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Biomedical Applications of Polysaccharides

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Abstract- Polysaccharides are the most complex carbohydrates, composed of monosaccharide units bound together by glycosidic linkages. They are obtained from renewable sources such as plants, algae and microorganisms like fungi and bacteria. They are getting more attention because they exhibit a wide range of biological activities, such as anti-tumor, immunomodulatory, antimicrobial, antioxidant, anticoagulant, antidiabetic, antiviral, and hypoglycemia activities, making them one of the most promising candidates in biomedical and pharmaceutical fields. In this review, we will give insight into the most recent updated applications of polysaccharides.

Keywords- Carbohydrates, Polysaccharides, Medicinal Applications, Biological activities.

I. INTRODUCTION

Polysaccharides also known as glycans are ubiquitous biopolymers that occur widely in nature [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), 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].

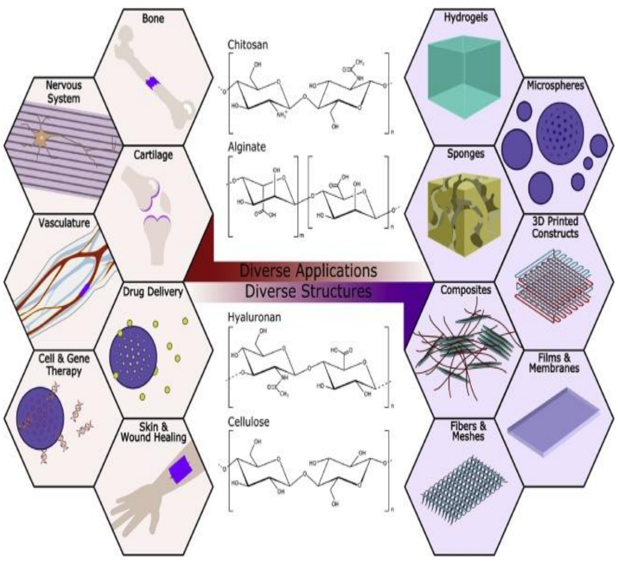

Fig 1. Various Applications of Polysaccharides.

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], 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 [6].

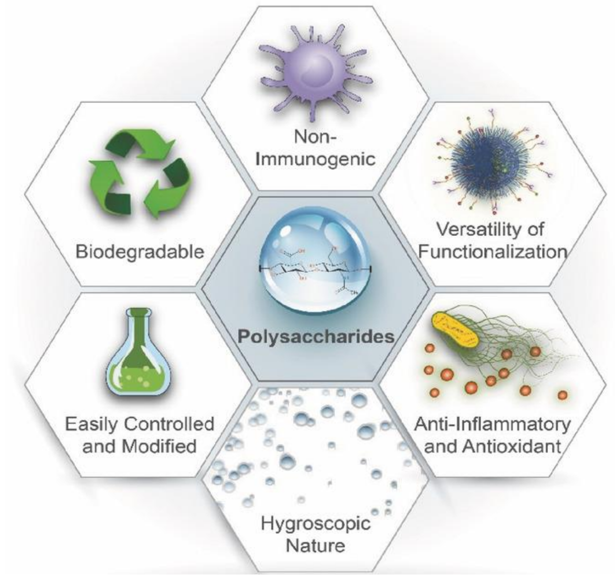

Fig 2. Polysaccharides.

The use of microbial polysaccharides in the field of biotechnology and biomedical sciences was started many years ago [7]. 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 [8] include food, energy, wood, paper, textiles, fibers, and oil drilling [9].

II. APPLICATIONS OF POLYSACCHARIDES

1. 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 [10]. Polysaccharides were also proved an important modulator since they can enhance immunity through different mechanisms, such as stimulation of macrophages, splenocytes, and thymocytes [11].

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 [12], 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 [13].Since the 80s of the last century, polysaccharides vaccines were available for different infectious diseases like Pneumonia and meningitis. 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 through interacting with the immune system [14].

2. 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 [16]. Moreover, the abundance of polysaccharides sources and their low cost made them substances of choice and used in many biomedical and biotechnological applications [17].

For instance, polysaccharides obtained from algae have been extensively used in biomedical applications such as wound management, regenerative medicine and to control drug delivery [18]. The ability of polysaccharides-based biomaterials to form hydrogels is another advantage of these new emerging classes of biomaterials, e.g., heparin-loaded hydrogels, which have been used successfully to deliver bone morphogenetic proteins [19]. The polysaccharide was proved to improve the mechanical properties, which can overcome the poor biological performance of synthetic polymers [20].

3. 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; they also gain more attention in tissue engineering [21], cosmetics, and wound healing fields.

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 [22].

