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Review Article

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Progress on Biological Activities of Polysaccharides: A Review

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Abstract Polysaccharides are a class of important polymers and play pivotal roles in many life processes. In recent years, polysaccharides have attracted much attention in the field of biochemistry and pharmacology. They possess a variety of biological activities, including anti-tumor, immune regulation, anti-oxidant and anti-virus, anti-lipid and anti-aging activities. They can be widely used in multifarious fields, including food, cosmetic, textile, pharmaceutical industries and so on. In this paper, the biological activities of the polysaccharides are investigated to promote their potential applications for healthcare.

Keywords Polysaccharides; biological activity; immunomodulatory activity; antitumor activity; antioxidant activity

Introduction

Polysaccharide is composed of at least ten monosaccharide molecules. They can be found in plants, animals, fungi and bacteria. Bioactive polysaccharides are very important to the composition and various physiological functions of living organisms. They are a class of biological macromolecules closely related to human life and play an important role in sustaining life activities [1].

It is well known that polysaccharides is important energy source in food. Since the 1960s, polysaccharides have aroused great interest as broad-spectrum immune promoters. Especially the discovery of the anti-tumor activity of fungal polysaccharides, more and more attention has been paid to the polysaccharides. So far, more than 300 kinds of polysaccharides have been isolated from natural products [2]. The physiological activities, chemical structure and structure-activity relationships of these active polysaccharides have become the frontier of the polysaccharides research, and great progress has been made. It has been gradually recognized that polysaccharides are not only an energy source and a supporting tissue structure, but more importantly are involved in biological reactions such as biosynthesis, cell proliferation, viral and bacterial infection, tumor cell metastasis, and regulation of intestinal flora [3]. Polysaccharides have a variety of biological functions and are widely used in functional food and clinical practice, and most of them are non-toxic, which makes the development, utilization and research of polysaccharides biological resources increasingly active, becoming a research hotspot of natural drugs, biochemistry and life science. Many polysaccharides have been developed as drugs, such as Astragalus polysaccharides, lentinan and Tremella polysaccharides.

Bioactivity of Polysaccharides

Immunomodulatory Activity

Immunomodulatory effect is the basis for polysaccharides to perform the pharmacological functions. Polysaccharides can not only activate T, B lymphocytes, macrophages, natural killer cells (NK) and other immune cells, but also activate complement and promote the generation of cytokines, such as interleukin-2 (Il-2) and tumor necrosis factor (TNF), so as to realize its multi-pathway and multi-level regulation of the immune system. As an important member of the host immune defense front, macrophages collaborate with a variety of other cell types, such as neutrophils, to defend themselves against pathogens. Polysaccharides play an important role in immune regulation by influencing the production of reactive oxygen species, secretion of cytokines, proliferation and phagocytosis of macrophages.

Wu et al [4] extracted and purified polysaccharides from *Fructus Corni*. In vitro immunodulatory analysis showed that polysaccharides from *Fructus Corni* could improve the biological activity of interleukin-2 (IL-2), which is a type of cytokine signaling molecule in the immune system. In other study, *Fructus Corni* polysaccharides exhibit an enhanced effect on specific humoral immunity, nonspecificimmunity and specific cellular immunity, and these actions of the polysaccharides increase markedly when they combined with wine [5]. Huang et al [6] found that polysaccharides from dried litchi pulp (LPD) exhibited a better stimulator to spleen lymphocyte proliferation, NK cells cytotoxicity and macrophage phagocytosis. Bian et al [7] found that Licorice polysaccharides affected the production of various cytokines *in vitro* by increasing IL 2, IL 6, IL 7 levels and a decreasing TNF-α levels. Purified polysaccharides from stem lettuce contain sulphate groups, triple helical structures and can promote macrophage proliferation without cytotoxicity [8]. Zhou et al [9] investigated the mechanisms of APS on EAC tumor-bearing mice and macrophage RAW 264.7. The concentrations of nitric oxide, TNF-α, IL-1β and IL-6 were increased after APS treatment. APS might regulate immunity of host organism through the activation of TLR4-mediated MyD88-dependent signaling pathway.

