MAHSA International Journal of Health and
Medicine, V4, Issue 1; September, 2024
e-ISSN: 2805-5705

**Review Article** **Open Access**

# Extraction, Purification and Biological Activities of Polysaccharides from Microorganism: A Review

Xiao-Lian Wei[1, 2], Rola Ali-Saeed[2, *]

[1] School of Basic Medicine, Youjiang Medical University for Nationalities, Baise, 533000, Guangxi, PR China. [2] Department Preclinical Sciences, Faculty of Dentistry, MAHSA University, 42610, Selangor, Malaysia. [3] Department of Biochemistry, Faculty of Medicine, Bioscience, and Nursing, MAHSA University, 42610 Jenjarom, Selangor, Malaysia.

[*]**Corresponding Author(s):** Rola Ali-Saeed, Department Precliinical Sciences, Faculty of Dentistry, MAHSA University, 42610, Selangor, Malaysia. E-mail Addresses: rolaali@mahsa.edu.my

Received: 05 August 2024 Accepted: 19 October 2024 Published: 20 October 2024

**Abstract**

Microbial polysaccharides, as a class of natural compounds, represent one of the primary active ingredients produced by microorganisms. Due to their unique chemical structures, microbial polysaccharides exhibit diverse biological activities such as anti-tumor, antiviral, antibacterial, and immunomodulatory effects, demonstrating immense potential for applications in various fields including medicine, food, and cosmetics. In recent years, microbial polysaccharides have garnered increasing attention from researchers. This article comprehensively reviews the advancements in the extraction techniques, purification methods, and biological activity research of microbial polysaccharides. Additionally, it enumerates some recent applications and development prospects of microbial polysaccharides across various sectors. This comprehensive overview aims to provide insights into the discovery of more high-quality microbial polysaccharide resources, elucidate the intrinsic relationship between polysaccharide structure and function, reveal the mechanisms of polysaccharide bioactivity, and facilitate further exploitation and utilization of microbial polysaccharides.

**Keywords:** Microorganisms; Polysaccharides; Extraction; Purification; Biological activity

## 1. Introduction

Polysaccharides are a class of polymer carbohydrates widely present in plants, fungi, algae and bacteria, and their molecular structure is composed of multiple monosaccharide molecules connected by glycosidic bonds, which has a high degree of complexity and diversity, and is one of the most important active components of organisms, with obvious biological activities such as antitumor (1), antiviral (2), anticoagulation (3), immunomodulatory (4) and neuroprotective (5). Polysaccharides are numerous and diverse, and can be divided into microbial polysaccharides, plant polysaccharides, and animal polysaccharides according to their sources (6). However, due to the obvious difference between the growth environment and metabolic pathways of microorganisms and animals and plants, the polysaccharides produced by them often have the characteristics of novel structure and diverse activities. In addition, microbial polysaccharides feature high controllability in production processes, no influence from external factors, short production cycles, and relatively low production costs. They can be produced in batches through fermentation for industrialization and are safe and non-toxic. Therefore, microbial polysaccharides have become an important source of new drugs (7). The extraction and purification processes of microbial polysaccharides are complex and diverse. To ensure the extraction efficiency and purity of polysaccharides, different extraction methods are required for different polysaccharide types and microbial sources. In terms of biological activity, microbial extracellular polysaccharides exhibit various biological activities, such as antioxidant, antitumor, and antibacterial effects. These biological activities make microbial polysaccharides have broad application prospects in the fields of medicine and health care. This article mainly reviews the extraction, separation, purification, and biological activities of microbial polysaccharides, aiming to provide a theoretical basis for the further development and utilization of microbial polysaccharides.

## 2. Extraction and purification of microbial polysaccharides

### 2.1 Extraction

With the development of technology, many methods for extracting polysaccharides from microorganisms have been reported. Table 1 shows the advantages and disadvantages of different methods for extracting microbial polysaccharides.

