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**Review Article**

# Application of Microbial Polysaccharides in Pharmaceutical Field: A Review

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**Abstract:** Polysaccharides have accepted consideration because they are found in all living organisms such as, animals, plants, microorganisms and algae, as they have many essential biological activities for the organism, and have many pharmacological and biomedical actions, making them one of the most hopeful compounds in the fields of pharmaceutical and biomedicine. They are anti-inflammatory; wound healing feature, anticoagulant, antiviral, antioxidant, antidiabetes agent. Because of the multiple physical and chemical properties of polysaccharides, it is possible to change these properties into improved properties, as this is the basis of their various uses in the biomedical and pharmaceutical fields. In this review, the applications of polysaccharides in these areas will be clarified, with their potential as alternatives to proper treatments.

**Keywords:** Biopolymers, Microbial Polysaccharides, Pharmaceutical applications.

## INTRODUCTION

Biopolymers have recently gained great importance as they are safe to use and environmentally friendly. Polysaccharides are the most abundant chemical compounds in nature, as they occur naturally in plants and microorganisms such as fungi and bacteria as well as algae. Most of these polysaccharides have unique physical properties as they are soluble in water and have a high molecular weight. In the past years, interest in the extracellular polysaccharides produced by microorganisms has increased due to the entry of these polysaccharides into the food industry and pharmacy, as well as medicine, especially in the field of vaccines [1].

Polysaccharides are usually described as exogenous polysaccharides, to distinguish them from other polysaccharides that can be found inside the cell. Polysaccharides play a major and important role in all living organisms. They work to store energy in the cells, other of specific biological functions such as adhesion to external surfaces, protective barrier to the cell as well as an essential component of biofilm structure formation [2].

Polysaccharides manufactured in microorganisms are secreted out of the cell to form a thick layer surrounding the surface of microorganism to protect it or they form a physical barrier that prevents harmful substances from entering the cell, such as the capsule in bacteria, which is usually difficult to separate from the cell mass or to prevent the cells from drying out. Polysaccharides may inhibit phagocytosis by other microorganisms or cells of the immune system. These polysaccharides also have an important role in adhesion and host penetration [3]. Polysaccharides are of great importance in all aspects of biotechnology such as the use of xanthan mainly in food applications, as well as dextran which is used in pharmaceuticals. Extracellular polysaccharides such as cellulose, scleroglucan, cordlan, pullulan, dextran, xanthan, gellan, alginate, are used in many fields, such as, medicine, pharmaceuticals, food, cosmetics as well as in the oil industry [4].

**Chemical Structures of Polysaccharides**

Polysaccharides are possesses unique physical, chemical and biological properties. More than 90% of the mass of carbohydrates in nature is in the form of polysaccharides. Polysaccharides are polymers that contain many monosaccharide units, so these polysaccharides have a high molecular weight [5].

Most polysaccharides contain more than 20 units of oligosaccharides. The number of monosaccharides that make up the polysaccharide is called the degree of polymerization, and this depends on the type of polysaccharide [6]. Few of polysaccharides of natural origin contain the number of monosaccharide units less than (100), as most polysaccharides have a degree of polymerization between (200-3000) units of monosaccharides.

An example of polysaccharides with a large degree of polymerization is cellulose, which contains between (7000 - 15000) units of monosaccharide. The monosaccharide that makes up the polysaccharide are linked by glycoside bonds, where the polysaccharide molecules can be either linear or branched, so all sugars have only one reducing end [7]. Polysaccharides containing repeating units of one type of monosaccharide are called homo- polysaccharides, such as starch, glycogen and cellulose, each of which consists of repeating glucose molecules linked to each other by glycoside bonds. But if the polysaccharides consist of different types of monosaccharide, they are called hetero-polysaccharides, such as hyaluronic acid, Keratansulfate, heparin and chondroitin sulfate [8].

