p* as the side chains.	Immunomodulatory activity	[45]
Basidiomycotina Heterobasidiomycetes Holobasidiomycetidae Aphyllophorales						
Cantharellaceae						
Cantharellus cibarius	WCCP-N-b	Gal:3-O-Me-D-Gal:Glc:Man = 14.4:4.6:1.0:1.2	18	A linear methylated galactan which was composed of α-(1 → 6)-α-D-Gal*p* and 3-*O*-Me-D-Gal*p*	Immunomodulatory activity	[46]
	CC-1	Glc:Xyl = 5:1	61,056	Backbone composed of (1 → 4)-β-D-Glc*p* which branched at *O*-6 and the branches were mainly composed of 6 → 1)-α-D-Xyl*p*	Immunomodulatory activity	[47]
Craterellus cornucopioides	CCP	Man:Gal:Glc:Xyl = 48.73:17.37:15.97:17.93	1970	(1 → 3)-β-D-Man*p*-(1 → 6)-α-D-Gal*p* backbone distributed by(1 → 4)-α-D-Xyl*p*-t-α-D-Man*p* and t-β-D-Glu*p* units at *O*-6.	Immunomodulatory activity	[48,49]
Ganodermataceae						
Ganoderma atrum	PSG-1	Man:Gal:Glc = 1:1.28:4.91	1013	The main glycosidic linkage types composed of→3)-Glc*p*-(1→3)-Glc*p*-(1 → 3)-Glc*p*-(1 → , which was heavily substituted *via* (1 → 6) glucosidic bonds with -R, where -R would be	Immunomodulatory activity	[50–57]

				one of these fragments: T-Glc*p*-(1-[→6)-Glc*p*-(1]$_n$→, T-Glc*p*-(1 → 4)-GlcA*p*-(1→, or T-Glc*p*-(1 → 4)-GlcA*p*-(1-[→6)-Glc*p*-(1]$_n$→		
Ganoderma lucidum	GSG	ND	8	GSG is a branched glucan that contains (1 → 3)-linked, (1 → 3,6)-linked, (1 → 6)-linked and (1 → 4) linked D-glucopyranosyl residues of either β or α configuration.	Immunomodulatory activity	[58]
Ganoderma sinense	GSP-2	Only Glc	32	Backbone composed of (1 → 4)-and (1 → 6)-β-D-Glc*p*, bearing the side chains of (1 → 3)-and terminal β-D-Glc*p* at O-3 position of (1 → 6)-β-D-Glc*p*, as well as trace amounts of Gal and Man residues	Immunomodulatory activity	[59]
Hericiaceae						
Hericium erinaceus	HEP-S	Rha:Fuc:Man:Glc:Gal = 1.47:0.93:1.36:8.68:4.08	18.3	The main glycosidic linkage types composed of (1→)-α-D-Glc, (1 → 3,4)-α-D-Glc, (1 → 6)-α-D-Gal, (1 → 3,4)-β-D-Man, (1 → 3,6)-α-Rha and (1 → 2)-β-L-Fuc	Immunomodulatory activity	[60]
	HEP-W	Rha:Fuc:Man:Glc:Gal = 0.98:1.59:0.89:5.60:7.06	15.9	The main glycosidic linkage types consisted of (1→)-α-D-Glc, (1 → 3,6)-α-D-Glc, (1 → 2,6)-α-D-Gal, T-β-Gal, (1 → 3,4)-β-D-Man, (1 → 3)-α-Rha, and (1 → 2)-β-L-Fuc	Immunomodulatory activity	[61]
Polyporaceae						
Bjerkandera fumosa	DBFM3	Man:GlcAc:Gal = 1:18.16:0.702	180	(1 → 6), (1 → 3,6), (1 → 3) linkages and pyranose conformation	Immunomodulatory activity	[62]
Cryptoporus volvatus	PRA-1	2,3,4,6-Me4-Glc:2,4,6-Me3-Glc:2,4--Me2-Glc = 5.72:1.00:2.41	24,190;109.6;4.12	Hyperbranched (1 → 3), (1 → 6)-β-D-glucan with a degree of branching of 0.89, backbone composed of →1)-D-Glc*p*-(3 → linkages and side chains having the major branching points at *O*-6 positions	Immunomodulatory activity	[63]
Fomitiporia punctate	G1	Ara:Fru:Gal:Glc = 1.6:3.8:19.7:19.7	151	Furanoid rings; β-glycosidic bonds between the sugar units	Anti-HIV activity	[64]
Grifola frondosa	GF-P	Fuc:Gal:Glc:Man:Rib:GlcAc = 5.8:10.5:72.2:7.8:2.2:1.2	19.6;722.7	Contained the highest amount of (1 → 3,6)-β-D-glucans. The degree of branching (0.38) of (1 → 3,6)-β-D-glucans	Immunomodulatory activity	[65]
	GFP1	Glc:Fuc = 2.3:0.5	40.5	(1 → 6)-β-D-Glc*p* backbone with a single (1 → 3)-α-D-Fuc*p* side-branching unit	Anti-EV 71 activity	[66]
Inonotus obliquus	IOI-WN	Ara:Rha:Fuc:Xyl:Man:Gal:Glc:GlcAc:GalAc:3-*O*-methyl Gal = 1.4:1.3:1.7:6.9:6.8:17.5:53.1:1.0:1.8:8.7	60	(1) The neutral polysaccharides were heterogeneous and branched and consisted of a (1 → 3)-linked β-Glc backbone with (1 → 6)-linked kinks in the chain at approximately every fifth residue, with branches of (1 → 6)-linked β-Glc in addition to substantial amounts of (1 → 6)-linked α-Gal with 3-*O*-methylation at about every third Gal residue.	Immunomodulatory activity	[67]
	IOI-WAC	Ara:Rha:Fuc:Xyl:Man:Gal:Glc:GlcAc:GalAc:3-*O*-methyl Gal = 2.1:5.1:1.3:8.8:8.2:11.2:37.9:5.1:15.7:4.6	15			
Phellinus igniarius	*P. igniarius* polysaccharides	Rha:Man:Ara:Gal:Xyl:Glc = 1.31:14.51:2.63:20.65:3.32:57.58	18.518	The glycosidic linkages were mostly 1 → 3, 1 → 6 or 1 → 3,6. main chain of →3)-β-D-Glc*p*-(1 → with →6)-β-D-Glc*p*-(1 → side chain	Immunomodulatory activity	[68]
Phellinus pini.	PPE	Man:Gal:Glc = 38.40:1.00:1.76	38	Backbone of (1 → 2)-linked Man, which was heavily substituted *via* (1 → 6) glucosidic bonds with (1 → 3)-linked Man, and terminated mainly with Man, as well as a	Immunomodulatory activity	[69]

(continued on next page)

Table 1 (*continued*)

Classification	Polysaccharides name	Monosaccharide composition	MW (kDa)	Structural feature	Biological activity	Ref.
Polyporus umbellatus	ZPS	>90% Glc	227	small amount of Gal and Glc. (1 → 6, 1 → 4)-linked β-D-Glc*p* backbone, substituted at *O*-3 position of (1 → 6)-linked β-D-Glc*p* by (1 → 3) linked β-D-Glc*p* branches	Immunomodulatory activity	[70]
Steccherinaceae						
Sarcodon aspratus	HBP	Only Glc	430	Backbone of (1 → 6)-β-D-Glc*p*, which occasionally branched at *O*-3 position on along the backbone and substituted by the side chains that consisting of (1 → 3)-β-D-Glcp, (1 → 4) linked-β-D-Glc*p* and non-reducing end β-D-Glc*p*	Immunomodulatory activity	[71]
Basidiomycotina Heterobasidiomycetes Phragmobasidiomycetidae Auriculariales						
Auriculariaceae						
Auricularia auricular	CEPSN-1	Glc:Man:Gal:GlcAc = 98.90:0.11:0.38:0.61	4.6	Backbone chain composed of (1 → 4)-α-D-Glc*p* in glucopyranose type	Immunomodulatory activity	[72]
	CEPSN-2	Glc:Man:Gal:Ara:Fuc:GluAc:GalAc = 97.56:0.14:1.04:0.11:0.45:0.50:0.20	6.7			
Basidiomycotina Heterobasidiomycetes Phragmobasidiomycetidae Tremellaceae						
Tremellaceae						
Tremella	TP	Man:Xyl:GlcAc = 57.50:32.09:10.14	1500	Backbone was composed of (1 → 3)-β-D-Man*p*, and the side chain composed of (1 → 6)-β-D-Xyl*p* was attached to the C2 of the backbone Man*p*	Immunomodulatory activity	[73]
Tremella aurantialba	TAP-3	Man:Xyl:GlcAc = 3.0:1.0: 1.0.	624	Backbone was composed of (1 → 3) and (1 → 2)-α-Man*p*, side chains formed by β-Xyl*p* and β-Glc*p*A linked to the C-2 position of α-Manp, and acetyl groups connected to the sixth hydroxyl positions of Man*p*	Immunomodulatory activity	[74]
Basidiomycotina Hymenomycetes Gasteromycetidae Phallales						
Phallaceae						
Dictyophora indusiata	DIP	Man:Rib:Rha:GlcAc:Glc:Gal:Xyl:Ara:Fuc = 23.55:0.46:0.043:1.014:59.84:12.95: 0.36:0.17:1.58	650	β-(1 → 3)-D-Glc with side branches of β-(1 → 6)-Glc units	Immunomodulatory activity	[75]
Basidiomycotina Hymenomycetes Holobasidiomycetidae Agricales						
Agaricaceae						
Agaricus bisporus	ABS	Glc:Man:Gal:Gal-Me:Fuc:Ribe = 51.4:6.8:33.9:3.0:1.6:3.3	ND	(1 → 6), (1 → 4)-α-Glc, (1 → 6)-β-Glc, and mannogalactan	Anti-inflammatory activity	[76]
Agaricus blazei	FR-S	ND	3.5	(1 → 6)-(1 → 3)-β-D-glucan	Anti-HSV activity	[77]
Bolbitiaceae						
Agrocybe aegerita	AAPS	Rha:Fuc:Man:Glc = 2.90:10.25:3.70:38.27	18.1	α-LRha*p*-(1 → 6)-β-D-Glc*p*-(1 → 2)-α-L-Fuc*p*-(1 → 6)-α-D-Glc*p*-(1 → 5)-α-L-Ara*f*-(1 → 4)-β-D-Glc*p*A-(1 → 5)-α-L-Ara*f*-(1 → 6)-α-D-Man*p*-(1 → 6)-α-D-Man*p*-(1 → 2)-α-L-Fuc*p*-(1 → 6)-β-D-Gla*p*-(1 → 2)-α-L-Rha*p*-(1 → 6)-β-D-Gal*p*-(1→, which linked with two side chains α-L-Fuc*p*-(1 → 6)-β-D-Glc*p*-(1 →	Immunomodulatory activity	[78]

				6)-β-D-Man*p*-(1 → and α-D-Xyl*p*-(1 → 2)-α-L-Fuc*p*-(1 → 5)-α-D-Ara*f*-(1 → 6)-β-D-Gal*p*-(1 → at O_{H2} at H-4-Ara and the terminal Gal*p* residues, respectively.		
Boletaceae						
Boletus speciosus	BSF-X	Glc:Gal = 2:1	141.309	Backbone of 1, 4-β-D-Glc of which branches were mainly composed of two 1, 6-α-D-Gal residue and a 4-β-D-Glc at the end of the branches	Immunomodulatory activity	[79]
	BEP	Glc:Gal:Rha:Ara = 2.9:3.2:1.3:1.6	113.432	Backbone consisting of (1 → 6)-linked-α-D-Glc*p*, (1 → 2,6)-α-D-Gal*p*, (1 → 6)-α-D-Gal*p*, and (1 → 3)-α-D-Rha*p* residues, which were branched at O-2 position of (1 → 2,6)-α-D-Gal*p* residue with a single terminal (1→)-α-L-Ara*f* residue	Immunomodulatory activity	[80]
Leccinum rugosiceps	LRP-1	Gal:Rha:Fuc:Man:Glc:Gala = 25.77:1.98:4.99:27.45:39.13:0.68	18.82	Backbone mainly composed of →1-α-D-Fuc*p*-3→, →1-α-D-Rha*p*-3→, →1-β-D-Glc*p*-6→, →1-β-D-Glc*p*-3→, →1-α-D-Glc*p*-4→, →1-β-D-Gal*p*-6→ and →1-α-D-Man*p*-6→.	Immunomodulatory activity	[81]
Pleurotaceae						
Lentinus edodes	RPS	ND	3.08	→3)-L-Rha*p*-(1→, →6)-D-Glc*p*(1→, →3,6)-D-Man*p*-(1→, →3)-L-Ara*p*-(1→, D-Man*p*-(1→, and →6)-D-Gal*p*-(1→,	Anti-inflammatory activity	[82]
	ERPS	ND	1.16	→3)-L-Rha*p*-(1→, →6)-D-Glc*p*-(1→, →3)-D-Man*p*-(1→, →6)-D-Gal*p*-(1→, and L-Ara*p*-(1→		
Pleurotus abalonus	LA	Glc:Rha:GlcA:Xyl:Gal = 26.3:2.7:1.0:1.4:1.8:1.2	120	$[→6)$-α-D-Glc*p*$(1→]_n$	Anti-HIV activity	[83]
Pleurotus citrinipileatus	PCPS	1, 5, 6-Tri-*O*-acetyl-2, 3, 4-tri-*O*-methyl glucitol:1, 3, 5, 6-tetra-*O*-acetyl-2, 4-di-*O*-methyl glucitol = 2:1	450	Backbone mainly composed of β-(1 → 6)-Glc*p* withβ-(1 → 6)-Glc*p* residues branched	Immunomodulatory activity	[84,85]
Pleurotus eryngii	WPEP-N-b	Gal:Man:3-O-Me-D-Gal:Glc = 43.8:39.3: 11.7:9.20	21.4	Backbone mainly composed of α-(1 → 6)-D-Gal*p* and 3-O-Me-D-Gal*p*, branched at *O*-2 with single t-β-D-Man*p*, and β-(1 → 6)--D-Glc*p* residues are present as minor components either in side-chains or backbone	Immunomodulatory activity	[86]
	EPA-1	Man:Glc:Gal = 2.20:1.00:3.20	99.7	Backbone mainly composed of (1 → 6)-Gal residue	Immunomodulatory activity	[87]
Pleurotus florida	PfloVv5FB	1,5-Di-*O*-acetyl-2,3,4,6-tetra-Omethyl--D-glucitol:1,5,6-tri-*O*-acetyl-2,3,4-tri-*O*--methyl-D-glucitol:1,3,5,6-tetra-*O*--acetyl-2,4-di-*O*-methyl-D-glucitol = 1:2:1	187	Repeating unit of the polysaccharide has a backbone of three (1 → 6)-linked β-D-Glc*p* units, where one of them is substituted at *O*-3 position with the β-D-Glc*p* moiety	Immunomodulatory activity	[88]
Pleurotus ostreatus	Heteropolysaccharide	Glc:Gal = 7:1	187	Backbone mainly composed of →3)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1 → 6)-β-D-Glc*p*-(1 → 3)-β-D-Glc*p*-(1 → 6)-β-D-Glc*p*-(1 → 6)-β-Glc*p*-(1 → The branches consisted of (1 → 3)-α-D-Gal*p*, and (1 → 3)-α-D-Glc*p*	Immunomodulatory activity	[89]
Pleurotus pulmonarius	β-Glucan	Xyl:Man:Gal:Glc = 2:5:3:90	ND	(1 → 3)β-D-Glc*p* main chain substituted at *O*-6 of every third unit by single β-D-Glc*p* nonreducing end units	Anti-inflammatory activity	[90]
	PEIsR	Man:Gal:3-Omethyl-Gal =37.0:39.7:23.3	64	Main chain of (1 → 6)-α-D-Gal*p* and 3-*O*-methyl-α-D-Gal*p* units. Some of the α-D-Gal*p* units were substituted at *O*-2 by non-reducing end units of β-D-Man*p*	Anti-inflammatory activity	[91]

(continued on next page)

Table 1 (*continued*)

Classification	Polysaccharides name	Monosaccharide composition	MW (kDa)	Structural feature	Biological activity	Ref.
Pluteaceae						
Volvariella volvacea	VGPI-a	Only Glc	1435.6	(1 → 4)-D-Glc*p* backbone with the substitution at C-6 with 1-D-Glc*p* residue	Immunomodulatory activity	[92]
Tricholomataceae						
Armillaria mellea	AMPS-1-1	Glc:Gal:GlcA = 89.06:9.59:1.34	123	(1→)-β-D-Glc*p*, (1 → 3,6)-α-D-Glc*p* and (1 → 3)-β-D-Glc*p* residues	Immunomodulatory activity	[93]
	AMPS-2-1	Glc:Gal:GlcA:Man = 65.28:22.87:2.87:8.98	676	(1 → 3,6)-α-D-Glc*p* and (1 → 6)-β-D-Glc*p* residues		
Flammulina velutipes	FVP2	Gal:Glc:Man = 19.96:60.66:19.38	18.3	(1 → 3)-β-D-Gal, (1 → 6)-α-D-Glc and (1 → 3,6)-α-D-Man	Improves gut microbiota function	[94]
	FVPB2	Gal:Man:Fuc:Glc = 1.9:1.2:1:2.5	15	Backbone mainly composed of →2)-α-D-Galp-(1 → 4)-α-D-Galp-(1 → 6)-α-D-Glc*p*-(1 → 3)-β-D-Glc*p*-(1→ The branches consisted of (1 → 3)-α-D-Man*p*, and (1 → 6)-α-L-Fuc*p*	Immunomodulatory activity	[95]
Tricholoma crassum	PS	Glc:Gal:Man = 3:1:1	200	Backbone mainly composed of →6)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1 → 6)-α-D-Glc*p*-(1 → The branches consisted of (1 → 3)-α-D-Gal*p*-(1 → 4)-β-D-Man*p*	Immunomodulatory activity	[96]

