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Natural Sulfated Polysaccharides from Renewable Sources as Biocompatible Nanocarriers for Drug and Gene Delivery: A Promising Avenue in Nanomedicine

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Abstract

Background: Natural Sulfated Polysaccharides (SP) derived from seaweeds have recently gained considerable attention as promising biomaterials for nanomedicine applications, particularly in drug and gene delivery systems. Their inherent biocompatibility, biodegradability, and ability to interact with a wide range of biomolecules make them attractive alternatives to synthetic polymers, which often exhibit toxicity and undesirable immune responses. **Aim:** This review aims to provide a comprehensive overview of sulfated seaweed polysaccharides as nanocarriers for drug and gene delivery, highlighting their structural characteristics, biological properties, and emerging biomedical applications. **Method:** Relevant literature on sulfated polysaccharides derived from seaweeds was systematically examined to analyse their chemical structure, classification, physicochemical characteristics, and biological activities. Particular emphasis was placed on their role in nanocarrier design, drug encapsulation strategies, gene delivery mechanisms, and safety considerations, including toxicity, immunogenicity, and biodegradability. **Results:** The findings indicate that the degree of sulfation and structural composition significantly influence the biological activity and delivery efficiency of SP-based nanocarriers. Various encapsulation and controlled release mechanisms, including pH-responsive, enzyme-sensitive, and other stimuli-responsive systems, have been successfully employed. Sulfated polysaccharides have demonstrated promising potential for delivering therapeutic molecules such as siRNA, DNA, and mRNA. In addition, their applications in cancer therapy—particularly targeting the tumour microenvironment in breast, lung, and colorectal cancers—along with their roles in regenerative medicine and wound healing, have been widely reported. **Conclusion:** Sulfated seaweed polysaccharides represent a versatile and sustainable platform for developing advanced nanocarrier systems in nanomedicine. Despite their significant potential, challenges related to formulation stability, large-scale production, and reproducibility remain. Future research focusing on surface modification, hybrid formulations, and theranostic applications may further enhance their clinical translation and therapeutic effectiveness.

Major Findings: Sulfated seaweed polysaccharides demonstrate significant potential as biocompatible and biodegradable nanocarriers for drug and gene delivery. They enable efficient encapsulation and controlled release of therapeutic agents such as siRNA, DNA, and mRNA, with promising applications in cancer therapy, regenerative medicine, and wound healing.

Keywords: Biocompatibility, Cancer Therapy, Drug Delivery, Gene Therapy, Nanocarriers, Sulfated Polysaccharides

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1. Introduction

The natural world is a dynamic factory of polymers, with living organisms consistently producing a vast array of biopolymers throughout their life cycles. These biopolymers, sourced from plants, animals, bacteria, and fungi, exhibit remarkable diversity in their monomeric building blocks and overall structural complexity.

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Among the key examples are proteins, nucleic acids, polyhydroxyalkanoates, polyphenols, and notably, polysaccharides[1]. This inherent diversity provides a foundation for numerous biological functions and technological applications. Polysaccharides, the most abundant biological macromolecules in nature, are complex carbohydrates produced by a wide range of organisms[2]. Natural polysaccharides are a diverse group of biopolymers composed of many monosaccharide units linked together[3]. Beyond their structural and energy storage roles, they possess a remarkable capacity to carry biological information, rivalling even nucleic acids and proteins in structural diversity[4]. These high molecular weight polymers are composed of monosaccharide units linked by glycosidic bonds, with common examples including glycogen, cellulose, and starch[5]. The specific arrangement of these sugars, including branching patterns, monosaccharide types, and three-dimensional structure, varies significantly depending on the source, contributing to their diverse functionalities[6].

The versatile nature of polysaccharides makes them invaluable in diverse pharmaceutical applications, notably drug delivery systems. Beyond this, they are utilised for encapsulation, gene therapy, wound healing, tissue engineering, and even the creation of specialised contact lenses for targeted drug delivery[7].

Their intrinsic biocompatibility and biodegradability make them attractive for biomedical applications, particularly as carriers in drug delivery systems where they facilitate targeted delivery and controlled release of therapeutic agents[8]. This has led to their utilisation in drug delivery systems, where they facilitate targeted delivery and controlled release of therapeutic agents. Additionally, polysaccharides serve as biomaterials in tissue engineering, wound healing, and regenerative medicine, leveraging their cell growth-supporting properties[9]. Furthermore, their immunomodulatory capabilities have positioned them as valuable components in vaccine development and immunotherapy. Heparin, a SP, serves as a prominent example, showcasing its therapeutic versatility as a widely used anticoagulant[10].

The biological activity of polysaccharides is intricately linked to their chemical composition, molecular weight, and overall structure[11]. Notably, sulfation often enhances their physiological properties, contributing to health maintenance and disease prevention[12]. This has led to the emergence of SP as a promising class of materials for nanomedicine. SPs offer distinct physicochemical characteristics and biological activities, providing advantages over synthetic polymers in drug and gene delivery systems[13].