Hot water extraction method is simple, easy to control, and is a classic method to extract polysaccharides from natural resources (8). In short, an appropriate amount of hot water is added, with the temperature controlled at 80-100℃, and the extraction is carried out for 1-3 hours. In order to improve the extraction rate of polysaccharides, multiple extractions can be performed. After filtering the extract to remove impurities, crude polysaccharides can be obtained by ethanol precipitation. It should be noted that high temperature may lead to partial degradation or structural changes of polysaccharides, affecting their biological activity and function.

Organic solvent extraction of polysaccharides is also a commonly used method. The principle of this method is to add organic solvents to the fermentation broth, which can reduce the solubility of polysaccharides, thereby causing polysaccharides to precipitate or coagulate. Ethanol, acetone, etc. are the most commonly used organic solvents for extracting microbial polysaccharides, among which ethanol is the most widely used. When ethanol is added to the fermentation broth, as the concentration of ethanol in the solution increases, the solubility of polysaccharides gradually decreases, forming a precipitate. At

present, the ethanol precipitation method has been widely used in the extraction of microbial polysaccharides (9,10).

Ultrafiltration, as a new membrane separation technique, relies primarily on sophisticated microporous membranes to effectively separate substances based on their molecular weight, achieving the purpose of isolating components of varying molecular masses. Compared to traditional separation methods, ultrafiltration boasts remarkable advantages: it swiftly and easily extracts extracellular polysaccharides from fermentation broth, minimizing disruption to the polysaccharides' biological activities and preventing the deactivation of heat-sensitive biomolecules. Furthermore, ultrafiltration is characterized by low energy consumption and minimal material loss, making it a favored approach among researchers in the field of polysaccharide extraction and separation (11).

In the extraction of fungal polysaccharides, enzyme-assisted extraction method is widely utilized due to their ability to hydrolyze the cell wall matrix of fungi. Commonly used enzymes include cellulase, trypsin, papain, and others. However, the application of enzymatic extraction is subject to various constraints, as changes in temperature, pH, and enzyme concentration can all affect enzyme activity. Furthermore, the relatively high cost of enzymes poses an additional challenge. These factors collectively constitute the primary challenges of enzyme-assisted extraction methods and contribute to the difficulty in scaling up this approach for large-scale applications (12).

Furthermore, spray drying boasts rapid heat transfer, fast water evaporation, and short drying time, and has been employed in the extraction and separation of certain bioactive substances(13). The acid-base extraction method, on the other hand, utilizes acids (such as HCl) or bases (such as NaOH) to disrupt cell walls, thereby releasing polysaccharides within the cells (14). The ultrasonic-assisted extraction method harnesses the cavitation effect of ultrasonic waves to facilitate the rupture of cell walls and the release of polysaccharides, thereby enhancing yield and efficiency (15). Parameters such as the power, frequency, and duration of ultrasonic waves may potentially affect polysaccharide yield, necessitating optimization based on specific conditions.

**Table 1: Comparison of microbial polysaccharide extraction methods**

| Method | Advantage | Disadvantage |
|---|---|---|
| Ultrafiltration | Efficient, fast, low energy consumption and low loss of biological activity. | The requirements for equipment are high and the cost is high. |
| Spray drying method | Fast heat transfer and short drying time. | It is easy to cause local overheating and affect the activity of polysaccharides. |
| Organic solvent precipitation method | Easy to operate and low cost. | Organic solvents are volatile, the dosage is large, and the extraction rate is not high. |
| Hot water method | Easy to operate and easy to control. | High temperature may cause degradation and structural changes of some polysaccharides. |
| Alkali extraction method | High yield. | The processing time is long, the temperature is high, the polysaccharides are degraded, and the molecular weight is reduced. |
| Acid extraction method | High yield. | The time is long, the temperature is high, the polysaccharide is degraded, and the molecular weight is reduced. |
| Ultrasound-assisted extraction | The extraction time is short, the energy consumption is low, the extraction rate is high, and the operation is simple. | The temperature rise is difficult to monitor, and the molecular weight of polysaccharides is reduced. |
| Enzyme-assisted extraction | The reaction conditions are mild, the extraction efficiency is high, and the product is not easy to deteriorate. | Enzymes are expensive and easily inactivated. |

