

Polysaccharides: Classification, Chemical Properties and Future Perspective Applications in Biological Medicine

Pushpraj Singh

Assistant Professor
Dept. of Chemistry,
Govt. Girls Degree College,
Chhibramau, Kannauj,
Uttar Pradesh, India

Abstract

Polysaccharides are most abundant naturally occurring macromolecular polymers which almost exist in all living forms, and have important biological functions. They are getting more attention because they exhibit a wide range of biological and pharmacological activities, such as antitumor, immunomodulatory, antimicrobial, antioxidant, anticoagulant, antidiabetic, antiviral, and hypoglycemia activities, making them one of the most promising candidates in biomedical and pharmaceutical fields. Polysaccharides can be obtained from many different sources, such as plants, microorganisms, algae and animals. Due to their physicochemical properties, they are susceptible to physical and chemical modifications leading to enhanced properties, which is the basic concept for their diverse applications in biomedical and pharmaceutical

fields. In this review, we will give insight into the most recent updated applications of polysaccharides and their potentialities as alternatives for traditional and conventional therapies. Challenges and limitations for polysaccharides in pharmaceutical utilities are discussed as well.

Keywords: Carbohydrates, Polysaccharides, Biological activities, Pharmacological applications, Future prospects.

Introduction

Polysaccharides also known as glycans are essential macromolecules which are obtained from renewable sources such as algae, plants, and microorganisms such as fungi and bacteria (Fig. 1) [1]. Together with other biomolecules like proteins and nucleotides, polysaccharides are an essential component and exert many activities in the biological system such as cell-cell communication, adhesion, and molecular recognition in the immune system [2]. Polysaccharides, which belong to the third major class of biopolymers (carbohydrates) (Fig. 2), play crucial roles in many different physiological processes and tumor metastasis [3], they can also provide structure, protection, adhesion, and stimuli responsiveness, they also have crucial roles in the immune system, blood clotting, fertilization, pathogenesis prevention, and therapeutic efficacy [4]. Natural polysaccharides can be obtained from different sources like algal origin, e.g., alginate, plant origin, e.g., pectin and gums, microbial origin, e.g., dextran, and animal origin, e.g., chitosan [5, 6], and can be considered as an essential functional material that plays important roles in many physiological and biological activities including antioxidant, antitumor, anti-hyperglycemic, and immune regulation activities [7, 8]. The use of microbial polysaccharides in the field of biotechnology and biomedical sciences was started many years ago [9, 10]. The diversity of sources that could produce polysaccharides made it a

substance of choice as starting materials which were modified chemically and used in different medical and non-medical fields [11], including food, energy, wood, paper, textiles, fibers, and oil drilling [12, 13].



Fig. 1: Examples of polysaccharides from different sources

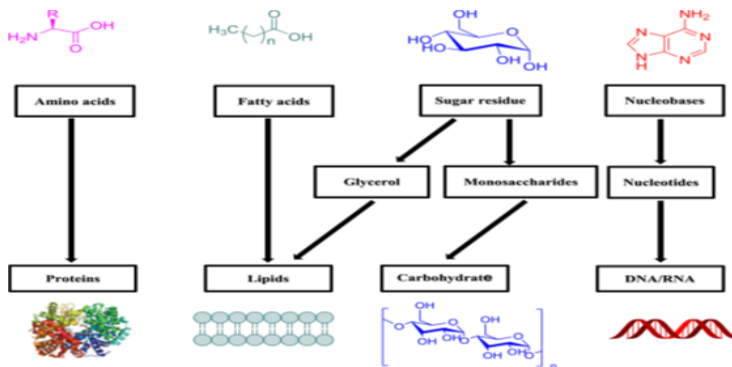


Fig. 2: Major macromolecules found in the body with its precursors

Classification, Chemical Structure, Sources and Physicochemical Properties of Polysaccharides