SPs hold significant promise in various biomedical applications due to their properties, which support their biomedical use. Their ability to encapsulate therapeutic agents, including small molecules, proteins, and nucleic acids, makes them ideal for drug delivery applications. They can be formulated into nanoparticles for controlled release and targeted delivery, enhancing treatment efficacy. Furthermore, SPs play a crucial role in gene delivery by complexing with nucleic acids to form protective nanoparticles that enhance cellular uptake and intracellular delivery. Their ability to be conjugated with imaging agents also enables bioimaging, facilitating *in vivo* tracking of drug delivery systems. Finally, the biocompatibility and support for cell growth and differentiation make them suitable for use as scaffolds in tissue engineering and regenerative medicine[14].

This review delves into the utilisation of SP as a promising material for advanced drug and gene delivery systems. It examines their unique physicochemical properties and biological activities that make them attractive candidates for biomedical applications, focusing on their versatility in encapsulating and delivering diverse therapeutic agents. Providing a comprehensive overview of SP in biomedicine, the review explores their structure, classification (based on composition, glycosidic linkages, and sulfation degree), and the influence of sulfation on their properties. It also addresses safety considerations, including immunogenicity, toxicity, biodegradability, and regulatory aspects. Mechanisms of action in drug and gene delivery are explored, covering encapsulation strategies, drug release mechanisms, and interactions with biological systems. Finally, the review acknowledges current limitations, such as formulation challenges and scalability, and explores potential solutions and future research directions, including novel modifications and the integration of advanced technologies.

2. Chemistry and Structural Properties of SP

Characterised by their negative charge, SP are present in the cell walls of marine algae, commonly

known as seaweeds. These biopolymers are primarily constituted by cellulose and hemicellulose, exhibit high carbohydrate content, and are concomitantly low in calories and fat. The negative charge is due to the cross-linkage of sulfate group ions with complex molecules of polysaccharides. Sulfate groups are present in their sugar structure's backbone to withstand the extreme marine conditions like high salinity, leading to alterations in their polymeric structure, turning into SP, whose biological activity and commercial applications are very high[15].

The biological activity of SP is influenced by its structural features, particularly the Degree of Sulfation (DS), sulfation pattern, molecular weight, and composition of backbone. An increased DS enhances negative charge density, promoting stronger electrostatic interactions with biomolecules and improving anticoagulant, antiviral, and anticancer activities. However, excessive sulfation may increase cytotoxicity, indicating the need for optimised sulfation levels. The position of sulfate groups on the sugar residues also affects receptor binding and biological response. Molecular weight influences pharmacokinetics and bioactivity, where lower molecular weight SP often show better tissue penetration, while higher molecular weight variants support sustained release and gel formation. Additionally, differences in monosaccharide composition and glycosidic linkages determine drug binding efficiency and interaction with biological systems.

The primary classification of SP is based on the stereochemistry of their constituent galactans, leading to the designation of agarans and carrageenans. Figure 1 provides a visual chemical representation of SP. Agarans are defined by the presence of 4-linked

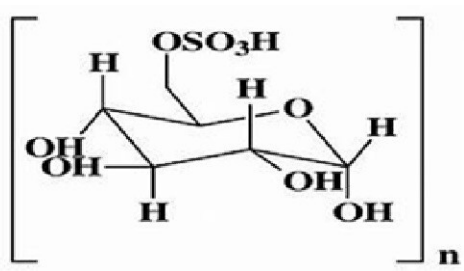


Figure 1. Chemical structure of sulfated polysaccharides illustrating the backbone sugar units and the position of sulfate groups.

α-galactose residues of the L-series, while carrageenans are characterised by the corresponding D-series configuration[15,16].

Table 1 shows the diverse biological activities of various SPs derived from different sources. These activities highlight their potential therapeutic applications in various fields, including medicine, pharmaceuticals, and cosmetics. Recent studies further substantiate the expanding biomedical applications of SP, particularly in nanocarrier development, cancer therapy, and regenerative medicine.

2.1 Carrageenan: SP of Red Seaweeds

Red seaweeds, belonging to the Rhodophyta phylum, have a rich history as a food source, dating back at least 2800 years. While the red algae themselves are edible, the carrageenan extracted from them is not digested by the human body. Instead, it acts primarily as a source of dietary bulk. This indigestibility, however, doesn't diminish carrageenan's value. Its unique chemical composition, primarily consisting of repeating galactose and 3,6-anhydrogalactose (3,6-AG) units linked by alternating α-1,3 and β-1,4 glycosidic bonds, is the key to its functional properties as shown in Figure 2a. This specific structure grants carrageenan the remarkable ability to form thermos-reversible gels or highly viscous solutions. Consequently, it has become a widely used gelling, stabilising, and emulsifying agent across the food, pharmaceutical, and cosmetic industries. Carrageenan is a versatile material for drug delivery due to its gel-forming ability and biocompatibility. It can be used to create hydrogels for controlled drug release, act as a binder and disintegrant in tablets, and be formulated into nanoparticles for targeted drug delivery[17,18].