**Microbial Sources of Polysaccharides**

**Bacterial Polysaccharides**

Polysaccharides produced by microbes are classified based on their biological functions into: intracellular stored polysaccharides, glycogen, as well as capsular polysaccharides that are closely bound to the cell surface (such as O antigen) and bacterial extracellular polysaccharides (such as xanthan, sphingan, alginate, cellulose) that important in the formation of biofilms and pathogenicity [9].

The polysaccharides in bacteria also include peptidoglycan, which is a structural component of the cell wall, as well as lipopolysaccharides, capsules, exogenous polysaccharides, and important virulence factors such as Poly-N-acetylglucosamine in *Staphylococcus aureus*. Due to the wide variety of polysaccharides present in bacteria, it has various applications, such as the food industry, pharmaceutical industries, biomedical industries, as well as in the field of biological treatment in the recovery of metals from industrial waste [10]. Different types of polysaccharides have been isolated and characterized from different types of marine bacteria, such as *Bacillus*, *Halomonas*, *Planococcus*, *Enterobacter*, *Alteromonas*, *Pseudo alteromonas*, *Vibrio* and *Rhodococcu* [11].

**Fungal Polysaccharides**

The polysaccharides establish around 75% of fungal bio-mass and ensure a structural governed of the mycelium. Concerning the yeast polysaccharides, we can find chains of glucose molecules side branched β-(1,3)-glucans [12]. The most typical examples of polysaccharides in fungi is chitin, a constituent of the fungal cell walls of mycelia and spores of the Ascomycetes, Basidiomycetes and Phycomycetes [13]. This aminoglucan, one of the most plentiful natural polysaccharides, is a copolysaccharide compose of D-glucosamine and N-acetyl-D-glucosamine units β-(1,4) linked with the degrees of acetylation. The fungal chitin is especially associated with other polysaccharide structures such as β-glucan, α-glucan or other galactomannan as in the case of *Aspergillus fumigates* [14].

The chitosan, a deacetylated derivate form of the chitin is gave in the Mucorales, such as, *Aspergillus niger* and *Fusarium moniliform*. These two aminoglycans have a large variety of applications in the pharmacological, biomedical, agricultural, and biotechnological industries. In the filamentous *Mucor* sp, the fibrillar wall is essentially composed of the chitin and chitosan [15]. Two polyuronans, called mucoric acid and mucoran have been described from M.rouxii. Mucoric acid is a homopolysaccharides Consists of of D-glucuronic acid alike to the bacterial glucuronan. Mucoran is a heteropolysaccharide compose of the D-glucuronic acid, D-mannose, D-galactose, and L-fucose. Several β-glucan polysaccharides have been discovered in the fungal cells, such as, the pachyman a branched β-(1,3)-glucan with several β-(1,6) linked residues was isolated from the Chinese medicine comprising the cell wall of Poria cocos mycelia [16]. The polysaccharide Grifolan produced from *Grifola frondosa* is a high molecular weight β-(1,3)-glucan which is known to encourage the production of cytokine from the macrophages. A branched β-(1,3) glucan called lentinan has been isolated from shiitake mushroom. Lentinan has essential effects on the immune system and is occupied in Japan for the treatment of the cancer [17].

Many fungal species are able to exude the Exopolysaccharides, particularly the β-(1,3), (1,6) glucans. Two main fungal neutral extracellular homopolysaccharides, called scleroglucan and schizophyllan. Scleroglucan is a natural branched homopolysaccharide comprise (1,3)-linked β-D-glucopyranosyl units with every third unit a β-D-glucosyl linked in (1,6) . It is synthesized by the fungus *Sclerotium*sp. It has been shows several interesting pharmacological properties in the gastroenterology, antitumor, antiviral and antimicrobial agent [18]. Schizophyllan is a neutral polysaccharide produced by the fungus Schizophyllan commune, comprise (1,3)-β-D-linked backbone of glucose residues with (1,6)-β-D-glucosyl side groups. In the family of α-D-glucans, the pullulan synthesized by the polymorphic fungus Aureobasidium pullulanase in a range of liquid fermentation system is made up of linear α links between the maltotriose and maltotetraose molecules [19]. The pollutant aquire a very high solubility in the water even in the presence of the ions. These have applications in the pharmaceutical, cosmetics, and foods. The biological activities of the carboxymethyl derivates of the linear α-(1,3)-D-glucans from *Agrocybe cylindracea* and *Amanita muscaria* have been investigated, they induced the macrophage secretion [20].