## 2.2 Isolation and purification of microbial polysaccharides

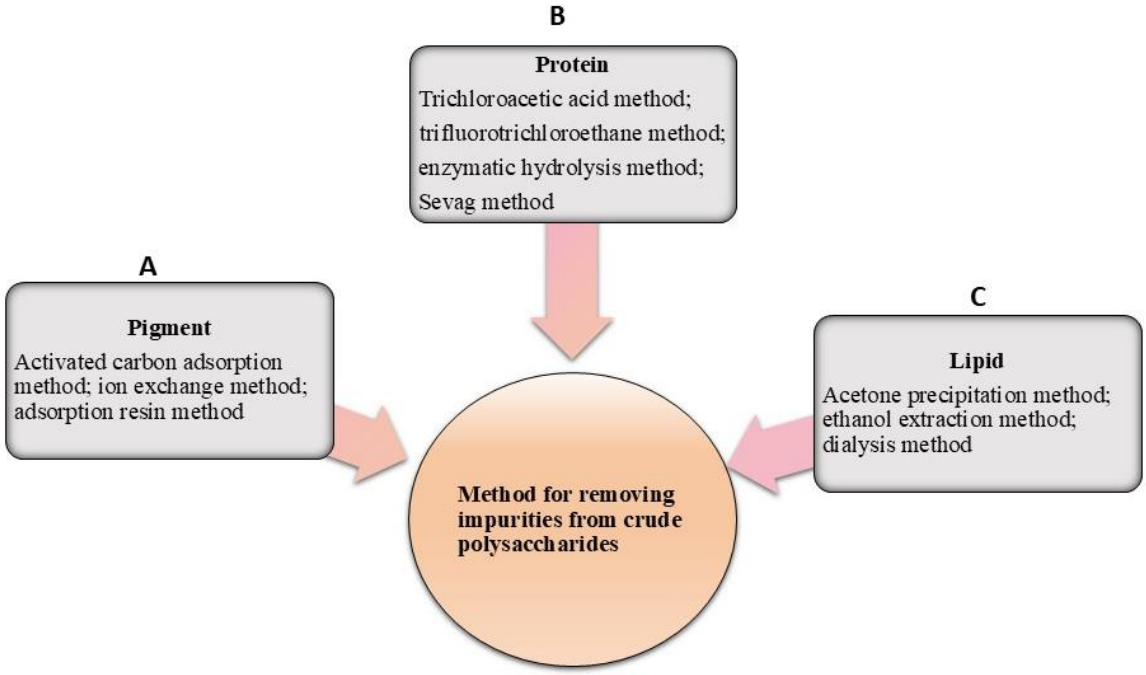


**Figure 1** Methods for removing impurities from microbial crude polysaccharides.

A: methods for removing pigment; B: methods for removing protein; C: methods for removing lipid.

The crude polysaccharides obtained after crude extraction from microorganisms often contain impurities such as proteins, pigments, and lipids, which may adversely affect the analysis of physicochemical properties, structural identification, and biological activity assessment of polysaccharides. Therefore, it is necessary to remove the impurities from crude polysaccharides (22). Common methods for removing impurities from microbial crude polysaccharides is shown in Figure 1. In the process of removing impurities from microbial polysaccharides,

the removal of proteins is crucial. Commonly used methods for deproteinization include trichloroacetic acid (TCA) method, trifluorotrichloroethane method, enzymatic hydrolysis method, and Sevag method. The TCA method involves adding trichloroacetic acid to the crude polysaccharide solution, causing proteins to denature and precipitate for removal. However, due to the strong acidity of trichloroacetic acid, it can not only denature proteins but also hydrolyze polysaccharide chains, ultimately resulting in significant polysaccharide loss (23). The trifluorotrichloroethane method involves mixing the crude polysaccharide solution with an equal volume of trifluorotrichloroethane, stirring for 10 minutes, and then centrifuging to obtain the upper aqueous layer. This process is repeated twice to remove proteins from the crude polysaccharides. While this method is relatively efficient, the solvent trifluorotrichloroethane is a volatile liquid, making it unsuitable for large-scale industrial production. The trifluorotrichloroethane