The absorption of the drug can be increased by loading it in bioadhesive polysaccharides nanoparticle carriers [23]. Other naturally occurring polysaccharides include pectin, guar gum, amylose, inulin, dextran, chitosan, and chondroitin sulphate, which have been investigated for colon-specific drug release and their ability to be used as pharmaceutical excipients [24].

These polysaccharides can deliver drugs to the colon as prodrugs or coating tablets [25]; 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 [26].

Chitosan is one of the most biopolymers that has been widely used as a drug and vaccine delivery system in many preparations, 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 [27] attention as nanometric carriers for the drug delivery system.

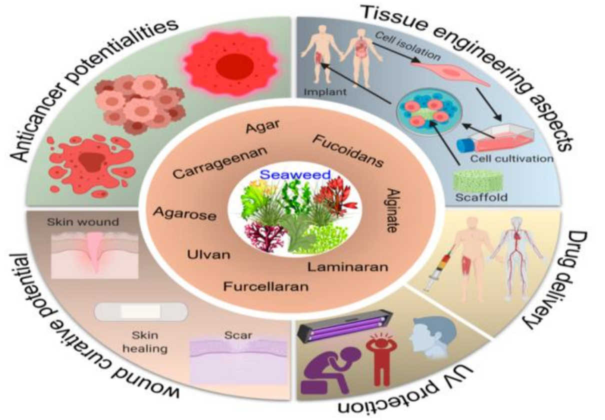

Fig 3. Applications of Polysaccharides in Drugs, Vaccine Delivery and Tissues Engineering.

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 [28]. Hydrogels based on cross-linked polysaccharides are used in key applications, such as drug delivery systems and tissue engineering; the hyper-branched polymer is considered an excellent carrier for gene delivery nanoparticles [29].

4. Antitumor and Immunomodulatory Activities:
The tumor is a major health problem, and a leading cause of death worldwide [30]. Antitumor activities can be found in many plants and marine polysaccharides [31]. A wide variety of natural polysaccharides proved to be effective antitumor agents, e.g., lentinan and schizophyllan [32]. It has been indicated that polysaccharide-protein conjugate has antitumor activity and can also enhance the activity of conventional chemotherapeutical drugs [33].

Recently, many researchers have proved the immunosuppressive activity of polysaccharides against tumor growth [34]. 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 [35].

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 [36], and Lentinus edodes, which exhibited a marked antitumor effect against subcutaneously transplanted sarcoma. Besides the antitumor activity, mushrooms 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 [37]. Algae polysaccharides are also of great importance because they have a diversity of pharmacological activities, including antitumor activity [38].

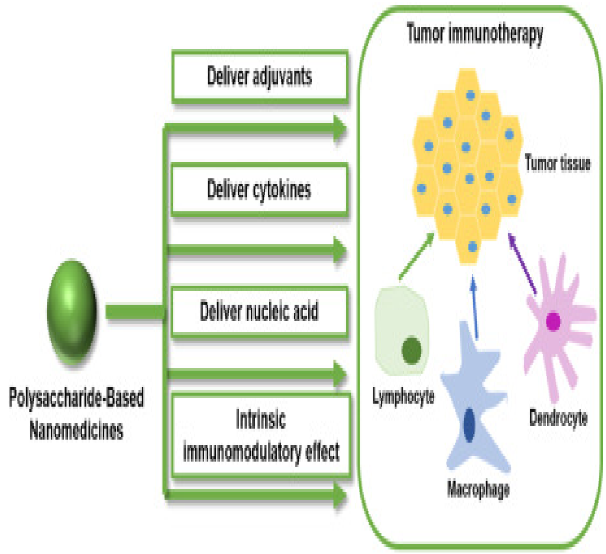

Fig 4. Antitumor Activity of Polysaccahrides.

5. Antioxidative Applications:
Reactive oxygen species (ROS) may cause damages 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 [39], and improve human health.

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 [40] that could protect the human body against free radicals and decreased the complications of many diseases.

Owing to its biological importance, chemical properties of plant polysaccharides have been extensively investigated for their wide range of applications, such as antitumor, immunestimulation, and antioxidant activities [41]. 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 [42]. Many of these natural polysaccharides, such as Hyriopsis cumingii, were evaluated for their antioxidative ability against different types of free radicals [43]. Another example is the polysaccharides derived from the traditional Chinese medicinal herb Astragalus, which showed potent antioxidant and antitumor activity [44].

Sulfated polysaccharides derived from seaweed and red alga also possess many activities like anticoagulant/ antithrombotic, antiviral, immuno-inflammatory, antilipidemic, and antioxidant activities [45].

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 [46].

6. Other Applications:

6.1 Anti inflammatory Activity: Natural polysaccharides have been widely used in nanomaterials for controlling inflammatory pathologies [47], and were experimentally tested for their anti-inflammatory activities [48]. 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 [49].

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 [51].

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 [52].

