NATURAL POLYSACCHARIDES AS BIOACTIVE AGENTS: A COMPREHENSIVE REVIEW OF ANTI-INFLAMMATORY AND ANTIOXIDANT MECHANISMS

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Abstract
Natural polysaccharides are high molecular weight biopolymers widely distributed in plants, animals, and microorganisms, known for their biocompatibility, biodegradability, and non-toxic nature. These compounds exhibit significant antioxidant and anti-inflammatory activities, making them promising candidates for pharmaceutical and biomedical applications. Polysaccharides play a crucial role in scavenging reactive oxygen species (ROS), enhancing antioxidant enzyme systems, and regulating key signaling pathways such as NF-κB, thereby reducing oxidative stress and inflammation. Their structural diversity enables a wide range of biological functions, including immune modulation, cell signaling, and tissue protection. Recent studies highlight their therapeutic potential in managing chronic diseases such as cancer, diabetes, cardiovascular disorders, and inflammatory conditions. Additionally, polysaccharides are increasingly utilized in drug delivery systems and nanocarriers due to their stability and functional versatility.
The structural diversity of polysaccharides, including homopolysaccharides and heteropolysaccharides derived from plant, animal, microbial, and marine sources, contributes to their wide range of biological functions. These include immune modulation, cell signaling regulation, and protection against cellular damage. Recent research highlights their therapeutic potential in the prevention and management of chronic diseases such as cancer, diabetes, cardiovascular disorders, and inflammatory conditions.
Furthermore, natural polysaccharides are increasingly being utilized in advanced drug delivery systems and nanocarrier development due to their functional versatility and ease of modification. Overall, they represent a promising and sustainable alternative to synthetic compounds, although further studies are required to fully elucidate their mechanisms of action and expand their clinical applications.

Introduction
Natural polysaccharides are a type of natural biomacromolecule found in plants, fungi, algae, animals, and bacteria. They are nontoxic, stable, biodegradable, biocompatible, and have antioxidant properties. Polysaccharides can reduce cellular damage, control antioxidation-related signal pathways, enhance the intracellular antioxidant enzyme system, lower substances that readily produce ROS, and shield bodily tissue from ROS-induced damage by scavenging free radicals and modulating the immune system. More than ten monosaccharide molecules joined by various glycoside linkages with intricate molecular structures make up polysaccharides that are taken from natural sources.[1]
Several polysaccharides, including starch, dextran, alginate, pectin, chitin, chitosan, hyaluronic acid, albumin, gelatin, and guar gum, are applied to manufacture nanocarriers for cancer therapy. Polysaccharides are a type of biopolymer that comes from carbs. They play a big role in the immune system, blood clotting, fertilization, stopping diseases before they start, and how well medicines work.[2]
Antioxidants are an essential defense system of the body that protect against damage caused by reactive oxygen species (ROS), which are continuously generated during various physiological processes. Oxidative stress plays a major role in the development of several diseases, including chronic inflammation, cardiovascular disorders, and cancer. Antioxidants help reduce the production of reactive oxygen species and effectively prevent oxidative stress. Among natural antioxidants, polysaccharides are high-molecular-weight biopolymers that exhibit significant antioxidant activity and contribute to disease prevention.[3]

These antioxidants originate from both endogenous sources within the body and exogenous dietary sources. In recent decades, there has been increasing interest in replacing synthetic dietary antioxidants with natural alternatives, leading to a focus on plant-based sources and low-cost agricultural raw materials for the discovery of new antioxidants. The body's innate defense system against these free radicals is critical, and it can be strengthened further by dietary antioxidant supplementation. Antioxidants are generally classified into two types: synthetic and natural. The primary target site for free radical damage and antioxidant defense in the body is the cellular level.[4]

