OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences

Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article | **Food Science and Technology**

Natural Polysaccharides as Immunomodulator for COVID-19; A Review

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DOI: 10.36348/sjmps.2022.v08i02.004 | **Received:** 30.12.2021 | **Accepted:** 06.02.2022 | **Published:** 11.02.2022

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Abstract

Natural Polysaccharides have been considered to be the most promising materials in recent years because of their numerous advantages including their accessibility, non-toxic, biocompatible, biodegradable, and ease of modification.Natural substanceswith pharmacotherapy potential are currently viewed as a promising future alternative to conventional therapy.With the rapid development of analytical techniquesandbiotechnologies,a large number of methods for identifying and quantifying polysaccharides without causing adverse effects have been created, resulting in the use of natural substances with established safety. Some bioactive polysaccharides obtained from natural sources have received a lot of attention in the field of biochemistry and pharmacology in recent years.Natural polysaccharides have been found in studies to boost innate immunity by activating upstream immune cells, hence regulating adaptive immunological pathways such as T cells and improving the efficacy of immunotherapy, implying that polysaccharides have a promising future in immunotherapy. As there is no targeted therapy available but these natural polysaccharides have been shown to possess complex, important and multifaceted biological activities including antitumor, anticoagulant, antioxidant, antiviral, immunomodulatory and antihyperlipidemic activities. Their properties are mainly due to their structural characteristics and are useful for combating various diseases as well improving immunity. Thus, polysaccharides can be used as an activating agent of immune system, minimising the damage caused by infectious agents such as SARS-CoV-2. Finally, these biopolymers can still be exploited to produce new treatments and vaccines.The present paper summarizes an overview of natural polysaccharides with immune boosting properties.

Keywords: COVID-19, Polysaccharides, Immunomodulation, Functional Foods, immunity.

1. INTRODUCTION

The SARSCoV2 virus, also known as COVID19, was used to study the severe acute respiratory syndrome outbreak, which highlights the need to develop population immunity. The negative effects of the SARSCoV2 pandemic around the world are unprecedented, with thousands of lives lost, growing inequality as well as countless economic losses. On the other hand, major technological advances have been made in knowledge of the disease condition and therapeutic pathways, polysaccharides, due to their properties, have the potential to be used as a potential drug with ability to modulate the immune response (Barbosa *et al.*, 2021).Technologies together with electro-osmotic dehydration, excessive hydrostatic pressure, ultrasound-assisted extraction, supercritical fluid technology, and pulsed electric powered field, amongst limitless others were carried out withinside the extraction of polyphenols, polysaccharides and diverse molecules of excessive industrial value (Zinoviadou *et al.*, 2015).Value-added compound extraction technology is one of the most relevant steps in the molecular search process, Moreover, they can be consumed easily, as they are harmless, biocompatible and biodegradable. Polysaccharides are well tolerated by the human body, with excellent bioactivity and biocompatibility so these biopolymers could also be employed to create new medications and vaccinations (Sindhu *et al.*, 2021).The biopolymer family includes polysaccharides, which are among the most important components. They are monosaccharide-based natural macromolecules. More than 300 different types of natural polysaccharide compounds have been discovered so far. Plants, animals, and microbes all have them, and they perform a range of physiological activities. Polysaccharides became a significant focus of research in pharmacology, especially immunopharmacology, in the 1950s, after their immunoregulatory and anti-tumor effects were discovered. (Yim *et al.*, 2019).These specific polysaccharides have the potential to have a significant impact on the adaptive, acquired, and innate immune systems. This is often accomplished through interactions with T-cells, leukocytes, monocytes, and, most significantly, macrophages.Polysaccharides has the ability to enrich and modulate the host's immunological response to infections. Biological response modifiers (BRMs) are polysaccharides that have these properties, and study on them is one of the most active fields of polysaccharide research. Various studies have been conducted to demonstrate the structural features of these bioactive components and how they interfere with the cellular units of the host individual. In the fields of biological research and pharmaceutical sciences, these natural polysaccharides offer a wide range of applications. Polysaccharides come in a variety of chemical and physical forms in nature. These polysaccharide variations serve as the foundation for biomaterials used in tissue engineering, drug transport vehicles, visco-supplementation, and controlled drug release in target sites, among other applications (Dumitriu *et al*., 2002).

