Sulfated polysaccharides: Immunomodulation and signaling mechanisms

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Abstract

Background

Polysaccharides are natural macromolecular polymers that are widely distributed in various food resources and have attracted much attention due to their significant bioactivities. Sulfated polysaccharides refer to polysaccharides containing sulfate groups on sugar units. A large number of studies have characterized and evaluated the biological relevance of sulfated polysaccharides, which shows great potential in terms of immunological activity.

Scope and approach

Through a critical analysis of current research literature regarding sulfated polysaccharides, this review will give an overview of the immunomodulatory properties and signaling mechanisms of natural or modified sulfated polysaccharides. The effects of the degree of substitution (DS), molecular weight, and structure on immunomodulatory effects will also be discussed.

Key Findings and Conclusions

The mechanisms by which sulfated polysaccharides exert their immunological activity is mainly due to the regulation of macrophage function, natural killer cells, and T/B lymphocytes, together with the stimulation of the immune responses of lymphocytes and the activation of the complement system. The immunological activity of sulfated polysaccharides depends not only on the source of the polysaccharide but also on structural characteristics, such as molecular weight and DS. Studies on the mechanisms of immune function have shown that the action of sulfated polysaccharides is a complex process that

may be regulated by one or more pathways. Nevertheless, the link between the immunological mechanisms and structure of sulfated polysaccharides requires further exploration.

Keywords: sulfated polysaccharide; immunity; mechanism

1 Introduction

Immunity refers to the biological organisms' protection against foreign bacteria, viruses, and other harmful substances (Zhao et al., 2016). The immune function of the body is accomplished through the interaction of lymphocytes, monocytes, and other related cells and their products (Kim et al., 2012). Numerous active substances, such as polysaccharides, lipids, proteins, peptides, and volatile oils, can maintain the health of the body by regulating the immune function of the body (Xiao, Muzashvili & Georgiev, 2014).

Polysaccharides are natural macromolecular compounds that are polymerized and consist of more than 10 monosaccharide units linked through glycosidic bonds (Xie et al., 2016a). Polysaccharides are widespread in nature and found in higher plants, algae, bacteria, and animals. These compounds exert various biological activities, such as immunity enhancement, anti-oxidation, anti-tumor, hypoglycemic, anti-thrombotic, and anticoagulant (Xie et al., 2016a; Xie et al., 2010). The immunological activity of polysaccharides is the most important biological activity, and polysaccharides can regulate the function of the immune system through multiple pathways (Yu et al., 2017). Sulfated polysaccharides have become one of the hotspots in the field of polysaccharide research in recent years due to their outstanding immunological activities.

Sulfated polysaccharides refer to polysaccharides containing sulfate groups on the hydroxyl groups of sugar units and include those extracted directly from plants and artificially synthesized and sulfuric acid derivatives of natural neutral polysaccharides (Wang, Xie, Shen, Nie & Xie, 2018). After sulfation of polysaccharides, the sulfated hydroxyl groups show changes in steric hindrance and electrostatic repulsion; moreover,

68 the flexion and extension of the polysaccharide chain and the water solubility increase,
69 resulting in the alteration of biological activities (Zhang et al., 2005b). Numerous scientific
70 studies have shown that sulfated polysaccharides exhibit better biological properties than
71 those that are not sulfated; the former also exert significant biological activities, such as
72 immunity, anti-virus, and anti-oxidantion (Wang et al., 2014).

73 The immunological activity of sulfated polysaccharides has attracted widespread
74 attention in recent years (Figure 1). The immune system is resistant to pathogens, protects
75 the body from infection, and maintains overall health (Zhao et al., 2016). Sulfated
76 polysaccharides are an immune regulator with immunomodulatory function and can
77 maintain homeostasis by regulating macrophages, T/B lymphocytes, natural killer cells
78 (NK cells), and complement systems. Sulfated polysaccharides can promote not only the
79 release of various cytokines (Kim et al., 2012) but also the generation of antibodies and
80 activate the complement system (Glovsky et al., 1983). Studies have shown that sulfate
81 modified polysaccharides can regulate macrophage phagocytosis and play a role in
82 promoting the secretion of nitric oxide (NO), interleukin (IL)-6, and other cytokines by
83 macrophages (Kim, Cho, Karnjanapratum, Shin & You, 2011). Sulfate modification
84 improves immune function and can significantly enhance the activities of normal and
85 immunosuppressed mouse macrophages (Geng, Xing, Sun & Su, 2016), which may be
86 related to the regulation of the signal transduction function of immune cells. With the
87 increasing number of research on the biological activities of sulfated polysaccharides, the
88 present work on the immune activity of sulfated polysaccharides will have an important
89 impact on their application in many fields.

The immunological activity of sulfated polysaccharides is closely related to their structural characteristics, such as molecular weight, conformation, and DS (Pan et al., 2017). Sulfated modification increased the immune activity of *Lycium* polysaccharides and showed a correlation between the DS and immune activity (Wang et al., 2010). Fucoidan with high sulfate contents has better immune activity on macrophages, and the effect can be reduced by removing sulfate groups (Ferreira, Passos, Madureira, Vilanova & Coimbra, 2015). In general, sulfation of polysaccharides could not only change the steric hindrance and electrostatic repulsion effect of the sulfate groups but also change the water solubility and flexion of the chain (Liu et al., 2009b). Hence, sulfation can improve the structural characteristics of polysaccharides and enhance their immune competence.

Based on their physiochemical properties, many of the new polysaccharides can help improve the nutritional value of foods, therefore, it has been widely applied in the field of functional foods. Moreover, polysaccharides have been widely used in food industry as packaging material and food additives. This paper reviews recent advances in research on the immunization of sulfated polysaccharides mainly from food resources, summarizes the immunomodulatory mechanisms, and the effects of structural characteristics of sulfated polysaccharides on immune activities so as to better understand the signal transduction pathways involved in immune responses moderated by sulfated polysaccharide.

2 Immunomodulatory effects of sulfated polysaccharides

The immunomodulatory activity of sulfated polysaccharides is an important biological activity function with multiple-paths, links, and targets. In recent years, many reports have been published about the immune activity of sulfated polysaccharides. Some

112 typical examples of sulfated polysaccharides with immune functions are listed in Table 1.
113 Sulfated polysaccharides play a key role in keeping the body healthy by improving the
114 defense ability of the immune system and enhancing the immune regulatory activity.
115 Current studies suggest that sulfated polysaccharides mainly exert immunomodulatory
116 effects by promoting the proliferation of macrophages, lymphocytes, and NK cells,
117 increasing the release of cytokines and regulating the immune system (Jiang et al., 2014;
118 Karnjanapratum & You, 2011; Pérez-Recalde, Matulewicz, Pujol & Carlucci, 2014;
119 Surayot & You, 2017; Zvyagintseva et al., 2000).

120 *2.1 Effects of sulfated polysaccharide on macrophages*

121 Macrophages are immune cells with multiple functions; in particular, they can
122 regulate the immune system by presenting antigens and releasing active mediators (Zirk,
123 Hashmi & Ziegler, 1999). Higher levels of sulfate groups in fucoidan are associated with
124 higher stimulatory activity by macrophages (Qiao et al., 2010). Moreover, the removal of
125 sulfate groups significantiy decreases the activity. The regulatory effect of sulfated
126 polysaccharides on macrophages is reflected in its influence on phagocytic activity,
127 cytokine secretion, and intracellular enzymatic activity (Yuan et al., 2015).