method involves mixing the crude polysaccharide solution with an equal volume of trifluorotrichloroethane, stirring for 10 minutes, and then centrifuging to obtain the upper aqueous layer. This process is repeated twice to remove proteins from the crude polysaccharides. While this method is relatively efficient, the solvent trifluorotrichloroethane is a volatile liquid, making it unsuitable for large-scale industrial production (24). The enzymatic method primarily utilizes a suitable concentration of protease to specifically degrade proteins within crude polysaccharide solutions. Common enzymes employed include trypsin (25), papain (26), and pepsin (27). This approach boasts mild reaction conditions, effectively preventing damage to the polysaccharide structure while preserving its biological activity. However, its limitation is the inability to completely remove all proteins from the polysaccharides. The Sevag method is the most commonly used approach for protein removal. It is mixed chloroform and butanol in a 4:1 ratio and added this mixture to the crude polysaccharide solution. By vigorous shaking, the proteins in the sample are denatured into an insoluble state, followed by centrifugation to remove them, thereby achieving the purpose of removing proteins and purifying polysaccharides (28). Although this method has a relatively low efficiency in removing proteins, often requiring repetition of the process three times or more to achieve satisfactory results, its mild process conditions have minimal impact on the polysaccharide structure, avoiding polysaccharide denaturation. As such, it is highly favored in scientific research.

After removing proteins from crude polysaccharides, the resultant mixture still comprises various substances with diverse relative molecular weights. To obtain fractions with a uniform distribution of relative molecular masses, further purification of the polysaccharides is necessary. Commonly employed methods for this purpose include precipitation using quaternary ammonium salts, membrane separation techniques, and column chromatography. The quaternary ammonium salt precipitation method leverages the unique property of quaternary ammonium salts, which, when their pH is below 9, can interact with acidic polysaccharides, forming precipitates that can be readily separated, thereby isolating the acidic polysaccharides effectively. Membrane separation technology embodies a highly selective process, where a mixture of molecules with varying particle sizes is passed through a semipermeable membrane, enabling the achievement of selective separation based on their size. Column chromatography is the most classic purification method, including macroporous resin column chromatography, gel filtration chromatography, and ion exchange column chromatography (29). In many cases, it is difficult to obtain polysaccharide components with good homogeneity by purifying crude polysaccharides by only one method, so two or more methods are generally used for purification to obtain components with higher purity. For example, Cao et al. (30) used DEAE-Sepharose Fast Fiow ion exchange column chromatography to purify crude polysaccharides from Lactobacillus plantarum and further purified them by Seph-arose CL-6B gel column chromatography, resulting in many single-component exopolysaccharides with high sugar content.

## 3. Biological activities of microbial polysaccharides

As natural products, microbial polysaccharides exhibit a variety of biological activities, with the currently proven ones including antioxidant, antitumor, antiviral, and immunomodulatory effects (Figure 2).

### 3.1 Immunomodulatory activity

It is well known that abnormalities in the immune system can lead to the development of a variety of diseases. Many studies have shown that microbial polysaccharides have immunomodulatory effects. Neumann et al. (31) found that the synergistic effect of bacterial lipopolysaccharide (LPS) and macrophage activating factor can increase the number of macrophages induced and enhance the phagocytic ability of macrophages. Zhu et al. (32) studied the effect of zymosan on the function of immune in mice. The results showed that zymosan significantly promoted the proliferation of splenic lymphocytes and the secretion of cytokines in mice, and there was a clear dose-effect relationship between the proliferation effect, the secretion of cytokines, and the concentration of zymosan. Guo et al.(33) found the exopolysaccharide Ebosin produced by *Streptomyces* sp. 139, not only could improve the inflammatory response of LPS-induced keratinocytes through the IKK / NF-kapaB pathway, but also reduce psoriatic skin damage and reduce the expression of imiquimod (IMQ) -mediated inflammatory factors in psoriasis mice. The experimental results of Li et al. (34) showed that *Bifidobacterium* EPS promoted the proliferation of splenic lymphocytes, significantly increased the serum half hemolytic value ($HC_{50}$) of mice, and stimulated the production of serum antibodies in mice. In addition, the immunoregulatory effects of *Bifidobacterium* EPS on T and B lymphocytes showed a certain dose-dependent relationship. It could not only selectively enhance the activity of suppressive lymphocytes, but also improve the function of T helper lymphocytes by enhancing the activity of B lymphocytes, ultimately enhancing both specific and non-specific immune activities.