Consumption of healthy foods, particularly those with functional characteristics, has become a need in the midst of the current crisis created by the COVID19 pandemic, primarily as a strategy to prevent and boost the immune system (Galanakis 2020).Using new technology to produce biologically active molecules from natural sources and waste is one of the current perspectives(Galanakis 2018). Polysaccharides are found in all living things, are a component of structural biochemistry, and play important roles in the cellular environment (Ng *et al*., 2020). Polysaccharides can be produced and refined from natural foods such as mushrooms, yeasts, fruits, algae, and cereals, and these biopolymers can be used as strong agents in the activation of the immune system, particularly the adaptive system, as revealed by recent studies *(Mohan et al.*, 2020). These biopolymers also have unique biological qualities such as antioxidant activity (Yuan *et al*. 2020), anti-inflammatory activity (Xiong *et al*. 2017), antiviral activity (Wang *et al*. 2020), and biocompatible, biodegradable, and non-toxic properties (Chen *et al*. 2020). As a result, polysaccharides can be employed as an immune system activator, diminishing the effects caused by infectious agents like SARS-CoV-2.

2. Immunity and classification of immunomodulators

Immunity is the body's most important underlying structure, and it is a complicated system with multiple defenses.The skin serves as the primary barrier/shield; nevertheless, the temperature and pH of the body may be incompatible with the present standard. Whether microorganisms enter the body or not, acquired or innate immune systems combat them. Immunity is of two varieties as shown in Fig 1 (Turvey &Broide, 2010).

Innate Immunity is one of the most important immunological defences against foreign and dangerous items. Innate immunity is a type of immune defence that is pre-programmed with receptors and ready to respond immediately. There is no requirement for genetic recombination or any other procedure in this case (Nicoholson, 2016).

Acquired immunity, also known as adaptive immunity, is a type of immunity that develops through time. It's mainly found in the blood, tissue fluids, or on the cell surface. The main key as an antigen-specific receptor in the shape of a 'Y' is immunoglobulin, commonly known as the antibody receptor (Kumar *et al.*, 2012).

Immunomodulators are drugs that stimulate, inhibit, and modulate many aspects of the immune system, both innate and adaptive. Scientifically, the immunomodulators are categorized as shown in Fig. 2 (Billiau & Matthys, 2001).

Immuno-adjuvants- These are immune stimulants that are used to boost the effectiveness of preparations/shots. They are referred to as "Genuine Immune System Modulators." They are frequently used as selectors between cellular and humoral assistant/helper T1 (TH1) and helper T2cells (TH2), immune-protective, immune-destructive, and immunoglobulin E vs. immunoglobulin G (IgE vs. IgG) reactions [because to structural similarity], an enormous problem for vaccine/shot designers (Gertsch, Viveros-Paredes & Taylor, 2011).

Immuno-stimulants- These are designed to boost the body's resistance to infection, which is inherently unreliable. They can function through adaptive or innate immunological responses. They raise the body's basic level of immunological defence. Immunopotentiators and promoter agents are two types of these substances (Giorgi, 2019).

Immunosuppressants are a class of medications that are inherently and operationally heterogeneous, and are used in combination to treat a variety of tissue/organ transplant rejection and autoimmune disorders (Narayanaswamy, 1981).

3. Immunomodulatory polysaccharides

3.1 Polysaccharides obtained from mushrooms

Mushrooms are moulds, or eukaryotic organisms, and they belong to the Eukarya domain (classification above kingdom). The fruiting of some fungi belonging to the phyla Basidiomycota and Ascomycota is known as a mushroom and their productive body is made up of a base (stape) and a cap (also called pileus).Mushrooms are rich in heteropolysaccharides. Several edible and medicinal mushrooms were explored with structural characteristics and biological effects. Mushrooms have several different types of heteropolysaccharides, that is, polysaccharides with more than one type of monomer in the monosaccharide chain*(Ruthes et al.,* 2016).These heteropolysacharides have important biological activities, such as anti-tumor, antioxidant, anti-inflammatory, and immunomodulatory activity.