Inflammation represents the initial protective response of the immune system to tissue injury, infection, or physiological stress. However, persistent or chronic inflammation is closely associated with the development and progression of several diseases, including arthritis, atherosclerosis, and cancer. Inflammation is a physiological process of the body that results from damage, illness, and stress and is the initial reaction of the immune system. Prolonged and chronic inflammation can be harmful and contribute to the pathophysiology of diseases including fever, asthma, atherosclerosis, and arthritis, but generally inflammation is a natural defensive response through the release of NO and pro-inflammatory cytokines.[5]

Natural Polysaccharides

Natural polysaccharides are non-renewable and possess high levels of biocompatibility and biodegradability, natural polysaccharides—which are the subject of this study—are among the most widely used biopolymers in food, pharmaceutical, and medical applications.[6]

One of the most important biomacromolecules for the growth and development of living things are polysaccharides, which are carbohydrate polymers made up of at least 10 monosaccharides connected by glycosidic bonds. Three essential steps are typically involved in the preparation of polysaccharides: extraction, pre-purification, and dehydration. The physicochemical and functional changes of polysaccharides in response to various processes or conditions were thoroughly examined in this work.[7]

The immune system, blood coagulation, fertilization, pathogenesis prevention, and therapeutic efficacy all depend on polysaccharides, which are members of the third major class of biopolymers (carbohydrates). Polysaccharides affect a variety of biological processes in cells, including lubrication, energy storage, structure support, and cell signal transduction.[8]