128 *2.1.1 Phagocytic activity of macrophages*

129 Phagocytosis is one of the basic functions of macrophages, and to some extent can
130 reflect the state of the bodys' immune function. Macrophages can remove damaged cells
131 and pathogens by phagocytosis to maintain homeostasis of the body (Stuart & Ezekowitz,
132 2005). Sulfated polysaccharides can regulate immunity by affecting the phagocytic activity
133 of macrophages. Sulfated polysaccharides from *Ganoderma atrum* (*G. atrum*) exerts better

134 immunological activity by enhancing the phagocytic ability of macrophages than *G. atrum*
135 polysaccharides; the phagocytic activity is affected by concentration and DS of the
136 polysaccharide (Chen et al., 2015). Sulfated polysaccharides from *Longan* can increase the
137 phagocytosis of mouse macrophages, and the highest phagocytic ability was found when
138 100 μg/mL polysaccharide was uesd (Jiang et al., 2014).

139 *2.1.2 Cytokines secreted by macrophages*

140 Macrophages can exert their functions by secreting NO and various cytokines, such as
141 IL, interferon (IFN), and tumor necrosis factor (TNF) (Meram & Wu, 2017). Sulfated
142 polysaccharides regulate immune function by regulating the secretion of different types
143 and amounts of cytokines by macrophages. Sulfated polysaccharides from *Monostroma*
144 *nitidum* can stimulate macrophages to produce cytokines such as NO and prostaglandin E2
145 (PGE2), by stimulating RAW 264.7 macrophages. (Karnjanapratum & You, 2011).
146 Sulfated polysaccharides from *Capsosiphon fulvescens* (Karnjanapratum, Tabarsa, Cho &
147 You, 2012) can stimulate macrophages to produce NO, PGE2, and cytokines and are
148 related to the expression of induced nitric oxide synthase (iNOS) and cyclooxygenase 2
149 (COX2). Research suggests that the immunological activity induced by the proliferation of
150 macrophages and the release of cytokines may be due to the ability of sulfated
151 polysaccharides to regulate a variety of related genes (Jose & Kurup, 2017).

152 NO is a biologically active cell messenger that is secreted by macrophages. NO is a
153 short-lived biologically active free radical from L-arginine catalyzed by NO synthase
154 (NOS), which plays a key role in killing pathogenic microorganisms and tumor cells
155 (Huang, Mei & Zhang, 2011). Sulfated polysaccharides could act as the irritants of

RAW264.7 cells to produce large amounts of NO and PGE2 by enhancing mRNA expression (Karnjanapratum, Tabarsa, Cho & You, 2012). Evidence indicates that macrophages release NO in a concentration-dependent manner stimulated by sulfated polysaccharides (Wang, Yang, Zhao, Lu & Zhu, 2016).

TNF-α is a cytokine produced by monocytes/macrophages and is active in regulating inflammation and autoimmunity. Previous studies demonstrated that sulfated polysaccharides could induce the secretion of cytokines, such as TNF-α, in macrophages in a concentration-dependent manner (Jiang et al., 2014), the secretion of TNF-α is critical for the activation and subsequent processes of NK cells.

IL is a cytokine that is generated by a variety of cells and regulates the interaction between white blood cells and other cells (Yu et al., 2017). IL is involved in the immune response in the host and plays a crucial role in maintaining homeostasis. Sulfated polysaccharides enhance immune activity by regulating the secretion of IL-6 and IL-1β (Wang, Yang, Zhao, Lu & Zhu, 2016). Sulfated polysaccharides from *Enteromorpha prolifera* (*E. prolifera*) can regulate immune T cells by up regulating the secretion of IL-2 and IFN-γ (Kim, Cho, Karnjanapratum, Shin & You, 2011).

2.1.3 Enzyme activities in macrophages

Macrophages contain numerous enzymes, and their activity can reflect the functional status of macrophages to some extent. Acid phosphatase (ACP) and acid α-naphthyl naphthalene esterase are present in macrophage lysosomes and are involved in many lysosomal digestive functions. ACP is strongly related to the inhibition or activation of macrophages (Yuan et al., 2015). Sulfated polysaccharides can influence the function of

178 macrophages by regulating the activity of enzymes. The ACP activities in macrophages are
179 remarkably enhanced in a dose-dependent manner after treatment with sulfated
180 polysaccharides (Di et al., 2017).

181 *2.2 Effects of sulfated polysaccharides on lymphocytes*

182 Lymphocytes are the primary immune cells in the body and mainly include T and B
183 lymphocytes. T lymphocytes are mainly involved in cellular immune response, and B
184 lymphocytes mainly participate in humoral immune responses (de Araújo et al., 2011).
185 Numerous studies have confirmed that sulfated polysaccharides can affect lymphocytes
186 and regulate immunity (Choi, Kim, Kim & Hwang, 2005). The regulatory effect of sulfated
187 polysaccharides on lymphocytes is reflected in its effect on proliferation and cytokine
188 secretion.

189 *2.2.1 Proliferation of lymphocytes*

190 Proliferation of lymphocytes can reflect immune function to a certain extent and
191 therefore can be used as a basis for evaluating immune strength (Thekisoe, Mbati &
192 Bisschop, 2004). Lymphocyte proliferation induced by concanavalin A (ConA) or
193 lipopolysaccharide (LPS) is a basis for assessing the immunological activities of B or T
194 lymphocytes. Normal T lymphocytes can be divided into cluster of differentiation antigen
195 CD4+ helper cells and CD8+ cytotoxic cells. Activated CD4+ regulatory T cells play a
196 critical role in immune responses to self and non-self antigens (Sánchez-Fueyo, Weber,
197 Domenig, Strom & Zheng, 2002). Polysaccharides can significantly enhance the activity of
198 immune competent cells through sulfate modification. Sulfated polysaccharide from
199 *Porphyra haitanensis* (*P. haitanensis*) regulates the proliferation of lymphocytes induced

by ConA and LPS. This finding further comfirms the immunologic activity of sulfated polysaccharides (Liu et al., 2017a).

2.2.2 Cytokines secreted by lymphocytes

Cytokines released by lymphocytes are crucial information molecules in immune regulation and include IFN and IL-2 (Spellberg & Edwards, 2001). Sulfated polysaccharides can improve the immune function by promoting cytokine secretion in lymphocytes. Sulfated polysaccharides from *P. haitanensis* promote the release of TNF-α and IL-10 from mouse lymphocytes to improve immunity (Liu et al., 2017a). *E. prolifera* sulfated polysaccharides can significantly increase IFN-γ and IL-2 secretion without altering the release of IL-4 and IL-5 (Kim, Cho, Karnjanapratum, Shin & You, 2011).