The fungus *Phallus atrovovatus* exhibits significant polysaccharide concentrations, primarily β-glucan and β-glucan fractions, according to a study. The polysaccharides obtained from this mushroom are known to have immune system modulating activity, as fractions of up to 50 µg of polysaccharides have been shown to significantly reduce myeloperoxidase (MPO) activity, as well as cytokine secretion TNF-, IL-6, and IL-10, indicating anti-inflammatory activity (Chaiyama *et al*., 2020).Polysaccharide-rich fractions from the *Pleurotus ostreatus* edible mushroom (Barbosa *et al*., 2020). The extracts were found to have a variety of polysaccharides, including glucans, according to the study. In the DPPH models, the extracts' antioxidant activity revealed a radical reduction capability of up to 80%. The extracts' antioxidant capacity was further confirmed in tests using a cell model, which indicated the extracts' ability to protect cells from oxidative damage caused by hydrogen peroxide.

3.2 Polysaccharides obtained from herbs

Herbs have long been used to cure a variety of ailments, and modern pharmacological research has revealed that the major or key components of herbal remedies typically contain a large number of substances. Polysaccharides have been found as key active components in herbal medicines, responsible for a variety of pharmacological effects.Although the actual mechanism of these effects is still being investigated, and numerous polysaccharides have been found to have immunostimulatory properties. This regulatory process appears to be mediated by immune cells, particularly macrophages (Schepetkin *et al*., 2006).Polysaccharides can also influence macrophage activity in a variety of sophisticated microbicidal tasks, including surveillance (O'Riordan *et al.,* 2002), chemotaxis (Truma *et al*., 2008), phagocytosis (Bratosin *et al.,* 1998), and target organism destruction. Polysaccharides primarily activate macrophages through interactions with specialised cell receptors known as pattern recognition receptors. Toll-like receptor 4 (TLR4), CD14 (Hua *et al*., 2007), dectin-1 (Hollmig *et al*., 2009), and mannose receptor (Zamze *et al.,* 2002) were used by macrophages to bind and interact with polysaccharides. The activation of receptors can result in downstream signaling and pro-inflammatory factor synthesis.Ando and Kataoka discovered that polysaccharides isolated from *Carthamus tinctorius* triggered macrophages via TLR4, resulting in downstream pathways and TNF- and NO expression (Ando *et al*., 2002). Schepetkin and Quinn isolated a polysaccharide from *Juniperus scopulorum* cones which composed of arabinogalactan,that can enhance macrophage functions which showed significant immunomodulatory effect by activating phagocytic ability (Wang *et al*., 2007), increasing the cytotoxic activity against the tumour cells, reactive oxygen species (ROS) and nitric oxide (NO) production, and secretion of cytokines and chemokines, such as tumour necrosis factor (TNF-α), interleukin-1β (IL-1β), IL-6 &IL-12(Rabinovich *et al*., 2009).

In human monocytic THP-1 cells, Luk discovered that polysaccharides isolated from the Tripterygium wilfordii suppressed TNF-secretion and the expression of certain proteins (CD11c, CD18, CD14, and CD54) (Wong *et al.,* 2012 & Luk *et al*., 2000). Polysaccharides produced from herbs have also been shown to stimulate macrophage hematopoiesis (Schepetkin *et al.,* 2006). Polysaccharides from Chelidonium majus increased the number of granulocyte–macrophage colony-forming cells in experimental mice (Song *et al*., 2002). Meanwhile, a polysaccharide from Aloe barbadensis promoted monocyte formation and had a strong hematopoietic effect (Hamman *et al*., 2008).

Angelica sinensis (Angelica sinensis) root (Oliv.) Diels, a well-known Chinese herbal medicine, has been used as a tonic, hematopoietic agent, and anti-inflammatory for eons (Jin *et al.*, 2012). Polysaccharide is one of the main active ingredients in the herb, according to modern phytochemical and pharmacological studies, and is responsible for several important biological activities, which include angiogenesis, immunomodulatory, antimutagenic, antioxidant, radioprotection, and hypoglycemic activity.