Abbreviations: glucose (Glc), xylose (Xyl), rhamnose (Rha), mannose (Man), fucose (Fuc), fructose (Fru), galactose (Gal), arabinose (Ara), ribose (Rib), glucuronic acid (GlcA), and galacturonic acid (GalA).
Due to table typesetting, the classification of "subphyla, class, order" in the table and Table S2 is presented in the form of "no indentation", "family" is indented by 1 character, "genus and species" is indented by 2 characters.

by boosting the immunity of anti-viral capabilities. A polysaccharide (PSG-1) was isolated and purified from *Ganoderma atrum*, and the main glycosidic linkage types composed of →3)-Glc*p*-(1→3)-Glc*p*-(1 → 3)-Glc*p*-(1 → , which was heavily substituted *via* (1 → 6) glucosidic bonds with -R, where -R would be one of these fragments: T-Glc*p*-(1-[→6)-Glcp-(1]$_n$→, T-Glc*p*-(1 → 4)-GlcA*p*-(1→, or T-Glc*p*-(1 → 4)-GlcA*p*-(1-[→6)-Glc*p*-(1]$_n$→. GSG isolated from *Ganoderma lucidum* is a branched glucan that contains (1 → 3)-linked, (1 → 3,6)-linked, (1 → 6)-linked and (1 → 4) linked D-glucopyranosyl residues of either β or α configuration. In *Hericiaceae Hericium erinaceus* polysaccharides, Mw are approximately in the range of 16.15–46 kDa [60,61,131–138], and it's worth noting that HEP could directly anti-MDRV, composed of Glc:Gal:Man:Ara (51.02:42.24:4.5:2.2), molecular weight of 16.18 kDa [132,133]. As showed in Tables 1 and S2, most of the EMFs polysaccharides with antiviral-biological activity are collected in *Polyporaceae* polysaccharides. For instance, *Fomitiporia punctate* polysaccharide (G1) could be anti-HIV [64], with furanoid rings and β-glycosidic bonds between the sugar units; *Grifola frondosa* polysaccharide (GFP1) could anti-EV 71 [66], which (1 → 6)-β-D-Glc*p* backbone with a single (1 → 3)-α-D-Fuc*p* side-branching unit; and *Inonotus obliquus* polysaccharide (IOPs) could anti-FCV [139], unclear structure. Therefore, we can try to speculate that β-glycosidic bonds play a critical role in the antiviral efficacy of EMFs polysaccharides. In addition, other *Polyporaceae* EMFs polysaccharides often through the enhancement of immune or anti-inflammatory effect, and achieve tacit anti-virus effect. In *Basidiomycotina Heterobasidiomycetes Phragmobasidiomycetidae Auriculariales* polysaccharides, interestingly, the polysaccharides (AAPt, AAP1, and AAP2) and sulfate derivatives (sAAPt, sAAP1, and sAAP2) of the widely consumed *Auricularia auricular* have anti-NDV activity [140]. In *Tremellaceae* (*Tremella* and *Tremella aurantialba*) polysaccharides, Mw is approximately in the range of 4–1500 kDa [73,74,141–152]. Among these polysaccharides from *Tremella*ceae, only *Tremella* polysaccharides (sTPStp and sTPS70c) could anti-NDV [149]. Other polysaccharides reach indirectly by improving the immunity of anti-viral properties. The *Basidiomycotina Hymenomycetes Holobasidiomycetidae Agricales* as another important classification of EMFs polysaccharides against viruses, most of antiviral-biological activities of EMFs polysaccharides are gathered here (Tables 1 and S2). Taking several typical EMFs as examples, *Agaricus blazei* polysaccharides (FR-S, MI-S, PLS, SPLS), have anti-HSV activity with (1 → 6)-(1 → 3)-β-D-glucan and the sulfate group generally occurs at the C4 of configuration β (1 → 6) and preferably at the C6 of configuration α (1 → 4) in F3; PLS isolated from *Agaricus blazei* have anti-PV-1 activity and PLS, β-glucan also derived from *Agaricus blazei* could anti-BoHV-1 with β (1 → 6)-D-Glc with branches made of β (1 → 3)-D-Glc [77,153–156]. On the other hand, *Lentinus edodes* polysaccharides, PLWM and LEP (structure unknown), could be anti-HBV and PV-1 respectively [157,158]; Efs (structure unclear) derived from *Pleurotus ostreatus* could anti-BIDV [159]; *Pleurotus pulmonarius* polysaccharides (PBG, structure unknown), also have anti-HPV activity [160]; *Flammulina velutipes* polysaccharides (FVP1, structure unknown) could also anti-HBV [120]. It is important to note that *Pleurotus tuber-regium* polysaccharides S-TM8-1–6 (structure unknown) have the ability of anti-HSV and Flu A [161]. Therefore, it can be speculated that the polysaccharides of EMFs after chemical modification (sulfation, phosphorylation, and methylation modification) may have better antiviral effects and the antiviral ability of chemical modified polysaccharides increases with the degree of modification within an optimal scope. Besides the EMFs polysaccharides described above, other polysaccharides of *Agricales* often fight viruses indirectly by enhancing immunity, anti-inflammatory activity and modulating the active function of the gut microbiota.

Unfortunately, we were unable to derive a specific paradigm to summarize the antiviral activity from the structure of EMFs polysaccharides owing to the relatively large differences in the classes of EMFs. Therefore, more studies on the Structure-activity relationships of the polysaccharides of EMFs are still needed (Fig. 3).

Fig. 2. Common EMFs with direct or indirect antiviral effects.

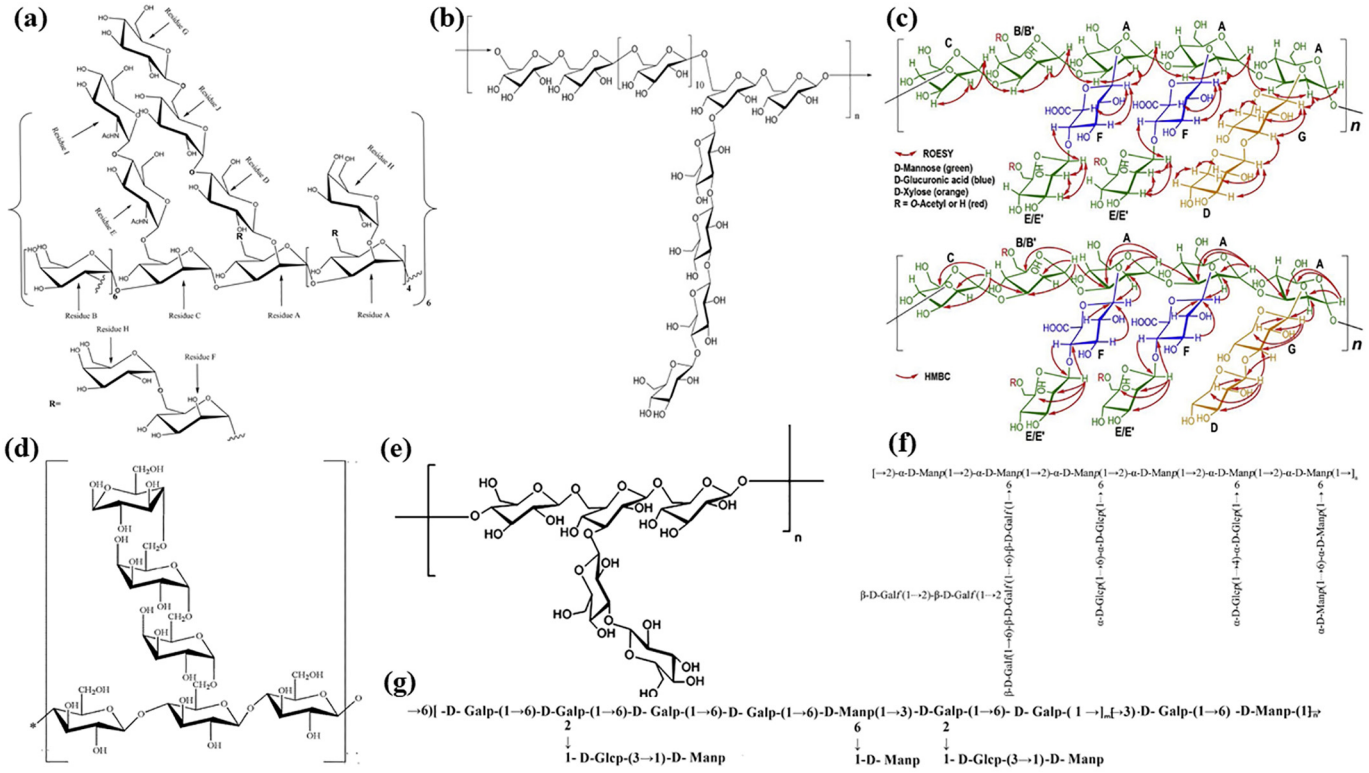

Fig. 3. Structures of common EMFs polysaccharides with direct or indirect antiviral effects. (a) Proposed structure of MIPW50–1 (*Morchella importuna* polysaccharide); (b) Putative structure of HBP (*Sarcodon aspratus* (Berk.) polysaccharide); (c) NOESY and HMBC correlations of TAP-3 (*Tremella aurantialba Bandoni* et Zang glucuronoxylomannan); (d) The structure of polysaccharide BSF-X (*Boletus speciosus Frost* polysaccharide); (e) Proposed structure of the polysaccharides from the fruiting bodies of *G. sinense*; (f) The proposed main structure of the galactoglucomannan SB1–1 (*Shiraia bambusicola* polysaccharide); (g) One possible structure of *Pleurotus eryngii* polysaccharide (EPA-1) ($m = 5, n = 2$).

3. Antiviral mechanisms of EMFs polysaccharides

It is well known that binding to cell surface through electrostatic interactions is the first step for a virus to invade a cell, while unstable reversible binding grows into stable irreversible adsorption to accomplish the subsequent invasion process (Nigel Dimmock et al., 2006). Numerous studies have demonstrated that the sulfate polysaccharides could interfere with the viral adsorption process on cells by blocking

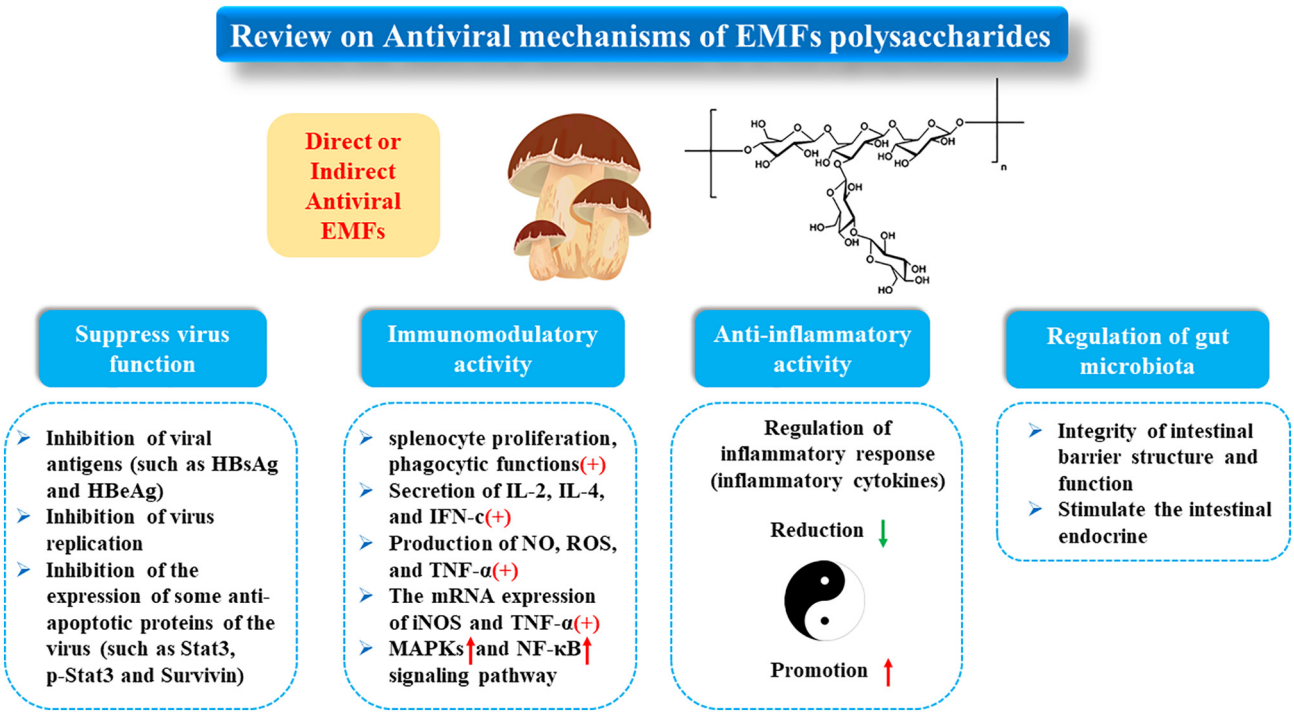

Fig. 4. Review on Antiviral mechanisms of EMFs polysaccharides.

the positive charge of the cell surface through the negative charge of the sulfate group [162]. For example, HIV-1conserved domains (gp120), defined as an envelope glycoprotein mediates virus attachment and entry, bind to $CD4^+$ T cells. On the other hand, different variable domains (in particular V3), as the third variable part of the HIV-1 gp120, could bind to the chemokine co-receptor [163]. These interactions described above clarify the mechanisms of virus attachment, uptake, intracellular transport, and eventual penetration into the cytoplasm [1]. In the past decades, natural EMFs polysaccharides exhibit antiviral activity through four core strategies (Fig. 4): suppressing virus function, improving immunomodulatory activity, regulating anti-inflammatory activity, and population balance of gut microbiota.

3.1. Suppress virus function

There is a relatively small body of literatures that is devoted to direct antiviral activity from EMFs polysaccharides. EMFs polysaccharides are structurally diverse and heterogeneous and the antiviral activities of these polysaccharides are also determined by their structure, especially their advanced structures (Tables 1 and S2). Also, there is a growing body of literatures that recognize the sulfate EMFs polysaccharides often have better antiviral activity. Although the S-TM8 fractions were inactive in inhibiting virus replication for Flu A, they showed a different degree of inhibitory effect toward the three enveloped viruses [161]. Besides, S-TM8s showed relatively higher anti-HSV-1 and HSV-2 activity, which IC_{50} values were 10-fold lower than those for RSV [161]. In 2004, a seminal article was issued entitled evaluation of sulfate fungal β-glucans of *Pleurotus tuber-regium* as a potential water-soluble antiviral agent, which had a major impact on the study of the antiviral activity of sulfate EMFs polysaccharides, the anti-virus (HSV-1, HSV-2, RSV and Flu A) activity of sulfate *Pleurotus tuber-regium* polysaccharides (S-TM8-1 to S-TM8-6) were evaluated [161]. In a study conducted by Gomes and colleagues, it was shown that sulfate derivative *Agaricus blazei* polysaccharides (MI-S) demonstrated a potential inhibitory activity against HSV-1 [KOS and 29R (acyclovir-resistant) strains] and HSV-2 strain 333, with selectivity indices ($SI = CC_{50}/IC_{50}$) higher than 439, 208, and 562, respectively [154]. However, in a follow-up study, Gomes et al. also found that FR-S, sulfate derivative also derived from *Agaricus blazei* polysaccharides, presented no *in vitro* antiherpetic action at 1 mg/mL, FR-S displayed potential anti-HSV-1 and anti-HSV-2 activities in both simultaneous and post-infection treatments, resulting in SI higher than 393. The reduction of viral adsorption upon cell pretreatment with FR-S also suggested its interaction with cellular components. FR-S inhibited HSV-1 ($EC_{50} = 8.39$ μg/mL) and HSV-2 ($EC_{50} = 2.86$ μg/mL) penetration more efficiently than heparin [77]. Similarly, Zhao and his team reported that sulfate *Tremella* polysaccharides ($sTPS_{tp}$ and $sTPS_{70c}$) could be substantially anti-NDV activity. And the antiviral activity in discrete processing stages of polysaccharide has been tested in their research [149]. As a pre-adding polysaccharide, the virus inhibitory rate of $sTPS_{tp}$ (1.563 μg/mL) was the highest (97.1%) and considerably higher than those of the other four groups. Next was $sTPS_{70c}$ group (85.99%) and significantly higher than the non-sulfated TPS_{tp} and TPS_{70c} groups. As simultaneously adding polysaccharide and NDV after mixed, the virus inhibitory rate of $sTPS_{tp}$ (1.563 μg/mL) group was the highest (94.42%) and significantly higher than those of the other four groups (0.0782 μg/mL $sTPS_{70c}$, TPS_{tp}, TPS_{70c}, and TPS_{tc}), and the following were 0.782 μg/mL TPS_{tp} (81.55%) group and significantly higher than those of the other three groups. As a post-adding polysaccharide, the virus inhibitory rate of $sTPS_{tp}$ (1.563 μg/mL) group was the highest (83.14%) and the following was 6.25 μg/mL $sTPS_{70c}$ (73.26%), which were significantly higher in comparison with other three non-sulfated polysaccharide groups (1.563 μg/mL TPS_{tp}, 3.907 μg/mL TPS_{70c} and TPS_{tc}) [149]. To determine the effects of sulfate on the antiviral activity of polysaccharides, in a follow-up study, Hu and colleagues compared the anti-NDV activity of *Auricularia auricula* polysaccharides (AAPt, AAP1, and AAP2) and sulfate polysaccharides (sAAPt, sAAP1, and sAAP2) [140]. As pre-adding polysaccharide, the virus inhibitory rate in sAAP1 group was the highest (43.38%), and the following was the AAP1 (36.71%), sAAPt (35.40%), sAAP2 (24.60%), AAP2 (22.90%) and AAPt (16.78%), respectively. Nguyen [140] argued that the virus inhibitory rate of sAAP1 group was the highest and the following was sAAPt group in post-adding polysaccharide, in which two groups were significantly greater than that of AAP2 group. As simultaneous-adding polysaccharide and NDV, the virus inhibitory rate in sAAP1 and sAAPt group was the highest, 70.90%, and 65.75%, respectively, which was markedly higher than that in APPs groups. The following was sAAP2 (51.95%) which was also significantly higher than the non-sulfate group, AAP2 (24.74%).