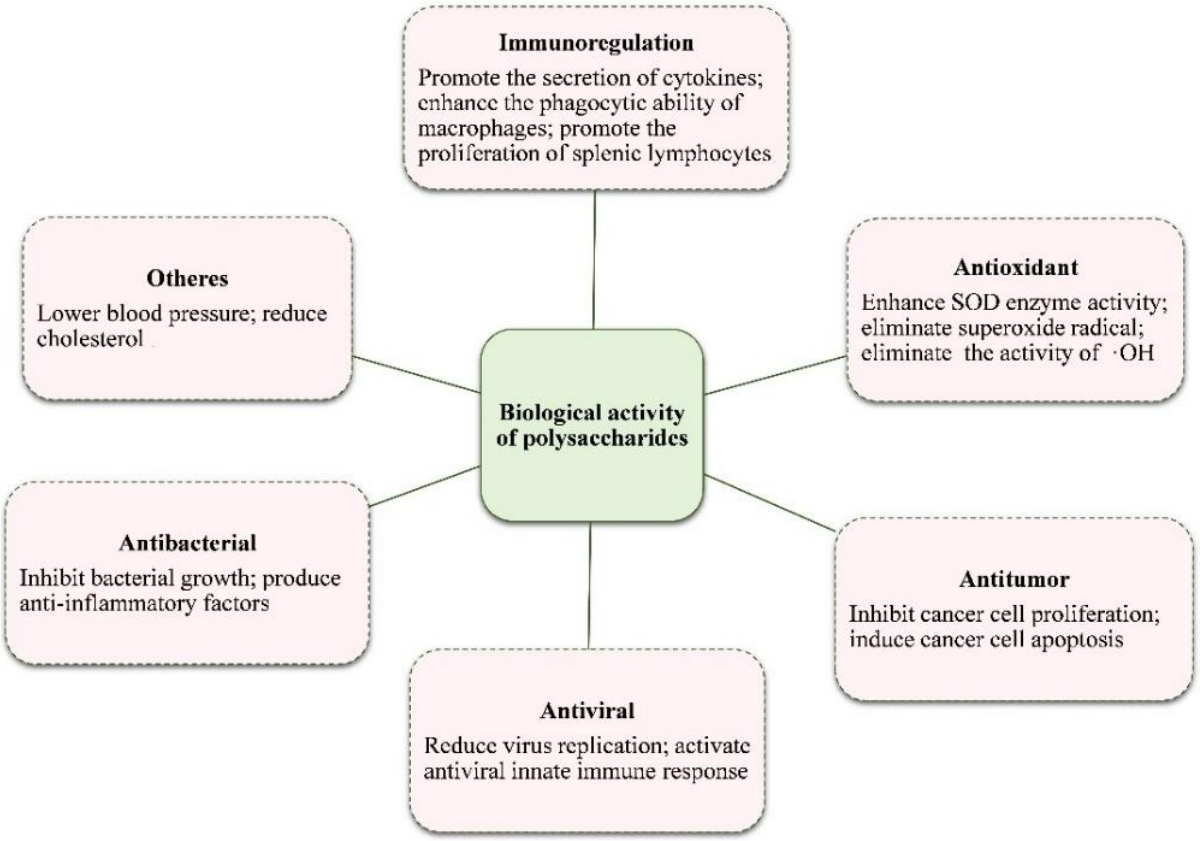


**Figure 2** Biological activities of microbial polysaccharides

### 3.2 Antioxidant activity

Excessive accumulation of superoxide radicals and lipid peroxides in the body can cause continuous damage to cells, ultimately leading to cell aging, apoptosis, and carcinogenesis. Microbial polysaccharides can play an antioxidant role by increasing the activity of superoxide dismutase, scavenging free radicals, and resisting lipid peroxidation.