2.2 Agar: SP from Red Algae

Classifying red algae, particularly those producing agar, has presented its own set of taxonomic challenges. Similar to the green algae example, genetic studies have sometimes led to revisions in the classification of red algae genera. While researchers extract agar from various genera and species of red algae using diverse methods, the term "agar" generally refers to a group of galactan polysaccharides extracted from red seaweed. Agar is composed of two main components: agarose, a neutral polysaccharide with repeating units of agarobiose (a disaccharide of D-galactose and

3,6-anhydro-L-galactopyranose), and agaropectin, a charged, SP with a more complex and variable structure is shown in Figure 2b. Agarose, a component of agar, is widely used in drug delivery for creating controlled release matrices, tissue engineering scaffolds, and wound dressings due to its ability to form gels and support cell growth[19].

2.3 Fucoidan: SP of Brown Seaweeds

Fucoidan, a group of SP, was initially isolated from brown algae (Phaeophycophyta) and certain echinoderms by Kylin in 1913. Though originally termed "fucoidin," it is now referred to as fucoidan, following IUPAC recommendations. The chemical structure of fucoidan is complex and varies depending on the source, but generally consists of a backbone of α-L-fucopyranose units linked by (1→3) and/or (1→4) glycosidic bonds, with sulfate groups attached at different positions, as shown in Figure 2c. However, it's important to note that these terms, including "fucosan," are often used interchangeably. Fucoidan, a biocompatible and biodegradable polysaccharide, shows promise in drug delivery due to its targeted delivery potential. It can be modified to target specific cells, form complexes with DNA/RNA for gene delivery, and be incorporated into wound healing formulations[20,21].

2.4 Ulvan: Sulfated Polysaccharide of Green Seaweeds

The classification of green algae has proven to be a complex and evolving field, particularly with recent genetic discoveries that have led to the merging of genera such as Enteromorpha and Ulva. While diverse extraction techniques are applied to various green algae species, the term "ulvan" has emerged as the standard designation for SP originating from these green seaweeds. Ulvan is characterised by a repeating disaccharide backbone composed of uronic acid (either glucuronic acid or iduronic acid) and sulfated rhamnose is seen in Figure 2d. Ulvan, with its biocompatibility and biodegradability, is an emerging polysaccharide in drug delivery. It can form nanoparticles for controlled release, facilitate mucoadhesive drug delivery to mucosal tissues, and act as a scaffold in tissue engineering. Notably, among the SP discussed, ulvan remains the least extensively studied[22]. Ulvan is characterised by a repeating disaccharide backbone composed of uronic acid (either glucuronic acid or iduronic acid) and sulfated rhamnose is seen in Figure 2d. Ulvan, with its biocompatibility and biodegradability, is an emerging polysaccharide in drug delivery. It can form nanoparticles for controlled release and facilitate mucoadhesive drug delivery to mucosal tissues. Notably, among the SP discussed, ulvan remains the least extensively studied[22].

2.5 Heparin: A Family of SP from Animal Tissues

While the classification of algae presents one type of challenge, glycosaminoglycans (GAGs) like heparin pose another. Critically, the fine structure in Figure 2e of these GAGs, which significantly affects their function, is often less studied than their overall classification, making detailed characterisation and standardisation an active area of research[23]. Heparin, though commonly described as a single anticoagulant agent, is actually a heterogeneous group of structurally related sulfated polysaccharides whose activity depends on sulfation pattern and chain length. Its activity is influenced by factors like sulfation degree, the presence of specific sugar units (*e.g.*, iduronic acid), and chain length. Beyond its anticoagulant properties, heparin is utilised in drug delivery for drug conjugation to improve pharmacokinetics, gene delivery through complex formation with DNA/RNA, and targeted drug delivery to specific cells like liver cells[24].

2.6 Chondroitin Sulfate: A Diverse Group of GAGs from Cartilage and Other Tissues

Chondroitin sulfate, primarily found in cartilage, also exists in various forms with differing sulfation patterns and chain lengths, impacting its biological functions. Similar to heparin, although their general structures are understood, the specific arrangement of sulfate groups, the length of the polysaccharide chains, and other modifications can vary considerably depending on the source and extraction method. This microheterogeneity makes it difficult to define a single, precise structure for "chondroitin sulfate." Although these GAGs are isolated from diverse sources (*e.g.*, animal tissues) using various methods and possess significant structural complexity, the

term "chondroitin sulfate" generally describes a family of SPs sharing characteristic structural features and biological activities. Critically, the fine structure shown in Figure 2f of these GAGs, which significantly affects their function, is often less studied than their overall classification, making detailed characterisation and standardisation an active area of research. Chondroitin sulfate's biocompatibility and ability to interact with various molecules make it useful for cartilage regeneration, targeted drug delivery to cartilage tissue, and ophthalmic drug delivery by increasing drug residence time[23].