In addition to the above sulfate EMFs polysaccharides, CMP40 derived from *Cordyceps militaris* was found to significantly improve the immune activity of NDV vaccination, which could be as the candidate of a new-type immune adjuvant [111]. The *Cordyceps militaris* polysaccharide (APS) also was reported to anti-H1N1 [117]. In a study investigating *Ganoderma lucidum* polysaccharide (APBP) by Oh et al., it was shown that combinations of APBP with acyclovir (ACV) on HSV-1 and HSV-2 were measured potent synergistic effects [130]. A recent study by Wu and colleagues' involved *Hericium erinaceus* polysaccharide (HEP) on the lymphocyte homing in Muscovy duck reovirus (MDRV) infected ducklings [132,133]. Results showed that HEP dramatically improved intestinal morphological structure and related indexes, and significantly inhibited the reduction of colonic mucosal IELs, goblet cells, and mast cells caused by MDRV infection [132,133]. Furthermore, *Fomitiporia punctate* polysaccharide (G1) [64] and *Pleurotus abalonus* polysaccharide (LA) [83] could inhibit HIV activity.

3.2. Immunomodulatory activity

Since the outbreak of COVID-19, there has been recognized that improved immunity plays an indispensable role in the prevention and elimination of the virus, as well as disease recovery [165,166]. A growing number of researches are also continuing to explore effective immune boosting foods in people's daily diets to achieve indirect antivirals effect. It is universally known that viruses Cells are non-cellular microorganisms that usually need to be parasitized in living cells to reproduce, and cellular immunity plays an important part in obliterating viral infections [166–168]. From the traditional perspective of viral infections and individual immune responses, immunomodulatory drugs have attracted attention for their ability to rapidly enhance cellular immunity and help fight viral infections. Immune cells including macrophages, neutrophils, monocytes, lymphocytes, and NK cells are the primary targets of coupling between polysaccharides of activating or stimulating immunization and specific proteins, which can directly or indirectly enter into dialogue with the host immune system, initiate a series of molecular interactions, lead to the activation of the immune system [165,166,169]. Immunomodulatory activity is one of the most expressive abilities of EMFs polysaccharides. Pharmacological tests showed that EMFs enhanced humoral immunity and nonspecific (or innate) immunity even at low doses. The immunomodulatory activity of EMFs polysaccharide is considered a critical basis for the antiviral effects mentioned above. The immunoreactivity of separate families (*Morchellaceae*, *Clavicipitaceae*, *Cantharellaceae*, *Ganodermataceae*, *Hericiaceae*, *Polyporaceae*, *Tremellaceae*, *Pleurotaceae*, *Pluteaceae*, *Russulaceae*, and *Tricholomataceae*) of EMFs polysaccharides will be described in the following section.

3.2.1. Morchellaceae (Morchella conica and Morehella esculenta) polysaccharides

In vivo and *in vitro* experiments during the past decades have elucidated some mechanisms by which the MCP, EPMC, and IPMC derived from *Morchella conica* were found to significantly improve the immune activity though modulating NO production, stimulating splenocyte proliferation, and inducible nitric oxide synthase (iNOS) expression in RAW264.7 cells [39,103]. Meng et al. illustrated that a novel

polysaccharide (MSP-II) extracted from *Morehella esculenta* could stimulate NO production, proliferation, and phagocytosis of RAW 264.7 [98]. Moreover, Yao et al. discovered that a polysaccharide fraction (MIPW50-1) from *Morehella esculenta* could significantly improve NO production, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and phagocytosis of RAW264.7, rising immunomodulatory activity through the TLR4/JNK and Akt/NF-κB signaling pathways in RAW264.7 cells [40]. Additionally, MIPW50-1, MEEP, MCP, MEP-SP2 and MEP-SP3 derived from *Morehella esculenta* were capable of stimulating macrophage function, NO production, and the proliferation of T and B lymphocytes [39,40,102,105]. However, interestingly, Cui and colleagues reported that *Morehella esculenta* polysaccharide just selectively activated T cells and macrophages, but not B cells [104].

3.2.2. Clavicipitaceae (Cordyceps militaris, Cordyceps sinensis, and Hirsutella sinensis) polysaccharides

Most recently, He et al. discovered that a polysaccharide (CMP-III) from *Cordyceps militaris* could significantly promote macrophage phagocytosis and secretion of NO, TNF-α and IL-6, which involved MAPKs and NF-κB signaling pathways [41]. Similarly, other studies indicated that PLCM could enhance NO production, ROS, TNF-α, and RAW264.7 macrophages phagocytic though activated MAPK and NF-κB. Meanwhile, antibodies specific for the extracellular domain of TLR2, TLR4, or the macrophage receptor Dectin-1 significantly attenuated PLCM-induced secretion of TNF-α [109]. In addition, several other polysaccharides (CMP—W1, CMP—S1, CP2c2-S2, CM, and CPMN Fr III) isolated from *Cordyceps militaris* also can enhance immunity and thus indirectly play an anti-viral role [106,107,113,114].Meng et al. found a novel *Cordyceps sinensis* polysaccharides UM01 PS, which promoted mouse RAW 264.7 macrophages proliferation, phagocytic activity, the release of NO and multiple cytokines and chemokines. UM01 PS not only induced differentiation of RAW 264.7 macrophages into dendritic-like cells but also promoted phenotypic and functional maturation of mouse JAWS II dendritic cells [43]. Besides, Cheung and colleagues found UST 2000 could induce cell proliferation and the secretion of IL-2, IL-6 and IL-8. In addition, the phosphorylation of extracellular signal-regulated kinases (ERK) was induced transiently by the treatment of cordysinocan [116]. Additional *in vitro* studies further illuminated HS002-II derived from *Hirsutella sinensis* showed that the NO, TNF-α, IL-1β, and NF-κB using murine macrophages cell line (RAW264.7), which exhibited significant immunomodulatory activity by stimulating the IκB-NF-κB pathway [44].

3.2.3. Cantharellaceae (Cantharellus cibarius and Craterellus cornucopioides) polysaccharides

Yang et al. reported a polysaccharide (WCCP-N-b) of *Cantharellus cibarius* could significantly increase macrophage phagocytosis, the release of NO and secretion of TNF-α, IL-6, and IL-1β [46]. On a cellular mechanistic level, WCCP-N-b activated MAPKs and NF-κB signaling pathways *via* TLR2. CC-1 and JBP-1 were found that could encourage the proliferation of B cells and T cells [47,119]. Guo and colleagues found a novel *Craterellus cornucopioides* polysaccharides CCP [48,49], it was found that the BALB/c mice models in the preventive groups treated with CCP had better immunoregulatory activity by spleen and thymus weight indices evaluation and histopathological analysis, indicating a protective function of CCP against the immunosuppression induced by cyclophosphamide (CTX). Moreover, CCP displayed definite and positive synergistic effects on the T- or B-lymphocyte proliferation induced by ConA or LPS, respectively, promoted the natural killer (NK) cell activity and markedly increased phagocytic activity to activate peritoneal macrophages in immunosuppressive mice. Besides, CCP could increase the protein expression of the G-protein coupled cell membrane receptor TLR4 and the production of its downstream protein kinases (TRAF6, TK1, p-IKKα/β, and NF-κB p50), while enhancing the production of cytokines (IL-2, IL-6, TNF-α, and IFN-α) through both preventive and therapeutic treatments *via* regulation of the TLR4-NFκB pathway in the peritoneal macrophage of immunosuppressive mice [48,49].

3.2.4. Ganodermataceae (Ganoderma atrum, Ganoderma lucidum and Ganoderma sinense) polysaccharides

In the past decade, there are a large number of published studies from Xie Mingyong's team that described the immunomodulatory effects of *Ganoderma atrum* polysaccharides (PSG-1) [51–57,121,122,170]. Li et al., found PSG-1 treatment could boost basal lymphocyte proliferation (T and B cells) as well as enhance IL-2 production [52,53]. Zhang et al., also demonstrated that PSG-1 treatment could significantly increase the thymus and spleen index and the phagocytosis of macrophages, while the production of TNF-α, IL-1β, and NO also grew [56]. Furthermore, it was reported that PSG-1 acted on TLR4, signaled *via* the p38 MAPK pathway, and then activated NF-κB and stimulated TNF-α production, in the meantime increased the expression of TLR4 and NF-κB, the degradation of IjBa and the phosphorylation of p38 MAPK. *Ganoderma atrum* polysaccharide also dose-dependently motivated the release of TNF-α and IL-1β and induced NF-κB activation by elevation of p65 nuclear translocation. Moreover, Yu et al. indicated that PSG-1 plays a major role in the protection against myelosuppression and immunosuppression and oxidative stress in cyclophosphamide (Cy)-treated mice as a potential immunomodulatory agent [170]. It is worth noting that the signaling pathways underlying the immunomodulatory effects of reishi polysaccharide on splenic lymphocytes from Ca^{2+} and calcineurin (CaN) activity perspective [121]. PSG-1 was first evaluated to increase the nuclear factor activity of activated T cells (NFAT), but this activity could be attenuated by treatment with CaN inhibitors (cyclosporine A and FK506), which provides a new perspective of research for subsequent studies on the immunoreactivity of EMFs polysaccharides.

Interestingly, Ming-Yong Xie's team conducted a study on mannose receptor (MR) mediated macrophage immune responses to *Ganoderma atrum* polysaccharides in 2017, which is not covered by many authors conducting studies on EMFs polysaccharide immunoreactivity [52]. They reported that MR was essential for the immune response to PSG-1 since enhanced phagocytosis in normal macrophages and the increased concentrations of IL-1β and TNF-α when the concentration of MR was raised. Interestingly, anti-MR antibody at least debilitated PSG-1-mediated anti-inflammatory responses, nevertheless it could not affect TNF-α secretion, suggesting that another receptor might be associated with PSG-1-triggered immunomodulation [52]. Xiang et al., reported that PSG-1 could improve the Th17 cell-specific production of IL-17A and IL-6, the expression of transcription factors (STAT3, RORγt), and phosphorylation of STAT3 in cyclophosphamide-induced immunosuppressed mice [51]. Besides, the Treg cell-specific cytokines (TGF-β1, IL-10) expression, and the transcription factor (Foxp3) were increased. It also raised the ratio of Th17 cells to Treg cells and restored the Th17/Treg ratio.

In the study of *Ganoderma lucidum* polysaccharides, GSG was just as an effective inducer of MAPKs- and Syk-dependent secretion (TNF-α and IL-6) in peritoneal macrophages, while dectin-1 could effectively recognize GSG and partially intervene its biological activities [58]. In other *vitro* studies, cy-treated mice compared to low-dose (2.5 mg/kg, i.p), Gl-PS could advance recovery of bone marrow cells, red blood cells, and white blood cells, as well as splenic natural killer T cells, and improved the proliferation responses of T and B cell (day 8), cytotoxic T lymphocyte activity (day 5), also NK cell and lymphokine-activated killer cell activity (days 7–9). Additionally, macrophage phagocytosis was increased (day 12). Meanwhile, Gl-PS turned out to promote the maturation of bone marrow-derived DC *in vitro* and also increase the initiation of DC-induced immune response [127,129].

In the study of *Ganoderma sinense* polysaccharides, GSP-4 was reported that could considerably stimulate the production of TNF-α, IL-1β, IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in human peripheral blood mononuclear cells (PBMCs).

GSP-4 also improved the iNOs mRNA expression in a dose-dependent manner [125]. Han et al. concluded that GSP-6B could also significantly induce the production of IL-1β and TNF-α in PBMC and exhibited no toxicity to either PBMC or a human macrophage cell line THP-1, while activating dendritic cells (DC) by encouraging the secretion of IL-12 and IL-10 [126].

3.2.5. Hericiaceae (Hericium erinaceus) polysaccharides

A large number of *in vitro* and *in vivo* studies have demonstrated that *Hericium erinaceus* polysaccharides could improve immunity. Sheng et al. found that ConA-stimulated proliferation of splenic lymphocytes was considerably increased after HEP treatment [134]. In another study described by Wu et al. illuminated that the polysaccharide HEP-W was able to stimulate proliferation of T and B lymphocytes and secretions of IL-2, IL-4, and IFN-γ [61]. Recent pieces of evidence have reported that HEP holds macrophage activation activity through enhancing capacities of phagocytic, production of NO, and proinflammatory cytokines. Meanwhile, the mRNA and protein expressions of iNOS, IL-6, and TNF-α needed to be improved [60,61,131,134,136]. Furthermore, although the action mechanism of HEP isolated from the fruiting body in activating RAW 264.7 cells has been affirmed, mycelium or culture broth was not clear [131]. Wu et al. [61] asserted that a heteropolysaccharide (HEP—W) could active the macrophage activity through myeloid differentiation protein 88 (MyD88)/IRAK-1/TRAF6/PI3K/protein kinase B (Akt)/MAPKs signaling pathways, and TLR2 synergism with mannose receptor (MR) to co-regulate the immunomodulatory response in RAW 264.7 cells. However, it is worth noting that the possible mechanism of macrophage, induced elution with 0.05 M NaCl solution, immunomodulatory activity was chiefly through PI3K/Akt/MAPKs/NF-κB and MyD88/IRAK/TRAF-6/IKKs/IKBs/NF-κB signaling pathways, which might be ascribed to their distinctions in structural features caused by different elution solvent [60]. In another study, HEP from the fruiting body was reported as induce DCs maturation and suppress DCs endocytosis. Meanwhile, exposure stimulated DCs was significantly stimulated secretion of IL-12 and IFN-γ cytokines that promoted TH1 responses after polysaccharide (sHEP and HEP) treatments. Further study demonstrated that the HEP could up-regulate the MAPK and down-regulate NF-κB signaling pathways of TLR4 [136,137].

3.2.6. Polyporaceae polysaccharides

Polyporaceae is the most widely used EMPs of the classification (family), such as *Bjerkandera fumosa*, *Coriolus versicolor*, *Cryptoporus volvatus*, *Grifola frondosa*, *Inonotus obliquus*, *Phellinus igniarius*, *Phellinus pini*, *Polyporus umbellatus*, *Poria cocos*, and *Trametes orientalis*. There is a large amount of literature has confirmed that *Polyporaceae* polysaccharide has a significant effect on improving immunity. A novel polysaccharide (DBFM3) isolated from *Bjerkandera fumosa* was found that could increase the lymphocyte proliferation in the presence of mitogen A or lipopolysaccharide [62]. *Coriolus versicolor* polysaccharide's immune function is widely known. Also, a study carried out to evaluate the antiviral effect of *Coriolus versicolor* polysaccharide CV-S2-Fr.I combined with INF-γ suggested that they could co-induce the production of NO. However, CV-S2-Fr.I used alone was invalid on NO proliferation [171]. A separately published report revealed evidence that *Coriolus versicolor* polysaccharide (CVP) markedly accelerated the mouse splenocytes proliferation. Besides, CVP-induced B cell proliferation may be considerably constrained by anti-mouse immunoglobulin (Ig) blocking antibody (Fab) or in cells from TLR4-mutant mice (C3H/HeJ), as well as phosphorylation of ERK-1/2 and p38 MAPK distinctly rose in a time-dependent manner, which was the nuclear translocation of the cytosolic NF-κB p65 subunit after CVP-treatment stimulation [172]. Furthermore, the polysaccharide (mPRSon) isolated from *Polyporus rhinocerus* was also demonstrated to boost immunity on bone marrow dendritic cells, while could also activate functional maturation of BMDCs [173]. Meanwhile, the expression of membrane phenotypic marker CD86 was increased by mPRSon treatment, while binding to the dectin-1 receptor and encourage the release of macrophage inflammatory protein 1α (MIP-1α), MIP-2, and IL-2 [173].

In research of *Grifola frondosa* polysaccharides, Ma et al. revealed that GFP-A prompted the function of phagocytes [174]. Other *in vitro* studies have shown that GFP-A exhibited the same splenic cell proliferation as ConA or LPS, while the indices of thymus and spleen were increased, the levels of LDH and ACP in the spleen were rose, and the mRNA levels of IL-1β, IL-2, IL-6, and IFN-γ in splenocyte were also elevated. It is worth noting that GFP-A can significantly improve the expression of $CD4^+$ and $CD8^+$ T lymphocytes, which were restrained by the CTX in peripheral blood [174]. In research of *Inonotus obliquus* polysaccharides, PFIO was in a position to enhance NO, ROS production, TNF-α secretion, and phagocytosis of phagocytes, while cell proliferation, and IFN-γ/IL-4 secretion in mouse splenocytes [175]. The phosphorylation of three MAPKs as well as the nuclear translocation of NF-κB, resulting in the activation of RAW264.7 macrophages was induced after PFIO treatment. PFIO also induced the inhibition secretion of TNF-αthrough the TLR2 receptor [175]. Similarly, other studies reported that the polysaccharide fraction (DEPS) could not only tremendously produce the secretion of TNF-α, IFN-γ, IL-1β, and IL-2 in PBMCs but also showed no toxicity to PBMCs [176]. Chen et al. found that the proliferation of spleen cells and lymphocytes induced by ConA and LPS was enhanced in a dose-dependent manner after IP3a treatment [177]. At the same time, IP3a could promote cytokine secretion (IL-2, IL-6, IL-12 and TNF-α) and macrophage phagocytosis in mice. It is worth noting that IP3a could increase Bax expression and inhibit Bcl-2 expression significantly [177]. However, other recent studies have not measured the expression of these two metrics (Bax and Bcl-2). Furthermore, the polysaccharide isolated from *Phellinus igniarius* was also illuminated to improve the cellular immunity as evidenced by the fact that a heteropolysaccharide (PISP1) accelerated the proliferation of mouse spleen lymphocytes [178].