Liu et al. (35) found that the exopolysaccharides of *Lactobacillus paracasei* and *Lactobacillus plantarum* exhibited ferrous ion chelating capacities of 54.18% and 29.34% respectively at a concentration of 10 mg/mL, demonstrating anti-lipid peroxidation effects. Xu et al. (36) discovered that the exopolysaccharide EPSa of *Bifidobacterium animalis* RH showed excellent performance in antioxidant tests, with its anti-lipid peroxidation activity and free radical scavenging ability surpassing that of ascorbic acid, and also inhibited erythrocyte hemolysis in a concentration-dependent manner. Ghareeb et al.(37) extracted an acidic exopolysaccharide (EPS) from the marine Streptomyces vinaceusdrappus strain AMG31 and demonstrated that it possesses significant antioxidant properties. Specifically, it efficiently scavenged 93.8% of DPPH radicals and exhibited potential efficacy in combating Alzheimer's disease by significantly inhibiting butyrylcholinesterase activity, especially at a concentration of 100 μg/ml, where it attains a maximum inhibition rate of 84.5%. Pan et al.(38) isolated and purified an extracellular polysaccharide (EPS-1) from *L. lactis* subsp.

lactis 12 and evaluated its antioxidant capacity. The results indicated that EPS-1 exhibited remarkable antioxidant activity, with its total antioxidant capacity, superoxide anion scavenging ability, and hydroxyl radical scavenging ability all increasing with concentration. This discovery not only reveals the potential of EPS-1 in reducing oxidative damage but also provides a scientific basis for its healthy applications in functional foods and antioxidants.

### 3.3 Antitumor activity

Tumor is a disease in which cell proliferation is out of control, abnormal differentiation, and abnormal apoptosis. At present, many tumor treatment methods used in clinical practice have great toxic side effects on the body (39), therefore, it is very important to develop non-toxic new anti-tumor drugs. Li et al. (40) extracted polysaccharides from the fermentation broth of marine *Bacillus* sp. QLc-04 and studied their ability to inhibit HeLa cells. When the concentration reached 500 mg/mL, the inhibition rate of HeLa cell proliferation was as high as 62.25%, but the mechanism of inhibiting cancer cell proliferation remains to be further explored. Ma et al. (41) screened the extracellular polysaccharide component (REPS2-A) of *Rhodotorula mucilaginosa* to evaluate its potential inhibitory effects on 10 common cancer cells. The results showed that the extracellular polysaccharide component REPS2-A could arrest the liver cancer cell cycle at the G1/S phase, thereby hindering further cell division and proliferation. Additionally, this polysaccharide component also triggered the apoptosis process of liver cancer cell Hep G2, displaying a significant dose-dependent effect. The aforementioned discoveries regarding the inhibition of cancer cell proliferation by microbial polysaccharides have provided new perspectives and potential candidate drug molecules for the field of cancer treatment, which carry significant scientific importance and clinical application prospects.