Anti-Tumor Activity

It is generally believed that the anti-tumor effects of the polysaccharides are proceeded in three main ways. First, the activation of the immune system. The regulations of polysaccharides on immune function mainly includes cellular immunity and humoral immunity. Yang et al [10] extracted and purified the water-soluble polysaccharides from *Kaempferia galanga* L. (KGPs). They establish H22 tumor-bearing mice model to observe the antitumor activity. The antitumor experiments *in vivo* revealed that KGPs could effectively protect the spleen and thymus of tumor-bearing mice from solid tumors and heighten the immunoregulatory ability of $CD4^+$ T cells, the cytotoxic effects of $CD8^+$ T cells and NK cells, and in the end resulting in the inhibiting effects on H22 solid tumors. Zhu et al [11] obtained two polysaccharides from *Astralus* and the animal experiment showed that the APS-I and APS-II treatment could protect the organs of animal like liver, spleen and thymus. Li et al [12] found that polysaccharides from *Astragalus* (AP) was composed of Glucan, which could directly activate leukocytes, stimulating their phagocytic, cytotoxic, and antimicrobial activity. AP administration dose-dependently signifificantly increased proliferation of spleen lymphocytes and increased blood IL-2 levels and NK activities. Second, direct toxicity to tumor cells. Polysaccharides inhibit tumor cell growth by changing cell membrane fluidity and regulating the expression inhibition of genes related to cell proliferation, apoptosis and angiogenesis. For example, Wang et al [13] investigated the effect of *Fructus Corni* polysaccharides on apoptosis and expression of related gene in lung carcinoma cells A549. It was found that *Fructus Corni* polysaccharides display a strong inhibiting effect against the cell multiplication and expression of antiapoptotic protein Bcl-2, and promote the expression of proapoptotic protein Bax. Miao et al [14] extracted four water-soluble polysaccharides (LSPa1, LSPb1, LSPb2 and LSPc1) and found that three acidic polysaccharides (LSPb1, LSPb2 and LSPc1) had more potent anti-proliferative effect on human laryngocarcinoma Hep-2 cells than neutral polysaccharide LSPa1. Furthermore, the tumor volume and tumor weight were also obviously suppressed after two weeks treatment of LSPc1 to mice engrafted with Hep-2 cancer cells. In addition, the antitumor activity of polysaccharides is also related to other factors. Deng et al [15] found that the antitumor activity of polysaccharides from *Lycium barbarum* was related to their molecular weights. They separated four water-soluble LBP fractions with serial different molecular weights (MWs) from LBP, designated LBP-2, LBP-3, LBP-4, and LBP-5. *In vivo* and *in vitro* experiments were performed. *In vivo* results showed that polysaccharides with different molecular weights had different inhibitory effects on tumor growth. LBP-2, LBP-3, LBP-4, and LBP-5 could inhibit the tumor growth in H22 tumor-bearing mice by 18.18%, 37.97%, 9.09%, and 14.44%, respectively. Only lbp-3 was significantly found to reduced tumor weight in H22 tumor-bearing mice. *In vitro*, the results showed that all the LBP fractions had significant inhibition on H22 cells, in which LBP-3 had the best activity. Meanwhile, LBP-3 could induce mitochondrial membrane potential destruction, apoptosis, and S phase arrest in H22 cells. Nurmamat et al [16] found that the physical and chemical properties and biological activities of polysaccharides were influenced by extraction temperatures. Water-soluble polysaccharides (CMPs-4 and CMPs-80) from cordyceps militaris (C. militaris) were extracted at 4 ºC and 80 ºC respectively. *In vitro* antitumor experiments showed that CMPs-80 possessed weaker inhibitory effects on human esophagus cancer Eca-109 cells by inducing cell apoptosis more than CMPs-4 did. Thus, polysaccharides extracted from cold water have better biological activity and have potential anti-tumor effect. It is known that Astragalus polysaccharides exert anti-tumor activity.

Antioxidant Activity

It is known that antioxidant activity means that some antioxidants can protect cells against the damaging effects of reactive oxygen species (ROS) [17], such as singlet oxygen, superoxide and hydroxyl radicals. The antioxidant activity of polysaccharides may be due to the fact that the structure of polysaccharides has a hemiacetal hydroxyl, or reductive end, which leads to the reduction of free radicals and thus the scavenging of free radicals, but the specific antioxidant mechanism remains to be studied. At present, it is believed that the antioxidant mechanisms of polysaccharides include the following four aspects. First, the hydrogen atoms in the structure of polysaccharides can react with free radicals to form water, and the reaction to form a single electron can be further reduced; Second, polysaccharides trap free radicals produced in lipid reactions, or chelate with metal ions, which are essential for the formation of free radicals; Third, polysaccharides can enhance the activity of some antioxidant enzymes in the body, such as superoxide dismutase, so as to better play the antioxidant capacity; Fourth, polysaccharides can regulate the immunity of the body, thereby indirectly achieving antioxidant effect. Wang et al [18] found that the polysaccharides from *Tricholoma lobayense* had a notable activity in scavenging $\bullet O_2^-$ in a concentration-dependent manner, which is a highly toxic species that could be generated by numerous biological and photochemical reactions; H_2O_2-induced MEH and formation of MDA were effectively inhibited; it was showed that the polysaccharides could obviously inhibit AAPH-induced oxidative modification of HSA. Moreover, Microalgal polysaccharides also showed potent scavenging activity toward different free radicals. Polysaccharides isolated from marine invertebrates showed *in vitro* and *in vivo* antioxidant activities could alleviate the diseases mediated by free radicals. Numerous antioxidant studies *in vivo* have revealed that fucoidan derived from brown algae can alleviate body damage caused by oxidative stress through regulating the antioxidant defense system in the body. Fucoidan from *Costaria costata* inhibits the oxidative stress in the liver of CCl_4-induced mice by down regulating the malondialdehyde (MDA) level and upregulating the superoxide dismutase (SOD) level [19].