## Pharmaceutical Applications of Polysaccharides

### Anti-Inflammatory Activity

The first response of the body's immune system is inflammation when infection occurs. The interest in polysaccharides produced from natural sources has increased significantly, as they are safe to use as well as their effectiveness in treating infections [21]. It has been observed that the polysaccharide produced from mushrooms has great importance in the treatment of many health problems such as fighting inflammation and pain, as well as it is an anti-tumor and an antioxidant, as it has activity in stimulating immunity.

Some researchers have noticed that small differences in the chemical composition of the polymer lead to different effects when the anti-inflammatory properties of these sugars were tested. Reliance on the use of raw extracts of mushrooms makes it difficult to determine the compound responsible for its vital activity, as there are a few researchers who isolated molecules in their pure form for the purpose of evaluation, in addition to the lack of clinical observational studies without suitable placebo or other identical controls [22]. With the advancement of science in the field of biotechnology, it became possible to obtain polysaccharides from mushrooms, so the research in this field has a future promising in the possibility of finding medicines from natural sources with few or no side effects Artem [23].

Natural compounds produced by bacteria that have similar activity to anti-inflammatory drugs have been enumerated through their modulating effect on cytokines. Natural components of bacterial origin such as polysaccharides, fatty acids, peptides act mainly through cytokines such as TNF-α, IL-1β and IL-6, which are the main pro-inflammatory cytokines, and IL-10, which is anti-inflammatory cytokines [24].

Congenital polysaccharides came to be broadly investigated as encouraging hopeful for the advancement of new nutraceutical products and medicinal agents. Many previous studies have shown the notable in vitro and in vivo anti-inflammatory and immunomodulatory activities of polysaccharides from various sources such as Mushrooms fungi, Bacteria, herbal plants and macroalgae [25]. Mushrooms have many health advantages such as anti-inflammatory activities, immunomodulatory and anticancer, which can be accredited at least fractionally to the polysaccharide component. *Ophiocordyceps sinensis* (a fungus that grows on insects) is a precious medicinal fungus in conventional Chinese medicine for health advertising and therapeutic treatment. Greatest of the *O. sinensis* fungal polysaccharides have been extracted from the mycelial biomass, but very little exopolysaccharides from mycelial fermentation [26].

The literature on the molecular properties and anti-inflammatory activities of exopolysaccharides produced by *O. sinensis* fungus is scarce. A high-molecular weight exopolysaccharide from the Cs-HK1 fungus species usually arise from the fruiting body of *O. sinensis* fungus. The mycelial culture of the Cs-HK1 fungus in a liquid medium has been capable to make a big amount of exopolysaccharides, which possesses a complex constitution and broad molecular weight range. a partially purified exopolysaccharides from Cs-HK1 mycelial fermentation indicated significant anti-inflammatory activities in both cell culture and animal patterns. It is an important to purify the polysaccharides to know the most active moieties, in order to better understand the molecular properties and to understand the mechanism of action and the relationship between polysaccharides and anti-inflammatory activity [27].

### Wound healing feature

[28] said “The effecting of natural polysaccharide decreases scar formation in severe wound injury due to its rich content of Glycosaminoglycans which was known to promote wound healing and leads to rapid granulation, vascularization, and reepithelialization, thus yielding a minimum scar formation certainly”. It was recently found that polysaccharides have the property of treating and healing wounds and fighting infections caused by bacteria as well as trauma. It has been clearly observed that polysaccharides, when used, begin to coagulate the blood in the affected area, and then begin to remodel the cellular layers of the skin, which in turn leads to wound healing [29]. Polysaccharides have an adhesive property, which leads to the bonding of wounds and the production of new cells in the inflamed area. This property was proven by observing the wound healing of mice in the laboratory when they were injured in the epidermal layer by a sterile blade, then a polysaccharide was applied to the affected area and left for (10-20) days, the wound healing was completely observed [30].