2.2.3 Secretion of lymphocyte antibodies

Antibody is an immunoglobulin produced by the proliferation and differentiation of B lymphocytes after antigen stimulation and can exert an immunological activity in combination with corresponding antigens. The level of antibodies in poultry reflects the humoral immune function of birds (Qiu, Hu, Cui, Zhang & Wang, 2007). Sulfated polysaccharides can increase antibody levels and improve immune function in animals. The immune activity is significantly enhanced after sulfated modification of *Lycium barbarum* polysaccharides. Sulfated *lyceum barbarum* polysaccharides can cause early generation of antibodies, rapidly increase and persist for a long time, thereby enhancing the immune response of chickens and improving the immune effect of the vaccine (Wang et al., 2010). The serum antibody titers increase due to sulfate modification of polysaccharides from *Auricularia auricula*, indicating that sulfated polysaccharides can

enhance humoral immune activity (Nguyen et al., 2012).

2.3 Natural killer cells

As an important part of the immune system, NK cells are differentiated from lymphoid stem cells of bone marrow. These cells can recognize and lyse target cells and provide an early source of immunomodulatory cytokines (De, Ménasché & Fischer, 2010). Through their cytotoxic activity and production of lymphokine, NK cells participate in immune function in the body against infection and tumor formation and for immune and hematopoietic regulation (Robertson & Ritz, 1990). Various cytokines regulate the development, activation, proliferation, chemotaxis, and killing of NK cells. IL-2 and IL-15 can stimulate the proliferation of NK cells and secrete various cytokines. The activated NK cells can secrete soluble cytokines, such as IFN and TNF, to enhance the immune response of the body (Raulet, 2006). Sulfated polysaccharides can exert immune function in a variety of ways; for example, they can enhance receptor expression and increase the release of granzyme-B, perforin, and various cytokines (Surayot & You, 2017). Sulfated polysaccharides from *Polysiphonia senticulosa* Harvey exert immunomodulatory activity by increasing the viability of NK cells (Zhao et al., 2017).

2.4 Complement system

Complement system consists of more than 30 proteins on the plasma and cell surface and widely exists in serum, tissue fluid, and cell membrane surface. This system participates in the destruction or elimination of pathogenic microorganisms as well as in specific and non-specific immune mechanisms (Fujita, 2002). The complement system comprises several common activation pathways, including classical complement,

alternative complement, and mannose-binding lectin (MBL) pathways, which play a crucial role in the body's microbial defense response and immune regulation (Ricklin, Hajishengallis & Yang, 2010). Sulfated glycosaminoglycans exert immunological activity, play a regulatory role in the complement system, and can be used as potential complement modulators to treat complement-associated diseases (Li et al., 2015). Some naturally sulfated polysaccharides and sulfate modified polysaccharides have activity in regulating the complement system. Water-soluble sulfated polysaccharides from the brown seaweed have significant effects on the human's complement system (Zvyagintseva et al., 2000).

2.4.1 Classical complement pathway

The complement system consists of nine proteins (C1 to C9). C1 consists of three subunits, namely, C1q, C1r, and C1s (Lambris, Reid & Volanakis, 1999). With the exception of C1q, all the components exist in the form of enzyme precursor in serum and require antigen-antibody complexes or other factors to activate and exert their biological activity; this process is called the classical complement pathway (Fujita, 2002). Sulfated polysaccharides (fucans) alter the classical and alternative pathway activation pathways in whole serum in a dose-dependent manner (Blondin, Fischer, Boisson-Vidal, Kazatchkine & Jozefonvicz, 1994). Sulfated polysaccharides from the fruits of *Capparis spinosa* L. effectively inhibit the classical complement system without inducing undesirable anti-coagulant activity in a certain concentration range (Wang, Wang, Shi, Duan & Wang, 2012).

2.4.2 Alternative complement pathway

Alternative complement pathway is directly initiated by C3, which requires neither an

antigen-antibody complex nor activation of C1, C2, and C4 (Lambris, Reid & Volanakis, 1999). Sulfated derivatives from polysaccharides isolated from the roots of *Saussurea costus* strongly inhibit complement activation by classical and alternative pathways (Fan, Fei, Bligh, Shi & Wang, 2014). Sulfated polysaccharides are worth considering for their potential application to therapeutic complement inhibition given their ability to modulate complement activation from alternative and classical complement pathways (Tissot et al., 2003c).

2.4.3 Mannose-binding lectin pathway

MBL is a calcium-dependent protein that is structurally similar to C1q. Lectins recognize the mannose receptors on the surface of some pathogen cells and activate the MBL complement system to exert immunity (Gadjeva, Thiel & Jensenius, 2001). MBL binds to the bacterial mannose residue at first and then to serine protease to form MBL-associated serine protease (MASP). MASP has a biological activity similar to the activated C1, and the reaction process is similar to the classical complement pathway (Wong, Kojima, Dobó, Ambrus & Sim, 1999). The MBL pathway can be activated by specific carbohydrate structures found in microorganisms (Yamada & Kiyohara, 1999); however, few studies have investaged the effects of sulfated polysaccharides on this pathway.

3 Mechanisms

Sulfated polysaccharides regulate the function and metabolism of immune cells through multiple signal transduction pathways. Through this important mechanism, sulfated polysaccharides exert the immunomodulatory effect by activating the signaling pathways of macrophages (Figure 2), T/B lymphocytes (Figure 3), NK cells (Figure 4), and

288 complement system (Figure 5).

289 *3.1 Regulation of macrophages signaling pathway*

290 Macrophages have multiple pattern recognition receptors on the surface. Sulfated
291 polysaccharides are usually too large to cross the cell membrane of macrophages.
292 Stimulation may occur through interactions between molecules and surface receptors,
293 where sulfate groups play a role (Leiro, Castro, Arranz & Lamas, 2007). These pattern
294 recognition receptors recognize and bind sulfated polysaccharides at first and then transmit
295 signals into cells through various signal transduction pathways, causing a series of
296 signaling cascade reactions to regulate the expression of related genes (Nakamura, Suzuki,
297 Wada, Kodama & Doi, 2006).

298 *3.1.1 Toll-like receptors 2/4-mediated signal transduction pathway*

299 Toll-like receptors (TLRs) are a class of protein recognition receptors that are widely
300 found on the surface of macrophages, neutrophils, and lymphocytes (Roeder et al., 2004).
301 At present, only TLR4 and TLR2 have been found to bind to glycosyl ligands in TLR
302 family members, both of which play a key role in innate and acquired immunity. TLRs
303 bind to polysaccharide ligands and activates TNF receptor-associated factor 6 (TRAF6)
304 through myeloid differentiation factor 88 (MyD88)-mediated signaling pathway or TLR
305 related interfere on factor (TRIF)-mediated signaling pathway (Schepetkin & Quinn,
306 2006). TRAF6 activates nuclear factor-kappa B (NF-κB) and mitogen-activated protein
307 kinase (MAPK) to signal transduction in two different pathways. Sulfated polysaccharides
308 can promote the expression of key molecular genes, including TRAF6 and C-Jun N-
309 terminal kinase-1 (JNK1), in activator protein-1 (AP-1) and NF-κB pathways to exert

immunostimulatory activity (Zheng et al., 2016). *Pinus massoniana pollen* sulfated polysaccharides exert immunological activity mainly through TLR4-mediated macrophage activation, and its possible signaling pathway is TLR4 → PI3K → PLC → IP3R (Geng, Xing, Sun & Su, 2016).