The model of scavenging the stable DPPH radical is a widely used method to evaluate the free radical scavenging ability of natural compounds [20]. Li et al [21] draw a conclusion that SPF obtained by the optimum ultrasonic assisted extraction technology through orthogonal experiment method, exhibited a strong DPPH scavenging activity. Free radicals are harmful to living organisms [22]. To reduce the damage caused by free radicals, both synthetic and natural antioxidants are used. However, synthetic antioxidants are thought to cause liver damage and carcinogenesis [23]. Therefore, it is important to develop natural nontoxic antioxidants to protect humans from free radicals. The antioxidant properties of exopolysaccharides (EPSs) have been reported from many types of EPSs derived from filamentous fungi [24]. Raza et al. reported that P. polymyxa SQR-21 produced one type of EPS using yeast extract and galactose as the best N and C sources, respectively. Their EPS showed good superoxide scavenging and moderate inhibition of lipid peroxidation [25]. In antioxidant assays *in vitro*, Liu et al found that both crude EPS and its purified fractions (EPS-Ⅰ and EPS-Ⅱ) were found to have moderate DPPH radical scavenging activity, hydrogen peroxide scavenging activity, lipid peroxidation inhibition effects [26]. Liu et al successfully acetylated, phosphorylated and benzylated the levan-type EPSs from P. polymyxa EJS-3 to obtain the derivatives of acetylated levan (AL), phosphorylated levan (PL) and benzylated levan (BL). For the antioxidant and antitumor activities *in vitro* of the natural polysaccharide and its derivatives, AL, BL and PL all exhibited higher reducing power, scavenging activity against superoxide radicals and scavenging activity of hydroxyl radicals compared to the natural polysaccharide EPS-1. The enhanced activities of the derivatives were probably due to the introduction of acetyl, benzyl or phosphoryl groups into the EPS-1 molecules, which increased the electron-donating ability and affinity with the receptors on immune cells. The results suggested that the derivatives could be explored as promising antioxidant [27]. It is reported that Se plays an important role in increasing the antioxidant activity of Se-containing polysaccharides. Wang et al [28] synthesized a novel derivative of *Artemisia sphaerocephala* polysaccharide (ASP), SeASP, by H_2SeO_3/HNO_3. They found that SeASP showed higher scavenge hydroxyl and superoxide radical activities than native ASP.

Anti-aging Effect

Aging is an activity in the process of occurrence and development of life. It is a process of loss and degeneration of body from constitution material, organization structure to physiological function. It is believed that accumulation of oxidative stresses contributes to the aging processes. Modern pharmacological research shows that polysaccharides can play an anti-aging role by enhancing antioxidant enzyme activity, eliminating free radicals in the body, enhancing immunity and other ways. Yuan et al [29] found that sulfated *Flammulina velutipes* polysaccharides showed superior antioxidant and protective abilities against the d-galactose-induced aging by increasing the antioxidant enzyme activities, decreasing lipid peroxidation, improving the inflammatory response and ameliorating the anile condition of mice in the *in vivo* animal experiments, Acetylated polysaccharides from *Pleurotus djamor* have the same effect [30]. Angelica polysaccharide can reduce the expression of p16, p53 and p21 proteins in the brain tissues of aging mice and delay aging. Le et al [31] investigated monosaccharide compositions of acidic-extractable polysaccharides (AcAPS) and its major purified fractions (AcAPS-1, AcAPS-2 and AcAPS-3) from the fruiting body of *Agaricus bisporus*. In the *in vitro* assays, AcAPS-2 showed superior scavenging activities on hydroxyl and DPPH radicals. For *in vivo* anti-aging analysis, AcAPS-2 showed superior effects on hepatic and nephric protection by improving serum enzyme activities, biochemical levels, lipid contents and antioxidant status, respectively.