### 3.4 Antiviral activity

Microbial polysaccharides can exert antiviral effects by activating immune cells, inducing the production of proinflammatory cytokines and chemokines, among other mechanisms. Arena et al. (42) demonstrated that a polysaccharide, EPS-2, secreted by *Geobacillus thermodenitrificans* strain B3-72, can interfere with the replication of herpes simplex virus type 2 (HSV-2) in human peripheral blood mononuclear cells (PBMCs), effectively suppressing viral proliferation. Further analysis revealed that a series of essential immunoregulatory factors, including IL-18, IL-12, IFN-α, IFN-γ, and TNF-α, were significantly present and upregulated in the culture supernatants of PBMCs. The synergistic action of these cytokines and chemokines enhances the antiviral immune response of host cells. KANMANI et al. (43) confirmed that the extracellular polysaccharide (EPS) produced by *Lactobacillus delbrueckii* subsp. bulgaricus TUA4408L can significantly enhance the ability of porcine intestinal epithelial cells to resist rotavirus infection, primarily by inhibiting viral replication within the cells. Furthermore, they revealed that EPS activates the antiviral innate immune response of host cells by regulating the Toll-like receptor 3 (TLR3) immune signaling pathway, thereby strengthening the defense mechanism. Meanwhile, Kim et al. (44) also demonstrated that the EPS produced by *Lactobacillus plantarum* LRCC5310 exhibits marked anti-rotaviral activity. Its mechanism of action primarily involves reducing the duration of diarrhea, inhibiting pathological changes in intestinal epithelial tissue, and decreasing rotavirus replication in the intestine, ultimately weakening the virus's

pathogenicity. Therefore, microbial polysaccharides, through their unique immunomodulatory mechanisms, exhibit significant antiviral activity, providing valuable natural resources and research clues for the development of novel antiviral therapies.

### 3.5 Other biological activities

Apart from the biological activities such as immunomodulation, antitumor, antioxidant, and antiviral effects, microbial polysaccharides also possess other biological activities. For instance, the exopolysaccharide (EPSS5) produced by *Streptomyces rochie* strain OF1 exhibited antibacterial activity against *Klebsiella pneumoniae,* methicillin-resistant *Staphylococcus aureus* (MRSA)*,* and *Escherichia coli*(45)*.* Exopolysaccharides (EPS) from *lactic acid bacteria* can effectively inhibit the growth of *Enterobacter sakazakii, Escherichia coli, Listeria monocytogenes, Staphylococcus aureus, Candida albicans, Yersinia pestis*, and *Salmonella typhimurium* (46-49), exhibiting certain antibacterial activities. The research by DINIC'M et al. (50) revealed that the extracellular polysaccharide (EPS) produced by *Lactobacillus plantarum* BGCG11 can elevate the expression levels of the anti-inflammatory cytokines IL-6 and IL-10, demonstrating high anti-inflammatory activity in rats. Kiho et al. (51) extracted a polysaccharide, CS-F10, from the mycelium of the *Cordyceps sinensis* fungus, which showed hypoglycemic activity. It can reduce the level of glucose transporter GLUT2 protein in the liver, thereby inhibiting hepatic glucose output and ultimately reducing blood glucose to normal levels. The research conducted by Shao et al. (52)has shown that the exopolysaccharide PJ1-1, extracted from the mangrove-endophytic fungus *Penicillium janthinellum* N29, possesses significant effects in lowering blood glucose levels and improving glucose tolerance. Furthermore, PJ1-1 can effectively reduce the levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol in the serum, while simultaneously increasing the level of high-density lipoprotein cholesterol in the serum, thereby contributing to the alleviation of dyslipidemia. Keerthi et al. (53) found that the EPS from *Lactobacillus plantarum* BR2 can reduce cholesterol by 45%.

## 4. Applications of several important microbial polysaccharides

Due to their various activities, microbial polysaccharides have been widely used in food, medical, healthcare, and industrial industries. For example, Xanthan Gum produced by *Xanthomonas campestris* has been widely used in papermaking and textile industries due to its excellent thickening, suspending, and stabilizing properties, which can improve the processing performance and final product quality of paper and textiles (54). Pullulan possesses numerous superior properties such as film-forming ability, oxygen barrier, biodegradability, and stability, all while being safe and non-toxic (54,55). In the food industry, it finds extensive applications in preservation, quality enhancement, thickening, shaping, and as an edible packaging material. Within the medical sector, pullulan is utilized as anticoagulant medical materials, hemostatic agents, capsule-forming agents, and suture threads for wound closure. Additionally, in cosmetics, it is incorporated into products like lotions, facial masks, skin protectants, and hair styling agents. Gellan Gum has been widely used in candies (56), fruit juice (57,58) and other foods. In addition, it has also been applied in the fields of slow drug release (59,60) and microbial culture medium (61).