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 administrated Insulin- loaded dextran-chitosan nanoparticulate polyelectrolyte complex is increased with extended hypoglycemic effect [53].

Other examples of polysaccharides with hypoglycemic and hypocholesterolemic effects include sulfated polysaccharides extract from Bullacta exarate, chitosan, and Kefiran.

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 [54].

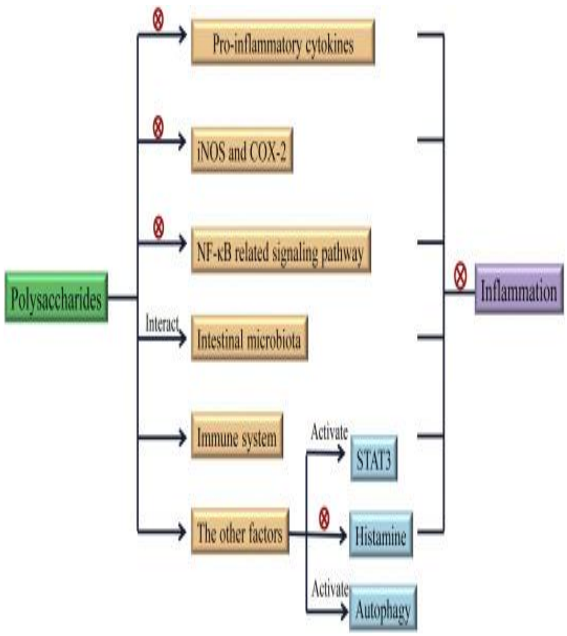

Fig 5. Anti inflammatory Activity of Polysaccharides.

6.2 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 [55].

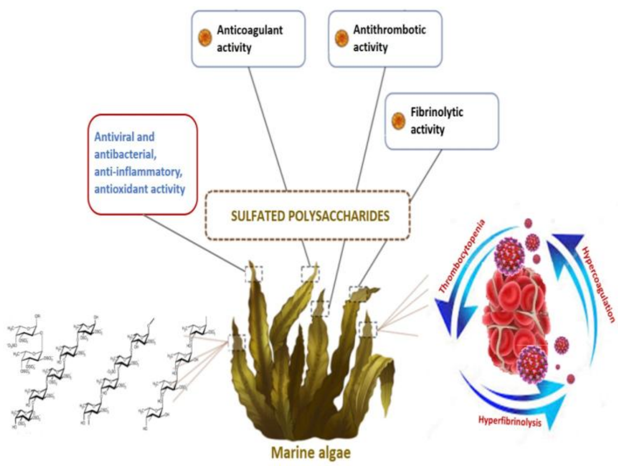

Fig 6. Anticoagulant Activity of Polysaccahrides.

6.3 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 [60].

Different microalgae species can produce sulfated exopolysaccharides which play an important biological role as antiviral agents [61]. 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 macrophagocytes to promote their phagocytic ability and induce the secretion of IL-2, IFN-γ, and antibodies [62]. Microalgae polysaccharides also possess a lot of biological properties, such as antioxidant, antibacterial, and antiviral activity [63].

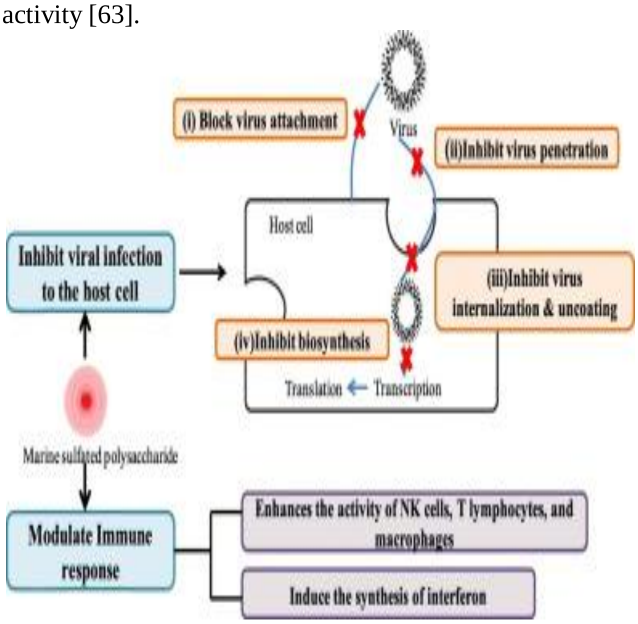

Fig 7. Antiviral Activity of Polysaccahrides.

2.7 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 [64]. 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 Hedysarummultijugummaxim, coptidis rhizoma, and forsythiae fructus [65]. 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 [66].

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 [67].

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. Aerogens, 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 [68].

III. 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 immune-regulatory, anti-tumor, anti-virus, anti-inflammatory, anti-oxidative, 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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