Antiviral Activity of Polysaccharides

Most polysaccharides have inhibitory effects on various viruses, for example human immunodeficiency virus(HIV), influenza virus and so on. The mechanism of anti-virus actions of polysaccharide can be divided into five types. First, direct virucidal action. Polysaccharides can directly interact with the surface of the virus through the negative charge they carry, thus inhibiting the ability to infect the virus, or directly kill the virus, making the virus lose its appeal. Second, inhibition of viral adsorption. Third, inhibition of virus internalization and uncoating. Fourth, inhibition of virus transcription and replication. Fifth, improvement of host antiviral immune responses, that is to regulate the body's immune system, enhance the body's anti-virus immune response. The experimental results of Gu et al. proved that pohygonatum sibiricmu polysaccharides had protective effect on cells, increased the activity of cells infected by herpes simplex virus, and had obvious inhibitory effect on viruses [32]. A large number of pharmacological studies have proved that lentinan polysaccharides and *Grifola Frondosa*polysaccharides have anti-HIV effect. The main anti-hiv mechanism is to interfere with the adhesion of HIV to host target cells, inhibit the expression of HIV antigen, inhibit the synthesis of syncytium, inhibit the activity of reverse transcriptase and enhance the immune function [33]. Xing et al [34] found that the activity of HIV was inhibited by the addition of polysaccharides from *Grifola Frondosa* to helper T lymphocytes infected with HIV. In recent years, it has been found that the antiviral activity of polysaccharides are associated with their molecular weights and the content of sulfates. Tang et al found that low molecular weight carrageenans and their derivatives showed significant inhibition effects against influenza virus FM1-induced pulmonary edema in mice, and the 3 kDa k-carrageenan with proper acetylation degree and sulfation degree possesses best antiviral activity *in vivo* [35]. Heparinoid polysaccharides can interact with the positive charge regions of cell surface glycoproteins, leading to the shielding effect on these regions, thus preventing the binding of viruses to the cell surface. The marine heparinoid polysaccharides have similar pharmacological activities to the natural heparin, and all can inhibit the infection and replication of different kinds of viruses.

Lipid-lowering Effect of Polysaccharide

With the improvement of people's living standard, the number of dyslipidemia in our country is increasing day by day, even many young people and children have joined the ranks of high cholesterol, high triglyceride. Hyperlipidemia is a systemic chronic metabolic disease caused by dyslipidemia *in vivo*. Its main harm is to accelerate systemic atherosclerosis, which causes coronary heart disease, thrombosis and other cardiovascular and cerebrovascular diseases. Previous studies have verified that polysaccharides are capable of decreasing the lipid content. The mechanism of polysaccharide lowering blood lipid may correlate the following aspects [36]. First, inhibit exogenous lipid absorption or promote cholesterol excretion. Exogenous lipids are absorbed into the body through the small intestine, and then circulates through enterohepatic circulation. Most of them are absorbed back to the liver for reuse, while a small part is excreted in the feces. Polysaccharides can block lenterohepatic circulation, reduce reabsorption, promote bile acid excretion, reduce cholesterol content in the blood. Second, affects the transport or distribution of lipids. Some polysaccharides have the effect of phospholipid, after binding with apolipoprotein, changed the conformation of apolipoprotein, make it more easy to bind with lipids, accelerate the transport of blood lipid back to the liver, accelerate cholesterol clearance. Third, affects endogenous lipid synthesis and metabolism. Polysaccharides can competitively inhibit hepatic HMG-CoA and limit endogenous cholesterol synthesis. TG synthesis can be reduced by reducing mRNA expression of fatty acid synthase. Polysaccharides can also promote cholesterol metabolism by affecting the activity and content of enzymes related to fat metabolism. Fourth, reduce blood lipid by antioxidant. Polysaccharides can increase the activity of SOD, GSH-Px, CAT and other antioxidant enzymes, improve the body's antioxidant capacity, reduce the generation of free radicals, reduce the generation of MAD, through the elimination of excess free radicals in the body to reduce the membrane lipid peroxidation so as to achieve the purpose of lowering blood lipids.