3.1.1.1 MAPK signal transduction pathways

MAPK signaling cascades play a major role in different states of various immune cells. Among the numerous signaling pathways after infection, the stress-activated MAPK cascade is focused on the JNK, and p38 MAPKs is an indispensable factor in immune signaling (Zhang & Tsao, 2016). In unstimulated cells, MAPK continues to remain in a state of rest. When the cells are stimulated, MAPK is activated by the phosphorylation of the two sites, and the phosphorylation transcription factors produced by the activated MAPK enter the nucleus to regulate the transcription of related genes (Widmann, Gibson, Jarpe & Johnson, 1999). The research indicates that marine microalga *Gyrodinium impudicum* sulfated polysaccharides promotes macrophage activation and increases the release of NO; this immune activity may be achieved through the JNK and NF-κB pathways (Bae, Yim, Hong & Pyo, 2006). When JNK and Janus kinase-2 (JAK2) inhibitors are added, the immunogenic gene expression of sulfated polysaccharide is blocked, indicating that TLR4-mediated MAPK signaling pathway is a potential signaling pathway for activation of macrophages by the sulfated polysaccharides (Liu et al., 2017a).

3.1.1.2 NF-κB signal pathways

NF-κB is a transcription factor that regulates various genes associated with immune and inflammatory responses. In the cytoplasm of unstimulated cells, NF-κB combines with

the inhibitor of NF-κB (IκB) and becomes an inactive complex form. When cells are stimulated, the IκB kinase (IKK) complex is activated. IκB is phosphorylated under the catalysis of IKK and dissociates with NF-κB, thereby converting NF-κB into an activated form (Hasegawa et al., 2008). Previous studies reported that sulfated polysaccharides could stimulate the TLR4 receptor-mediated NF-κB signaling pathway in a concentration-dependent manner (Wu, Shiu, Hsieh & Tsai, 2016). Sulfated polysaccharides from *Grifola frondos* can induce tumor cell apoptosis through the NF-κB pathway to exert immunity (Wang et al., 2013a).

3.1.2 CD14, complement receptor 3 (CR3) mediated signal pathways

CD14 is a receptor with high affinity for sulfated polysaccharides and a marker for determining whether macrophages differentiate. CR3 is a multifunctional protein complex that is present on almost all T cell surfaces (Ross, 2000). CD14 and CR3 can form a transmembrane complex that mediates signal by activating phospholipase (PLC), which in turn activates protein kinase (PKC) and phosphatidylinositol 3-kinase (PI3-K) through MAPK or NF-κB signaling pathway and regulates the expression of related genes (Mörk et al., 1998). Sulfated polysaccharides bind to CD14 and activate the signal transduction cascade to activate the immunological activity of macrophages (Ginsburg, 2002).

3.1.3 Mannose receptors (MR)-mediated signal pathway

MR is an important pattern recognition receptor and endocytic receptor in the innate immune system; MR is mainly expressed by macrophages and can recognize mannose, fucose, and acetyl glucosamine (Gazi & Martinez-Pomares, 2009). MR has a variety of immune-related functions, including roles in innate and adaptive immunity. MR promotes

macrophages to ingest microorganisms, such as bacteria, yeasts, and parasites by identifying polysaccharides on their cell walls in the innate immune response (Taylor, Conary, Lennartz, Stahl & Drickamer, 1990). Previous studies showed that MR receptors are associated with the binding and interaction of sulfated carbohydrates. MR receptors participate in innate and adaptive immune responses through the carbohydrate recognition domain in combination with sulfated oligosaccharides (Susanne et al., 2002).

3.1.4 Scavenger receptors (SR)-mediated signal pathways

SR is a transmembrane glycoprotein that exists in various immune cells. SR can be identified and combined with Gram-negative bacteria, LPS, and so on (Murphy, Tedbury, Homer-Vanniasinkam, Walker & Ponnambalam, 2005). The pathway of SR macrophage activation may be consistent with the CR3 receptor. Sulfated polysaccharides can bind to the SR receptor family to exert their activity (Gough & Gordon, 2000). Sulfated polysaccharides can also release NO through the SR receptor-activated macrophages and induce iNOS gene expression through the NF-κB and p38 MAPK pathways (Ilchmann et al., 2010).

3.1.5 Dectin-1-mediated signal pathway

As a type II transmembrane protein, dectin-1 is a c-type lectin-like receptor mainly expressed on the surface of monocytes/macrophages, and neutrophils (Nakamura, Suzuki, Wada, Kodama & Doi, 2006). Ligands can bind to dectin-1 and regulate cellular signaling, responding to the MAPK signaling pathway or the NF-κB signaling pathway (Herre et al., 2004). The immunomodulatory mechanism of sulfated polysaccharides regulates the expression of immune-related cytokines and proteins by binding to the dectin-1 receptor on

the cell surface and activating the MAPK signaling pathway (Abram & Lowell, 2007).

In summary, the signal transduction pathways of sulfated polysaccharides to stimulate macrophage immune responses are mainly summarized as follows (Figure 2), including TLR2/4 → IRA → TRAF6 → NF-κB/MAPKs, CR3/CD14 → PLC → P13-K/PKC → NF-κB/MAPKs, MR → endocytosis, SR → PLC → P13-K/PKC→ NF-κB/MAPKs, Dectin-1 → MAPKs.

3.2 Molecular channels regulated by T/B lymphocytes

Sulfated polysaccharides can stimulate the immune responses of lymphocytes through complex signal transduction pathways. The molecular channel of polysaccharide-activated T lymphocytes is mainly involved in the T-cell receptor (TCR), but TCR has weak affinity for antigens and generally forms a complex with CD3 to recognize the receptor and mediate T-cells activation (Abram & Lowell, 2007).

3.2.1 Membrane immunoglobulin (mIg) complex receptor-mediated signal pathway

There are a slew of mIg receptors are found on the surface of B lymphocytes, which form complex receptors with CD19 and CD79b to regulate B cell activation. Protein tyrosine kinase (PTK) will be activated when IgM/CD79 binds to polysaccharides (Zhang & Huang, 2005a). Under the catalytic action of PTK, MAPK is further activated and produces activator protein-1 (AP-1), which regulates the expression of B lymphocyte related genes (Han et al., 2003). Sulfur-containing polysaccharides can induce the proliferation of spleen lymphocytes, allow their differentiation into IgM secretory plasma cells, and increase the expression of CD71+/CD25+ and mIg (Zhang, Liu, Peng, Han & Yang, 2014).

3.2.2 Toll-like receptors 2/4 receptor-mediated signal pathway

TLR2/4 receptors are transmembrane proteins found in T and B lymphocytes. The expression level of TLRs is relatively low on the surface of T lymphocytes (Yang, Yin & Zhang, 2012b). Sulfated polysaccharides from Pine Pollen enhance B lymphocyte proliferation and antibody production through the TLR4 receptor (Liu, Li & Geng, 2014). Once sulfated polysaccharides bind to the TLR on the surface of T lymphocytes, the protein forms a complex with the adaptor protein MyD88 to activate the transduction pathways, such as MAPK and NF-κB pathways (Makarenkova et al., 2012). When sulfated polysaccharides activate B lymphocytes, TLR4 is the surface receptor and activates the downstream calcium signaling pathway (Liu, Li and Geng 2014).