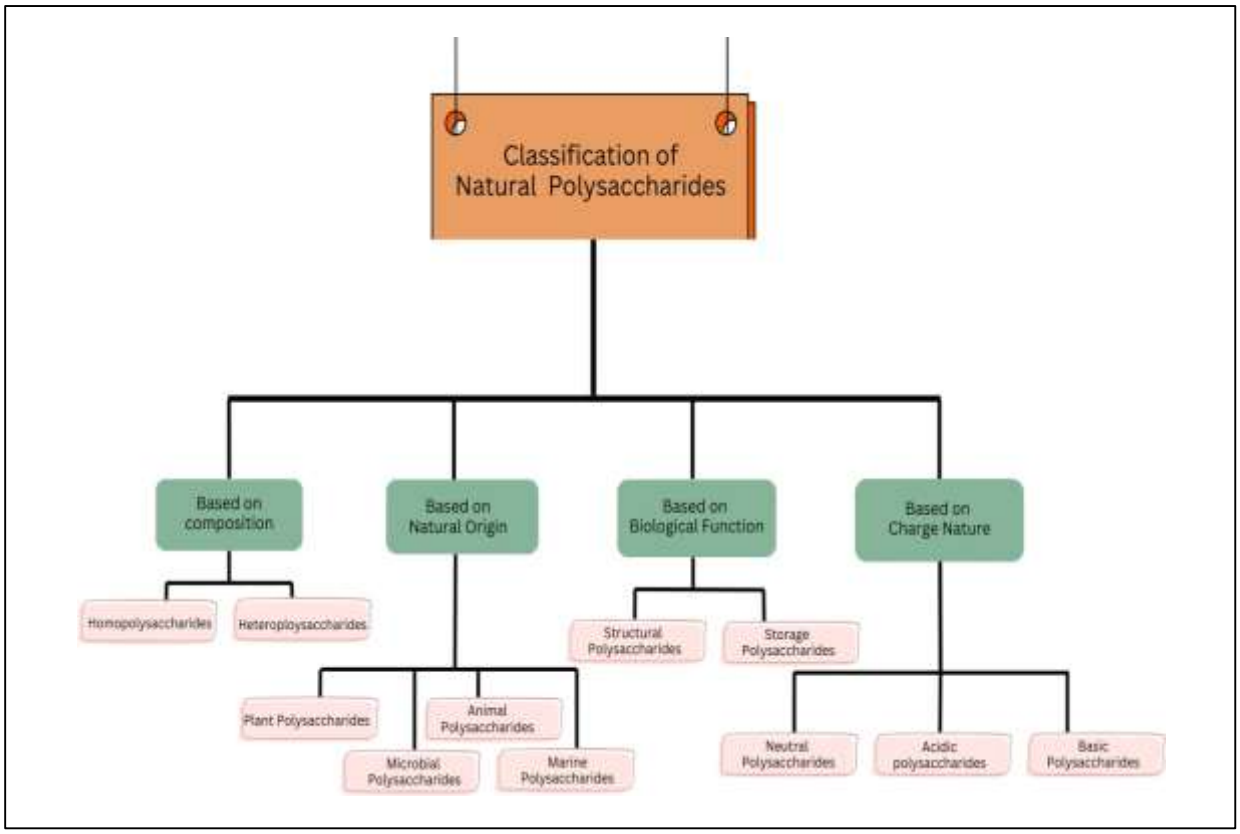

Figure.1 Classification of Natural Polysaccharide

- **Based on composition**

➢ **Homopolysaccharides**- A unique class of polymeric carbohydrates known as homopolysaccharides (HoPSs), or homoglycans, are distinguished by the presence of a single kind of monosaccharide unit repeated throughout their molecular structure. Starch, cellulose, pullulan, glucan, and inulin are common examples of homopolysaccharides; they are all mostly made up of monosaccharide residues connected by glycosidic linkages.

Bacterial homopolysaccharides (HoPSs) can be broadly classified into four major categories, which are further subdivided according to the nature of the glycosidic linkage and the specific carbon atom involved in bond formation. These categories include α-glucans (such as dextran, alternan, reuteran, and mutan), β-glucans, β-fructans, and α-galactans. [9]

➢ **Heteropolysaccharide**- Heteropolysaccharides, also known as heteroglycans, are complex polysaccharides composed of two or more different types of monosaccharide units linked together by glycosidic bonds. In nature, heteropolysaccharides are extensively distributed and present in a diverse range of creatures, including plants, mammals, fungus, bacteria, and algae. These polymers are commonly found in plants, animals, fungi, and microorganisms, where they play important roles in structural support, cell signaling, protection, and biological activity.[10]

- **Based on Natural Origin**

➢ **Plant Polysaccharides**- Plant polysaccharides have been researched for their important bioactivities in medicine over the last few decades. Certain plant polysaccharides have demonstrated significant antibacterial properties against a range of both Gram-negative and Gram-positive bacteria. Different antibacterial properties are displayed by the polysaccharides that are derived from algae or from the roots, leaves, branches, seeds, or other portions of woody, shrubby, or herbal plants.[11]

Numerous polysaccharides have been identified in various plant species, and details regarding the composition and functions of several of these polysaccharides have been clarified. The great majority of plant polysaccharides were discovered to be comparatively non-toxic and to have no adverse effects. For the therapeutic use of immunomodulating polysaccharides made from microorganisms and chemical synthesis,

side effects are in fact an unresolved issue.[12]

➢ **Animal Polysaccharides-** Animal polysaccharides are naturally occurring biopolymers obtained from animal sources such as chitin, chondroitin sulfate, hyaluronic acid, and heparin. These polysaccharides possess excellent biocompatibility, biodegradability, and low toxicity, making them highly valuable in pharmaceutical and biomedical applications. They play an important role in drug delivery, tissue engineering, wound healing, and regenerative medicine due to their unique biological and physicochemical properties. animal-derived polysaccharides exhibit antioxidant, anti-inflammatory, and antimicrobial activities, which enhance their therapeutic potential in modern healthcare research.
One category of biological macromolecules includes animal polysaccharides. These natural biopolymers have many benefits for biological applications, including non-toxicity, non- antigenicity, biocompatibility, and biodegradability. Animal-based polysaccharides are long chains of sugar molecules made by animals. They're part of structures like connective tissues, shells, and fluid lubricants in the body. These differ from plant polysaccharides (like starch and cellulose) because they often contain nitrogen and are linked with proteins.[13]