In research of *Polyporus umbellatus* polysaccharides, the treatment of BMDCs with PPS demonstrated effective activity of improving the cell-surface expression of CD86, and increasing production of both IL-12 p40 and IL-10 in a dose-dependent manner *via* monoclonal antibodies to TLR4. Additionally, the same treatment of BMDCs with PPS was found that could increase T cell-stimulatory ability and reduce phagocytosis [179,180]. PPS (f-PPS) was bound specifically to BMDCs. Interestingly, binding intercepted by unlabeled PPS and anti-TLR4, but not by anti-TLR2 and anti-CR3 monoclonal antibodies, which has not been previously described by others. Similarly, *in vitro* studies further demonstrated that PPS was able to effectively promote the NO production and cytokine expression in macrophages. The evaluation of C3H/HeN mice treated with PPS showed that the proliferation of splenocytes and the production of TNF-α, IL-1β, and NO of peritoneal macrophages were markedly alleviated after treatment, as well as function-blocking antibodies to TLR-4, but not TLR-2 and CR3, obviously restrained production of TNF-α and IL-1β after PPS treatment [179,180]. On the other hand, a separately published report revealed evidence that a polysaccharide named ZPS isolated from *Polyporus umbellatus* was an effective activator of B cell, macrophages, and dendritic cells. Interestingly, a substantial reduction caused by ZPS branches was not only to motivate B cells *in vitro* but also to induce specific IgM production *in vivo* [70].

In research of *Poria cocos* polysaccharides, PCPs were reported to improve the function of the mononuclear phagocyte system, antigen-presenting cells and humoral immunity [181,182]. The immunomodulatory activity of two polysaccharides, P1 and P2, from *Poria cocos* was investigated [183]. In another animal study, polysaccharides fractions from *Poria cocos* were considered to boost immunity by activating T cells in Balb/c mice. After the treatment of ovalbumin-immunized mice given PRF (200 mg/kg), the proportion of cytotoxic T cells among splenocytes was remarkably heightened, suggesting that PRF had the potentiality to modulate the specific immune response by activating T cells [184]. In another interesting study, similarly, a polysaccharide (PCSC) was illuminated that could substantially promote NO production

and activate NF-κB/Rel that upregulated the transcription of iNOS [185]. It was universally known that p38 kinase was the basis of LPS-induced signal transduction through activating the synthesis of some cytokines [166]. So, it is worth noting that p38 kinase was overexpression in RAW 264.7 cells after PCSC treatment. Besides, when p38 kinase inhibitor was added to the culture medium of RAW 264.7 cells, overexpression levels of NF-κB/Rel and NO production were reduced. However, it could not happen when using inhibitors of mitogen-activated protein kinase/extracellular signal-regulated kinase 1. Beyond that, NO production could also be prevented by treating cells using anti-CD14, anti-TLR4, and anti-CR3 antibodies, suggesting PCSC could interact with these cell membrane receptors and consequently upregulate p38 kinase pathway [185].

3.2.7. Tremellaceae (Tremella and Tremella aurantialba) polysaccharides

Jiang et al. illuminated that *Tremella* polysaccharides (TP) improved the number of leukocytes in the peripheral blood which were significantly decreased by cyclophosphamide [73]. Zhou et al. found that *Tremella* polysaccharides (TP) could significantly enlarge the TI and SI (thymus and spleen index), moderate pathological features of immunosuppression (the arrangement of the liver sinusoid, disordered hepatic plates, infiltrated massive inflammatory cells and fatty degeneration of hepatocytes in the liver, intermixed red and/or white pulp, demolished and/or disappeared splenic corpuscles, extended splenic sinusoid, and decreased lymphocytes of the spleen in the spleen) [142]. TP exhibited a preventive effect for cyclophosphamide-induced immunosuppressed mice, which could also up-regulate serum levels of immune factors (IL-2, IL-12, INF-γ, and IgG), reduce the level of TGF-β in serum, noticeably raise mRNA expression of IL-1β, IL-4 and IL-12 in liver and spleen, and restrain mRNA expression of TGF-β [142].

In the research of *Tremella aurantialba* polysaccharides, TAPA1 could stimulate the proliferation of mouse spleen lymphocytes *in vitro* [147]. Du et al. compared with TAPA1, TAPA1-ac indicated considerable immunostimulation effects on the proliferation of mouse spleen lymphocytes (MSLs) and the production of NO by macrophages RAW264.7, while TAPA1-deac exhibit significant lower effects [147]. Additionally, it's worth noting that the immune activity above may be related to the content and concentration of acetyl groups, suggesting that acetylation of TAPA1 was an effective way of improving immunostimulating activities [147]. Other *in vitro* animal experiments show that TAP-3 as an immunopotentiator could produce strong immune enhancement effects, such as promoting the production of NO, IL-1β, and TNF-α secretion by macrophages. Further research indicated that the crucial membrane receptor of TAP-3 was identified to be TLR4, and the chain length was indispensable for its immunoregulatory activity [74].

3.2.8. Pleurotaceae polysaccharides

Pleurotaceae is the other most widely used EMPs of the classification (family), which were commonly known as mushrooms, for instance, *Lentinus edodes*, *Pleurotus albidu*, *Pleurotus eryngii*, *Pleurotus ferulae*, *Pleurotus florida*, *Pleurotus nebrodensis*, *Pleurotus ostreatus*, *Pleurotus pulmonarius*, and *Pleurotus tuber-regium*. In some of the earlier studies, the *Lentinus edodes* polysaccharide (L-II) could significantly increase the concentration of TNF-α, IFN-γ in serum in the polysaccharide groups compared with the model control group, but IL-2 not [186]. Moreover, L-II could raise the production of NO and catalase activity in macrophages [186]. Lo et al. researched *Lentinula edodes* polysaccharides *in vitro* macrophage stimulated activities from 10 regionally different strains [187]. Additional *in vitro* studies further illuminated the potential mechanism of action that stimulated immune activates treatment by *Lentinus edodes* polysaccharides associated with the upregulation of MHC II, CD80/CD86, and TLRs in spleen dendritic cells (DCs) [187]. Zhou et al. found that α-(1–3)-β glucan (lentinan) from *Lentinus edodes* could enhance the production of IL-12, IFN-γ, and NO in spleen cells of infected mice [188]. Additional animal studies further illuminated that lentinan could enhance expression of MHC II, CD80/CD86, and TLRs (TLR2/TLR4), and increase the production of IL-12 in spleen dendritic cells (DCs) co-cultured with parasitism red blood cells (pRBCs). Moreover, both the amount of $CD4^+$, $CD25^+$ regulatory T cells, and the levels of IL-10 secreted dropped by pre-treatment with lentinan in the spleen of malaria-infected mice. Meanwhile, apoptosis of $CD4^+$T cells in the spleens of mice pretreated with lentinan was considerably reduced [188]. Kojima et al. found that IA-a and IA-b could potently phagocytosis and cytokine production in RAW264.7 cells [189]. Similarly, other studies indicated that LEP1 and LEP2 could dramatically improve by LEP1/-2 treatment. Production of NO, TNF-α, and IL-6 were higher in LEP1/-2-treated groups than in the cLEP-treated group. Also, LEP1/-2 had a greater improving effect on mRNA transcription of iNOS, TNF-α, and IL-6 genes. On the other hand, the phosphorylation of kinases ERK and JNK was heavily promoted by LEP1/-2 treatment, suggesting this improving immunocompetence *via* MAPK signaling pathway [190].

In the research of *Pleurotus eryngii* polysaccharides, Xu et al. found that a water-soluble polysaccharide EPA-1 could significantly induce macrophage to release the lever of NO, TNF-α, IL-1, and IL-6 through up-regulating signal protein of p38, ERK, JNK in MAPKs and translocation of nuclear NF-κB [87]. Similarly, other studies also indicated that WPEP-N-b boosted the degradation of IκB-α, and increased phosphorylation of MAPKs and the NF-κB p65 subunit, which demonstrated this polysaccharide activates RAW264.7 cells through MAPK and NF-κB signaling pathways and the TLR2 [86]. In the research of *Pleurotus florida* polysaccharides, PS and glucan were found that could stimulate macrophages, splenocytes, and thymocytes. PfloVv5FB could exhibit strong immune activation of macrophages, splenocytes as well as thymocytes [191–194].

Additionally, other studies in research of *Pleurotus nebrodensis* polysaccharides reported a novel polysaccharide (PN50G) [195]. The phagocytosis of macrophages was significantly enhanced, and remarkable changes were noted in the morphology of PN50G-treated cells. Compared with the control group, the production of TNF-α, IL-6, IL10, and iNOS in the macrophages, as well as the RNA expressions were strongly induced after PN50G treatment. Pro-/anti-inflammatory cytokine secretion ratios (IL-6/IL-10, TNF-α/IL-10, NO/IL-10) by lipopolysaccharide-stimulated RAW264.7 macrophages were significantly declined by PN50G in a dose-dependent manner under an immoderate immune experimental model [195]. Most recently, Cui and colleagues demonstrated that the phagocytosis of macrophages was markedly improved after exposure to PN-S, with observed remarkable changes in morphology. PN-S was reported to improve RAW264.7 cells to progress *via* S and G2/M phases [196,197]. Additionally, PN-S could enhance the production of IL-6, NO, INF-γ, and TNF-α in the macrophages, with upregulating mRNA expressions of IL-6, iNOS, INF-γ, and TNF-α being monitored in a dose-dependent manner. Additional animal studies further illuminated that PN-S treatments considerably changed the CY-in reduced weight loss, boosted the TI and SI, and promote prolife action of T lymphocyte, B lymphocyte, and macrophages. PN-S also raised the activity of natural killer cells and increased the IgM and IgG levels in the serum [196,197].

In research of *Pleurotus ostreatus* polysaccharides, POP was able to improve concanavalin A (ConA)-or lipopolysaccharide (LPS)-induced lymphocyte proliferation [198]. The heteroglycan (WPOP-N1) isolated from *Pleurotus ostreatus* was reported that could stimulate macrophages, splenocytes, and thymocytes, and markedly be growing in secretion level of TNF-α in the serum [199]. Additionally, WPOP-N1 raised the phagocytic capability of peritoneal macrophages *in vitro*, as well as the secretion of TNF-α, NO, and the amount of TNF-α and iNOS transcript increased substantially when the peritoneal macrophages were susceptible to WPOP-N1. Meanwhile, further molecular experiments showed that the stimulation of peritoneal macrophages by WPOP-N1 induced the phosphorylation of p65 and a marked down-regulation of IκB expression [199]. In the research of *Pleurotus*

pulmonarius polysaccharides, purified β-glucan was able to effectively increase NO, TNF-α and IL-1β production in macrophages, while these effects being very similar to those of *Escherichia coli* serotype lipopolysaccharide (LPS), while not modifying the response of LPS-activated macrophages [200].

3.2.9. Tricholomataceae (Armillaria mellea, Flammulina velutipes, Tricholoma crissum, Tricholoma lobayense, and Tricholoma matsutake) polysaccharides

In the research of *Armillaria mellea* polysaccharides, the water-soluble *Armillaria mellea* polysaccharide (AMP) was reported which could stimulate lymphocyte proliferation induced by concanavalin A or lipopolysaccharide in a dose-dependent manner [201]. Similarly, Chen et al. reported that a polysaccharide fraction (AMPs-2-1) isolated from *Armillaria mellea* could promote proliferation of splenocyte lymphocytes and phagocytosis of macrophages RAW264.7, exhibited significant immunomodulatory activities [93].

A polysaccharide (FVSPs) was extracted from the base of *Flammuliana Velutipes*. In this research, FVSPs was shown a high ability to significantly increase the proliferation and phagocytic activity of macrophage [202]. Interestingly, another study revealed an enhancing-immune polysaccharide (PFVM) derived from *Flammuliana Velutipes* in terms of the number of T lymphocyte subsets ($CD3^+$, $CD4^+$, and $CD8^+$) [203]. The percentage of $CD3^+$ and $CD4^+$ T lymphocyte, the ratio of $CD4^+/CD8^+$, and the levels of IL-2 and TNF-α were significantly enlarged in polysaccharide of PFVM. On the other hand, the percentage of $CD8^+$ T lymphocyte was reduced in polysaccharide of PFVM dose-dependent manner indicated that the T lymphocyte immune function was stimulated after a long term exposure of PFVM [203].

In the research of other *Tricholomataceae* polysaccharides, *Tricholoma crissum* polysaccharide (PS) were reported that could exhibit splenocyte, thymocyte as well as macrophage activations [96]. Zhang et al. found that polysaccharide TLH-3 extracted from *Tricholoma lobayense* could significantly enhance the phagocytic activity, production of NO, and secretion of the cytokine TNF-α, IL-6 [204]. Furthermore, TNF-α and IL-6 were blocked by the inhibitor of TLR4 (Toll-like receptor4), which indicated TLR4 was a receptor of TLH-3 as well as immunomodulatory activity of TLH-3 was mediated by TLR4 [204]. Moreover, immunofluorescence suggested that TLH-3 leads to the nuclear translocation of NF-κB subunit p65, which demonstrated that NF-κB levels in nuclei increased and cytoplasmic IκB-α degraded after TLH-3 treatment [204]. Similarly, other studies reported that TMF-II derived from *Tricholoma matsutake* would comparably increase and/or highly upregulate the production of NO production and expression of IL-1β, IL-6, IL-12, and TNF-α to LPS [205]. On the other hand, TMF-II provoked the phosphorylation of IκBα, a vital step for NF-κB activation and translocation. It is worth noting that the upstream signaling enzymes (SRC and AKT) were observed the responsible upstream signaling components in the induction of NO production, even though TMF-II strongly upregulated the phosphorylation of all MAPK pathways [205]. In another study, TMC-2 also derived from *Tricholoma matsutake* was demonstrated that could strongly increase the production of NO and TNF-α [206]. Additionally, phagocytic uptake and ROS generation were also improved by TmC-2 treatments. Interestingly, TmC-2 stimulated CD29-mediated cell-cell or cell-fibronectin adhesions in monocytes, while CD43-mediated cell adhesion was down-regulated. The enhancement of proliferation and IFN-γ production was strikingly reported in TmC-2-treated splenic lymphocytes. Further molecular experiments showed that the activation mediated by up-regulating intracellular signaling cascades such as PI3K/Akt and MAPK (ERK and p38) and by the involvement of surface receptors (dectin-1 and TLR-2) [206].

3.3. Anti-inflammatory activity

Inflammation is a defense reaction produced by the living tissues of the vascular system after the organism is stimulated by various injury factors, and the pathological process is the exudation, degeneration, and hyperplasia of tissues in the inflamed area [166]. The clinical data from this novel coronavirus study revealed that pathogenic coronavirus infection initially presents as a mild influenza-like illness with fever, dyspnea, and cough, which progresses to atypical interstitial pneumonia and diffuse alveolar damage, with more severe cases of the disease dyspnea and/or hypoxemia develops 1 week after the onset of symptoms, with rapid progression to acute respiratory distress syndrome in severe cases (ARDS), septic shock, intractable metabolic acidosis and coagulopathy, COVID-19 infection [33,34]. The pathogenesis of severe lung injury caused by a severe inflammatory response and acute lung injury may be through an acute inflammatory response and the cytokines IL-1, IFN-γ, interferon-inducible protein 10 (IP-10), monocyte chemotactic protein-1 (MCP-1), IL-4 and IL-10 secretion is increased, and the patients' strength of the cytokine storm following infection correlates with the severity of the disease [166].

Numerous previous studies have demonstrated that anti-inflammatory activity is very common in diverse sources of EMFs polysaccharides. Its mechanism of action was determined by the following anti-inflammatory mechanisms, the foremost being inflammatory factors that promote inflammatory responses, such as TNF-α, and interleukins (IL-1β, IL-2, IL-6, IL-8, and IL-12). Among them, TNF-α, as an important inflammatory factor, can induce lymphocytes and epithelial cells to produce a variety of adhesion molecules, induce the production of chemokines, prompting inflammatory cells to localize to inflammation, further causing inflammation, tissue damage, and other pathological changes [166]. The second category is anti-inflammatory factors that reduce or inhibit the inflammatory response, such as IL-4, IL-5, and IL-10. Among them, IL-10 is the most popular and prominent anti-inflammatory cytokine, which can exert its anti-inflammatory effects through multiple pathways. The role of MAPK in the production of pro-inflammatory cytokines, such as antagonizing the secretion of pro-inflammatory cytokines, enhances the effect of 5-HT, modulating MAPK, and enhancing the production of pro-inflammatory cytokines [166]. Other anti-inflammatory cytokines such as IL-4 and IL-13 may also have similar characteristics to IL-10. The anti-inflammatory details in separate families (*Morchellaceae*, *Xylariaceae*, *Ganodermataceae*, *Polyporaceae*, *Phallaceae*, *Agaricaceae*, *Pleurotaceae*, *Russulaceae*, and *Tricholomataceae*) of EMFs polysaccharides will be described as followed.