Polysaccharides isolated from Cyclocaryapaliurus(Batalin) Iljinskaja were studied for their structural features, extraction procedures, and biological activities. This plant's leaves contain essential chemical components, particularly polysaccharides, and have been utilised for millennia in the preparation of beverages and food. Several studies reviewed by the authors investigate into various polysaccharide extraction techniques, as well as a set of modern spectroscopy techniques linked to others like chromatography and nuclear magnetic resonance, for structural polysaccharide elucidation. Finally, the author lists the key biological activities connected with Cyclocaryapaliurus(Batalin) Iljinskaja's pure and modified polysaccharides, which include anti-cancer, anti-inflammatory, antioxidant, antibacterial, anti-hyperlipidemic, and anti-diabetic properties (Kakar *et al*., 2020).

3.3 Polysaccharides obtained from cereals

The presence of biopolymers such as starch, dietary fibre, and polysaccharide complex coupled with polyphenol molecules gives cereal grains and pseudocereals appealing nutritional qualities. Although cereal grains like rice, barley, and sorghum comprise highly branched and nutritionally important starch polysaccharides, these biopolymers are ineffective in boosting immunity since the majority of them are digested and used for energy production (Filho *et al*., 2017).When compared to cereal grains, pseudocereals are more attractive for getting polysaccharides, owing to the enormous chains of polysaccharide complexes with biomolecules, metal ions, and polyphenols. We'll look at the inherent features of polysaccharides and their relationship to improved immunity, despite the fact that both types of grains are nutritionally significant. Pseudocereals grains like amaranth (Amaranthus spp.), buckwheat (*Fagopyrum esculentum* and *F. tataricum*), and quinoa (Chenopodium quinoa) are high in dietary fibre, polysaccharides connected to metal ions like iron and zinc, and polysaccharide-protein complexes (Beniwal *et al*., 2019).We'll look at the inherent features of polysaccharides and their relationship to improved immunity, despite the fact that both types of grains are nutritionally significant. Isolated homogalacturonans divided into interspersed chains, with units of ramnogalacturonane and side chains of xyloglucans, disaccharides, trisaccharides, and cellulose from A. caudatus, and demonstrated that the fraction was composed of homogalacturonans divided into interspersed chains, with units of ramnogalacturonane and side chains of xyloglucans, disaccharides, trisaccharides (Lamothe *et al*., 2015).The presence of a variety of polysaccharides in Quinoa seeds, particularly pectins and insoluble fibres (Zhang *et al*., 2020). It was observed in a percentage of insoluble fibre homogalacturonans interspersed with ramnogalacturonan units and side chains of xyloglucans, trisaccharides, and cellulose, a structure similar to that of *A. caudatus* (Lamothe *et al*., 2015).Furthermore, comparisons of grain polysaccharides and fibre fractions from common sources, such as fruits and vegetables, indicate many similarities, namely in composition and immunomodulatory potential (Chai *et al*., 2020).

3.4 Polysaccharides obtained from fruits

Fruits are one of the most popular foods in the world, and they can be eaten in a variety of forms, including dehydrated, in jams, juices, desserts, cakes, and biscuits. Currently, the presence of polysaccharides has been identified in over 53 fruits (Mohan *et al*., 2020). Fruit polysaccharides have antioxidants, immunomodulatory, anti-diabetic, anti-cancer, anti-tumor, anti-glycation, hepatoprotective effects, anti-inflammatory effects, and anti-microbial activity. The isolation of a new polysaccharide from Chinese wild fruits (*Passiflora foetida*) and demonstrated that it was a heteropolysaccharide with a structure consisting → 1) -α-D-Manp→ 1,2) -β-D-Manplinked 1,2,6) -β-D-Manp residues and side chains consisted of → 1) -β-D-Galp, → 1,4) -α-D-Manp, → 1, 4) -β-D -Glcp, → 1,3) -α-D-Galp, → 1, 6) -β-D-Manp, → 1,6) -β-D-Galp, → 1,2,3) -β-D -Man and → 1,3,6) -β-D-Galp residues. Mannose is the major monosaccharide in this novel polysaccharide, and it has the ability to boost the immune system (Song *et al*., 2019).