➢ **Microbial Polysaccharides**-Hydrocolloids used in food, medicine, and other industrial purposes can be produced from renewable sources using microbial polysaccharides. Nowadays, xanthan, gellan, dextran, and alginate are some of the frequently used microbial polysaccharides. Cell wall polysaccharides are a structural component of the cell wall, whereas intracellular microbial polysaccharides are found inside a portion of the cytoplasmic membrane. Extracellular polysaccharides, also known as exopolysaccharides (EPS), can be loosely bonded to the cell surface in the form of slime or covalently linked to the cell surface in the form of capsules.[14]

➢ **Marine Polysaccharides-** Marine-based polysaccharides are long carbohydrate molecules naturally found in marine organisms. They often have unique chemical structures and bioactivities compared with land-plant polysaccharides. They are used in food, cosmetics, medicine, pharmaceuticals, biotechnology, and materials science. 70% of the earth's surface covered by marine life, the seas are the planet's greatest ecosystem, potentially home to over 80% of all plant and animal species.[15]

- **Based on Biological Function**

➢ **Structural Polysaccharides-** Plant structural polysaccharides differ in their monosaccharide makeup, the types of substitutions present, and the glycosidic bonds that connect their sugar units. The content of monosaccharides, substitution patterns, and glycosidic bonds between monomers are all different in plant structural polysaccharides. [16]

- **Based on Charge Nature**

➢ **Neutral Polysaccharides-** Neutral polysaccharide which is HJP-1a and other three acid polysaccharides HJP-2, HJP-3 and HJP-4 has been extracted from Z. jujuba cv. Hamidazao. HJP-1a was primarily made up of arabinose and galactose in a ratio of 56.9:20.0, with an average molecular weight of 3.115 × 104 g/mol. The homogeneous heteropolysaccharides HJP-2, HJP-3, and HJP-4 were primarily composed of galacturonic acid, arabinose, and galactose.[17]

➢ **Acidic Polysaccharides**-the rate of hydrolysis was determined for no of polysaccharides as a function of the ph. neutral carbohydrates were hydrolysed at a rate nearly proportional to acid concentration. acid hydrolysis is widely used tool for studying the chemical composition and structure of polysaccharides.[18]