3.2.3 T-cell receptor-mediated signal pathway

TCR specifically recognizes and binds to major histocompatibility complex molecules in lymphocytes. Most TCRs consist of α and β peptides, and a few TCRs consist of γ and δ peptides. After the TCR/CD3 complex binds to the polysaccharide, PTK is acticated, leading to the activation of T lymphocyte immune response through the PI3-K or MAPK pathway (Crabtree & Clipstone, 1994). PKC affects the flow of calcium ions, which regulate NFAT into cells. Sulfated polysaccharide polymers are linked to the TCR/CD3 complex to activate T lymphocytes; the complex then activates the intracellular PKC and MAPK pathways, and finally promotes the expression of relevant factors (Miao, Li, Fu, Ding & Geng, 2005).

In summary, the signal transduction pathways of sulfated polysaccharide-stimulated B lymphocyte immune response are mainly summarized as TLR2/4 → TRAF6 → NF-κB,

TLR2/4 → PTK → MAPKs → AP-1 and IgM → PTK → MAPKs → AP-1 (Figure 3). The signaling pathways that stimulate T cell immune response by sulfated polysaccharides are mainly summarized as TCR/CD3 → PTK → PI3-K → PKC/PLCγ → Ca^{2+} → NFAT and TCR/CD3 → PTK → MAPKs → AP-1 (Figure 3).

3.3 Signaling pathways regulated by natural killer cells

NK cells can be activated by CD3 molecules on the membrane surface, as well as by multiple cytokines and other pathways. Evidence reveals that sulfated fucan-activated NK cells are most likely to be achieved by CR3 receptors (Surayot, Lee & You, 2018). The surface of NK cells contains natural killer group 2-member D (NKG2D) and killer cell immunoglobulin-like receptors (KIR). KIR can be divided into inhibitory and activation receptors, all of which can act in the activation of NK cells. Heparan sulfate interacts directly with the NK cell receptor KIR2DL4 to activate NK cells and induce cytokine production (Brusilovsky et al., 2013). NK cells surface also has an IL-2 affinity receptor, which enhance the activity of NK cells. The effect of polysaccharides on the function of NK cells may be due to their different structural characteristics and their ability to bind to cell surface receptors (De, Ménasché & Fischer, 2010). Sulfated fucan (SF) may enhance the activity of NK cells by secreting IFN-γ. SF enhances NK cell activity by secreting IFN-γ, releasing perforin, and enhancing the expression of NKp30 (Surayot, Lee & You, 2018). Sulfated polysaccharides, such as fucoidan, dextran sulfate, and κ-carrageenan, can interact with NK cell receptors in C-type lectin domain (Brennan, Takei, Wong & Mager, 1995). In summary, sulfated polysaccharides can activate NK cells via receptors, such as CR3, KIR, NKG2D, and IL-2 (Figure 4).

3.4 Regulatory mechanisms for activation of the complement system

The complement system has multiple functions, including defense of the body, activation of inflammation, and regulation of the immune system. Sulfated polysaccharides can exert their immunological activity through the following three pathways of the complement system.

3.4.1 Classical complement pathway

Activator is an immune complex formed by the binding of an antibody (IgG1, IgG2, IgG3, or IgM) to the corresponding antigen. When the complement is activated during lysis or hemolysis reaction, 11 components can be divided into three functional units: the unit of recognition: C1q, C1r, and C1s; activation units: C2, C3, and C4; and film attack units: C5, C6, C7, C8, and C9. Sulfated polysaccharides can bind to C1q to regulate the activity of the complement system (Tissot, Daniel & Place, 2003b). Fucoidan regulates the human complement system by interacting with the protein C4 in the classical pathway. Therefore, the classical activation pathway of the complement system can be divided into three stages: recognition, activation, and attack (Berger et al., 1988). Fucoidan binds to C1q by interaction involving lysine residues, thereby preventing the formation of the C1r (2)-C1s (2) subunit required for complete activation of C1. In addition to C1q, fucoidan can form a complex with protein C4 to regulate the first step of the classical pathway activation (Tissot et al., 2003c). A recent study has found that sulfated polysaccharides from tea can enhance the inhibition of the classical complement pathway; and exert a targeted inhibitory effect on activation of the complement system (Wang et al., 2013b).

3.4.2 Alternative complement pathway

In the alternative pathway, C3b obtained by hydrolysis of C3 can bind to a variety of surface antigens and form a complex with factor B. The alternative C3 convertase C3bBb is produced by the involvement of factor D, which cleaves C3 into C3b that can bind to the surface of the microorganism. C3b in combination with C3bBb can form an alternative C5 convertase (C3bBb3b) to yield C5b-9 (Li, Sun & Li, 2015). Sulfated polysaccharides extracted from *Kjellmaniella crsaaifolia* regulates the classical and alternative complement pathways and may affect immune diseases associated with the pathway (Zhang et al., 2015).

3.4.3 Mannose-binding lectin pathway

Lectin activation pathway does not require antibody initiation and can be directly associated with pathogenic microorganisms; this pathway can be easily recognized. Unlike the alternative activation pathway but similar to the classical pathway, the lectin activation pathway requires the activation of C1 and C4 (Sell, 2008). MBL can be combined with sulfated polysaccharides, such as fucose (Turner, 2003), but the underlying mechanism remains unclear.

In summary, the pathway of the sulfated polysaccharides in exerting an immune response through the complement pathway is mainly classified into three types (Figure 5): C1 → C2/C4 → C4b2b → C4b2b3b → C5/C5b → C5b-9, C3 → C3b → C4b2b3b → C5/C5b → C5b-9 and C3 → C3b → C3bBb3b → C5/C5b → C5b-9.

4 Structure–activity relationships between sulfated polysaccharides and immunomodulation

4.1 Degree of substitution

The sulfate content of polysaccharides from different sources are variable, and DS is usually used to indicate the extent to which hydroxyl groups are substituted with sulfate groups on polysaccharide molecules. Many studies have explored the structure-activity relationship between different DS of sulfated polysaccharides and immunomodulation (Liang, Mao, Peng & Tang, 2014). The immune activities of sulfated polysaccharides are influenced by DS (Yang, Jia, Zhou, Pan & Mei, 2012a). Four sulfated polysaccharides with different DS from *Stichopus japonicus*, exert immunity by stimulating NK cells to enhance their toxicity to tumor cells. The cytotoxicity of NK cells in HT-29 cells is enhanced with increasing DS, but this phenomenon is not reflected in the toxicity of other tumor cells (Surayot, Lee & You, 2018). At high doses, the immunological activity of sulfated polysaccharides from *G. atrum* increases with increasing DS. At low doses, the highly substituted sulfated polysaccharides are less immunogenic than low DS sulfated polysaccharides (Chen et al., 2015). Hence, the immunological activity of the sulfated polysaccharide is not always positively associated with DS, indicating that its immunological activity depends not only on DS but also on other factors.