In addition, many microbial polysaccharides have been used clinically as anti-tumor drugs.

For example, lentinan has been made into anti-cancer injections and used in combination with chemotherapy drugs (such as FT) for the treatment of patients with gastrointestinal tumors. China and Japan have been able to produce and widely use them (62). *Hericium erinaceus* polysaccharide is widely used in the preparation of compound fungal polysaccharide preparations and traditional Chinese medicine compound preparations to protect gastric mucosa, effectively treat atrophic gastritis and combat *Helicobacter pylori* infection (63). In addition, the addition of *Hericium erinaceus* polysaccharide to the feed can improve the utilization of nutrients and promote the growth of broilers (64), reduce the deposition of cholesterol in the liver and abdomen of broilers, and increase the level of high-density lipoprotein cholesterol (65,66), opening up a new path for the production of healthy chicken products with low fat and low cholesterol. The above results indicate the broad application prospects and far-reaching influence of *Hericium erinaceus* polysaccharide in the livestock and poultry breeding industry.

## 5. Conclusion and Prospect

This paper comprehensively reviews the methods of extraction, isolation, and purification of microbial polysaccharides, their biological activities, as well as the current application status of some microbial polysaccharides. As mentioned above, microbial polysaccharides have demonstrated extensive application potential and enormous market value in various fields such as food, medical treatment, and healthcare. However, despite the significant progress made in the research of microbial polysaccharides, their true application value has not been fully realized. Therefore, further research and development of microbial polysaccharides hold vital practical significance and application value.

Microbial exopolysaccharides (EPS) exhibit broad development prospects due to their diverse biological activities, making in-depth research on them highly significant. Microorganisms are widely distributed in water, soil, and even within animals and plants, with many new species yet to be discovered. These new species often serve as potential sources of novel biologically active secondary metabolites(67). Especially in special environments such as deserts, deep seas, and volcanoes, microbial EPS may form novel structures and possess special functions, harboring immense developmental potential. Therefore, exploring microorganisms in these special environments can be considered. The biological activity of EPS is closely related to its structure, with activity not only depending on the quantity of molecules but also influenced by the degree of branching and conformation(68). Consequently, characterizing the structure of polysaccharides and delving into the chemical structure and composition of microbial EPS, particularly focusing on the characteristics of chemical structures such as glucan, galactan, and amide, is crucial for understanding their functions and applications. In the medical field, by revealing the molecular mechanisms of disease occurrence, researchers can design drugs targeting specific sites, thereby enhancing treatment efficacy and reducing side effects. EPS, as a class of biologically active biopolymers with diverse activities, have not fully elucidated molecular mechanisms underlying their bioactivity. In research, protein interactions and signaling pathways are two core directions. Exploring the interactions between microbial EPS and proteins through molecular biological methods can reveal the mechanisms of interaction between EPS and cells and their roles in physiological functions. Meanwhile,

research on signaling pathways can also effectively uncover the mechanisms by which EPS function within cells. Utilizing research tools in molecular biotechnology and cellular signal transduction, we can deeply explore the signaling pathways between EPS and host cells, revealing fundamental biological mechanisms and providing important foundations for further research and development of microbial polysaccharides.

In the current era of increasingly scarce resources, deeply exploring microbial polysaccharides from different sources is not only an effective utilization of natural resources but also a key to promoting the sustainable development of related industries.

**CRediT authorship contribution statement**

Both Xiao-Lian Wei and Rola Ali-Saeed contributed to the study conception and design. Xiao-Lian Wei wrote the first draft of the manuscript, Rola Ali-Saeed revised and edited the manuscript. All authors read and approved the final manuscript.

**Declaration of interest statement**

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

**Data availability**

Not Applicable.

**Acknowledgments**

This work was supported by the Baise City regional multi-incidence joint special plan program [grant number 20224138]; Financial Special Guangxi First-class Discipline Construction Fund- Young Academic Backbone program [grant number DC2200001901].

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