Some researchers indicate that some polysaccharides act as an anti-adhesion agent, which leads to the prevention of biofilm formation by microorganisms on wounds using polysaccharides [31]. When microorganisms are present in the form of biofilms, they cause an important medical problem as they become more resistant to antibiotics, and one of the important and promising means is the polysaccharides that prevent the formation of biofilms. The first polysaccharide that was shown to exert an effect on bacterial biofilms is galactan, where studies indicate that galactan has the ability to inhibit the formation of biofilms of *Pseudomonas aeruginosa*. The mechanism of action of galactan has been clarified that it does not interfere with the adh11esion of bacterial cells to the substrate, but it prevents the accumulation of bacterial biomass, and galactan not only inhibits the formation of biofilms, but works on the partial destruction of the previously formed biofilms and does not allow the formation of a suitable biofilm structure [32].

**Anti-Coagulant Activity**

The anticoagulant effect of some types of carbohydrates produced by marine bacteria is through suppression of thrombin or by initiation of antithrombin III as well as by prolongation of clotting time. It is also possible that these molecules have anticoagulant effects by blocking the movement of thrombin [33].

Anticoagulants are widely used in the medical and pharmaceutical fields to treat many pathological conditions such as myocardial infarction as well as strokes. Anticoagulant drugs such as heparin and coumarin are used for this purpose, as well as anti-platelet aggregation drugs. Heparin is among the most used drugs for this purpose, as this drug has been widely used in clinical applications in the treatment of thrombosis diseases. Heparin contains an anticoagulant substance, glycosaminoglycan, which contains sulfates in its composition, and it carries a negative charge that enables it to inhibit the activity of thrombin [34].

Low molecular weight heparin is a sulfuric polysaccharide that is used as anticoagulant medication but causes side effects such as bleeding and thrombocytopenia. Sulfur polysaccharides from *Catathelasma ventricosum* after sulfated modification have been shown to have many biological activities such as being antitumor, antioxidant as well as anticoagulant. The high sulfate content is a major factor in the anticoagulant activity of sulfur polysaccharides [35]. Polysaccharides obtained from various natural sources such as oysters, shrimp, lobster, marine algae, seaweed, marine fungi and corals, the polysaccharides derived from them can be considered as potential anticoagulant agents [36].

**Anti-viral Activity**

Several microbial are polysaccharides exhibit antiviral as well as immunomodulatory activities. Microbial polysaccharides have antiviral effects by interfering with the life cycle of viruses or modulating host immune responses. Microbial polysaccharides have potential uses as adjuvants for antiviral vaccines. Some sulfated polysaccharides obtained from microbes and algae have been approved as generally Recognized as Safe (GRAS), which can be used as biologically active ingredients [37].

The results of recent studies indicate that the human immune system plays a fundamental and important role in the body's immune response when infection occurs with viruses. Therefore, modern research should focus on finding innovative ways that improve the immune response to the host by supporting and developing the immune system, especially the adaptive immune system, which It needs to be stimulated by stimulants of the immune system as well as factors that work to regulate immunity, as it was found that the polysaccharides which found in some foods such as mushrooms, yeasts, algae, fruits and cereals contain important properties of biological activity, such as their ability to activate the functions of the immune system, and it was also found that these polysaccharides stimulate the production of Anti-inflammatory and antioxidants. Thus polysaccharides can be used as an activating agent of the immune system, reducing the damage caused by infectious agents such as SARS-CoV-2 [38].