4.2 Molecular mass

Different preparation methods and sources of polysaccharides often result in difference in monosaccharide composition and molecular weight, thereby affecting the immune activity. Sulfated polysaccharides with different molecular weights have different immune functions. Sulfated polysaccharides from the same source have different effects on immunity due to their different molecular weights and DS (Zhang, Lu, Zhang, Qin & Zhang, 2010). Sulfated polysaccharides have different abilities to up-regulate mRNA

508 expression by various cytokines in macrophages, and the extent of Con A-induced spleen
509 cell proliferation also varies; this change is related to molecular weight (Kim, Cho,
510 Karnjanapratum, Shin & You, 2011). Sulfated polysaccharides from *Gracilaria rubra*
511 exert their immunological activity by promoting the proliferation of RAW264.7 cells; the
512 activity gradually increases with decreasing molecular weight (Di et al., 2017). Sulfated
513 polysaccharides from *G. atrum* exert the best immunological activity when the molecular
514 weight is intermediate (Chen et al., 2015). The immunological activity of the sulfated
515 polysaccharideS is not determined by molecular weight and DS alone but is controlled by
516 various factors.

517 *4.3 Molecular structure and conformation*

518 Molecular structure of sulfated polysaccharide molecules, such as the flexibility and
519 spatial conformation of the chain, has a greater effect on activity than the primary
520 structure. The molecular and structural modification of polysaccharides is of great
521 significance in improving their immunological activity (Wang et al., 2017). The main
522 chain and branched chain of sulfated polysaccharides and their higher structure affect their
523 biological activity. The introduction of sulfate groups changes the physicochemical
524 properties of polysaccharides, especially their steric conformations; the change is a
525 determinant of activity changes (Zhang et al., 2005b). Sulfated modification of
526 polysaccharides from *Hypsizigus marmoreus* affects the molecular structure and
527 conformation and significantly improves the anticancer and immunomodulatory activities
528 of natural polysaccharides (Bao, Wonseok & You, 2010). Sulfated chitosans have different
529 immunological activities depending on their conformations; molecules with the same

conformation may have different immunological activities depending on DS (Yang et al., 2017). The structure and conformation of sulfated polysaccharides are diverse and complex; as such, the effects of these parameters on immune activity remain unclear. Nevertheless, the conformation of sulfated polysaccharides is also a known factor that affects their immunological activity.

In conclusion, the immunological activity of sulfated polysaccharides is related to their structural characteristics. The DS, molecular weight, conformation, and other factors will have an impact on the intensity of immunological activity (Figure 6). Such effect is determined by one or more of these factors, as reflected in the difference in immune activity. The relative importance of influence and interactions among these factors remains unclear. Future works must continue exploring mechanisms through which sulfated polysaccharides exert their maximum immune effect.

5 Future outlooks and conclusions

Recent studies have shown that sulfated polysaccharides are macromolecules that play a crucial role in regulating the bodys' immune system. Polysaccharides can bind to multiple surface receptors of immune cells and stimulate different signaling pathways to regulate the immune system. The results of many studies indicate that the immunological activity of sulfated polysaccharides is not only dependent on the source but also on structural features, such as molecular weight and DS, *etc*. However, the trends associated with these factors are uncertain. The immunological activity of sulfated polysaccharides is not affected by a single factor, but by a combination of various related factors (Figure 6). Studies on the mechanisms of immune function indicate that the action of sulfated

polysaccharides is a complex process that may be regulated by one or more pathways.

This field of research has attracted considerable attention because natural sulfated polysaccharides do not pose serious safety concerns given that they are produced by marine organisms or natural plants. Moreover, sulfation of polysaccharides may lead to good immune response. Scientists can further explore the link between the structure and immunological activity of sulfated polysaccharides and analyze the role of sulfates. With the advancements in molecular biology, genomics, proteomics, and molecular nutrition, the structure-activity relationship and molecular mechanisms involved in the immune function of sulfated polysaccharides will be elucidated. Sulfated polysaccharides are envisioned to play a wide role in immunology. However, studies of the immunity of sulfated polysaccharides present several weaknesses. Although simple and low-cost extraction techniques are available, they are still limited to laboratory research and cannot be easily incorporated into large-scale production. Further human (clinical) studies are needed to validate the efficacy of sulfated polysaccharide-based foods or drugs to establish a health claim. If these problems are resolved, a bright future will wait for these new products based on sulfated polysaccharides.

Conflicts of interest

The authors declare no conflict of interest.

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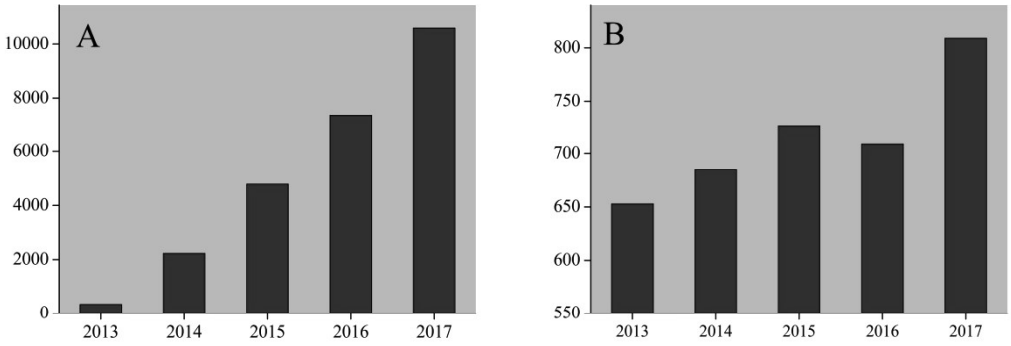

Fig.1 Research trends of sulfated polysaccharides in the past five years. (A) Citations in each year, and (B) Published Items in each year. Taken from the database of web of science (http://apps.webofknowledge.com). Topics entered: “sulfated polysaccharides”. Retrieve date: September 2018.