Morchella esculenta polysaccharide (EMP-1) and sulfated polysaccharide (SEMP-1) were found that the best-protecting effect in decreasing PM2.5-induced cell death, cell apoptosis and production of TNF-α and IL-1β, as well as accompanied by a vitiated level in ROS formation, caused by PM2.5 in rat alveolar macrophage NR8383 cells [99]. Moreover, SEMP-1 could decrease the expression of iNOS and COX-2 at both mRNA and protein levels with PM2.5 treatment. Besides, the PM2.5-induced phosphorylation of NF-κB was also decreased *via* suppressing nuclear translation of the NF-κB and inhibiting the degradation and phosphorylation of IκBα [99]. Similarly, other studies reported that acetylation of polysaccharide (PEMP and Ac-$PMEP_{1-3}$) extracted from *Morchella angusticeps* compared with the control group, PMEP and $AcPMEP_{1-3}$ boosted cell proliferation and the production of NO and TNF-α of RAW264.7 macrophages (cultured without lipopolysaccharide). On the other hand, compared with PMEP, Ac-PMEP3 improved cell viability and NO production by inducing the degradation of cytoplasmic IκBα and nuclear translocation of NF-κB subunit p65 as well as the expression of iNOS and phosphorylated-p38 [97]. The intensive search for alleviating PM2.5-induced lung injury in mice has resulted in the discovery of *Trametes orientalis* polysaccharide (TOP-2) intervention could moderate PM2.5-induced lung injury (pulmonary edema) in mice through its antioxidant and anti-inflammatory activities [207]. PM2.5 could notably raise the number of inflammatory cells and proportion of neutrophils in bronchoalveolar lavage fluid (BALF), and remarkably declined the percentages of macrophages in BALF, however, TOP-2 eliminated these effects. Additionally, TOP-2 could inhibit increasing levels of total protein, albumin, C-

reactive protein (CRP), myeloperoxidase (MPO), lactate dehydrogenase (LDH), alkaline phosphatase (AKP), acid sphingomyelinase (ASM), TNF-α, IL-1β and IL-6 in BALF after PM2.5 exposure. On the other hand, TOP-2 up-regulated the expressions of nuclear factor-erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) and inhibited the activation of NLR family pyrin domain-containing 3 (NLRP3) inflammasome in the lung tissue [207].

Furthermore, the polysaccharide isolated from the *Dictyophora indusiata* (DIP) was also shown to be anti-inflammatory activity as evidenced by the facts that DIP restrained NF-κB signal pathway through regulating TLR4 expression, phosphorylation of IκBα and nuclear translocation of NF-κB-p65 subunit [75]. Similarly, DIP decreased inflammasome activation through down-regulating NLRP3 expression in cytoplasmic pools, confining self-assembly of NLRP3 inflammasome, meanwhile the subsequent triggering of caspase-1 and the secretion of IL-1β and IL18 [75]. In another study, a glucogalactomanan polysaccharide (TJ3) isolated from *Agaricus bisporus* induced an inflammatory response through the ERK/MAPK and IjB/NFjB pathways in macrophages [208]. Huijeong et al. found that Lentinan (LNT) from shiitake could selectively attenuate AIM2 and non-canonical inflammasome activation as well as inducing pro-inflammatory cytokine production, which could selectively inhibit lacking in melanoma 2 (AIM2) inflammasome activation [209]. In addition, LNT improved pro-inflammatory cytokines and induced expression of inflammasome-related genes *via* toll-like receptor 4 signalings, which indicated that could as an anti-AIM2 and anti-non-canonical inflammasome candidate even if its enhancing of cytokine expression [209].

Ken-ichiro et al. reported that *Pleurotus citrinopileatus* polysaccharide (PCPS) was able to regulate the monocyte-to-macrophage differentiation early at the monocyte stage [84]. PCPS could inhibit the levels of secreted pro-inflammatory cytokines (TNF and IL-6), increase the secreted levels of the anti-inflammatory cytokine IL-10, and the expression levels of CCL2 and CCL8 mRNAs, similarly constrained mRNA expression of CCR2 in the IFNγ/LPS activated macrophages [84]. In previous study, Ken-ichiro et al. [85] found that PCPS improved the surface maturation markers (CD80, CD86, and HLA-DR) on DCs, which suggested its potential to induce DC maturation. Additionally, PCPS was a DCs activator to secrete the pro-inflammatory cytokines (TNF, IL-1β, IL-6, and IL-12), as well as the anti-inflammatory cytokine IL-10. At the same time, PCPs also enhanced mRNA levels of the chemokines (CCL2, CCL3, CCL8, CXCL9, CXCL10, and LTA). The secretion of TNF and IL-12 by PCPS-activated DCs could significantly be eased by an anti-Dectin-1 antibody, as well as by a Syk kinase and a Raf-1 inhibitor, suggesting that PCPS motivated Dectin-1 signaling at least partly *via* the Syk- and the Raf1-dependent pathways in DCs [85]. Song et al. reported that anti-inflammatory and hepatoprotective effects of exopolysaccharides (EPS) extracted and purified from *Pleurotus geesteranus* on alcohol-induced liver injury [210]. Changes in anti-inflammatory factors are essentially consistent with the other EMFs polysaccharides mentioned above. [210].

Marcia L.L. Silveira et al. found that an exopolysaccharide (PEIsR) produced by *Pleurotus sajor-caju* has anti-inflammatory activity. *In vivo* could be as a potent and effective antinociceptive and anti-inflammatory candidate [91]. On the other hand, Marcia et al. reported the LPS from *P. sajor-caju* demonstrated an immunomodulatory activity on THP-1 macrophages [91]. Further animal experiments showed that LPS significantly inhibited the inflammatory phase of pain sensation in mice induced by formalin, and effectively reduced the total number of leukocytes and the level of myeloperoxidase in mice induced by LPS [91].

3.4. Regulation of population balance of gut microbiota

The intestinal tract is an important digestive organ of the body and is also the main host site for symbiotic microflora, which plays an essential role in the maintenance of normal life activities such as immune and endocrine functions [211]. Normally, intestinal flora, host, and external environment maintain a dynamic balance, but due to drug metabolism, changes in the flora, abnormal intestinal dynamics, age, dietary habits, and immune dysfunction, this balance can be disrupted, causing an imbalance in intestinal flora and pathological changes in host organism [211,212]. In this novel coronavirus, it has also been shown that there is a correlation between changes in the intestinal flora of patients with neo-corneal pneumonia and the neo-corneal virus [35]. Many studies have shown that EMFs polysaccharide has the function of regulating intestinal function, including participating in the immune process by acting on the intestinal mucosa, protecting the integrity of the intestinal barrier structure and function, regulating the composition of intestinal flora and stimulating the intestinal endocrine, and so on.

A polysaccharide extracted and purified from *Dictyophora indusiata* was reported to advance recovery from antibiotic-driven intestinal dysbiosis and promote gut epithelial barrier function in a mouse model [213]. Among controls, daily oral administration of clindamycin and metronidazole for two weeks was evaluated to reduce bacterial diversity and richness and disorder rates of microflora at different taxonomic levels (altered Firmicutes/Bacteroidetes ratio and rose relative abundance of harmful flora (*Proteobacteria*, *Enterococcus*, and *Bacteroides*), however, DIP administration recovered the dysbiosis and improving beneficial flora, such as lactic acid-producing bacteria (*Lactobacillaceae*), and butyrate-producing bacteria (*Ruminococaceae*). Additionally, endotoxemia was reduced by DIP treatment *via* LPSs and pro-inflammatory cytokine (TNF-α, IL-6, IL-1β) levels, with the increased expression of tight-junction associated proteins (claudin-1, occludin, and zonula occludens-1), which indicated a comprehensive perception of the protective effects of a DIP in the restoration or rebuilding of gut microbiota and emphasized its vital function in the enrichment of intestines barrier integrity, decrease of inflammation, and lowering of endotoxin levels in mice [213]. On the other hand, Zhang et al. [214,215] systematically investigated that *Lentinula edodes* polysaccharide (L2) refreshed mice in terms of immune responses and gut microbiota. L2 was reported to restore the aging immune responses by improving cytokine levels in peripheral blood and partly alter the aging composition of intestines microbiota. The results of further group animal experiments suggest the advantageous effects of L2 on boosting immunity and enhancing gut health. Besides, analysis of Caco-2 cells and a Caco-2/RAW264.7 *co*-culture system indicated that *Lentinula edodes*-derived polysaccharide (L2) remarkably intensified immune responses by differentially affecting gene expressions of small intestine (55 genes), cecum (26 genes) and colon (25 genes), recognized 3 core regulation networks (in the small intestine, cecum, and colon) for assorted parts of the gut [214,215]. In another study, the fecal microbiota in PEP (a homogeneous *Pleurotus eryngii* polysaccharide) treatment was evaluated structural differences compared to the control group, while the *Porphyromonadaceae*, *Rikenellaceae*; *Bacteroidaceae* and *Lactobacillaceae* abundances were entirely boosted at the family level [216]. It is worth noting that the immune response produced by oral administration of high dose PEP also changed significantly. In summary, PEP intake could play a positive role in gastrointestinal health [216]. Also, a separately published report revealed evidence that a novel polysaccharide (FVP2) isolated from *Flammulina velutipes*, impact on gut microbiota in rats was reported by Jufeng Ye [94]. On the one hand, the concentrations of two short-chain fatty acids (isobutyric acid and butyric acid) and the abundance of beneficial bacteria in the caecum after the FVP2 treatment were significantly higher than those in control group, as well as butyric acid level was effectively improved, thus increasing the intestinal beneficial bacteria. On the other hand, FVP2 can maintain the integrity of intestinal mucosa by improving intestinal barrier function [94].

4. Conclusion and future perspective

Nowadays, there is a restricted range of antiviral drugs with certain toxic side effects, but with the emergence of new mutant and resistant

strains of viruses, the availability of highly effective, low-toxicity, antiviral drugs have been increasingly important. Research on antiviral drugs for resistant viruses is imminent. EMPs polysaccharide has the characteristics of multi-component, multi-pathway, multi-target effect, and has unique advantages in antiviral, not easy to generate drug resistance. The unique advantage of EMPs polysaccharides against viruses is their ability to operate directly on viruses, inhibit their proliferation and, more importantly, modulate the host immune response, alleviate inflammatory damage, and fully exploit antiviral effects through multiple pathways and targets, thus seeking out natural EMPs polysaccharides is an important way to develop highly effective and low-toxicity novel antiviral drugs, *in vivo*. As a potential antiviral drug, its antiviral effect still has to be validated through clinical practice. EMPs polysaccharide species are numerous, and their absorption and distribution in the body were varied greatly. Why the EMPs polysaccharide were still only in the laboratory stage due to the following reasons:

(1) The EMFs polysaccharide molecules are very large, and existing studies suggest that polysaccharides containing β-glycosidic bonds have some antiviral activity (especially β-glucan), in addition to which some degree of sulphation modification may also enhance the antiviral activity of polysaccharides, but the analysis of the structure-antiviral relationship of most polysaccharides is not yet clear. Also, there is no way to control the quality of each batch, limiting its industrial production;
(2) The most existing industrialized production methods of EMFs polysaccharide are water extraction and alcohol precipitation, so the products are mostly crude polysaccharides and the amount of refined polysaccharides were limited which cannot meet the requirements for industrialization. Even if there are some EMFs polysaccharides pharmaceutical products on the market, basically their functional ingredients are crude polysaccharides, so there are still big controversies in terms of safety and stability.
(3) As the mode of action of EMFs polysaccharides is multifaceted and coordinated, their effect is slow and not immediate, and the changes in their biological activity after oral and gastrointestinal digestion have to be taken into account, so they cannot meet clinical requirements for the time being;
(4) Most current researches related to EMFs polysaccharides are based on cellular and/or animal levels. Unfortunately, there are few preclinical and/or clinical studies on the effect and mechanism of EMFs polysaccharides. As a result, there is still a long way to go from laboratory to market. Therefore, further research is urgently needed on its constitutive relationship and action mechanism.

CRediT authorship contribution statement

Yuxi Guo: Writing original draft, Conceptualization. Xuefeng Chen: Visualization, Investigation, Writing review & editing. Pin Gong.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

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References

[1] J. Grove, M. Marsh, The cell biology of receptor-mediated virus entry, J. Cell Biol. 195 (2011) 1071–1082.
[2] T.P. Sheahan, A.C. Sims, S.R. Leist, A. Schafer, J. Won, A.J. Brown, S.A. Montgomery, et al., Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV, Nat. Commun. 11 (2020) 222–235.
[3] J.D. Croxtall, C.M. Perry, Lopinavir/ritonavir a review of its use in the management of HIV-1 infection, Drugs 70 (2010) 1885–1915.
[4] V. Nukoolkarn, V.S. Lee, M. Malaisree, O. Aruksakulwong, S. Hannongbua, Molecular dynamic simulations analysis of ritronavir and lopinavir as SARS-CoV 3CL(pro) inhibitors, J. Theor. Biol. 254 (2008) 861–867.
[5] L.J. Stockman, R. Bellamy, P. Garner, SARS: systematic review of treatment effects, PLoS Med. 3 (2006) 1525–1531.
[6] L.L. Ren, Y.M. Wang, Z.Q. Wu, Z.C. Xiang, L. Guo, T. Xu, et al., Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study, Chin. Med. J. 133 (2020) 1015–1024.
[7] B.R. Beck, B. Shin, Y. Choi, S. Park, K. Kang, Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model, Comput. Struct. Biotechnol. J. 18 (2020) 784–790.
[8] M.R. Dayer, S. Taleb-Gassabi, M.S. Dayer, Lopinavir; a potent drug against coronavirus infection: insight from molecular docking study, Arch. Clin. Infect. Dis. 12 (2017) 13823–13829.
[9] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, et al., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*, Cell Res. 30 (2020) 269–271.
[10] E. de Wit, F. Feldmann, J. Cronin, R. Jordan, A. Okumura, T. Thomas, et al., Feldmann, prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection, Proc. Natl. Acad. Sci. U.S.A. 117 (2020) 6771–6776.
[11] T.P. Sheahan, A.C. Sims, R.L. Graham, V.D. Menachery, L.E. Gralinski, J.B. Case, et al., Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses, Sci. Transl. Med. 9 (2017) 396–407.
[12] L. Delang, R. Abdelnabi, J. Neyts, Favipiravir as a potential countermeasure against neglected and emerging RNA viruses, Antivir. Res. 153 (2018) 85–94.
[13] A. Zumla, Z.A. Memish, M. Maeurer, M. Bates, P. Mwaba, J.A. Al-Tawfiq, et al., Emerging novel and antimicrobial-resistant respiratory tract infections: new drug development and therapeutic options, Lancet Infect. Dis. 14 (2014) 1136–1149.
[14] V. Loustaud-Ratti, M. Debette-Gratien, J. Jacques, S. Alain, P. Marquet, D. Sautereau, et al., Ribavirin: past, present and future, World J. Hepatol. 8 (2016) 123–130.
[15] B. Morgenstern, M. Michaelis, P.C. Baer, H.W. Doerr, J. Cinatl, Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines, Biochem. Biophys. Res. Commun. 326 (2005) 905–908.
[16] J. Blaising, S.J. Polyak, E.I. Pecheur, Arbidol as a broad-spectrum antiviral: an update, Antivir. Res. 107 (2014) 84–94.
[17] J. Blaising, P.L. Levy, S.J. Polyak, M. Stanifer, S. Boulant, E.I. Pecheur, Arbidol inhibits viral entry by interfering with clathrin-dependent trafficking, Antivir. Res. 100 (2013) 215–219.
[18] H. Wang, P. Yang, K. Liu, F. Guo, Y. Zhang, G. Zhang, et al., SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway, Cell Res. 18 (2008) 290–301.
[19] G. Li, E. De Clercq, Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nat. Rev. Drug Discov. 19 (2020) 149–150.
[20] J.R. Teijaro, Type I interferons in viral control and immune regulation, Curr. Opin. Virol. 16 (2016) 31–40.
[21] R. Channappanavar, A. Fehr, R. Vijay, J. Zhao, D.K. Meyerholz, S. Perlman, Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice, J. Immunol. 196 (2016) 181–193.
[22] A.S. Omrani, M.M. Saad, K. Baig, A. Bahloul, M. Abdul-Matin, A.Y. Alaidaroos, et al., Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study, Lancet Infect. Dis. 14 (2014) 1090–1095.
[23] R.C. Chen, X.P. Tang, S.Y. Tan, B.L. Liang, Z.Y. Wan, J.Q. Fang, et al., Treatment of severe acute respiratory syndrome with glucosteroids - the Guangzhou experience, Chest 129 (2006) 1441–1452.
[24] T.W. Auyeung, J.S.W. Lee, W.K. Lai, C.H. Choi, H.K. Lee, J.S. Lee, et al., The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study, J. Inf. Secur. 51 (2005) 98–102.
[25] N. Lee, K.C.A. Chan, D.S. Hui, E.K.O. Ng, A. Wu, R.W.K. Chiu, et al., Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients, J. Clin. Virol. 31 (2004) 304–309.
[26] D. Plantone, T. Koudriavtseva, Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic, and neurological diseases: a mini-review, Clin. Drug Investig. 38 (2018) 653–671.