3. Biocompatibility and Safety Profile

Natural polymers, derived from sources like microorganisms, algae, plants, and animals, have a long history of application in diverse biomedical fields, such as pharmaceuticals, tissue regeneration, drug delivery, and imaging. Their similarity to Extracellular Matrix (ECM) components further contributes to their biocompatibility, allowing them to avoid the chronic immunological reactions and toxicity frequently associated with synthetic polymers. They have limited recyclability[25]. Synthetic polymers, on the other hand, are produced through controlled artificial synthesis, offering greater control over their structure and properties. This allows for tailored design and functionality, making them particularly attractive for drug delivery applications[26]. Common examples include Poly (Lactic-Co-Glycolic Acid) (PLGA), Polyethene Glycol (PEG), and Polycaprolactone (PCL). These polymers can be engineered to respond to specific stimuli, such as changes in pH, temperature, or enzyme activity, enabling targeted drug delivery to specific tissues or cells. Synthetic polymers also enable the creation of sophisticated drug delivery systems with tailored release profiles, improved biocompatibility, and enhanced therapeutic efficacy[27].

SPs exhibit a broad spectrum of biological activities, including immunomodulatory and cytotoxic effects, which are influenced by their source and sulfation degree. For instance, Porphyridium cruentum SP (PcSP) have been shown to induce interleukin-6 and tumour necrosis factor-alpha (TNF-α), indicating its potential to modulate immune responses. TNF-α, a key regulator of inflammation and autoimmunity,

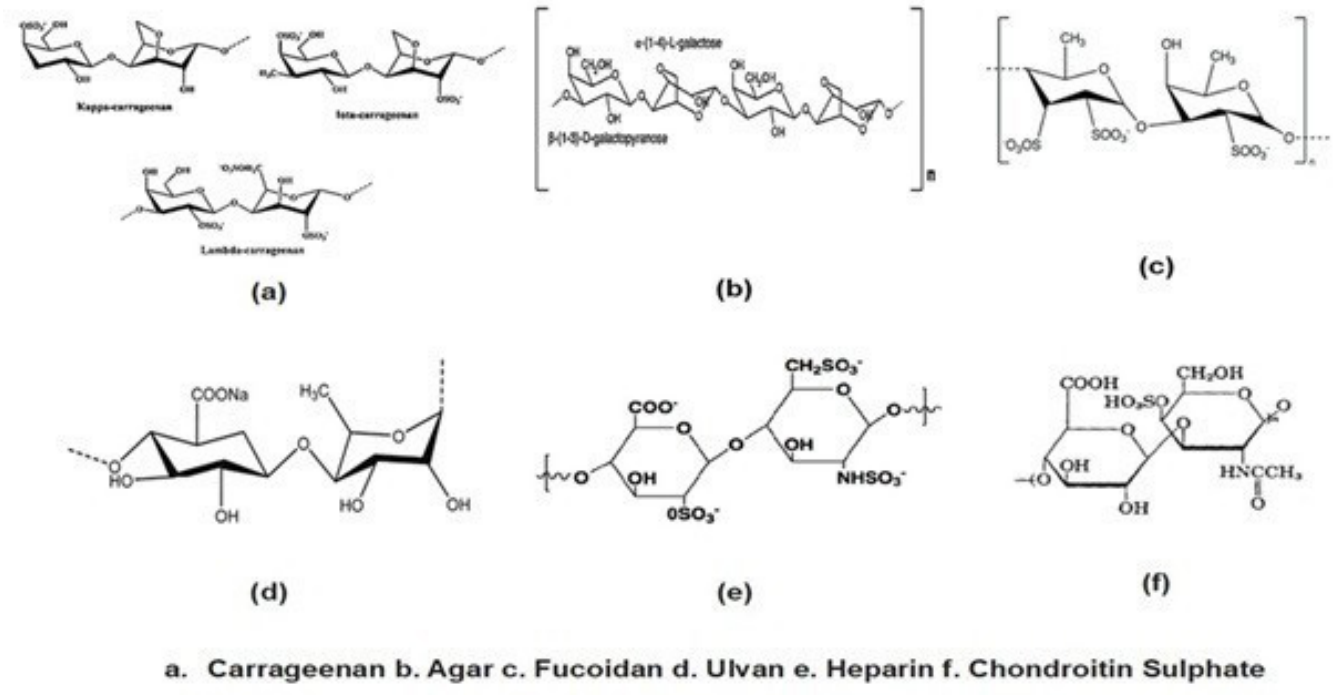


Figure 2. Classification of sulfated polysaccharides based on their biological source and structural characteristics.

acts through its receptors and accessory proteins, influencing NF-κB, which controls genes involved in inflammation, apoptosis, and autoimmunity[28].

The biocompatibility of SP is further supported by its biodegradability, particularly within the colon. Colonic microflora can effectively biodegrade various polysaccharides, making them suitable for colon-specific drug delivery. However, the rates of biodegradation are dependent on the polysaccharide type and the availability of colonic enzymes. Challenges related to degrading low-solubility polysaccharides can potentially be addressed through enzyme induction, highlighting the need for tailored SP selection and modifications[29].

Moreover, the safety profile of SP is enhanced by the development of greener synthesis methods. Research emphasises the importance of tailoring sulfation methods to control polymer properties and bioactivity. While traditional sulfation techniques exist, newer, less toxic reagents are increasingly favoured, promoting the use of SP in medicine, pharmaceuticals, and materials science[30]. This shift towards greener synthesis not only improves biocompatibility by reducing toxic residuals but also contributes to the sustainability of SP production.