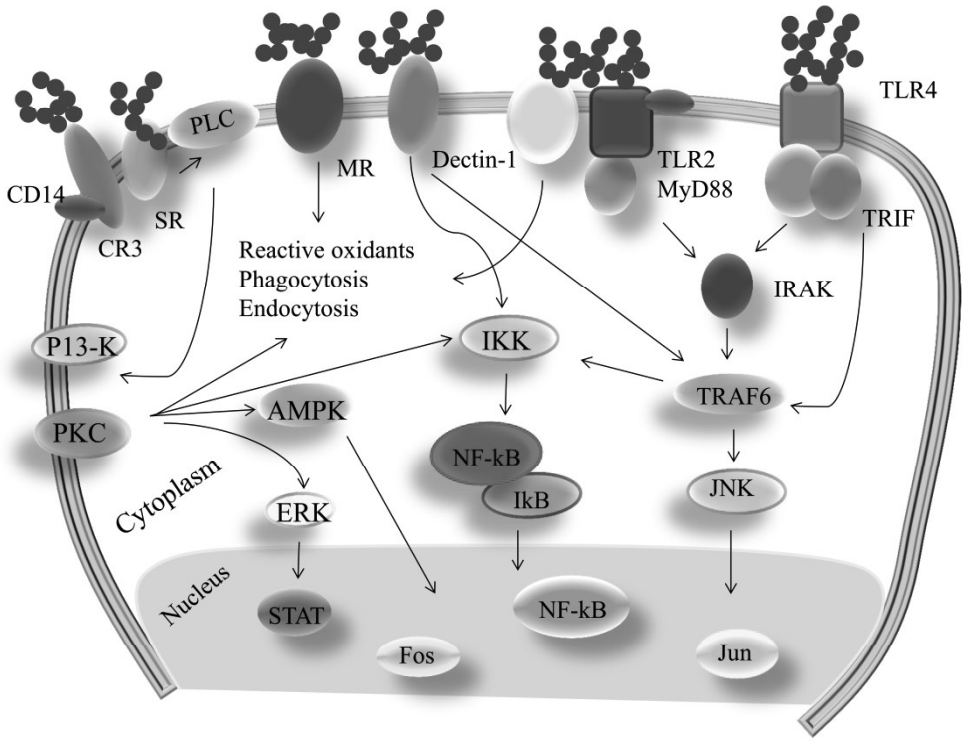

Fig.2 Signaling pathways involved in macrophage activation by sulfated polysaccharides. CR3: complement receptor 3; SR: scavenger receptors; MR: mannose receptors; Dectin-1: dendritic cell-associated C-type lectin-1; CD14: cluster of differentiation antigen 14; TLR2: Toll-like receptor 2; TLR4: Toll-like receptor 4; PLC: phospholipases C; MyD88: myeloid differentiation factor 88; TRIF: Toll/IL-1 domain containing adaptor inducing interferon β; PI3-K: phosphatidylinositol 3 kinase; PKC: protein kinase C; IRAK: interleukin-1 receptor associated kinase; IKK: inhibitor of nuclear factor kappa-B kinase; TRAF6: tumor necrosis factor receptor-associated factor 6; NF-κB: nuclear factor kappa-B; IκB: inhibitor of nuclear factor kappa-B; ERK: extracellular signal-regulated kinase; STAT: signal transducers and activators of transcription; JNK: Jun N-terminal kinase.

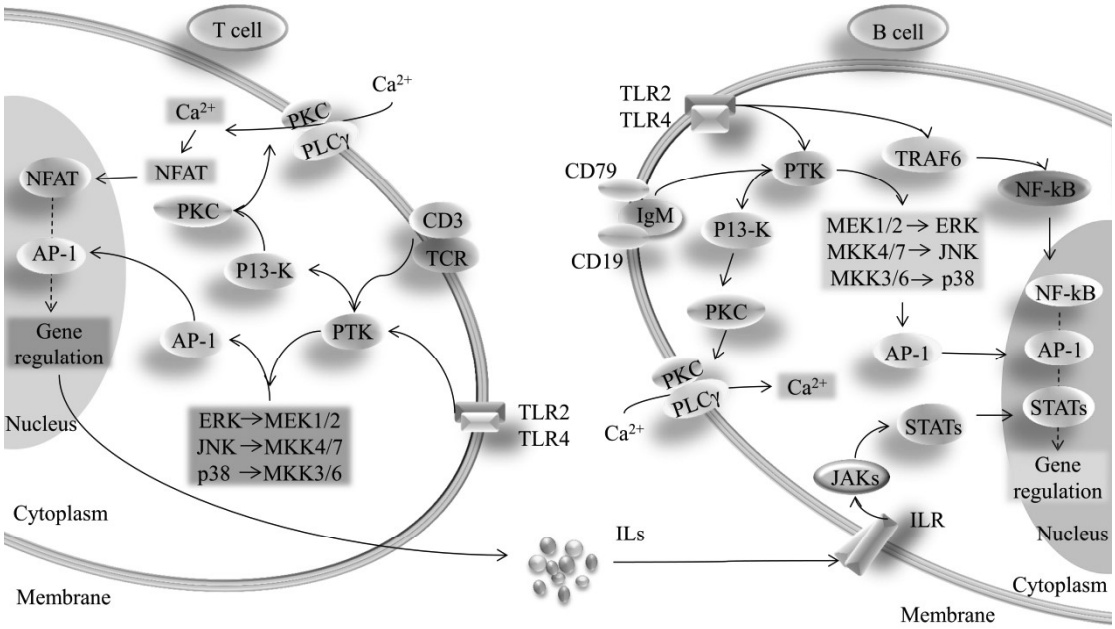

Fig.3 Signaling pathways involved in T / B lymphocytes activation by sulfated polysaccharides. CD3: cluster of differentiation antigen 3; CD79: cluster of differentiation antigen 79; TCR: T cell receptor; IgM: immunoglobulin M; ILR: interleukin receptor; MHC: major histocompatibility complex; IL-2: interleukin-2; IL-4: interleukin-4; IL-6: interleukin-6; IL-8: interleukin-8; PLCγ: phospholipase Cγ; PTK: protein tyrosine kinase; AP-1: activator protein-1; NFAT: nuclear factor of activated T cells.

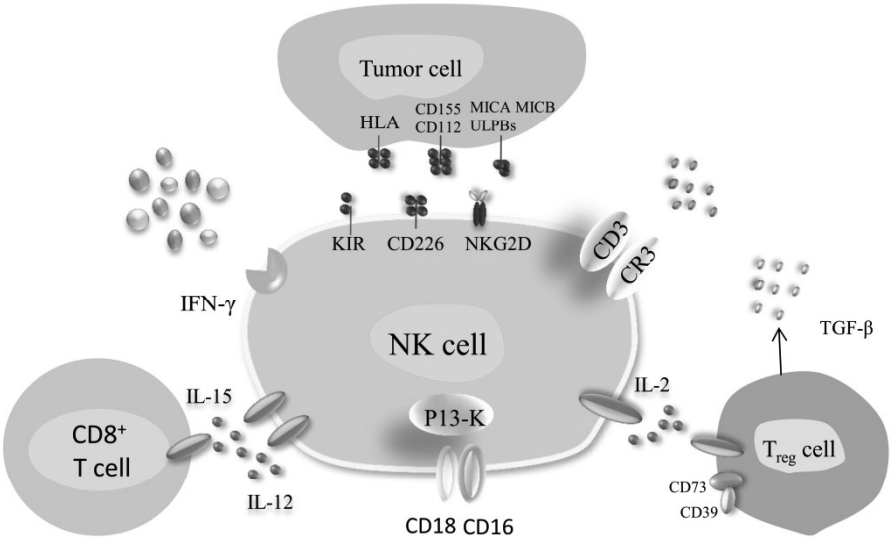

Fig.4 Signaling pathways involved in NK cell activation by sulfated polysaccharides. HLA: human leucocyte antigen; KIR: killer cell immunoglobulin like receptors; CD3: cluster of differentiation antigen 3; CR3: complement receptor 3; IFN-γ: Interferon-γ; IL-15: interleukin-15; IL-12: interleukin-12; P13-K: phosphatidylinositol 3 kinase; CD18: cluster of differentiation antigen 18; CD16: cluster of differentiation antigen 16; IL-2: interleukin-2; CD73: cluster of differentiation antigen 73; CD39: cluster of differentiation antigen 39; TGF-β: transforming growth factor-β.