Sources of Natural Polysaccharides

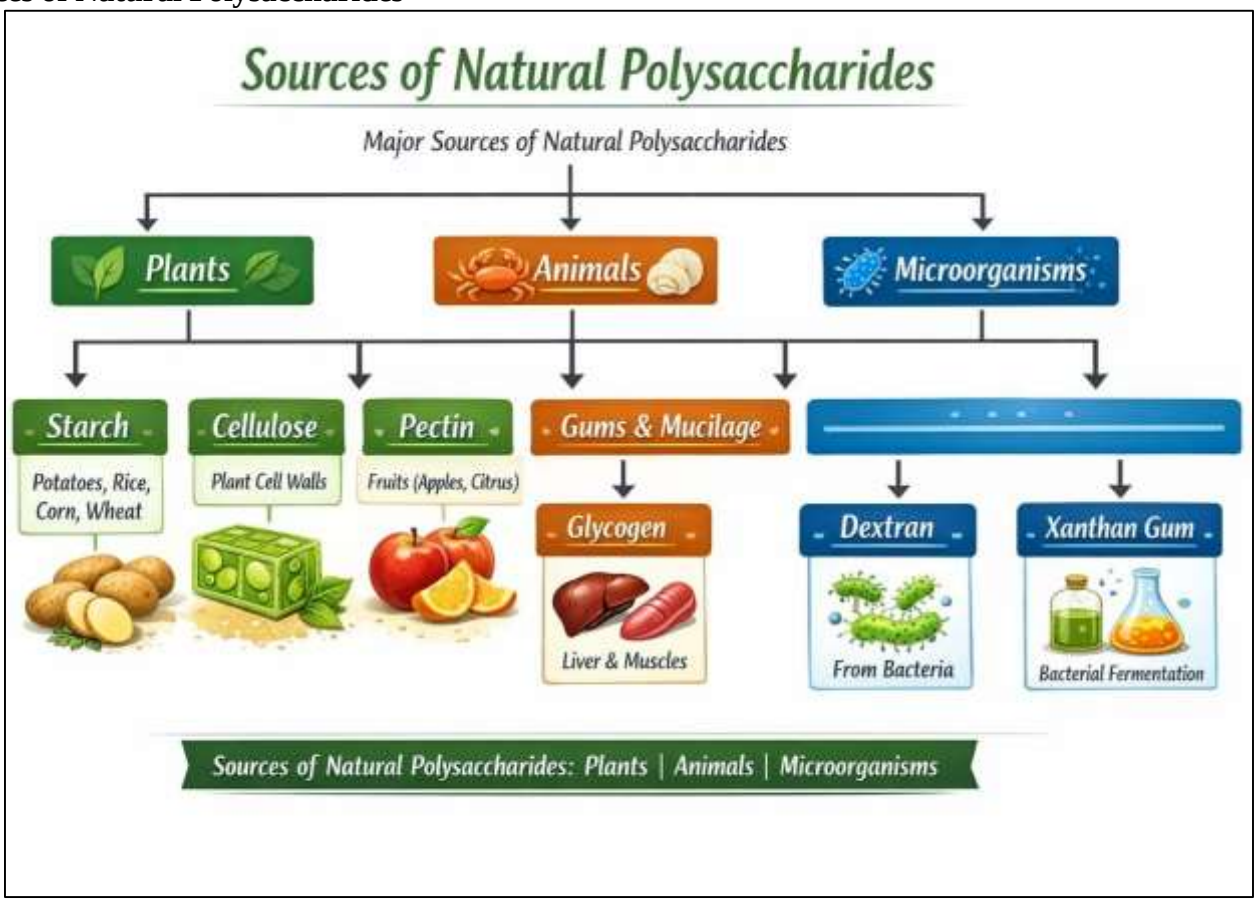

Figure.2 Sources of Natural Polysaccharide

Applications of Natural Polysaccharides

Natural polysaccharides and their derivatives are often preferred for medicinal use because they break down naturally, are safe and non-toxic, work well with biological tissues, and require less cost for processing. The function of bioactive polysaccharides in managing various metabolic disorders and their uses in the previously mentioned novel research fields are covered in this section.

Anti-Microbial and Antiviral

Several clinical studies have been shown that intake of pectin orally can significantly decrease the diarrhea and other intestinal problems in infants and children. This effect may occur because pectin helps lower the number of harmful bacteria such as Citrobacter, Salmonella, Enterobacter, Shigella, and Proteus in the intestine.[19]

Anti-Tumor/Cancer

The number of cancer cases and fatalities worldwide is rapidly growing, making the discovery of effective therapies even more vital. Natural polymers, such as polysaccharides, have received a lot of interest in recent years due to their unique physicochemical and biological properties. Aside from their direct potential to inhibit tumor growth, polysaccharides have flexible structures that can be exploited to make multifunctional nanocomposites. Chemical modification of these materials improves their stability and bioavailability, allowing therapeutic medicines to be administered more efficiently to tumor tissues. Many studies have investigated that dietary fibers' anti-cancer properties. Among them, pectin has been extensively studied and proven to inhibit tumor development and cancer cell dissemination in rat models treated with modified citrus pectin.[20]

Anti-Diabetic

Polysaccharides can enhance insulin sensitivity, lower the risk of complications from diabetes, and help regulate high blood sugar levels, according to numerous studies. Polysaccharides are seen as a viable strategy for managing diabetes because of these advantages. The precise processes underlying their antidiabetic benefits are still unclear, though.
Short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate can be produced in the human gut by

certain bacteria that break down undigested polysaccharides. By strengthening tight junctions and promoting the proliferation of intestinal epithelial cells, these substances help preserve the integrity of the intestinal barrier and lower systemic inflammation.
Additionally, through the action of SCFAs, the fermentation of polysaccharides may aid in the regulation of immune cells found in the lamina propria and mucosal epithelium, including regulatory and diabetogenic T cells. This mechanism can lower the chance of developing autoimmune diabetes by influencing the immunological milieu of the pancreas and gut.[21]