Many microbial polysaccharides are abundant in nature and are safe to use and biodegradable. Therefore, it is recommended to take an appropriate dose of sugars to regulate the physiological functions of the body to prevent viral diseases or reduce their damage, but more pharmaceutical and clinical investigations must be conducted to know the antiviral and immune-enhancing effects [39].

It has been found through the results of studies that sulfur polysaccharide extracted from seaweed has an inhibitory effect against the reproduction of viruses such as herpes simplex virus (HSV), human immunodeficiency virus (HIV), human cytomegalovirus, dengue virus, and respiratory syncytial virus (HRSV) [40].

Microorganisms produce different types of polysaccharides with exclusive properties that exhibit biological activity such as immune modulating and antiviral activities by interfering with the life cycle of viruses and modulating the host immune response thus aiding in the treatment of patients with COVID-19 [37]. The components of polysaccharides, structural compatibility, molecular weight and functional groups greatly influence the bioactivity of polysaccharides. Polysaccharides of microbial origin can be used as adjuvants for antiviral vaccines or in drug delivery systems, where some microbial polysaccharides are approved for use as safe, biocompatible, biodegradable and readily available, as they can be used as active ingredients. It is biologically antiviral, so an appropriate dose of polysaccharides may modify the physiological functions of the body to prevent viral diseases. More pharmacological and clinical research should be conducted to find out the antiviral and immune-enhancing mechanisms of action [5].

**Antioxidant Activity**

Microorganisms are an important source of bioactive compounds that are used in the fields of medicine, pharmacology, agriculture and industry. Microbes such as actinomycetes, bacteria, blue-green algae and lichens, can grow under controlled conditions at a faster rate making them a rich source of natural bioactive molecules [41].

There has been great importance in using natural antioxidants as food supplements and scientific importance in fungal biopolymers as antioxidants has developed because of their secure and useful functional properties in a assortment of products. Fungi, including *Ganoderma*, *Flammulina*, *Coriolus* and *Pleurotus* have been found to produce structurally special biologically-active substances that display abundant medicinal effects including antioxidative properties [42]. Polysaccharides are possible to be the prime antioxidants of some medicinal mushrooms, playing arole in removal of superoxide and hydroxyl radicals. Carbohydrates are chiefly current in these mushrooms as polysaccharides or glycoproteins.

The most abundant polysaccharides are chitin, glucans, and other hemicelluloses [43]. Exploration of natural antioxidants and their role in human health is a rapidly developing area. Free radicals are among the most unpaired electron-containing reactive molecules that can cause damage to nucleic acids, proteins, carbohydrates and fats, causing several diseases, including atherosclerosis, cancer and premature aging. The role of antioxidants is to remove free radicals in order to prevent cell damage by reducing oxidative stress, which leads to having a positive role in influencing human health, as it was found that consuming large amounts of foods containing antioxidants leads to a reduced risk of many diseases [44].

Although artificial antioxidants such as Bureau for Humanitarian Assistance (BHA), butylated hydroxytoluene (BHT) and propyl gallate (PG) and tertiary butyl hydroquinone (TBHQ) are most broadly used in foods, some researchers have showed that definite artificial antioxidants such as BHA and BHT may acquire weak carcinogenic effects in some animals at high levels. Natural sources of antioxidants are such as tocopherols, ascorbic acid, erythrobic acid or their salts and unoriginal such as ascorbyl palmitate [45].

Efforts in recent years have focused on evaluating and applying antioxidants in reducing the risk of human diseases. Many polysaccharides have been extracted and purified and modified in order to change their properties in order to expand their application range [46]. The results of studies also found the health benefits of polysaccharides in terms of antioxidant activity. The mucosal adhesion and uptake properties of chitosan have been used to deliver therapeutic proteins and antigens using intracellular mucosal pathways. The beneficial properties of polysaccharides in biomedical and pharmaceutical applications need more extensive research [2].

**Anti-Diabetic Activity**

Diabetes is a standout amongst the most widely recognized infections on the planet. Diabetes mellitus is a widespread metabolic disease caused by high blood sugar due to impaired insulin secretion. Two types of diabetes have been distinguished according to the World Health Organization, the first type is characterized by insufficient production of insulin in the human body, and the second type is characterized by insulin resistance [47].