Polysaccharides, the most complex form of carbohydrates that existed in nature [14], can be defined according to their chemical structure, which contains

monosaccharides units that linked by glycosidic bonds [15, 16], they are either sugars residues that glycosidically linked together or bonded covalently to other structures like peptides, amino acids, and lipids. Homopolysaccharides are homoglycans that consist of the same monosaccharides, whereas heteropolysaccharides are heteroglycans that consist of different monosaccharides (Fig. 3). Glucans are glucose homopolysaccharides, while mannans are mannose homopolysaccharides [14]. Hydrophilic groups like OH, COOH, and NH₂ groups can form a bioadhesive layer with epithelial and mucous membrane tissues [5]. The most common constituent of polysaccharides is d-glucose; however, d-fructose, d-galactose, l-galactose, d-mannose, l-arabinose, and d-xylose are also frequent, some monosaccharide derivatives found in polysaccharides include the amino sugars (d-glucosamine and d-galactosamine) as well as their derivatives (*N*-acetylneuraminic acid and *N*-acetylmuramic acid), and simple sugar acids (glucuronic and iduronic acids). Polysaccharides can be differentiated according to the nature of monosaccharides components, length of chains, and the branching of those chains. The glycosidic linkage through the anomeric carbon atom between the glycosidic bond donor and the acceptor form either linear or branched chains, which make them distinguished from proteins and peptides since the latter has only linear chains. Polysaccharides naturally have storage properties like starch or structural properties, e.g., cellulose (Fig. 4), which provides physical structure and stability [14]. Polysaccharides can also be classified based on polyelectrolyte to positively charged polysaccharides (chitosan) and negatively charged polysaccharides (alginate, heparin, hyaluronic acid, and pectin [5]. Another primary components of the cell surface and the cell-extracellular matrix (ECM), Glycosaminoglycans

(GAGs), they were studied extensively [17], heparin, heparan sulfate, hyaluronan, chondroitin sulfate, dermatan sulfate, and keratan sulfate are the most important GAGs polysaccharides in mammalian tissues [18], some biological importance of these GAGs will be explained in this review. Chemical modifications of polysaccharides like sulfation, phosphorylation, and carboxymethylation are very efficient procedures to modify and change the biological properties of polysaccharides[19], which render them suitable for drug delivery systems in different drugs preparations because they can be more stable, non-toxic, and biodegradable [20]. Chemical modifications such as grafting, cross-linking, complexation, and covalent coupling add more potentialities as drug delivery and subsequently improve therapeutic efficacy [4]. They can also be a suitable choice for the replacement of some excipients or synthetic polymers [15]. Traditional polysaccharides vaccines contain contaminants and impurities in their heterogeneous mixtures; therefore, the chemically synthetic polysaccharides-based vaccine can overcome these shortcomings [21].

The stability, hydrophilicity, and biodegradability [22], along with other properties like the diversity of the physico-chemical properties of natural polysaccharides provide the basis for its wide range of biological activities [16]. It has been established that the biochemical and physical properties of polysaccharides have been contributed to their biomedical applications [18].

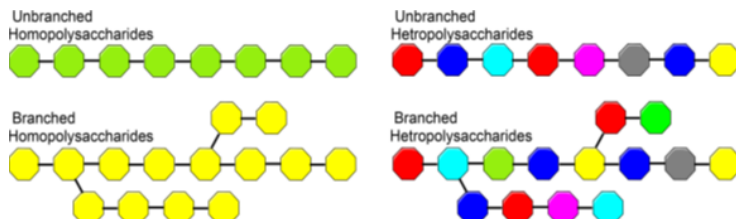


Fig. 3: Branched and unbranched homopolysaccharides and heteropolysaccharides, different, monosaccharides represented by different colors

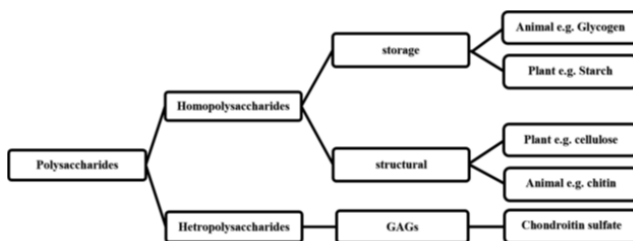


Fig. 4: Classification of polysaccharides according to the type of monosaccharides building blocks and their physiological properties