While synthetic polymers such as PLGA, PEG, and PEI offer precise structural control, reproducibility, and established regulatory familiarity, they may present limitations, including potential cytotoxicity, accumulation, and inflammatory responses. In contrast, natural SP provide inherent biocompatibility, biodegradability, and bioactive functionality, including immunomodulatory and tumour-targeting properties. However, natural SP faces challenges related to batch variability, structural heterogeneity, large-scale standardisation, and regulatory characterisation. Therefore, while synthetic systems offer manufacturing consistency and translational familiarity, SP provide biologically interactive advantages. Hybrid approaches integrating natural and synthetic materials may combine scalability with biological functionality.

4. SP as Nanocarriers for Drug Delivery

The growing interest in SP as nanocarriers stems from their inherent biocompatibility, biodegradability, and adaptable nature, making them highly suitable for drug delivery applications[31].

A primary mechanism for drug encapsulation within SP nanocarriers relies on electrostatic interactions. The negative charge imparted by the sulfate groups on SP allows them to readily associate with positively charged drugs or polymers. This attraction drives the formation of nanoparticles or larger complexes, effectively encapsulating the therapeutic payload[32,33].

Beyond electrostatic interactions, diverse mechanisms contribute to drug encapsulation. Hydrophobic interactions can be employed by modifying SP with hydrophobic moieties, enabling the encapsulation of hydrophobic drugs. Additionally, hydrogen bonding between the hydroxyl groups of SP and drug molecules plays a role in complex formation. The interaction allows for the creation of stable complexes, particularly with drugs containing complementary functional groups like hydroxyl, carboxyl, or amine groups. Doxorubicin, an anticancer drug, contains multiple hydroxyl groups that enable hydrogen bonding with SP, thereby enhancing encapsulation efficiency[34]. Curcumin primarily interacts through hydrophobic forces; however, its hydroxyl groups also contribute to hydrogen bonding with SP[35]. Physical entrapment of drugs within the SP matrix is achieved during nanoparticle or microparticle formation, often through techniques like nanoprecipitation or emulsion. In certain cases, covalent conjugation of drugs to SP can create robust and stable linkages. Drug release from SP nanocarriers is commonly governed by diffusion, where drug molecules migrate from the nanoparticle interior to the surrounding environment following concentration gradients[31,33].

Several mechanisms govern drug release from SP carriers. Biodegradation of the SP matrix by enzymes in the body leads to drug release as the polymer breaks down. pH-sensitive SP can be designed to swell or dissolve in response to pH changes, enabling targeted drug delivery to specific sites like the stomach or intestines. Researchers have developed SP-based nanoparticles using acetal or hydrazone linkages, which are sensitive to pH. When these nanoparticles encounter the acidic environment of a tumour or endosome (pH 5.0-6.5), the linkages break, causing the SP matrix to degrade and release the encapsulated drug[36].

Enzyme-sensitive SP release drugs when specific enzymes, present in target tissues or cells, break down the SP matrix. Stimuli-responsive SP offers controlled drug release in response to triggers like temperature, light, or magnetic fields. Several factors influence both encapsulation and release: the SP molecular weight, sulfation degree, and branching; the drug's size, charge, and hydrophobicity; the preparation method used for SP nanoparticles or complexes; and environmental factors like pH, temperature, and ionic strength. In conclusion, SPs are used for drug encapsulation and release through diverse mechanisms. Careful selection and modification of the SP, along with optimised preparation methods, enable the design of tailored drug delivery systems for specific therapeutic applications[37].

5. SP in Gene Delivery

SPs are used for gene delivery due to their biocompatibility, biodegradability, and ability to interact with nucleic acids. Their negative charge, conferred by sulfate groups, allows them to readily interact with positively charged molecules, such as cationic polymers or lipids, often used to condense nucleic acids (DNA, siRNA, mRNA)[38].

5.1 Mechanisms of Gene Delivery using SP Nanocarriers

SP can be used for gene delivery due to its ability to interact with nucleic acids and facilitate their entry into cells. One key mechanism underlying this interaction is the electrostatic interaction. The negatively charged sulfate groups on SP readily bind to positively charged molecules, such as cationic polymers or lipids, often used to condense nucleic acids like DNA, siRNA, and mRNA. This leads to the formation of complexes or nanoparticles, effectively protecting the genetic material[39].

Beyond simply binding to intermediary molecules, SP can also directly interact with nucleic acids. Although SP and nucleic acids are both negatively charged, direct electrostatic binding between them is unfavourable under physiological conditions. In most cases, complex formation occurs through intermediary cationic polymers or ions (e.g., chitosan, polyethyleneimine, or divalent cations), which bridge the negatively charged groups and facilitate stable nanoparticle formation. In certain formulations, hydrogen bonding, hydrophobic interactions, or ionic crosslinking may also contribute to complex stabilisation[40].