3.5 Polysaccharides obtained from Microbes

β-(1–3)-Glucans are generated from a variety of fungus and yeast strains. These are glucose homopolymers with 1–3 connected chains. When treated with β-(1–3)-glucans, the proportion of neutrophils and eosinophils increased. They also change the activity of macrophages and the activity of Phosphatase and NO generation were boosted by macrophages.β-(1–3)-Glucans increase the activity of mononuclear cells and neutrophils, as well as the proliferation of macrophages, resulting in a cellular and humoral immune response (Wakshull, Brunke-Reese & Lin- dermuth, 1999).Proinflammatory mediators such as IL-1, TNF-, IL-2, and eicosanoids are increased by insoluble β-(1–3)-glucans. Solubleβ-(1–3)-glucans, on the other hand, are known to inhibit bacterial sepsis. The number of circulating neutrophils and bone marrow proliferation are both increased by soluble-(1–3)-glucans (Patchen & Lotzova, 1980).

Mannan is a polysaccharide and protein blend obtained from Candida albicans mannan (5 percent by weight). Mannan may interact with macrophage Mannose binding lectins and stimulate the immune system through a non-self-recognition method. When the mannose receptor detects mannan, endocytosis and phagocytosis occur, resulting in enhanced cytokine synthesis and signaling (Vasta, Quesenberry, Ahmed, & O'Leary, 1999).Mannan has a down-regulatory effect that is mediated by the cytokine IL-4. Specific CD8 + T cells are responsible for the downregulatory activity. These cells can only be produced in the presence of CD4+ cells. IL-4 is produced by these cells. As a result, IL-4 is assumed to have a role in the process (Aderem& Underhill, 1999; Ng, 1998).PSK and PSP are protein-bound polysaccharides extracted from a variety of mushroom strains and are categorized as biological response modifiers. They have been shown to aid TNF activation and increase IFN- and IL-2 production.

They also raise the number of white blood cells in the body. Dendritic and cytotoxic T-cell infiltration is facilitated by PSP and PSK, which boosts the immunological response. As a result, they have antitumor action (Izcue, Coombes & Powrie, 2006; Siegelman, DeGrendele & Estess, 1999).

4. Polysaccharides modulating the immune system

After infection of the cells by SARS-CoV-2 alveolus cells are damaged and the body initiates a local immune response by recruiting defense cells such as macrophages and monocytes that immediately respond to infection, releasing cytokines, substances that modulate the immune response.Initiation of the inflammatory process as well as the elicitation of an immunological response. Neighboring epithelial cells, endothelial cells, and alveolar macrophages perceive the patterns and produce pro-inflammatory cytokines and chemokines (such as IL-6, IP-10, inflammatory protein macrophage 1a (MIP1), MIP1 and MCP1).Monocytes, macrophages, and T cells are immediately drawn to pro-inflammatory proteins, resulting in localised inflammation and the generation of interferon (IFN) by T cells. An extra buildup of immune cells in the lungs can occur in specific circumstances, resulting in a storm of pro-inflammatory cytokines that harm the pulmonary architecture and other organs. The first inflammation attracts specialised T cells, which can fight the virus and remove infected cells, resulting in a balanced immune response. The formation of neutralising antibodies aids in the prevention of viral infection, lowering the dangers associated with it. Finally, alveolar macrophages launch a coordinated attack against neutralised viruses and apoptotic cells, phagocytosing them and eliminating them. The procedure decreases viral load and lung damage, allowing for a speedier recovery. However, it is well understood that stimulating the immune system with drugs that modulate the immune response aids in the adaptation of the body in the face of serious infections, allowing for a more controlled reaction (He *et al*., 2020). Because of the few targeted studies, polysaccharides are not recommended as a treatment during infection, but they can modulate a sufficient immune response beforehand, preparing the body to fight infection in a balanced manner fig-3.