Applications of Polysaccharides

Application in Vaccine

The immune system plays an important role in responding to different external exposures like infectious diseases, inflammatory agents, and even carcinogens. Recently, cancer and infectious diseases become an emerging problem, and due to drawbacks like resistance, toxicity, and lack of immune responses of some available drugs, pharmaceutical companies are more concerned with the discovery of new safe and effective immune-stimulating alternatives, polysaccharides in this regard, are considered one of the best choices. It was proved that polysaccharides isolated from traditional Chinese medicine could activate or regulate T lymphocytes and macrophages, enhance the activity of interleukin, improve the antibody level, and regulate the immune function of the organism [23]. Polysaccharides were also proved an important modulator since they can enhance immunity through different mechanisms, such as

stimulation of macrophages, splenocytes, and thymocytes [24]. The carbohydrate-based vaccine is intensively studied for their potentiality to become vaccine candidates. Tumor-associated carbohydrate antigens and polysaccharides located on the surface of pathogenic microorganisms can be recognized by the host immune system [25], which opens a new era in glycobiology and vaccination availability since polysaccharides have a vital role in cell-cell recognition and interaction with the immune system. Many vaccine formulations contain polysaccharides based antigens such as bacterial capsular polysaccharides or tumor-associated carbohydrate antigens which have been used in many vaccines formulations [26]. Since the 80s of the last century, polysaccharides vaccines have been available for different infectious diseases like Pneumonia and meningitis [27, 28]. Unfortunately, conventional polysaccharide antigens (mainly high-purified capsular polysaccharides) have disadvantages such as short duration with a poor immunogenic response in infants and young children because of the absence of immunological memory and IgM to IgG class switch. To overcome these shortcomings, new polysaccharides vaccines are conjugated to strongly immunogenic protein carriers like diphtheria and tetanus toxins that induce T cell-dependent response and enhance the immunogenicity [21, 29] through interacting with the immune system [30].

Biomedical Applications

Since the last century, polysaccharides have found their place in the biomedical fields [15]. Owing to many properties of polysaccharides like biodegradability, biocompatibility, non-immunogenicity, and enhanced solubility and stability, they have been considered as potential candidates in many biomedical applications [3, 18], (Table 1). Moreover, the abundance of polysaccharides sources and

their low cost made them substances of choice and used in many biomedical [31], and biotechnological applications [32]. For instance, polysaccharides obtained from algae have been extensively used in biomedical applications such as wound management, regenerative medicine and to control drug delivery [33]. The ability of polysaccharides-based biomaterials to form hydrogels is another advantage of these new emerging class of biomaterials [14], e.g., heparin-loaded hydrogels, which have been used successfully to deliver bone morphogenetic proteins [18]. The polysaccharide was proved to improve the mechanical properties [34], which can overcome the poor biological performance of synthetic polymers [35].

Drugs, Vaccine Delivery and Tissues Engineering

Recently, polysaccharides have been extensively used as drug carriers, building blocks for drug delivery, bioactive materials, and excipients to enhance drug delivery [4], they also gain more attention in tissue engineering [63], cosmetics, and wound healing fields [12]. The ability of natural polysaccharides to be shaped and modified to do specific goals made them a potential candidate for many applications including drug and vaccine delivery. Xanthan gum, gellan gum, and scleroglucan are microorganisms-derived polysaccharides and have been studied extensively in drug delivery [64]. The absorption of the drug can be increased by loading it in bioadhesive polysaccharides nanoparticle carriers [5]. Other naturally occurring polysaccharides include pectin, guar gum, amylose, inulin, dextran, chitosan, and chondroitin sulfate, which have been investigated for colon-specific drug release and their ability to be used as pharmaceutical excipients [65]. These polysaccharides can deliver drugs to the colon as prodrugs or coating tablets [20, 66]; moreover, chitin and chitosan are low-immunogenic and tissue

compatible polysaccharides that proved to be effective in wound healing, tissue engineering, bone regeneration, and in delivery of drugs and vaccine [67, 68]. Chitosan (Fig. 5) is one of the most biopolymers that has been widely used as a drug and vaccine delivery system in many preparations [69], that is because a wide variety of antigen that could be encapsulated under mild conditions and without using organic solvents, which avoid the degradation and denaturation of the antigen during processing or after loading [68] attention as nanometric carriers for the drug delivery system [5]. Polycations, which are prepared by reductive amination reaction between primary amines and periodate oxidized polysaccharides, are considered a new class of non-viral gene delivery systems, cationic polysaccharides are also used as gene transfection vectors [70]. Hydrogels based on cross-linked polysaccharides are used in key applications, such as drug delivery systems and tissue engineering [71], the hyper-branched polymer is considered an excellent carrier for gene delivery nanoparticles [24].