Many types of fungi have shown high efficacy against hypoglycemia, insulin resistance and dyslipidemia. β-glucans, which is included in the composition of the mushroom, it is one of the compounds with various biological activities, and it is believed that this compound is responsible for the anti-diabetic effect of the fungi [48]. It has been widely proven that polysaccharides inhibit hyperglycemia, reverse insulin resistance, and prevent complications of diabetes. Therefore, polysaccharide therapy is a promising option for managing diabetes, according to the results of scientific research, it is believed that there are a number of mechanisms of action of natural polysaccharides extracted from different organisms on diabetes mellitus, they are: an increase in hepatic glycogen synthesis, an increase in plasma insulin levels and a decrease in the activity of the glucagon hormone that produced by alpha cells in the pancreas, a decrease in insulin resistance, an increase in insulin receptor sensitivity, an anti-inflammatory effect, an improvement in glucose utilization in tissues oceanic [49].

The results of the studies indicate that effects of polysaccharides on diabetes is due to the management of polysaccharides on gut microbiota and following improvement in the production of Bacteria produce molecules such as Short chain fatty acids, Lipopolysaccharides and Barium sulfides . The antidiabetes accomplish of polysaccharides perhaps via increase the plenty of Short chain fatty acids producing bacteria while decrease the numeral of

Lipopolysaccharides producing bacteria, giving to increase expression of tight junction proteins, facilitate the propagation of regulatory T cells , advance Glucagon-like peptide-1 release and decrease 12α-hydroxylated Barium sulfides levels in colon.

Polysaccharides be allowed to affect on microbial metabolites not directly, for example, tryptophan metabolites, branched chain amino acids, neurotransmitters and vitamins. Therefore, the modification of metabolite profiles and matching signal pathways by metabolomics and proteomics be allowed to further reveal the mechanisms of polysaccharides antidiabetic effects. It has been recorded that utilization of greater than 50 gram per day of fiber could considerably enhance the health. Polysaccharides perhaps believe as future attitudes for the advancement of protective even therapeutic options for diabetes based on gut microbiota management, but it still needs more works to detect new antidiabetic polysaccharides [50, 51].

**Future Prospects of Microbial Polysaccharides**

Although there is a great diversity in the molecular structures of the polysaccharides produced from microorganisms, only a few of these polysaccharides have been developed for commercial purposes due to the high production costs of these polysaccharides which are often related to substrate cost and availability in certain geographical areas, in addition to the challenges of cultivation and final processing [52]. The production and purification of these polysaccharides remains a major and obvious challenge, in order to obtain a high production of polysaccharides that are characterized by high purity and quality, work must be done to engineer the metabolism of the produced microorganisms by manipulating the genes responsible for encoding enzymes that catalyze the reorganization of metabolic pathways, or by altering regulatory pathways that affect gene expression and enzyme activity [53].

# CONCLUSION

- Polysaccharides that produced from microorganisms have unique properties that contribute to a differing of biological capabilities. This review showed that polysaccharides can regulate an immune response by different biochemical pathways.
- These biopolymers can be found in edible sources of microorganisms such as mushroom fungus, bacteria and algae. The prospective of natural polysaccharides for disease prevention is clear, as showed by several reports.
- Food containing these biopolymers can be used securely as they have no toxic effects. Polysaccharides achieved from these microorganisms, it can be a source for the development of new medicines and immunity-boosting therapies.
- Many researches around the world are devoted to the development of drugs for the treatment of different diseases using polysaccharides.
- Based on many studies carried out in the last few years, indicate that natural polysaccharides perhaps used for the production of many drugs and vaccines, because they can easily bind to different cell receptors.
- The biological effects of polysaccharides isolated from natural sources have become a catalyst for increasing human immunity, thus, reducing the risk of complex clinical cases if they develop a specific disease.

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