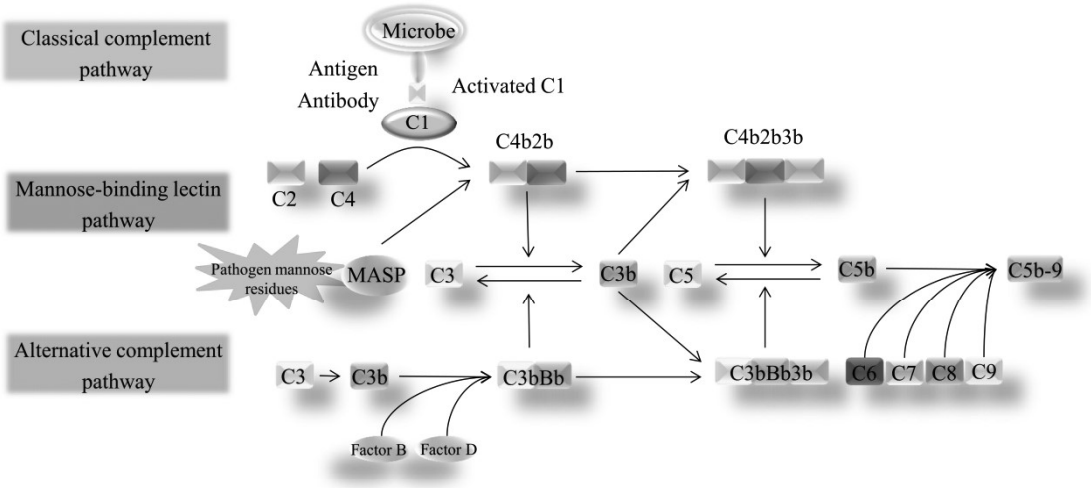

Fig. 5 Signaling pathways involved in complement system activation by sulfated polysaccharides. C4b2b: C3 convertase; C4b2b3b: C5 convertase; C3bBb: C3 convertase; C3bBb3b: C5 convertase; C5b-9: Membrane attack complex; MASP: Mannose-binding lectin associated serum proteinase.

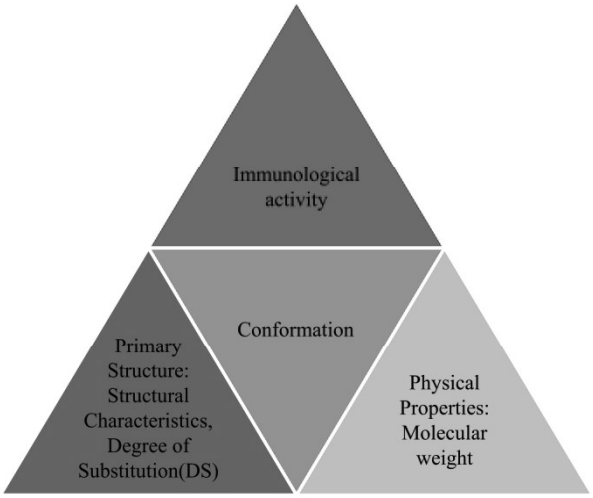

Fig. 6 Schematic diagram indicating the different factors which underpin the immunological activity of sulfated polysaccharides.

Table 1

The immunomodulatory effects of sulfated polysaccharides

Source	Compound name	Components	Mw (kDa)	Sulfuric radical (%)	Immunomodulation	References
Hyriopsis cumingii	HCPS	Rha, Ara, Fuc, Man, Glc, GalA	156	1.38	↑ splenocyte proliferation	(Qiao et al., 2010b)
Monostroma nitidum	F1, F2, F3	Rha, Glc, Xyl	94.40- 1387	1.80-17.70	↑ NO and PGE2 production from Raw 264.7 cells	(Karnjanapratum & You, 2011)
Nemalion helminthoides	N3, N4	Man, Xyl	13.60, 11.70	0.45, 0.84	↑ proliferation of macrophages; RAW264.7 product NO, IL-6 and TNF-α	(Pérez-Recalde, Matulewicz, Pujol & Carlucci, 2014)
Enteromorpha prolifera	F1, F2, F3	Rha, Glc, Xyl	37-1,281	0.15-0.19	↑ phagocytic activity, cytokine secretion and intracellular enzymatic activity in macrophages	(Kim, Cho, Karnjanapratum, Shin & You, 2011)
Ganoderma atrum	S-PSG-1, S-PSG-2, S-PSG-3	Man, Glc, GalA	6470, 4000, 1250	0.65, 0.78, 3.43	↑ macrophage phagocytosis capacity and TNF-α production	(Chen et al., 2015)
Porphyra haitanensis	PHPS	GalA	-	14.67	↑splenocyte proliferation; the subpopulation of Th cells.	(Liu et al., 2017a)
longan	LP1-S	Glc, Ara, Man	105	2.01	↑splenocyte proliferation; the production of NO, IL-6, IL-1β and TNF-α in macrophages.	(Jiang et al., 2014)
Capsosiphon fulvescens	F1, F2, F3	Rha, Xyl, Man	401.70-6232	5.20-13.40	↑ production of NO, PGE2 and cytokines, the expression of iNOS, COX2 from RAW 264.7 cells	(Karnjanapratum, Tabarsa, Cho & You, 2012)
Laminaria cichorioides	Fucoidan I, Fucoidan II	Fuc, Gal, Glc, Xyl, Rha	20–70	36, 38	↑ activation of human complement system	(Zvyagintseva et al., 2000)
Smilax glabra Roxb	SGRP1	Man, Fuc, Glc	12.60	-	↑ phagocytosis and secretion of NO, IL-6, TNF-α and IL-1β on RAW264.7 cells	(Wang, Yang, Zhao, Lu & Zhu, 2016)

Gracilaria rubra	GRPS-1-1, GRPS-2-1 GRPS-3-2	Gal, Fuc	1310, 691, 923	5.96, 8.46, 12.03	↑ RAW264.7 phagocytic activity and acid phosphatase	(Di et al., 2017)
Auricularia auricula	sAAPt, sAAP1, sAAP2	Man, Xyl, Glc, GalA	-	0.22, 1.46, 1.19	↑ humoral immune activity	(Nguyen et al., 2012)
lycium barbarum	sLBPS1.5, sLBPS1.9	-	-	1.51, 1.87	↑ lymphocytes proliferation, serum antibody titer	(Wang et al., 2010b)
Codium fragile	SP-F2	Man, Glc, GalA	-	11.70	↑ NK cell activation, and the expression of NKp30	(Surayot & You, 2017)
Laminaria ja ponica	Fucoidan	Fuc, Gal, Glc, Xyl, Rha	22-39	14	↑ activation of the human complement system	(Zvyagintseva et al., 2000)
Polysiphonia senticulosa Harvey	PS2	Xyl, GalA, Gal	35.40	17.50	↑ phagocytic activity of macrophages; proliferation of T lymphocyte; NK cells activity	(Zhao et al., 2017)
Fucus evanescens	Fucoidan I, Fucoidan II	Fuc, Gal, Man, Glc, Xyl, Rha	150–500	9, 25	↑ activation of human complement system	(Zvyagintseva et al., 2000)
Polymannurog uluronate.	SPMG	Man	8	1.02	↑ proliferative response of T lymphocytes	(Miao, Li, Fu, Ding & Geng, 2005)

Note: Xyl, xylose; Glc, glucose; Rha, rhamnose; Gal, galactose; Ara, arabinose; Man, mannose; Fuc, fucose; GalA, galacturonic acid; Mw, average molecular weight; NO, nitric oxide; PGE2, prostaglandin E2; IL-6, interleukin- 6; Th cells, helper T cell; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; iNOS, induced nitric oxide synthase; COX2, cyclooxygenase 2; NKp30, natural killer cell p30.