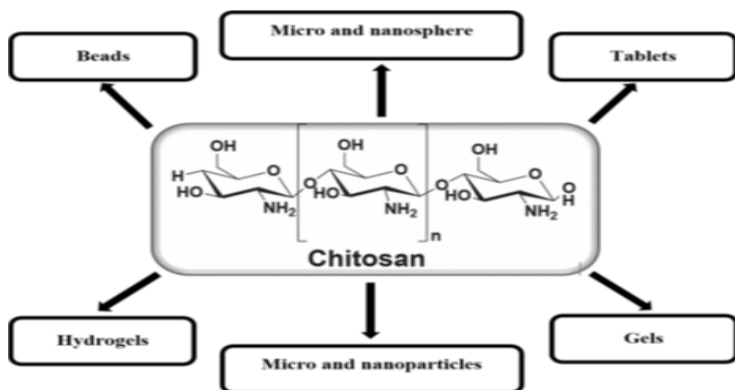


Fig. 5: Chitosan-based drug delivery systems
Antitumor and Immunomodulatory Activities

The tumor is a major health problem, and a leading cause of death worldwide [72]. Antitumor activities can be found in many plants [7] and marine polysaccharides [33]. A wide variety of natural polysaccharides proved to be effective antitumor agents, e.g., lentinan and schizophyllan [24]. It has been indicated that polysaccharide-protein conjugate has antitumor activity and can also enhance the activity of conventional chemotherapeutic drugs [72]. Recently, many researches have proved the immunosuppressive activity of polysaccharides against tumor growth [73]. Mushrooms are rich sources of many therapeutic agents and have been used for a long time as food and medicinal agents, regardless of the differences in the chemical structures and conjugated parts. It has been established that natural polysaccharides derived from mushrooms have been extensively studied for their potent antitumor and pharmaceutical activities [74, 75]. Examples of polysaccharides from mushrooms include *Ganoderma lucidum* which proved to have potent in vitro immune activation, and antitumor activity on the breast cancer cells [76, 77], and *Lentinus edodes*, which exhibited a marked antitumor effect against subcutaneously transplanted sarcoma [78]. Polysaccharides derived from mushrooms can produce their antitumor effects through the following proposed mechanisms oncogenesis prevention, immune system enhancement, and induce apoptosis of tumor cells through its direct tumor-inhibitory effect [79]. Besides the antitumor activity, mushroom polysaccharides exhibit a wide range of therapeutic activities and are used in clinical trials to increase the effectiveness of chemotherapeutic agents and minimize their side effects [80]. Algae polysaccharides are also of great importance because they have a diversity of pharmacological activities, including antitumor activity [81]. Polysaccharides activate effector cells, such as macrophages, T lymphocytes,

B lymphocytes, cytotoxic T lymphocytes, and natural killer cells to express cytokines, such as TNF- α , IFN- γ , and IL-1 β , cytokines invariably possess antiproliferative activity, cause apoptosis and differentiation in tumor cells (Fig. 6), and also secrete products like reactive nitrogen, oxygen intermediates, and interleukins [82]. Nanoparticles covered with saccharides display a higher circulation lifetime in the bloodstream. Additionally, they significantly accumulate in tumor tissues [83].