Gastro-Protective

The gastric mucosa is the thin, weak, and most active mucosal tissue in the stomach's inner wall. It helps break down food and use energy. Natural polysaccharides have been shown to have gastroprotective properties in both clinical and animal trials. Additionally, several of them have been used as building blocks to create gastroprotective compounds. For instance, piroxicam, a prodrug made from piroxicam maleate and pectin, shown protection against GU.
For instance, piroxicam, a prodrug made from piroxicam maleate and pectin, shown protection against GU. Chitosan-alginate polyelectrolyte complex nanoparticles loaded with amoxicillin may be used as a mucopenetrating delivery strategy for H. pylori. Given this, natural polysaccharides are promising substances for managing and treating GU or GL. [22]

Anti-Inflammatory

The body's immune system's initial reaction to damage, infection, and stress is inflammation. Numerous illnesses, including cancer, atherosclerosis, and arthritis, are closely linked to chronic inflammation. Scientists from all over the world are becoming more interested in polysaccharides because of their strong anti-inflammatory, immunomodulatory, and safe qualities. Scientist showed that seabuckthorn berry polysaccharide's anti-oxidative and anti-inflammatory properties may shield mice against carbon tetrachloride-induced hepatotoxicity. These activities involve a variety of targets and cell signaling pathways, which must be methodically summarized. One lesser-known but important aspect of the anti-inflammatory activity of animal polysaccharides is their ability to regulate immune signaling pathways rather than simply suppress inflammation. Certain animal polysaccharides, such as chondroitin sulfate and hyaluronic acid, can inhibit the activation of nuclear factor-kappa B (NF-κB) and reduce the production of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. Additionally, they help maintain extracellular matrix integrity and promote tissue hydration, which indirectly reduces chronic inflammatory damage. Recent studies also suggest that some animal polysaccharides can modulate gut microbiota, leading to reduced systemic inflammation and improved immune balance.[23]

Characteristics and Properties

Natural polysaccharides possess several important characteristics that contribute to their antioxidant and anti-inflammatory activities. They are biocompatible, biodegradable, non-toxic, and highly stable natural biomacromolecules, making them suitable for pharmaceutical and biomedical applications. Natural polysacharides are biopolymers which are obtained from plants, animals, and microorganisms.they can possess various funtional characterstics and properties which make them useful in food, pharmaceuticals, and biodegeradable film applications.

1. Mechanical Property

Natural polysaccharides can provide mechanical strength and help in preventing physical damage in food products when used in film or coating.

2. Barrier Property

Barrier property will act as the effective barrier against oxygen, carbon dioxide and water vapor, thereby helping in maintaining food quality and extending shelf life.

3. Antimicrobial Property

Antimicrobial property of natural polysaccarides will exhibit antimicrobial activity which helps in reducing microbial spoilage and protects food from harmful microoragnisms.

4. Antioxident property

They help in preventing lipid oxidation, thus maintaining the fresheness and nutrional values of food products.

5. Biodegeradibility

Natural polysaccahrides are biodegradable in nature, making them environmentally friendly and suitable for sustainable applications.[24]

A Comprehensive Review of Anti-inflammatory and Antioxidant Mechanism

Table 1. Natural polysaccharides and their antioxidant effects.[25]

Category	Polysaccharides	Main Monosaccharides	Protective Mechansim
Plant polysaccharide	Cellulose	Glucose	Reduce oxidative stress indirectly by improving gut health and decreasing ROS generation
	Pectin	Galacturonic acid, rhamnose, galatose	Scavenges free radicals, enhances antioxidant enzymes (SOD,CAT) and reduces lipid peroxidation
	Starch	Glucose	Exhibits mild antioxidant activity; modified starch reduces ROS levels and oxidative damage
	Gum	Arabinose, galactose, rhamnose	Protect cell from oxidative damage by scavenging free radicals and chelating metal ions
	Mucilage	Arabinose, galactose,uronic acids	Inhibits oxidative stress by neutralizing energy balance and indirectly reduces oxidative stress
Animal polysaccharides	Chitosans	Glucosamine, N-acetylglucosamine	Protect albumin from oxidation by scavenging peroxy free radicals