[27] J. Dyall, C.M. Coleman, B.J. Hart, T. Venkataraman, M.R. Holbrook, J. Kindrachuk, et al., Repurposing of clinically developed drugs for treatment of Middle East Respiratory Syndrome Coronavirus Infection, Antimicrob. Agents Chemother. 58 (2014) 4885–4893.
[28] M.J. Vincent, E. Bergeron, S. Benjannet, B.R. Erickson, P.E. Rollin, T.G. Ksiazek, et al., Chloroquine is a potent inhibitor of SARS coronavirus infection and spread, Virol. J. 2 (2005) 69–78.
[29] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, S.P.J. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2020) 271–280.
[30] J.F. Rossingol, Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus, J. Infect. Public Health 9 (2016) 227–230.
[31] J.F. Rossignol, Nitazoxanide: a first-in-class broad-spectrum antiviral agent, Antivir. Res. 110 (2014) 94–103.
[32] J.F. Rossignol, S. La Frazia, L. Chiappa, A. Ciucci, M.G. Santoro, Thiazolides, a new class of anti-influenza molecules targeting viral hemagglutinin at the post-translational level, J. Biol. Chem. 284 (2009) 29798–29808.
[33] M.L. Holshue, C. DeBolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce, et al., Washington State-nCo, first case of 2019 novel coronavirus in the United States, N. Engl. J. Med. 382 (2020) 929–936.
[34] S.H. Alfaraj, J.A. Al-Tawfiq, A.Y. Assiri, N.A. Alzahrani, A.A. Alanazi, Z.A. Memish, Clinical predictors of mortality of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: a cohort study, Travel Med. Infect. Dis. 29 (2019) 48–50.
[35] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (2020) 270–273.
[36] P. Cao, S. Wu, T. Wu, Y. Deng, Q. Zhang, K. Wang, et al., The important role of polysaccharides from a traditional Chinese medicine-lung cleansing and detoxifying decoction against the COVID-19 pandemic, Carbohydr. Polym. 240 (2020) 116346–116355.
[37] Lainian Huang, Zhibin Lin, Guoliang Chen, Medicinal and Edible Fungus, Shanghai Science and Technology Press, Shanghai, China, 2010 1.
[38] X. He, J. Fang, Q. Guo, M. Wang, Y. Li, Y. Meng, L. Huang, Advances in antiviral polysaccharides derived from edible and medicinal plants and mushrooms, Carbohydr. Polym. 229 (2020) 115548–115563.
[39] C.A. Su, X.Y. Xu, D.Y. Liu, M. Wu, F.Q. Zeng, M.Y. Zeng, et al., Isolation and Characterization of Exopolysaccharide With Immunomodulatory Activity From Fermentation Broth of *Morchella conica*, Daru, vol. 21, 2013 5–10.
[40] Y. Wen, D. Peng, C. Li, X. Hu, S. Bi, L. Song, et al., A new polysaccharide isolated from Morchella importuna fruiting bodies and its immunoregulatory mechanism, Int. J. Biol. Macromol. 137 (2019) 8–19.
[41] B.L. He, Q.W. Zheng, L.Q. Guo, J.Y. Huang, F. Yun, S.S. Huang, J.F. Lin, Structural characterization and immune-enhancing activity of a novel high-molecular-weight polysaccharide from *Cordyceps militaris*, Int. J. Biol. Macromol. 145 (2020) 11–20.
[42] Y. Zhang, Y. Zeng, Y. Cui, H. Liu, C. Dong, Y. Sun, Structural characterization, antioxidant and immunomodulatory activities of a neutral polysaccharide from *Cordyceps militaris* cultivated on hull-less barley, Carbohydr. Polym. 235 (2020) 115969–115878.
[43] L.Z. Meng, K. Feng, L.Y. Wang, K.L. Cheong, H. Nie, J. Zhao, S.P. Li, Activation of mouse macrophages and dendritic cells induced by polysaccharides from a novel *Cordyceps sinensis* fungus UM01, J. Funct. Foods 9 (2014) 242–253.
[44] L. He, P. Ji, J. Cheng, Y. Wang, H. Qian, W. Li, et al., Structural characterization and immunostimulatory activity of a novel protein-bound polysaccharide produced by *Hirsutella sinensis* Liu, Guo, Yu & Zeng, Food Chem. 141 (2013) 946–953.
[45] T. Wang, Z. Dong, D. Zhou, K. Sun, Y. Zhao, B. Wang, et al., Structure and immunostimulating activity of a galactofuranose-rich polysaccharide from the bamboo parasite medicinal fungus *Shiraia bambusicola*, J. Ethnopharmacol. 257 (2020) 112833–112840.
[46] G. Yang, Y. Qu, Y. Meng, Y. Wang, C. Song, H. Cheng, et al., A novel linear 3-*O*-methylated galactan isolated from *Cantharellus cibarius* activates macrophages, Carbohydr. Polym. 214 (2019) 34–43.
[47] D. Zhao, X. Ding, Y. Hou, W. Hou, L. Liu, T. Xu, et al., Structural characterization, immune regulation and antioxidant activity of a new heteropolysaccharide from *Cantharellus cibarius* Fr, Int. J. Mol. Med. 41 (2018) 2744–2754.
[48] M.Z. Guo, M. Meng, C.C. Feng, X. Wang, C.L. Wang, A novel polysaccharide obtained from *Craterellus cornucopioides* enhances immunomodulatory activity in immunosuppressive mice models via regulation of the TLR4-NF-kappa B pathway, Food Funct. 10 (2019) 4792–4801.
[49] M.Z. Guo, M. Meng, S.Q. Duan, C.C. Feng, C.L. Wang, Structure characterization, physicochemical property and immunomodulatory activity on RAW264.7 cells of a novel triple-helix polysaccharide from *Craterellus cornucopioides*, Int. J. Biol. Macromol. 126 (2019) 796–804.
[50] M. Ying, B. Zheng, Q. Yu, K. Hou, H. Wang, M. Zhao, et al., *Ganoderma atrum* polysaccharide ameliorates intestinal mucosal dysfunction associated with autophagy in immunosuppressed mice, Food Chem. Toxicol. 138 (2020) 111244–111252.
[51] Q. Xiang, Q. Yu, H. Wang, M. Zhao, S. Liu, S. Nie, et al., Immunomodulatory effect of *Ganoderma atrum* polysaccharides on Th17/Treg balance, J. Funct. Foods 45 (2018) 215–222.
[52] W.J. Li, X.F. Tang, X.X. Shuai, C.J. Jiang, X. Liu, L.F. Wang, et al., Mannose receptor mediates the immune response to *Ganoderma atrum* polysaccharides in macrophages, J. Agric. Food Chem. 65 (2017) 348–357.
[53] W.J. Li, L. Li, W.Y. Zhen, L.F. Wang, M. Pan, et al., *Ganoderma atrum* polysaccharide ameliorates ROS generation and apoptosis in spleen and thymus of immunosuppressed mice, Food Chem. Toxicol. 99 (2017) 199–208.
[54] Q. Yu, S.P. Nie, J.Q. Wang, D.F. Huang, W.J. Li, M.Y. Xie, Signaling pathway involved in the immunomodulatory effect of *Ganoderma atrum* polysaccharide in spleen lymphocytes, J. Agric. Food Chem. 63 (2015) 2734–2740.
[55] Q. Yu, S.P. Nie, W.J. Li, W.Y. Zheng, P.F. Yin, D.M. Gong, et al., Macrophage immunomodulatory activity of a purified polysaccharide isolated from *Ganoderma atrum*, Phytother. Res. 27 (2013) 186–191.
[56] Z. Shenshen, N. Shaoping, H. Danfei, L. Wenjuan, X. Mingyong, Immunomodulatory effect of *Ganoderma atrum* polysaccharide on CT26 tumor-bearing mice, Food Chem. 136 (2013) 1213–1219.
[57] W.J. Li, S.P. Nie, X.P. Peng, X.Z. Liu, C. Li, Y. Chen, J.E. Li, et al., *Ganoderma atrum* polysaccharide improves age-related oxidative stress and immune impairment in mice, J. Agric. Food Chem. 60 (2012) 1413–1418.
[58] L. Guo, J. Xie, Y. Ruan, L. Zhou, H. Zhu, X. Yun, et al., Characterization and immunostimulatory activity of a polysaccharide from the spores of *Ganoderma lucidum*, Int. Immunopharmacol. 9 (2009) 1175–1182.
[59] K.S. Liu, C. Zhang, H.L. Dong, K.K. Li, Q.B. Han, Y. Wan, et al., GSP-2, a polysaccharide extracted from *Ganoderma sinense*, is a novel toll-like receptor 4 agonist, PLoS One 14 (2019) 1–12.
[60] F. Wu, C. Zhou, D. Zhou, S. Ou, X. Zhang, H. Huang, Structure characterization of a novel polysaccharide from *Hericium erinaceus* fruiting bodies and its immunomodulatory activities, Food Funct. 9 (2018) 294–306.
[61] F. Wu, C. Zhou, D. Zhou, S. Ou, H. Huang, Structural characterization of a novel polysaccharide fraction from *Hericium erinaceus* and its signaling pathways involved in macrophage immunomodulatory activity, J. Funct. Foods 37 (2017) 574–585.
[62] D. Liu, Q. Sun, J. Xu, N. Li, J. Lin, S. Chen, F. Li, Purification, characterization, and bioactivities of a polysaccharide from mycelial fermentation of *Bjerkandera fumosa*, Carbohydr. Polym. 167 (2017) 115–122.
[63] C. Liu, P.C.K. Cheung, Structure and immunomodulatory activity of microparticulate mushroom sclerotial beta-glucan prepared from *Polyporus rhinocerus*, J. Agric. Food Chem. 67 (2019) 9070–9078.
[64] F. Liu, Y. Wang, K. Zhang, Y. Wang, R. Zhou, Y. Zeng, et al., A novel polysaccharide with antioxidant, HIV protease inhibiting and HIV integrase inhibiting activities from *Fomitiporia punctata* (P. karst.) murrill (Basidiomycota, hymenochaetales), Int. J. Biol. Macromol. 97 (2017) 339–347.
[65] C.H. Su, M.N. Lai, C.C. Lin, L.T. Ng, Comparative characterization of physicochemical properties and bioactivities of polysaccharides from selected medicinal mushrooms, Appl. Microbiol. Biotechnol. 100 (2016) 4385–4393.
[66] C. Zhao, L. Gao, C. Wang, B. Liu, Y. Jin, Z. Xing, Structural characterization and antiviral activity of a novel heteropolysaccharide isolated from *Grifola frondosa* againstenterovirus 71, Carbohydr. Polym. 144 (2016) 382–389.
[67] C.W. Wold, C. Kjeldsen, A. Corthay, F. Rise, B.E. Christensen, J.O. Duus, K.T. Inngjerdingen, Structural characterization of bioactive heteropolysaccharides from the medicinal fungus *Inonotus obliquus* (Chaga), Carbohydr. Polym. 185 (2018) 27–40.
[68] P. Suabjakyong, K. Nishimura, T. Toida, L.J.L.D. Van Griensven, Structural characterization and immunomodulatory effects of polysaccharides from Phellinus linteus and *Phellinus igniarius* on the IL-6/IL-10 cytokine balance of the mouse macrophage cell lines (RAW 264.7), Food Funct. 6 (2015) 2834–2844.
[69] P. Jiang, L. Yuan, G. Huang, X. Wang, X. Li, L. Jiao, et al., Structural properities and immunoenhancement of an exopolysaccharide produced by *Phellinus pini*, Int. J. Biol. Macromol. 93 (2016) 566–571.
[70] H. Dai, X.Q. Han, F.Y. Gong, H. Dong, P.F. Tu, X.M. Gao, Structure elucidation and immunological function analysis of a novel beta-glucan from the fruit bodies of *Polyporus umbellatus* (Pers.) Fries, Glycobiology 22 (2012) 1673–1683.
[71] X.Q. Han, X.Y. Chai, Y.M. Jia, C.X. Han, P.F. Tu, Structure elucidation and immunological activity of a novel polysaccharide from the fruit bodies of an edible mushroom, *Sarcodon aspratus* (Berk.) S. Ito, Int. J. Biol. Macromol. 47 (2010) 420–424.
[72] Y. Zhang, Y. Zeng, Y. Men, J. Zhang, H. Liu, Y. Sun, Structural characterization and immunomodulatory activity of exopolysaccharides from submerged culture of *Auricularia auricula*-judae, Int. J. Biol. Macromol. 115 (2018) 978–984.
[73] R.Z. Jiang, Y. Wang, H.M. Luo, Y.Q. Cheng, Y.H. Chen, Y. Gao, et al., Effect of the molecular mass of *Tremella* polysaccharides on accelerated recovery from cyclophosphamide-induced leucopenia in rats, Molecules 17 (2012) 3609–3617.
[74] Q. Yuan, X. Zhang, M. Ma, T. Long, C. Xiao, J. Zhang, et al., Immunoenhancing glucuronoxylomannan from *Tremella aurantialba* Bandoni et Zang and its low-molecular-weight fractions by radical depolymerization: properties, structures and effects on macrophages, Carbohydr. Polym. 238 (2020) 116184–116192.
[75] Y. Wang, L. Lai, L. Teng, Y. Li, J. Cheng, J. Chen, et al., Mechanism of the anti-inflammatory activity by a polysaccharide from *Dictyophora indusiata* in lipopolysaccharide-stimulated macrophages, Int. J. Biol. Macromol. 126 (2019) 1158–1166.
[76] F.R. Smiderle, A.C. Ruthes, J. van Arkel, W. Chanput, M. Iacomini, H.J. Wichers, et al., Polysaccharides from *Agaricus bisporus* and *Agaricus brasiliensis* show similarities in their structures and their immunomodulatory effects on human monocytic THP-1 cells, BMC Complement. Alternat. Med. 11 (2011) 58–67.
[77] F.T. Gomes de Sousa Cardozo, C.M. Camelini, P.C. Leal, J.M. Kratz, R.J. Nunes, M.M. de Mendonca, et al., Antiherpetic mechanism of a sulfated derivative of *Agaricus brasiliensis* fruiting bodies polysaccharide, Intervirology 57 (2014) 375–383.
[78] X. Liu, D. Liu, Y. Chen, R. Zhong, L. Gao, C. Yang, et al., Physicochemical characterization of a polysaccharide from *Agrocybe aegirita* and its anti-ageing activity, Carbohydr. Polym. 236 (2020) 116056–116064.
[79] H. Zhu, X. Ding, Y. Hou, Y. Li, M. Wang, Structure elucidation and bioactivities of a new polysaccharide from Xiaojin *Boletus speciosus* Frost, Int. J. Biol. Macromol. 126 (2019) 697–716.