Zhong et al [37] found that hawthorn polysaccharide effectively controlled the absorption of fat by inhibiting the activity of pancreatic lipase. Polysaccharides from *Grateloupia filicina* can significantly reduce fasting blood glucose and TC, TG and LDL-C content in hyperglycemia mice, and increase HDL-C content in hyperglycemia mice [38]. Studies have shown that pumpkin polysaccharides can enhance the a-helix structure of apolipoprotein AⅠ, leading to a conformational change of apolipoprotein AⅠ, making it more conducive to lipid binding, which is similar to phospholipids. In addition, apolipoprotein AⅠcan also promote HDL maturation by activating lecithin cholesterol acyltransferase, so that cholesterol esterification transported to the liver, so as to speed up the removal of blood cholesterol and reduce blood lipids [39].

Hypoglycemic Activity

Long-term hyperglycemia can cause lesions in various tissues and organs of the whole body, leading to the occurrence of acute and chronic complications, such as impaired renal function, cardiovascular and cerebrovascular diseases. Diabetes has become a frequent and common disease in China, especially in the middle and old people over 40 years old. Therefore, it is very important to develop drugs and health food that are safe, have little side effect, prevent and treat hyperglycemia. It was found that most polysaccharides had significant hypoglycemic effect. Polysaccharide hypoglycemic mechanism is mainly manifested in insulin pathway and non-insulin pathway, and many drugs are not through a single pathway to hypoglycemic. First, the insulin pathway. Polysaccharides can protect and repair β cells. Direct stimulation of pancreatic β cells to increase insulin secretion; Improve glucose tolerance, promote the secretion of insulin; Improve the morphology and function of islet cells. Second, the non-insulin pathway. Polysaccharides can replace glucose and do not raise blood glucose. Regulate glucose metabolism, promote liver glycogen synthesis or reduce liver glycogen decomposition; Inhibit gluconeogenesis and promote the utilization of glucose in peripheral tissues. Antagonizes hyperglycemia. Third, the role of other pathways. Pumpkin polysaccharides, sea cucumber polysaccharides, lentinan etc have been found to have the effect of lowering blood glucose. The water-soluble polysaccharide from sweet corncob (SCP-80-I) significantly reduced the blood glucose level in a dose-dependent manner. The SCP-80-I reduced total cholesterol, triglyceride, and low-density lipoprotein-C levels significantly, and increased the level of high-density lipoproteins in streptozotocin-induced diabetic rats [40]. Wei et al [41] found that the extracellular polysaccharides from *Lachnum calyculiforme* had a strong hypoglycemic effect in alloxan diabetic mice with dose-dependent relationship through Diabetic mice experiments. Using fifty male wistar-imamichi rats which were injected peritoneally by normal saline (NS) as models, Yu lei [42] studied the effect of lycium barbarum polysaccharide on the hypoglycemic activity. The results showed that the diabetic rats body weight injected with LBP gained; the levels of fasting blood glucose (FBG), fasting insulin (FNs), serum il-6 and serum TNF reduced gradually, but the insulin sensitivity index (ISI) index increased and insulin resistance (IR) index decreased. LBP has the effect of lowering blood glucose in stz-induced diabetic rats, and the hypolipidemic effects that could be related to its reducing the level of serum inflammatory factor, improving lipid metabolism.

Other Activities

In addition to the above biological activities, polysaccharides have some other functions. The plantain seed polysaccharides showed protective effects on inflammation in animal models, which may be mediated through inhibition of the exudation of inflammatory factors, the lipid peroxidation and the elimination of free radicals [43]. Animal experimental data show that ganoderma lucidum polysaccharides, cordyceps sinensis polysaccharides, etc. enhance the function of spark phagocytic cells in mice and improve the resistance of mice to radiation through strengthening the hematopoietic system of mice [44]. Thus edible fungi polysaccharide has a certain anti-mutation effect. Zhang et al [45] found that lycium barbarum polysaccharides have protective and improving effects on germ cells. It can reduce the expression of apoptotic protein caspase-3 in testicular spermatogenic cells, reduce the expression of apoptotic promoting gene Bax, increase the expression of apoptotic inhibiting gene Bcl-2, inhibit the expression of Fas and FasL, and thus inhibit the apoptosis of spermatogenic cells.

Conclusions

In recent years, research on polysaccharides has been deepening at home and abroad. As an important bioactive substance, polysaccharides have many physiological functions such as regulating immunity, anti-tumor, anti-virus and anti-aging, and have been widely used in many industries. However, due to the complex structure of polysaccharides, it is difficult to purify polysaccharides. The mechanism by which polysaccharides exert their activity remains unclear. Therefore, researchers need to further study the purification method and mechanism of polysaccharides. It is believed that in the future, polysaccharides will be a new class of high - efficiency drugs to protect human health.

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