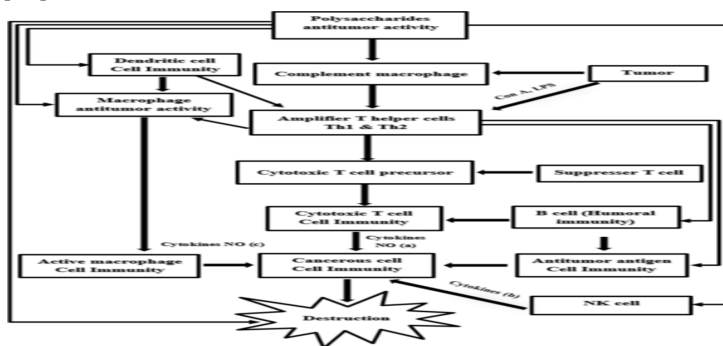


Fig. 6: Possible immune mechanism cytokines and fungus polysaccharides increased the production of IL-2, 3, 4, 6, 8, and 12, TNF- α , IFN- γ , IL-1 α , and IL-1 β generated from T cells. Cytokines b mushroom polysaccharides increased the production of IL-1, 2, 3, 12, TNF- α , and IFN- γ of NK cells. Cytokines c fungus polysaccharides could improve the release of IL-6 and 8, IL-1 β , TNF- α , and IFN- γ from macrophages. ConA was used as a specific T cell activator, and LPS was used as a general activator of B cells, macrophages, and DCs [82]

Antioxidative Applications

Reactive oxygen species (ROS) may cause damage to the human body, they attack different macromolecules such

as membrane lipids, proteins, and DNA, leading to many health disorders such as cancer, diabetes mellitus, neurodegenerative and inflammatory diseases with severe tissue injuries. Antioxidative agents are of great benefit in this regard since they can block or reduce the effect of these hazardous agents [84, 85], and improve human health [86]. Antioxidants from scientific resources are bearing many drawbacks like their carcinogenesis and liver damages; for these reasons, an alternative natural substitute will be of great advantage. Polysaccharides derived from plants are promising candidates because they exhibit strong antioxidant activities [87], that could protect the human body against free radicals and decrease the complications of many diseases [88]. Owing to its biological importance, chemical properties of plant polysaccharides have been extensively investigated for their wide range of applications, such as antitumor, immune stimulation, and antioxidant activities [89]. Moreover, the existence of natural antioxidants capable of scavenging these ROS will offer great help in this regard, this is the case with polysaccharides since they possess antioxidant activity which has been proved to protect and inhibit cardio and cerebrovascular disease caused by free radicals [24]. Many of these natural polysaccharides, such as *Hyriopsis cumingii*, were evaluated for their antioxidative ability against different types of free radicals [90]. Another example is the polysaccharides derived from the traditional Chinese medicinal herb *Astragalus*, which showed potent antioxidant and antitumor activity [91]. Sulfated polysaccharides derived from seaweed and red alga also possess many activities like anticoagulant/antithrombotic, antiviral, immuno-inflammatory, antilipidemic, and antioxidant activities [92, 93]. Antioxidative properties of polysaccharides are well proved, different kinds of polysaccharides have been used for this purpose include

seaweed polysaccharides, e.g., sulfated polysaccharides, plant polysaccharides, e.g., arabinogalactan, galactomannan, and pectic polysaccharides, and mushroom polysaccharides, e.g., β -glucans and glycoproteins [23].

Other Applications

Anti-inflammatory Activity

Natural polysaccharides have been widely used in nanomaterials for controlling inflammatory pathologies [15], and were experimentally tested for their anti-inflammatory activities [94]. The anti-inflammatory effect of polysaccharides could be through one of these mechanisms, e.g., the anti-inflammatory activity of TCM polysaccharides is mainly due to the inhibition of the expression of the chemotactic factor and adherence factor, as well as the activities of key enzymes in the inflammation process [19]. Other polysaccharides have an inhibitory effect on inflammatory-related mediators such as cytokines (IL-1b, IL-6, TNF-a) and NO (nitric oxide), and decreased the infiltration of inflammatory cells [50], sulfated polysaccharides derived from algae exhibit their anti-inflammatory effect through interfering with the migration of leukocytes to sites of inflammation [92].

Hypoglycemic and Hypocholesterolemic Activities Since the 1980s of the last century, polysaccharides have been extensively investigated in clinical trials for their hypoglycemic and hypocholesterolemic effect, *Ganoderma atrum* polysaccharide has potential for the treatment of hyperglycemia, hyperlipidemia, hyperinsulinemia, and insulin resistance, as well as a protective effect on kidney injury in the second type diabetes [24, 95]. Natural polysaccharides can be used as nanocarriers for proteins that enhance the

stability of loaded proteins and prolong their therapeutic effect, e.g., the bioavailability of orally administered Insulin-loaded dextran-chitosan nanoparticulate polyelectrolyte complex is increased with extended hypoglycemic effect [4]. Other examples of polysaccharides with hypoglycemic and hypocholesterolemic effects include sulfated polysaccharides extracted from *Bullacta exarata* [23], chitosan [96], and Kefiran [97]. Traditional Chinese medicine derived from *Tremella fuciformis* Mushrooms polysaccharides showed a significant dose-dependent hypoglycemic effect and improved insulin sensitivity by regulating PPAR- γ -mediated lipid metabolism when it was administered to mice [73].