[80] D. Wang, S.Q. Sun, W.Z. Wu, S.L. Yang, J.M. Tan, Characterization of a water-soluble polysaccharide from *Boletus edulis* and its antitumor and immunomodulatory activities on renal cancer in mice, Carbohydr. Polym. 105 (2014) 127–134.
[81] Y. Li, L. You, F. Dong, W. Yao, J. Chen, Structural characterization, antiproliferative and immunoregulatory activities of a polysaccharide from *Boletus Leccinum rugosiceps*, Int. J. Biol. Macromol. 157 (2020) 106–118.
[82] Z. Ren, W. Liu, X. Song, Y. Qi, C. Zhang, Z. Gao, et al., Antioxidant and anti-inflammation of enzymatic-hydrolysis residue polysaccharides by *Lentinula edodes*, Int. J. Biol. Macromol. 120 (2018) 811–822.
[83] C.R. Wang, N. Tzi Bun, L. Li, J.C. Fang, Y. Jiang, T.Y. Wen, et al., Isolation of a polysaccharide with antiproliferative, hypoglycemic, antioxidant and HIV-1 reverse transcriptase inhibitory activities from the fruiting bodies of the abalone mushroom *Pleurotus abalonus*, J. Pharm. Pharmacol. 63 (2011) 825–832.
[84] K.I. Minato, L.C. Laan, I. van Die, M. Mizuno, *Pleurotus citrinopileatus* polysaccharide stimulates anti-inflammatory properties during monocyte-to-macrophage differentiation, Int. J. Biol. Macromol. 122 (2019) 705–712.
[85] K.I. Minato, L.C. Laan, A. Ohara, I. van Die, *Pleurotus citrinopileatus* polysaccharide induces activation of human dendritic cells through multiple pathways, Int. Immunopharmacol. 40 (2016) 156–163.
[86] J. Yan, Y. Meng, M. Zhang, X. Zhou, H. Cheng, L. Sun, et al., A 3-O-methylated heterogalactan from *Pleurotus eryngii* activates macrophages, Carbohydr. Polym. 206 (2019) 706–715.
[87] D. Xu, H. Wang, W. Zheng, Y. Gao, M. Wang, Y. Zhang, et al., Charaterization and immunomodulatory activities of polysaccharide isolated from *Pleurotus eryngii*, Int. J. Biol. Macromol. 92 (2016) 30–36.
[88] K.K. Maity, S. Patra, B. Dey, S.K. Bhunia, S. Mandal, B. Bahera, et al., A beta-glucan from the alkaline extract of a somatic hybrid (PfloVv5FB) of *Pleurotus florida* and *Volvariella volvacea*: structural characterization and study of immunoactivation, Carbohydr. Res. 370 (2013) 13–18.
[89] K.K. Maity, S. Patra, B. Dey, S.K. Bhunia, S. Mandal, D. Das, et al., A heteropolysaccharide from aqueous extract of an edible mushroom, *Pleurotus ostreatus* cultivar: structural and biological studies, Carbohydr. Res. 346 (2011) 366–372.
[90] F.R. Smiderle, L.M. Olsen, E.R. Carbonero, C.H. Baggio, C.S. Freitas, R. Marcon, et al., Anti-inflammatory and analgesic properties in a rodent model of a (1 -> 3),(1 -> 6)-linked beta-glucan isolated from *Pleurotus pulmonarius*, Eur. J. Pharmacol. 597 (2008) 86–91.
[91] M.L.L. Silveira, F.R. Smiderle, F. Agostini, E.M. Pereira, M. Bonatti-Chaves, E. Wisbeck, et al., Exopolysaccharide produced by *Pleurotus sajor-caju*: its chemical structure and anti-inflammatory activity, Int. J. Biol. Macromol. 75 (2015) 90–96.
[92] F. Cui, L. Jiang, L. Qian, W. Sun, T. Tao, X. Zan, et al., A macromolecular alpha-glucan from fruiting bodies of *Volvariella volvacea* activating RAW264. 7 macrophages through MAPKs pathway, Carbohydr. Polym. 230 (2020) 115674–115685.
[93] R. Chen, X. Ren, W. Yin, J. Lu, L. Tian, L. Zhao, et al., Ultrasonic disruption extraction, characterization and bioactivities of polysaccharides from wild *Armillaria mellea*, Int. J. Biol. Macromol. 156 (2020) 1491–1502.
[94] J. Ye, X. Wang, K. Wang, Y. Deng, Y. Yang, R. Ali, et al., A novel polysaccharide isolated from *Flammulina velutipes*, characterization, macrophage immunomodulatory activities and its impact on gut microbiota in rats, J. Anim. Physiol. Anim. Nutr. 104 (2020) 735–748.
[95] W.H. Wang, J.S. Zhang, T. Feng, J. Deng, C.C. Lin, H. Fan, et al., Structural elucidation of a polysaccharide from *Flammulina velutipes* and its immunomodulation activities on mouse B lymphocytes, Sci. Rep. 8 (2018) 3120–3132.
[96] P. Patra, S.K. Bhanja, I.K. Sen, A.K. Nandi, S. Samanta, D. Das, et al., Structural and immunological studies of hetero polysaccharide isolated from the alkaline extract of *Tricholoma crassum* (Berk.) Sacc, Carbohydr. Res. 362 (2012) 1–7.
[97] Y. Yang, J. Chen, L. Lei, F. Li, Y. Tang, Y. Yuan, et al., Acetylation of polysaccharide from *Morchella angusticeps* peck enhances its immune activation and anti-inflammatory activities in macrophage RAW264.7 cells, Food Chem. Toxicol. 125 (2019) 38–45.
[98] X. Meng, C. Che, J. Zhang, Z. Gong, M. Si, G. Yang, et al., Structural characterization and immunomodulating activities of polysaccharides from a newly collected wild *Morchella sextelata*, Int. J. Biol. Macromol. 129 (2019) 608–614.
[99] W. Li, Z.N. Cai, S. Mehmood, L.L. Liang, Y. Liu, H.Y. Zhang, et al., Anti-inflammatory effects of *Morchella esculenta* polysaccharide and its derivatives in fine particulate matter-treated NR8383 cells, Int. J. Biol. Macromol. 129 (2019) 904–915.
[100] Z. Tietel, S. Masaphy, True morels (Morchella)-nutritional and phytochemical composition, health benefits and flavor: a review, Crit. Rev. Food Sci. Nutr. 58 (2018) 1888–1901.
[101] S. Li, A. Gao, S. Dong, Y. Chen, S. Sun, Z. Lei, et al., Purification, antitumor and immunomodulatory activity of polysaccharides from soybean residue fermented with *Morchella esculenta*, Int. J. Biol. Macromol. 96 (2017) 26–34.
[102] L. Fu, Y. Wang, J. Wang, Y. Yang, L. Hao, Evaluation of the antioxidant activity of extracellular polysaccharides from *Morchella esculenta*, Food Funct. 4 (2013) 871–879.
[103] M. Huang, S. Zhang, M. Zhang, S. Ou, Z. Pan, Effects of polysaccharides from *Morchella conica* on nitric oxide production in lipopolysaccharide-treated macrophages, Appl. Microbiol. Biotechnol. 94 (2012) 763–771.
[104] H.L. Cui, Y. Chen, S.S. Wang, G.Q. Kai, Y.M. Fang, Isolation, partial characterisation and immunomodulatory activities of polysaccharide from *Morchella esculenta*, J. Sci. Food Agric. 91 (2011) 2180–2185.
[105] C.J.G. Duncan, N. Pugh, D.S. Pasco, S.A. Ross, Isolation of a galactomannan that enhances macrophage activation from the edible fungus *Morchella esculenta*, J. Agric. Food Chem. 50 (2002) 5683–5685.
[106] X. Luo, Y. Duan, W. Yang, H. Zhang, C. Li, J. Zhang, Structural elucidation and immunostimulatory activity of polysaccharide isolated by subcritical water extraction from *Cordyceps militaris*, Carbohydr. Polym. 157 (2017) 794–802.
[107] X. Liu, Y. Huang, Y. Chen, Y. Cao, Partial structural characterization, as well as immunomodulatory and anti-aging activities of CP2-c2-s2 polysaccharide from *Cordyceps militaris*, RSC Adv. 6 (2016) 104094–104103.
[108] J.Y. Liu, C.P. Feng, X. Li, M.C. Chang, J.L. Meng, L.J. Xu, Immunomodulatory and antioxidative activity of *Cordyceps militaris* polysaccharides in mice, Int. J. Biol. Macromol. 86 (2016) 594–598.
[109] J.S. Lee, D.S. Kwon, K.R. Lee, J.M. Park, S.J. Ha, E.K. Hong, Mechanism of macrophage activation induced by polysaccharide from *Cordyceps militaris* culture broth, Carbohydr. Polym. 120 (2015) 29–37.
[110] D.T. Wu, L.Z. Meng, L.Y. Wang, G.P. Lv, K.L. Cheong, D.J. Hu, et al., Chain conformation and immunomodulatory activity of a hyperbranched polysaccharide from *Cordyceps sinensis*, Carbohydr. Polym. 110 (2014) 405–414.
[111] M. Wang, X. Meng, R. Yang, T. Qin, Y. Li, L. Zhang, et al., *Cordyceps militaris* polysaccharides can improve the immune efficacy of Newcastle disease vaccine in chicken, Int. J. Biol. Macromol. 59 (2013) 178–183.
[112] M. Wang, X.Y. Meng, R. Le Yang, T. Qin, X.Y. Wang, K.Y. Zhang, et al., *Cordyceps militaris* polysaccharides can enhance the immunity and antioxidation activity in immunosuppressed mice, Carbohydr. Polym. 89 (2012) 461–466.
[113] J.S. Lee, E.K. Hong, Immunostimulating activity of the polysaccharides isolated from *Cordyceps militaris*, Int. Immunopharmacol. 11 (2011) 1226–1233.
[114] J.S. Lee, J.S. Kwon, J.S. Yun, J.W. Pahk, W.C. Shin, S.Y. Lee, et al., Structural characterization of immunostimulating polysaccharide from cultured mycelia of *Cordyceps militaris*, Carbohydr. Polym. 80 (2010) 1011–1017.
[115] J.S. Lee, J.S. Kwon, D.P. Won, K.E. Lee, W.C. Shin, E.K. Hong, Study on macrophage activation and structural characteristics of purified polysaccharide from the liquid culture broth of *Cordyceps militaris*, Carbohydr. Polym. 82 (2010) 982–988.
[116] J.K.H. Cheung, J. Li, A.W.H. Cheung, Y. Zhu, K.Y.Z. Zheng, C.W.C. Bi, R. Duan, et al., Cordysinocan, a polysaccharide isolated from cultured *Cordyceps*, activates immune responses in cultured T-lymphocytes and macrophages: signaling cascade and induction of cytokines, J. Ethnopharmacol. 124 (2009) 61–68.
[117] Y. Ohta, J.B. Lee, K. Hayashi, A. Fujita, D.K. Park, T. Hayashi, *In vivo* anti-influenza virus activity of an immunomodulatory acidic polysaccharide isolated from *Cordyceps militaris* grown on germinated soybeans, J. Agric. Food Chem. 55 (2007) 10194–10199.
[118] Y. Wu, H. Sun, F. Qin, Y. Pan, C. Sun, Effect of various extracts and a polysaccharide from the edible mycelia of *Cordyceps sinensis* on cellular and humoral immune response against ovalbumin in mice, Phytother. Res. 20 (2006) 646–652.
[119] X.Q. Han, W.J. Li, C.H. Ko, X.M. Gao, C.X. Han, P.F. Tu, Structure characterization and immunocompetence of a glucan from the fruiting bodies of *Cantharellus cibarius*, J. Asian Nat. Prod. Res. 15 (2013) 1204–1209.
[120] K. Zhang, Y. Liu, X. Zhao, Q. Tang, J. Dernedde, J. Zhang, et al., Anti-inflammatory properties of GLPss58, a sulfated polysaccharide from *Ganoderma lucidum*, Int. J. Biol. Macromol. 107 (2018) 486–493.
[121] Q.D. Xiang, Q. Yu, H. Wang, M.M. Zhao, S.Y. Liu, S.P. Nie, et al., Immunomodulatory activity of *Ganoderma atrum* polysaccharide on purified T lymphocytes through Ca^{2+}/CaN and mitogen-activated protein kinase pathway based on RNA sequencing, J. Agric. Food Chem. 65 (2017) 5306–5315.
[122] H. Wang, Q. Yu, S.P. Nie, Q.D. Xiang, M.M. Zhao, S.Y. Liu, et al., Polysaccharide purified from *Ganoderma atrum* induced activation and maturation of murine myeloid-derived dendritic cells, Food Chem. Toxicol. 108 (2017) 478–485.
[123] U. Grienke, T. Kaserer, F. Pfluger, C.E. Mair, T. Langer, D. Schuster, et al., Accessing biological actions of *Ganoderma* secondary metabolites by in silico profiling, Phytochemistry 114 (2015) 114–124.
[124] Q. Yu, S.P. Nie, J.Q. Wang, X.Z. Liu, P.F. Yin, D.F. Huang, et al., Chemoprotective effects of *Ganoderrna atrum* polysaccharide in cyclophosphamide-induced mice, Int. J. Biol. Macromol. 64 (2014) 395–401.
[125] X.Q. Han, B.C.L. Chan, H. Yu, Y.H. Yang, S.Q. Hu, C.H. Ko, et al., Structural characterization and immuno-modulating activities of a polysaccharide from *Ganoderma sinense*, Int. J. Biol. Macromol. 51 (2012) 597–603.
[126] X.Q. Han, B.C.L. Chan, C.X. Dong, Y.H. Yang, C.H. Ko, G.G.L. Yue, et al., Isolation, structure characterization, and immunomodulating activity of a hyperbranched polysaccharide from the fruiting bodies of *Ganoderma sinense*, J. Agric. Food Chem. 60 (2012) 4276–4281.
[127] X.L. Zhu, A.F. Chen, Z.B. Lin, *Ganoderma lucidum* polysaccharides enhance the function of immunological effector cells in immunosuppressed mice, J. Ethnopharmacol. 111 (2007) 219–226.
[128] M.J. Hsu, S.S. Lee, S.T. Lee, W.W. Lin, Signaling mechanisms of enhanced neutrophil phagocytosis and chemotaxis by the polysaccharide purified from *Ganoderma lucidum*, Br. J. Pharmacol. 139 (2003) 289–298.
[129] L.Z. Cao, Z.B. Lin, Regulation on maturation and function of dendritic cells by *Ganoderma lucidum* polysaccharides, Immunol. Lett. 83 (2002) 163–169.
[130] K.W. Oh, C.K. Lee, Y.S. Kim, S.K. Eo, S.S. Han, Antiherpetic activities of acidic protein bound polysacchride isolated from *Ganoderma lucidum* alone and in combinations with acyclovir and vidarabine, J. Ethnopharmacol. 72 (2000) 221–227.
[131] X.Y. Wang, D.D. Zhang, J.Y. Yin, S.P. Nie, M.Y. Xie, Recent developments in *Hericium erinaceus* polysaccharides: extraction, purification, structural characteristics and biological activities, Crit. Rev. Food Sci. Nutr. 59 (2019) S96–S115.
[132] Z. Liu, M. Li, P. Yan, Z. Zhu, L. Liao, Q. Chen, et al., Transcriptome analysis of the effects of *Hericium erinaceus* polysaccharide on the lymphocyte homing in Muscovy duck reovirus-infected ducklings, Int. J. Biol. Macromol. 140 (2019) 697–708.
[133] Y. Wu, H. Jiang, E. Zhu, P. Lia, Q. Wang, W. Zhou, et al., *Hericium erinaceus* polysaccharide facilitates restoration of injured intestinal mucosal immunity in Muscovy