	Hyaluronis acid polysaccharides	Glucuronic acid, N-acetylglucosamine	The liver and serum, improve the total antioxidant capacity, and decrease MDA levels
	Glycogen	Glucose	Minimal antioxident activity, indirect metabolic support
	Chitin	N-acetylglucosamine	Scavenges free redical reduces oxidative stress by enchancing antioxidant enzymes
	Heparin	Glucosamine, uronic acid	Exhibits antioxidant activity by inhibiting lipid peroxidation and scavenging free radicals
Microbial Polysaccharides	Dextran	Glucose	Reduces ROS production and enchances cellular antoioxidant defense systems
	Xanthan gum	Glucose, mannaose, glucoronic acid	Enhances antioxidant enzyme activity (SOD,CAT) and decreases oxidative stress markers
	Gellan gum	Glucose, glucuronic acid, rhamnose	Protcts cells by reducing oxidative stress and stabilizing cell environment
	Levan	Fructose	Exhibits antioxidant activity by scavenging free radicals

Table 1. Natural polysaccharides and their anti-inflammatory effects.[26]

Category	**Polysaccahrides**	**Main Monosaccaharide**	**Protetctive Mechanism**
Pant Polysccahride	Arabinoxylan	Arabinose, Xylose	Inhibits NF-κB pathway and reduces pro-inflammatory cytokines (TNF-α, IL-6)

	Inulin	Fructose	Modulates gut microbiota and decreases inflammatory mediators
	Galactomannan	Mannose, Galactose	Suppresses inflammatory response and regulates immune pathways
	Xyloglucan	Glucose, Xylose, Galactose	Reduces inflammation by modulating cytokine production
Animal Polysaccharide	Chitosan	Glucosamine	Inhibits NF-κB pathway and reduces nitric oxide (NO) production
	Heparin	Glucosamine, uronic acid	Inhibits inflammatory mediators and reduces cytokine production
	Chondroitin sulfate	N-acetylgalactosamine, glucuronic acid	Suppresses pro-inflammatory cytokines (TNF-α, IL-6) and modulates immune response
	Keratan sulfate	Galactose, N-acetylglucosamine	Reduces inflammatory response and protects tissues from damage
	Hyaluronic acid	Glucuronic acid, N-acetylglucosamine	Regulates immune cell activity and reduces inflammation
Microbial Polysaccharide	Dextran	Glucose	Suppresses inflammatory mediators and reduces cytokine production
	Xanthan gum	Glucose, mannose, glucuronic acid	Inhibits NF-κB pathway and decreases pro-inflammatory cytokines
	Pullulan	Glucose	Modulates immune response and reduces inflammatory signaling pathways

	Levan	Fructose	Reduces inflammation by inhibiting cytokines and oxidative stress
	Curdlan	Glucose	Enhances immunomodulation and suppresses inflammatory pathways
	Gellan gum	Glucose, glucuronic acid, rhamnose	Reduces inflammatory response and stabilizes cellular environment

Conclusion: Natural polysaccharides are developing as extremely desirable bioactive macromolecules due to their superior features such as biocompatibility, biodegradability, nontoxicity, and stability. They are abundant in plants, animals, and microbes and serve important roles in a variety of biological processes including as immunological control, cell signaling, and structural support.

Natural polysaccharides have antioxidant and anti-inflammatory properties, including the ability to scavenge free radicals, decrease ROS, and control critical signaling pathways like NF-κB. These systems aid in the protection of cells from oxidative damage as well as the regulation of chronic inflammation, both of which contribute significantly to diseases such as cancer, diabetes, cardiovascular problems, and arthritis.

Overall, natural polysaccharides represent a promising and sustainable alternative to synthetic compounds in pharmaceutical and biomedical fields. However, more detailed studies are still required to fully understand their mechanisms of action, optimize their extraction and modification techniques, and improve their clinical applications.

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