Anticoagulant Activity

Among the diversity of polysaccharides properties, anticoagulant activity was extensively studied, unfractionated and low molecular weight heparins are sulfated polysaccharides that used as anticoagulant drugs, but unfortunately, they have side effects like bleeding and thrombocytopenia [81]. It was proved that polysaccharides, specially sulfated polysaccharides, have many biological activities like anti-tumor, antioxidant, and anticoagulant activities [23]. The high content of sulfate is a key factor in the anticoagulant activity of these sulfated polysaccharides [98]. Natural polysaccharides obtained from different marine sources like shellfish (shrimp, crab, squilla, lobster, and crayfish, etc.), marine macroalgae (seaweeds), marine fungi, microalgae, and corals [99], and plant-derived polysaccharide, e.g., pectin, could be considered as potential anticoagulant agents [100].

Antiviral Activity

The antiviral activity of polysaccharides was proved since the 50s of the last century, it has been established that sulfated polysaccharides from seaweeds have an inhibitory

effect against the replication of enveloped viruses including herpes simplex virus (HSV), human immunodeficiency virus (HIV), human cytomegalovirus, dengue virus, and respiratory syncytial virus [92]. Different microalgae species can produce sulfated exopolysaccharides which play an important biological role as antiviral agents [98]. Polysaccharides derived from Chinese traditional medicine have also been used for a long time as antiviral agents since they can improve and strengthen the immune system through activating macro phagocytes to promote their phagocytic ability and induce the secretion of IL-2, IFN- γ , and antibodies [19]. Microalgae polysaccharides also possess a lot of biological properties, such as antioxidant, antibacterial, and antiviral activity [32].

Polysaccharides in Corona Virus Disease (COVID-19)

Undoubtedly, the Covid-19 outbreak has become a major health challenge, especially with continuous searching for safe and effective therapeutic agents and vaccines [101]. Polysaccharides with their broad antiviral activity are considered one of the promising candidates in COVID-19 prevention and control from both sides as a therapeutic agent and carriers. GAGs, Traditional Chinese Medicine, and marine polysaccharides have shown potent anti-coronavirus activity. The entry of the virus to the host cell can be interfered with by sulfated polysaccharides by blocking the positive charge of the pathogen surface receptors. The cationically modified chitosan shows significant inhibition against the human coronavirus HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, which indicate its inhibitory effect against low-pathogenic human coronaviruses. Traditional Chinese herbal medicine contains potential anti-SARS-CoV-2 active compounds, especially *Hedysarum Multi Jugum Maxim*, *coptidis rhizoma*, and *forsythiae fructus* [102]. In vitro

experiments show that sulfated polysaccharides bind tightly to the S-protein of SARS-CoV-2, this interfering of protein binding to the heparan sulfate co-receptors has a potent inhibitory effect on viral infection [103]. Polysaccharides from different origins have also shown anti-pulmonary fibrosis activities, which render them an alternative agent for preventing or treating pulmonary fibrosis in COVID-19 patients [104]. One of the most complications of COVID-19 is the susceptibility of the infected patients to the bacterial secondary infection, polysaccharides can play a major role in this regard such as *Glycyrrhiza* polysaccharide displayed antimicrobial activity, inhibiting the growth of *B. cereus*, *Staphylococcus aureus*, *E. Aerogenes*, and *Escherichia coli*. The purified Chinese yam polysaccharide showed inhibitory activity against *E. coli*, with a minimum inhibitory concentration (MIC) of 2.5 mg/mL. A recent study found that *Poria cocos* polysaccharide could inhibit the growth of *S. aureus* and *E. coli*. *Asarum* polysaccharides in the Lung Cleansing and Detoxifying Decoction play an important role in relieving cough symptoms, which are prevalent in COVID-19 patients [105].