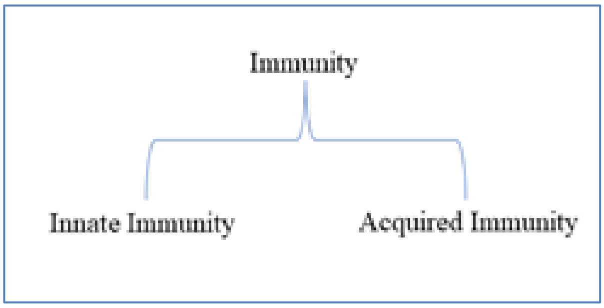

Fig-1

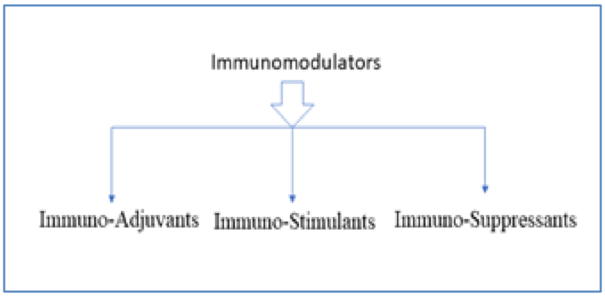

Fig-2

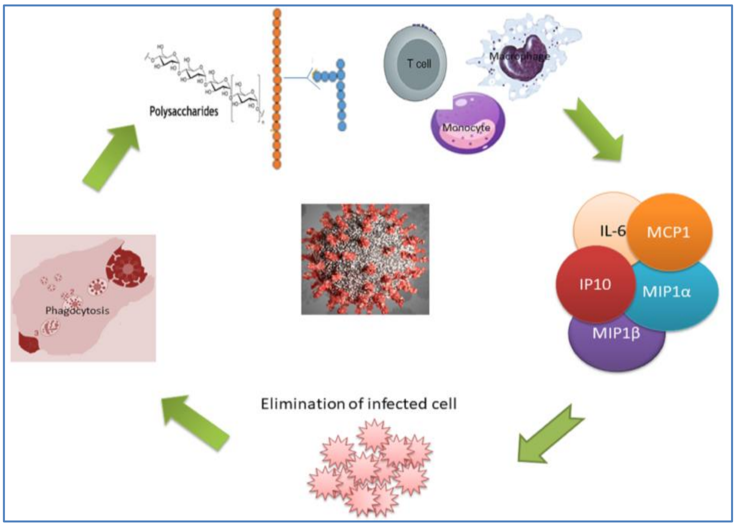

Fig-3

5. CONCLUSION

This review showed that polysaccharides derived from functional foods have unique structural features that contribute to a wide range of biological functions. Different polysaccharides draw huge attention because of their natural properties, for example, anticancer, antiviral, immunomodulating, antimicrobial, anticoagulant, antidiabetic, cancer prevention agent, and antitumor. Polysaccharides can regulate an immuneresponse by various biochemical pathways and upgrade the immune system and treats several other diseases. Thesebiopolymers can be found in natural and edible sources such as mushrooms, plants, fruits, and other form. Polysaccharides isolated and purified fromthese food sources may be the key in the development of new drugs andimmunity-boosting therapies. Foods rich in these biopolymers can beused safely since they have no toxic effects and biodegradable. Polysaccharides are an essential area for the creation of novel medications, despite the fact that there are still many unresolved problems in the area. The therapeutic value and extensive application prospects of polysaccharides make them an attractive avenue for the development of new drugsbased on various researches conducted, because they can easily bind to diverse cell receptors. Despite the fact that numerous studies, some of which are highly advanced, and research groups around the world are dedicated to developing vaccines and treatments to treat SARS-CoV-2, the disease continues to spread exponentially throughout the world. As a result, new methods for avoiding and enhancing efficient immune responses must be researched. In future investigation it will be required to look into mechanism of different polysaccharides and how they exert their biological effect on human being.

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