Cellular uptake is a crucial step in gene delivery, and SP-nucleic acid complexes are internalised by cells through various mechanisms. Endocytosis is a primary pathway where the cell membrane engulfs the complex, forming vesicles that transport it into the cell. The specific type of endocytosis involved can vary depending on the characteristics of the SP and the target cell type. Cellular uptake can be further enhanced through receptor-mediated endocytosis. This involves modifying SP with targeting ligands, such as antibodies or peptides, that bind to specific receptors on the cell surface, thereby promoting and increasing internalisation[41].

However, merely entering the cell is not enough. Trapped within endosomes, the nucleic acids must escape to exert their function. Endosomal escape is crucial, and SP facilitate this through various mechanisms. For instance, Native SP generally do not exhibit a classical proton sponge effect due to their anionic nature. However, when chemically modified or formulated in combination with polycationic polymers (e.g., chitosan or polyethyleneimine), the resulting hybrid systems may demonstrate buffering capacity that facilitates endosomal escape. Thus, the proton sponge mechanism in SP-based systems is typically attributed to incorporated cationic components rather than the SP backbone itself.

Alternatively, some SP can directly disrupt the endosomal membrane, allowing the nucleic acids to escape into the cytoplasm[40]. Finally, in DNA-based gene therapies, the DNA must reach the nucleus to be transcribed. Nuclear localisation, while SPs themselves typically lack nuclear localisation signals, the SP-DNA complexes can sometimes be transported to the nucleus through other cellular mechanisms[42].

5.2 Stability and Protection of Nucleic Acids

Protection from degradation and improved stability are key benefits that SP offer to nucleic acid delivery. SP protect nucleic acids from degradation by nucleases, enzymes that break down DNA and RNA. The formation of complexes or nanoparticles with SP shields the nucleic acids from these enzymes, preserving their integrity until they are released within

the cell. This protection is particularly crucial for siRNA, which is inherently susceptible to degradation in biological fluids. SP can significantly enhance the stability of siRNA, prevent its premature breakdown and ensure that it reaches its target with its sequence intact[43].

5.3 Case Studies of siRNA, DNA, and mRNA Delivery

SPs are widely used for siRNA delivery due to their ability to form stable complexes with siRNA, protecting it from degradation and enhancing cellular uptake and endosomal escape for efficient gene silencing[44]. Small interfering RNA (siRNA) holds immense therapeutic potential for gene silencing, but its delivery to target cells remains a significant hurdle[45].

Natural polysaccharides and their derivatives have emerged as promising building blocks for siRNA delivery nanocarriers due to their biocompatibility, biodegradability, and versatile chemical properties. siRNA itself holds immense promise for cancer therapy by silencing genes that drive tumour growth and metastasis. However, delivering siRNA to cancer cells is challenging due to its size, negative charge, and susceptibility to degradation. Lipid- and polymer-based carrier systems, including those based on SP, have been used to overcome these obstacles[46,47].

In a study, fucoidan-based nanoparticles were developed for the delivery of siRNA targeting Vascular Endothelial Growth Factor (VEGF) to treat ocular neovascularisation. The nanoparticles, composed of fucoidan, chitosan, and PEG, effectively encapsulated the siRNA and facilitated its targeted delivery to the retina. The delivered siRNA successfully silenced VEGF expression, leading to a significant reduction in abnormal blood vessel growth in a mouse model of retinopathy. This study highlights the potential of fucoidan as a safe and effective nanocarrier for siRNA delivery in the treatment of ocular diseases[45].

A study demonstrated the effective delivery of siRNA targeting the oncogene PLK1 using fucoidan-based nanoparticles. The nanoparticles, composed of fucoidan and chitosan, effectively condensed the siRNA and facilitated its cellular uptake in human lung cancer cells. The delivered siRNA successfully silenced PLK1 expression, leading to growth inhibition and apoptosis of the cancer cells. This study highlights the potential of fucoidan as a nanocarrier for siRNA delivery in cancer therapy[48].

A recent study explored the use of carrageenan-based hydrogels for mRNA delivery. The hydrogels, composed of kappa-carrageenan and polyethene glycol, provided sustained release of the encapsulated mRNA encoding for Erythropoietin (EPO) *in vitro* and *in vivo*. The delivered mRNA effectively translated into EPO protein, leading to increased red blood cell production in mice. This study demonstrates the potential of carrageenan-based hydrogels for mRNA delivery in the treatment of anaemia and other diseases. SP show promise in delivering various types of nucleic acids[44].

For DNA delivery in gene therapy, SP can condense plasmid DNA into nanoparticles, improving cellular delivery and protecting the DNA from degradation. However, a key challenge remains: efficiently transporting the DNA to the nucleus, as SP alone do not typically possess nuclear localisation signals. For mRNA delivery, SP offer a safer alternative as nuclear entry is not required. SP can protect mRNA from degradation and facilitate its delivery to the cytoplasm, where it can be directly translated into proteins[49-51].

5.4 Challenges and Future Directions

Despite the promise of SP in gene delivery, several challenges remain. Targeted delivery, while demonstrated by some SP inherent cell-type selectivity, requires further development of targeted SP nanocarriers to enhance delivery specificity and minimise off-target effects. Endosomal escape, a critical step for effective gene delivery, also needs improvement. Strategies to enhance this process are under active investigation. Finally, while generally biocompatible, some SPs can exhibit toxicity at high concentrations, necessitating careful evaluation of SP nanocarrier toxicity.