Polysaccharides, Future Prospective, Limitations and Challenges

Polysaccharides are the most abundant natural biopolymers, and recently they have gained more attention as applicable substances in different biomedical areas. Many properties are economically cheaper, could be modified chemically to suit specific purposes, and unlike synthetic polymers which have many drawbacks such as toxicity and long-time synthetic approaches, polysaccharides are comparably safe [106]. Another advantage of Polysaccharides is their resemblance to biological macromolecules like the natural extracellular matrix (ECM), which increases the

potentiality for using them in cell therapy approaches [1]. Over the past few years, there has been an increasing interest in the application of polysaccharide materials in the field of tissue engineering [107]. Mushrooms have been used for a long time, and recently they have gained more importance in cancer therapy, polysaccharides derived from mushrooms such as schizophyllan, lentinan, grifolan, polysaccharide-peptide complex (PSP), and polysaccharide-protein complex (PSK) can induce the immune response and produce the antitumor effect, which makes them promising candidates against tumor in the future [79]. The safety of polysaccharides is a crucial factor, and a strong advantage that will make use of their increase in the future, many other organic synthesis and chemical modifications caused severe environmental pollution which could be improved by substitution to natural polysaccharides [108]. From the drug delivery perspective, and due to their biocompatibility and biodegradability properties, polysaccharides have been increasingly used in many different forms to control the delivery of some drugs [109]. The diversity of functional groups located on polysaccharides structures such as hydroxyl, amino, and carboxylic acid groups could be furtherly modified to serve as a specific biological tool in different fields like vaccine adjuvants, drug carriers, tissue engineering scaffolds, and many other pharmacological activities [110]. Natural polysaccharides such as glycogen, cellulose, and starch were engineered onto biologically superior molecules by numerous methods such as chemical modification, co-polymer grafting, and atom transfer radical polymerization (ATRP) to promote its candidature in biopharmaceutics [9]. The conjugation between hydrophilic groups of polysaccharides with hydrophobic groups of drugs can form prodrugs with amphiphilic properties, which can be

self-assembled to form nanostructures with improved water solubility [83]. On the other hand, and since the polysaccharides are usually derived from natural sources, there are some limitations and challenges for polysaccharides in pharmaceutical and biological fields, such as batch-to-batch variations, microbial contamination, reduced viscosity during the storage, thickening, and uncontrolled rate of hydration. Fortunately, these drawbacks could be minimized by modifications such as grafting, cross-linking, and blending with other natural/synthetic/semi-synthetic polymers [111]. The high variability of polysaccharides in nature adds a new difficult task in extraction and purification of these polysaccharides, over and above, polysaccharides naturally found in complex with other compounds like proteins and lipids, and their isolation requires efficient and precise methods to avoid co-extraction and contamination with other compounds. Finally, the determination and fully understanding of the structural activity relationship of polysaccharides shall provide new opportunities in pharmaceutical and biological applications [112].

Conclusion

Polysaccharides are the most available natural biopolymers with diverse physical and chemical properties that render them a promising candidate in many biomedical areas. Polysaccharides have several advantages over other synthetic polymers; they are safe, economical, stable, hydrophilic, biocompatible, biodegradable, and prone to chemical modifications and tailoring for specific purposes in a wide variety of applications, such as preparation of pharmaceutical materials, drug release agent and plasma substitutes. Polysaccharides can be applied biologically in many different therapeutic fields like immunoregulatory, anti-tumor, anti-virus, anti-inflammatory, antioxidation, and

hypoglycemic activity. Over the past decades, polysaccharides have attracted extensive attention and can be considered as one of the most potent alternatives to conventional therapy. Even though carbohydrate-based pharmaceuticals are proved effective in different areas, they are not gaining as much interest as proteins or nucleic acid-based drugs. At the end of this review, we recommend further studies and investigation because many discoveries still lie ahead and many biological activities of a variety of polysaccharides are still not fully understood. Extensive investigation and elucidation of the structural activity relationship of polysaccharides are crucial to give more insight into the exact mechanisms of their biological activities and fully explore their future applications.

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