duck reovirus-infected Muscovy ducklings, Int. J. Biol. Macromol. 107 (2018) 1151–1161.
[134] X. Sheng, J. Yan, Y. Meng, Y. Kang, Z. Han, G. Tai, et al., Immunomodulatory effects of *Hericium erinaceus* derived polysaccharides are mediated by intestinal immunology, Food Funct. 8 (2017) 1020–1027.
[135] Z. Ren, T. Qin, F. Qiu, Y. Song, D. Lin, Y. Ma, et al., Immunomodulatory effects of hydroxyethylated *Hericium erinaceus* polysaccharide on macrophages RAW264.7, Int. J. Biol. Macromol. 105 (2017) 879–885.
[136] T. Qin, Z. Ren, Y. Huang, Y. Song, D. Lin, J. Li, et al., Selenizing *Hericium erinaceus* polysaccharides induces dendritic cells maturation through MAPK and NF-kappa B signaling pathways, Int. J. Biol. Macromol. 97 (2017) 287–298.
[137] S.C. Sheu, Y. Lyu, M.S. Lee, J.H. Cheng, Immunomodulatory effects of polysaccharides isolated from *Hericium erinaceus* on dendritic cells, Process Biochem. 48 (2013) 1402–1408.
[138] J.S. Lee, J.Y. Cho, E.K. Hong, Study on macrophage activation and structural characteristics of purified polysaccharides from the liquid culture broth of *Hericium erinaceus*, Carbohydr. Polym. 78 (2009) 162–168.
[139] J. Tian, X. Hu, D. Liu, H. Wu, L. Qu, Identification of *Inonotus obliquus* polysaccharide with broad-spectrum antiviral activity against multi-feline viruses, Int. J. Biol. Macromol. 95 (2017) 160–167.
[140] N. The Luong, J. Chen, Y. Hu, D. Wang, Y. Fan, J. Wang, et al., *In vitro* antiviral activity of sulfated *Auricularia auricula* polysaccharides, Carbohydr. Polym. 90 (2012) 1254–1258.
[141] Y. Wu, Z.X. Wei, F.M. Zhang, R.J. Linhardt, P.L. Sun, A.Q. Zhang, Structure, bioactivities and applications of the polysaccharides from *Tremella* fuciformis mushroom: a review, Int. J. Biol. Macromol. 121 (2019) 1005–1010.
[142] Y. Zhou, X. Chen, R. Yi, G. Li, P. Sun, Y. Qian, et al., Immunomodulatory effect of *Tremella* polysaccharides against cyclophosphamide-induced immunosuppression in mice, Molecules 23 (2018) 239–250.
[143] Y. Ruan, H. Li, L. Pu, T. Shen, Z. Jin, *Tremella* fuciformis polysaccharides attenuate oxidative stress and inflammation in macrophages through miR-155, Anal. Cell. Pathol. 2018 (2018) 8316–8324.
[144] C. Deng, Y. Sun, H. Fu, S. Zhang, J. Chen, X. Xu, Antioxidant and immunostimulatory activities of polysaccharides extracted from *Tremella aurantialba* mycelia, Mol. Med. Rep. 14 (5) (2016) 4857–4864.
[145] Z.W. Shi, Y. Liu, Y. Xu, Y.R. Hong, Q. Liu, X.L. Li, et al., *Tremella* polysaccharides attenuated sepsis through inhibiting abnormal $CD_4(+)CD_{25}$(high) regulatory T cells in mice, Cell. Immunol. 288 (2014) 60–65.
[146] T.H. Hsu, C.H. Lee, F.Y. Lin, S.P. Wasser, H.C. Lo, The fruiting bodies, submerged culture biomass, and acidic polysaccharide glucuronoxylomannan of yellow brain mushroom *Tremella* mesenterica modulate the immunity of peripheral blood leukocytes and splenocytes in rats with impaired glucose tolerance, J. Tradit. Complement. Med. 4 (2014) 56–63.
[147] X. Du, J. Zhang, Z. Lv, L. Ye, Y. Yang, Q. Tang, Chemical modification of an acidic polysaccharide (TAPA1) from *Tremella aurantialba* and potential biological activities, Food Chem. 143 (2014) 336–340.
[148] X. Zhao, Y. Hu, D. Wang, J. Liu, L. Guo, The comparison of immune-enhancing activity of sulfated polysaccharidses from *Tremella* and *Condonpsis pilosula*, Carbohydr. Polym. 98 (2013) 438–443.
[149] X. Zhao, Y. Hu, D. Wang, L. Guo, S. Yang, Y. Fan, et al., Optimization of sulfated modification conditions of *Tremella* polysaccharide and effects of modifiers on cellular infectivity of NDV, Int. J. Biol. Macromol. 49 (2011) 44–49.
[150] X.J. Du, J.S. Zhang, Y. Yang, Q.J. Tang, W. Jia, Y.J. Pan, Purification, chemical modification and immunostimulating activity of polysaccharides from *Tremella aurantialba* fruit bodies, J. Zhejiang Univ. Sci. B 11 (2010) 437–442.
[151] X. Du, J. Zhang, Y. Yang, L. Ye, Q. Tang, W. Jia, et al., Structural elucidation and immuno-stimulating activity of an acidic heteropolysaccharide (TAPA1) from *Tremella aurantialba*, Carbohydr. Res. 344 (2009) 672–678.
[152] F.C. Guo, R.P. Kwakkel, B.A. Williams, H.K. Parmentier, W.K. Li, Z.Q. Yang, et al., Effects of mushroom and herb polysaccharides on cellular and humoral immune responses of Eimeria tenella-infected chickens, Poult. Sci. 83 (2004) 1124–1132.
[153] L.C. Faccin, F. Benati, V.P. Rincao, M.S. Mantovani, S.A. Soares, M.L. Gonzaga, et al., Antiviral activity of aqueous and ethanol extracts and of an isolated polysaccharide from *Agaricus brasiliensis* against poliovirus type 1, Lett. Appl. Microbiol. 45 (2007) 24–28.
[154] F.T. Gomes de Sousa Cardozo, C.M. Camelini, A. Mascarello, M.J. Rossi, R.J. Nunes, C.R. Monte Barardi, et al., Antiherpetic activity of a sulfated polysaccharide from *Agaricus brasiliensis* mycelia, Antivir. Res. 92 (2011) 108–114.
[155] M.C. Minari, V.P. Rincao, S.A. Soares, N.M.P.S. Ricardo, C. Nozawa, R.E.C. Linhares, Antiviral properties of polysaccharides from *Agaricus brasiliensis* in the replication of bovine herpesvirus 1, Acta Virol. 55 (2011) 255–259.
[156] K.A. Yamamoto, L.C. Faccin Galhardi, V.P. Rincao, S.d.A. Soares, I.G. Pinto Vieira, N.M. Pontes Silva Ricardo, et al., Antiherpetic activity of an *Agaricus brasiliensis* polysaccharide, its sulfated derivative and fractions, Int. J. Biol. Macromol. 52 (2013) 9–13.
[157] V.P. Rincao, K.A. Yamamoto, N.M. Pontes Silva Ricardo, S.A. Soares, L.D. Paccola Meirelles, C. Nozawa, et al., Polysaccharide and extracts from *Lentinula edodes*: structural features and antiviral activity, Virol. J. 9 (2012) 37–42.
[158] F. Jiao, D. Li, S. Yang, J. Zhang, C. Zhang, L. Jia, Inhibition effects of polysaccharides on HBV replication and cell proliferation from *Lentinus edodes* waste material, Microb. Pathog. 123 (2018) 461–466.
[159] M. Selegean, M.V. Putz, T. Rugea, Effect of the polysaccharide extract from the edible mushroom *Pleurotus ostreatus* against infectious bursal disease virus, Int. J. Mol. Sci. 10 (2009) 3616–3634.
[160] P.E. Roopngam, Increased response of human T-lymphocytes by dendritic cells pulsed with HPV16E7 and *Pleurotus sajor-caju*-beta-glucan (PBG), Iran. J. Immunol. 15 (2018) 246–255.
[161] M. Zhang, P.C.K. Cheung, V.E.C. Ooi, L. Zhang, Evaluation of sulfated fungal beta-glucans from the sclerotium of *Pleurotus tuber-regium* as a potential water-soluble anti-viral agent, Carbohydr. Res. 339 (2004) 2297–2301.
[162] S. Mukherjee, K. Ghosh, F. Hahn, C. Wangen, H. Strojan, R. Mueller, et al., Chemically sulfated polysaccharides from natural sources: assessment of extraction-sulfation efficiencies, structural features and antiviral activities, Int. J. Biol. Macromol. 136 (2019) 521–530.
[163] C.C. Huang, M. Tang, M.Y. Zhang, S. Majeed, E. Montabana, R.L. Stanfield, et al., Structure of a V3-containing HIV-1 gp120 core, Science 310 (2005) 1025–1028.
[165] L. Makowski, M. Chaib, J.C. Rathmell, Immunometabolism: from basic mechanisms to translation introduction, Immunol. Rev. 295 (2020) 5–14.
[166] N. Mangalmurti, C.A. Hunter, Cytokine storms: understanding COVID-19, Immunity 53 (2020) 19–25.
[167] K. Leung, J.T. Wu, D. Liu, G.M. Leung, First-wave COVID-19 transmissibility and severity in China outside Hubei after control measures, and second-wave scenario planning: a modelling impact assessment, Lancet 395 (2020) 1382–1393.
[168] C. Liang, L. Tian, Y. Liu, et al., A Promising Antiviral Candidate Drug for the COVID-19 Pandemic: A Mini-Review of Remdesivir[J], Eur. J. Med. Chem. 201 (2020) 112527–112543.
[169] J. Saravia, J.L. Raynor, N.M. Chapman, S.A. Lim, H. Chi, Signaling networks in immunometabolism, Cell Res. 30 (2020) 328–342.
[170] Q. Yu, S.P. Nie, J.Q. Wang, X.Z. Liu, P.F. Yin, D.F. Huang, et al., Chemoprotective effects of *Ganoderma atrum* polysaccharide in cyclophosphamide-induced mice, Int. J. Biol. Macromol. 64 (2014) 395–401.
[171] S.C. Jeong, B.K. Yang, G.N. Kim, H. Jeong, M.A. Wilson, Y. Cho, et al., Macrophage-stimulating activity of polysaccharides extracted from fruiting bodies of *Coriolus versicolor* (Turkey tail mushroom), J. Med. Food 9 (2006) 175–181.
[172] S.F. Yang, T.F. Zhuang, Y.M. Si, K.Y. Qi, J. Zhao, *Coriolus versicolor* mushroom polysaccharides exert immunoregulatory effects on mouse B cells via membrane Ig and TLR-4 to activate the MAPK and NF-kappa B signaling pathways, Mol. Immunol. 64 (2015) 144–151.
[173] C. Liu, M.W. Choi, X. Xue, P.C.K. Cheung, Immunomodulatory effect of structurally characterized mushroom sclerotial polysaccharides isolated from *Polyporus rhinocerus* on bone marrow dendritic cells, J. Agric. Food Chem. 67 (2019) 12137–12143.
[174] X. Ma, M. Meng, L. Han, D. Cheng, X. Cao, C. Wang, Structural characterization and immunomodulatory activity of *Grifola frondosa* polysaccharide via toll-like receptor 4-mitogen-activated protein kinases-nuclear factor kappa B pathways, Food Funct. 7 (2016) 2763–2772.
[175] D.P. Won, J.S. Lee, D.S. Kwon, K.E. Lee, W.C. Shin, E.K. Hong, Immunostimulating activity by polysaccharides isolated from fruiting body of *Inonotus obliquus*, Mol. Cell 31 (2011) 165–173.
[176] X. Xu, J. Li, Y. Hu, Polysaccharides from *Inonotus obliquus* sclerotia and cultured mycelia stimulate cytokine production of human peripheral blood mononuclear cells *in vitro* and their chemical characterization, Int. Immunopharmacol. 21 (2014) 269–278.
[177] Y. Chen, Y. Huang, Z. Cui, J. Liu, Purification, characterization and biological activity of a novel polysaccharide from *Inonotus obliquus*, Int. J. Biol. Macromol. 79 (2015) 587–594.
[178] Y. Yang, L. Ye, J. Zhang, Y. Liu, Q. Tang, Structural analysis of a bioactive polysaccharide, PISP1, from the medicinal mushroom *Phellinus igniarius*, Biosci. Biotechnol. Biochem. 73 (2009) 134–139.
[179] X. Li, W. Xu, TLR4-mediated activation of macrophages by the polysaccharide fraction from *Polyporus umbellatus* (pers.) Fries, J. Ethnopharmacol. 135 (2011) 1–6.
[180] X. Li, W. Xu, J. Chen, Polysaccharide purified from *Polyporus umbellatus* (Per) Fr induces the activation and maturation of murine bone-derived dendritic cells via toll-like receptor 4, Cell. Immunol. 265 (2010) 50–56.
[181] Y. Pu, Z. Liu, H. Tian, Y. Bao, The immunomodulatory effect of *Poria cocos* polysaccharides is mediated by the Ca^{2+}/PKC/p38/NF-kappa B signaling pathway in macrophages, Int. Immunopharmacol. 72 (2019) 252–257.
[182] H. Tian, Z. Liu, Y. Pu, Y. Bao, Immunomodulatory effects exerted by *Poria cocos* polysaccharides via TLR4/TRAF6/NF-kappa B signaling *in vitro* and *in vivo*, Biomed. Pharmacother. 112 (2019) 108709–108717.
[183] S.X. Wang, Y.Y. Wen, C.X. Hu, Immunoactivities of the polysaccharides from Morus-alba, Chlamydomonas-mexicana and Poria-cocos, Phytother. Res. 9 (6) (1995) 448–451.
[184] C.Y. Ma, W.C. Chang, H.M. Chang, J.S.B. Wu, Immunomodulatory effect of the polysaccharide-rich fraction from sclerotium of medicinal mushroom *Poria cocos* FA Wolf (Aphyllophoromycetideae) on Balb/c mice, Int. J. Med. Mushrooms 12 (2010) 111–121.
[185] K.Y. Lee, H.J. You, H.G. Jeong, J.S. Kang, H.M. Kim, S. Dal Rhee, et al., Polysaccharide isolated from *Poria cocos* sclerotium induces NF-kappa B/Rel activation and NOS expression through the activation of p38 kinase in murine macrophages, Int. Immunopharmacol. 4 (2004) 1029–1038.
[186] Z. Ruan, J. Su, H.C. Dai, M.C. Wu, Characterization and immunomodulating activities of polysaccharide from *Lentinus edodes*, Int. Immunopharmacol. 5 (2005) 811–820.
[187] T.C.T. Lo, Y.H. Jiang, A.L.J. Chao, C.A. Chang, Use of statistical methods to find the polysaccharide structural characteristics and the relationships between monosaccharide composition ratio and macrophage stimulatory activity of regionally different strains of *Lentinula edodes*, Anal. Chim. Acta 584 (2007) 50–56.
[188] L.D. Zhou, Q.H. Zhang, Y. Zhang, J. Liu, Y.M. Cao, The shiitake mushroom-derived immuno-stimulant lentinan protects against murine malaria blood-stage infection

by evoking adaptive immune-responses, Int. Immunopharmacol. 9 (2009) 455–462.
[189] H. Kojima, J. Akaki, S. Nakajima, K. Kamei, M. Tamesada, Structural analysis of glycogen-like polysaccharides having macrophage-activating activity in extracts of *Lentinula edodes* mycelia, J. Nat. Med. 64 (2010) 16–23.
[190] T. Wang, H. He, X. Liu, C. Liu, Y. Liang, Y. Mei, Mycelial polysaccharides of *Lentinus edodes* (shiitake mushroom) in submerged culture exert immunoenhancing effect on macrophage cells via MAPK pathway, Int. J. Biol. Macromol. 130 (2019) 745–754.
[191] S.K. Roy, D. Das, S. Mondal, D. Maiti, B. Bhunia, T.K. Maiti, S.S. Islam, Structural studies of an immunoenhancing water-soluble glucan isolated from hot water extract of an edible mushroom, *Pleurotus florida*, cultivar Assam Florida, Carbohydr. Res. 344 (2009) 2596–2601.
[192] B. Dey, S.K. Bhunia, K.K. Maity, S. Patra, S. Mandal, S. Maiti, et al., Islam, chemical analysis of an immunoenhancing water-soluble polysaccharide of an edible mushroom, *Pleurotus florida* blue variant, Carbohydr. Res. 345 (2010) 2736–2741.
[193] K. Maity, E. Kar, S. Maity, S.K. Gantait, D. Das, S. Maiti, et al., Structural characterization and study of immunoenhancing and antioxidant property of a novel polysaccharide isolated from the aqueous extract of a somatic hybrid mushroom of *Pleurotus florida* and Calocybe indica variety APK2, Int. J. Biol. Macromol. 48 (2011) 304–310.
[194] S. Patra, K.K. Maity, S.K. Bhunia, B. Dey, S. Mandal, T.K. Maiti, et al., Structural characterization and study of immunoenhancing properties of heteroglycan isolated from a somatic hybrid mushroom (*PfloVv1aFB*) of *Pleurotus florida* and *Volvariella volvacea*, Carbohydr. Res. 346 (2011) 1967–1972.
[195] C. Wang, H. Cui, Y. Wang, Z. Wang, Z. Li, M. Chen, et al., Bidirectional immunomodulatory activities of polysaccharides purified from *Pleurotus nebrodensis*, Inflammation 37 (2014) 83–93.
[196] H.Y. Cui, C.L. Wang, Y.R. Wang, Z.J. Li, M.H. Chen, F.J. Li, et al., *Pleurotus nebrodensis* polysaccharide (PN-S) enhances the immunity of immunosuppressed mice, Chin. J. Nat. Med. 13 (2015) 760–766.
[197] H.Y. Cui, C.L. Wang, Y.R. Wang, Z.J. Li, Y.N. Zhang, The polysaccharide isolated from *Pleurotus nebrodensis* (PN-S) shows immune-stimulating activity in RAW264.7 macrophages, Chin. J. Nat. Med. 13 (2015) 355–360.
[198] Y. Sun, J. Liu, Purification, structure and immunobiological activity of a water-soluble polysaccharide from the fruiting body of *Pleurotus ostreatus*, Bioresour. Technol. 100 (2009) 983–986.
[199] F. Kong, F.E. Li, Z. He, Y. Jiang, R. Hao, X. Sun, et al., Anti-tumor and macrophage activation induced by alkali-extracted polysaccharide from *Pleurotus ostreatus*, Int. J. Biol. Macromol. 69 (2014) 561–566.
[200] S. Satitmanwiwat, K. Ratanakhanokchai, N. Laohakunjit, L.K. Chao, S.T. Chen, P. Pason, et al., Improved purity and immunostimulatory activity of beta-(1 -> 3)(1 -> 6)-glucan from *Pleurotus sajor-caju* using cell wall-degrading enzymes, J. Agric. Food Chem. 60 (2012) 5423–5430.
[201] Y. Sun, H. Liang, X. Zhang, H. Tong, J. Liu, Structural elucidation and immunological activity of a polysaccharide from the fruiting body of *Armillaria mellea*, Bioresour. Technol. 100 (2009) 1860–1863.
[202] G.T. Chen, Y.X. Fu, W.J. Yang, Q.H. Hu, L.Y. Zhao, Effects of polysaccharides from the base of *Flammulina velutipes* stipe on growth of murine RAW264.7, B16F10 and L929 cells, Int. J. Biol. Macromol. 107 (2018) 2150–2156.
[203] Z.F. Yan, N.X. Liu, X.X. Mao, Y. Li, C.T. Li, Activation effects of polysaccharides of *Flammulina velutipes* mycorrhizae on the T lymphocyte immune function, J Immunol Res (2014) (2014) 285421–285428.
[204] M. Zhang, X. Tian, Y. Wang, D. Wang, W. Li, L. Chen, et al., Immunomodulating activity of the polysaccharide TLH-3 from *Tricholomalobayense* in RAW264.7 macrophages, Int. J. Biol. Macromol. 107 (2018) 2679–2685.
[205] J.Y. Kim, S.E. Byeon, Y.G. Lee, J.Y. Lee, J. Park, E.K. Hong, et al., Immunostimulatory activities of polysaccharides from liquid culture of pine-mushroom *Tricholoma matsutake*, J. Microbiol. Biotechnol. 18 (2008) 95–103.
[206] S.E. Byeon, J. Lee, E. Lee, S.Y. Lee, E.K. Hong, Y.E. Kim, et al., Functional activation of macrophages, monocytes and splenic lymphocytes by polysaccharide fraction from *Tricholoma matsutake*, Arch. Pharm. Res. 32 (2009) 1565–1572.
[207] Y. Zheng, J. Fan, H.W. Chen, E.Q. Liu, *Trametes orientalis* polysaccharide alleviates PM2.5-induced lung injury in mice through its antioxidant and anti-inflammatory activities, Food Funct. 10 (2019) 8005–8015.
[208] X. Zhao, P. Hou, H. Xin, Y. Zhang, A. Zhou, C. Lai, et al., A glucogalactomanan polysaccharide isolated from *Agaricus bisporus* causes an inflammatory response via the ERK/MAPK and I kappa B/NF kappa B pathways in macrophages, Int. J. Biol. Macromol. 151 (2020) 1067–1073.
[209] H. Ahn, E. Jeon, J.C. Kim, S.G. Kang, S.I. Yoon, H.J. Ko, et al., Lentinan from shiitake selectively attenuates AIM2 and non-canonical inflammasome activation while inducing pro-inflammatory cytokine production, Sci. Rep. 7 (2017) 1314–1325.
[210] X. Song, Z. Liu, J. Zhang, Q. Yang, Z. Ren, C. Zhang, et al., Anti-inflammatory and hepatoprotective effects of exopolysaccharides isolated from *Pleurotus geesteranus* on alcohol-induced liver injury, Sci. Rep. 8 (2018) 10493–10505.
[211] A. Koh, F. Backhed, From association to causality: the role of the gut microbiota and its functional products on host metabolism, Mol. Cell 78 (2020) 584–596.
[212] B.A. Helmink, M.A.W. Khan, A. Hermann, V. Gopalakrishnan, J.A. Wargo, The microbiome, cancer, and cancer therapy, Nat. Med. 25 (2019) 377–388.
[213] S. Kanwal, T.P. Joseph, L. Owusu, X. Ren, M. Li, Y. Xin, A polysaccharide isolated from *Dictyophora indusiata* promotes recovery from antibiotic-driven intestinal dysbiosis and improves gut epithelial barrier function in a mouse model, Nutrients 10 (2018) 1003–1026.
[214] X. Xu, J. Yang, Z. Luo, X. Zhang, *Lentinula edodes*-derived polysaccharide enhances systemic and mucosal immunity by spatial modulation of intestinal gene expression in mice, Food Funct. 6 (2015) 2068–2080.
[215] X. Xu, J. Yang, Z. Ning, X. Zhang, *Lentinula edodes*-derived polysaccharide rejuvenates mice in terms of immune responses and gut microbiota, Food Funct. 6 (2015) 2653–2663.
[216] G. Ma, B.M. Kimatu, L. Zhao, W. Yang, F. Pei, Q. Hu, *In vivo* fermentation of a *Pleurotus eryngii* polysaccharide and its effects on fecal microbiota composition and immune response, Food Funct. 8 (2017) 1810–1821.