Hence, SP offer a very good platform for gene delivery due to their ability to interact with and protect nucleic acids. Their biocompatibility and biodegradability make them attractive candidates for developing safe and effective gene therapies. However, realising their full potential requires further research focused on optimising SP nanocarriers for targeted delivery, enhanced endosomal escape, and minimising potential toxicity.

6. Applications in Cancer Therapy and Other Biomedical Fields

SPs are attracting considerable interest due to their diverse applications in cancer therapy and other biomedical fields. One promising area is their potential to target the tumour microenvironment.

6.1 Role in Targeting the Tumour Microenvironment (TME)

The TME plays a critical role in cancer progression and metastasis, and SP can be engineered to interact with specific components of the TME, opening up new avenues for targeted therapeutic strategies[52].

Inhibition of tumour growth and metastasis as certain SP have demonstrated the ability to inhibit tumour growth and metastasis. They achieve this by interfering with key processes within the TME, such as angiogenesis (the formation of new blood vessels that feed tumours) and cell migration (the movement of cancer cells to distant sites). By disrupting these processes, SP can potentially slow down tumour progression and limit the spread of cancer cells[53].

These polysaccharides demonstrate ability in modulating the immune response within the TME. This immunomodulatory activity can be harnessed in several ways, such as activating immune cells to directly attack cancer cells or suppressing immunosuppressive signals that otherwise protect the tumour from immune attack. Furthermore, SP can serve as effective drug delivery vehicles, enabling targeted delivery of drugs or other therapeutic agents specifically to the TME. This targeted approach enhances treatment efficacy by concentrating the therapeutic payload at the tumour site and simultaneously reduces off-target effects, minimising damage to healthy tissues[54].

6.2 Applications in Specific Cancers

Preclinical studies have demonstrated the potential of SP in various cancer therapies. In breast cancer, SP have shown promising results in inhibiting cell growth and metastasis, allowing direct chemotherapeutic drug delivery and targeting of overexpressed receptors[53]. Studies shows that SP have role in treatment of lung cancer. They can be utilised to deliver drugs specifically to lung cancer cells or to target the TME within lung tumours. Furthermore, SP may also play a role in preventing or limiting lung cancer metastasis[55]. In colorectal cancer they had shown that SP can inhibit tumour growth and angiogenesis. Experimental findings support the use of SP in delivering drugs to colorectal tumours and modulating the immune response within the colorectal tumour microenvironment[56].

6.3 Potential in Regenerative Medicine and Wound Healing

Scaffold Materials in SP have valuable applications as scaffold materials in tissue engineering and regenerative medicine[57]. When incorporated into these scaffolds, SP can promote cell adhesion, proliferation, and differentiation, thereby supporting and facilitating tissue regeneration[58]. SP have been shown to accelerate wound healing by promoting the formation of new blood vessels and stimulating the production of growth factors. They can also reduce inflammation at the wound site[59].

6.4 Therapeutic Mechanisms of Sulfated Polysaccharides

The mechanisms by which SP exert their therapeutic effects are diverse and depend on the specific SP structure and application. Targeted drug delivery in SP can be used to deliver drugs specifically to cancer cells or other target tissues, improving treatment efficacy and reducing side effects[60]. Modulation of the immune system in SP can stimulate or suppress the immune system, which can be beneficial in cancer therapy and other diseases[61]. Inhibition of angiogenesis in SP can inhibit the formation of new blood vessels, which can starve tumours of nutrients and oxygen[60]. Promotion of tissue regeneration of SP can stimulate the growth and differentiation of cells involved in tissue repair[62].

7. Challenges and Future Perspectives

SP hold immense potential in nanomedicine, particularly for drug delivery and tissue engineering. However, translating their promising preclinical results into clinical success faces several challenges, primarily related to formulation, scale-up, and reproducibility[63-65].

7.1 Formulation Challenges

7.1.1 Stability

SP-based nanocarriers can exhibit instability due to various factors, including aggregation, degradation,

and premature drug release. This instability can compromise their therapeutic efficacy and safety. For example, changes in pH or temperature during storage or administration can affect the integrity of SP nanoparticles[64,66].

7.1.2 Scale-up

Scaling up the production of SP nanocarriers from laboratory to industrial scale presents significant challenges. Maintaining consistent particle size, morphology, and drug loading throughout the scale-up process is essential for ensuring batch-to-batch reproducibility. Variations in equipment, processing parameters, and even raw materials can introduce inconsistencies in the final product, affecting its quality and performance[67].

7.1.3 Reproducibility

Achieving reproducible formulations of SP nanocarriers is essential for clinical translation. Variations in the source of SP, the sulfation process, and the manufacturing method can affect the properties of the nanocarriers and their performance *in vivo*. This lack of consistency can hinder clinical trials and regulatory approval[68].

7.2 Potential Solutions

Surface modification of SP nanocarriers with polymers, lipids, or other molecules can enhance their stability and prevent aggregation. For example, coating SP nanoparticles with PEG can improve their circulation time in the bloodstream by reducing interactions with plasma proteins[69]. Hybrid Formulations combine SP with other materials, like lipids, polymers, or inorganic nanoparticles, allowing for the creation of hybrid formulations with enhanced properties. For example, incorporating SP into liposomes can improve both drug encapsulation and targeting capabilities. Similarly, creating nanocomposites of SP with inorganic nanoparticles can provide added stability and functionality to the resulting nanocarrier[70].

Controlled Sulfation, a solution which develops more controlled and precise sulfation methods, is key to improving the reproducibility of SP-based nanocarriers. This involves carefully controlling both the degree and pattern of sulfation to achieve the desired properties for specific applications.[30] Standardised characterisation techniques are crucial for ensuring quality control and reproducibility of SP nanocarriers. These techniques should include methods for measuring particle size, zeta potential, drug loading, and *in vitro* drug release[70,71]. Optimised manufacturing processes in successful clinical translation of SP nanocarriers, developing optimised and scalable manufacturing processes is essential. This requires careful control of process parameters and the use of appropriate equipment to ensure consistent and reliable production[72].

7.3 Emerging Trends in Sulfated Polysaccharide-based Nanomedicine

Stimuli-Responsive Nanocarriers in SP can be designed to respond to specific stimuli found at the target site, such as variations in pH, temperature, or enzyme activity. This stimuli-responsive design allows for controlled

Table 1. Classification of sulfated polysaccharides

Sulfated Polysaccharides	Biological Sources	Biological Activity
Carrageenan	Red Seaweeds	Antioxidant, Anti-microbial, Anti-inflammatory, Anti-cancer, anti-coagulant[7,77,78]
Agar	Red Algae	Anti-diabetic, Anti-coagulant, Antioxidant, Anti-tumour, Anti-viral, Laxative properties, Alpha-glucosidase inhibitor[79,80]
Fucoidan	Brown Seaweeds	Blood thinners, Antioxidants, Antiviral, Antineoplastic, Immunoregulatory, Anticomplementary, Anti-inflammatory, Cholesterol-lowering, Mucosal shielding agent[69,81,82,]
Ulvan	Green Seaweeds	Anti-septic, Anti-inflammatory, Anti-cancerous, Anti-viral, Anti-microbial properties[83,84]
Heparin	Animal Tissues	Anti- coagulant, Anti-inflammatory[85]
Chondroitin Sulfate	Cartilage and Tissues	Osteoarthritis and anti-inflammatory[86]

drug release, resulting in improved therapeutic efficacy and reduced side effects[73]. The targeted Delivery helps in targeting ligands, such as antibodies, peptides, or aptamers, which can be attached to SP to enhance their delivery to specific cells or tissues. This targeted approach aims to improve drug accumulation at the desired site, such as a tumour, and simultaneously reduce off-target toxicity by minimising exposure to healthy tissues[74].

Combination Therapy of SP nanocarriers offers the potential for co-delivery of multiple therapeutic agents, including drugs, genes, and imaging agents, to achieve synergistic therapeutic effects. This combined approach can be particularly advantageous in cancer therapy, where drug resistance poses a significant clinical challenge[75]. Theragnostic is an integrating therapy and diagnostics within a single SP nanocarrier that offers the potential for personalised medicine. For instance, SP nanocarriers can be designed to carry both a therapeutic drug and an imaging agent, enabling real-time monitoring of drug delivery and assessment of treatment response[76].

Despite significant progress in SP-based nanomedicine, translating promising preclinical results into clinical applications hinges on addressing challenges related to formulation, scale-up, and reproducibility. Emerging trends, including stimuli-responsive nanocarriers, targeted delivery, combination therapy, and theragnostics, offer exciting avenues for future development. Continued research and development in this field are crucial and likely to yield significant advancements in treating various diseases. SPs hold immense potential in nanomedicine, especially for drug delivery and tissue engineering, but these translational challenges must be overcome to fully realise their therapeutic potential.

8. Conclusion

SP represent structurally tunable natural biomaterials with significant potential in drug and gene delivery. Their functional adaptability enables targeted delivery, controlled release, and tumour microenvironment modulation. Addressing formulation reproducibility and translational challenges will be essential for clinical advancement. This review has highlighted the diverse applications of SP in various biomedical fields, particularly in targeted drug delivery, gene therapy, and cancer treatment. While significant progress has been made in preclinical studies, translating these promising results into clinical success requires addressing the challenges related to formulation, scale-up, and reproducibility. Future research directions should focus on optimising SP nanocarriers for targeted delivery, enhancing endosomal escape, and minimising potential toxicity. Exploring novel modifications, hybrid formulations, and stimuli-responsive designs will further enhance the therapeutic efficacy and safety of SP-based nanomedicine. Continued research in this area holds great promise for developing innovative and effective therapies for a variety of diseases.

9. References

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Author Contribution

R. P. Ramkumar - conceptualised, performed the literature survey and prepared the initial draft of the manuscript. V. Muruganantham - conceptualised, contributed to manuscript revision and final editing. R. Margret Chandira - conceptualised and supervised the study. All authors have read and agreed to the published version of the manuscript.