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Review

Innovative applications of sulfated polysaccharides from macroalgae in hydrogels and biomaterials production

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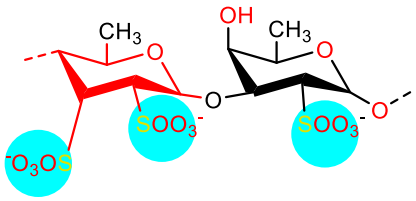
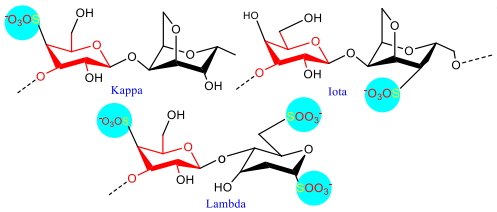
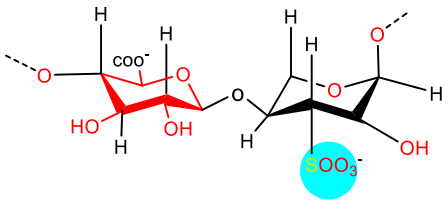
Abstract: Sulfated polysaccharides (SPs) produced by macroalgae, including fucoidan, carrageenan, and ulvan, are emerging as promising materials for biomedical and economic uses. Their distinct physicochemical characteristics make them very attractive. These natural compounds are not only biocompatible but also have incredible bioactivities, such as anticoagulant, anti-inflammatory, and antiviral effects. This versatility makes it feasible for use in tissue engineering, wound healing, and pharmaceutical delivery systems. In addition to their well-known anticoagulant, anti-inflammatory, and antiviral properties, in this review, we emphasized explicitly how the molecular structure and sulfation pattern of SPs control their crosslinking behavior and stimulus responsiveness. We incorporated new developments in 3D bioprinting, electrospinning, and ionic and thermal gelation, demonstrating how these manufacturing processes enable precise control over printability, mechanical properties, and drug release kinetics. The novelty of this work lies in presenting SPs not merely as passive matrices, but as active, tunable components that bridge marine polysaccharide chemistry with advanced biomaterial engineering. Overall, we present an innovative conceptual framework that describes macroalgal SPs as active, tunable, and sustainable components for cutting-edge biomedical technologies, linking materials engineering and marine biotechnology to influence drug delivery and regenerative medicine in the future.

Keywords: sulfated polysaccharides; biomaterials; 3D printing; microneedles

1. Introduction

Sulfated polysaccharides (SPs) are active biomolecules obtained from macroalgae that inhabit the marine environment, and have attracted much attention due to their diversity, abundance, and physicochemical properties [1]. The SPs are composed of mono-, di-, or oligosaccharides linked by glycosidic linkages with fucose, fructose, mannose, and galactose as standard monomer units in the broad spectrum of SPs [2,3]. One key factor that makes SPs more interesting is the negatively charged functional groups in the sugar backbone of these linear or branched polymers due to their high degree of sulfate functionalization and polyanionic structure [4].

Table 1. SPs from macroalgae sources and their physicochemical properties.

Biopolymer	Algae source	Physicochemical properties	Ref
Fucoidan 	-Saccharina -Focus -Dictyosiphon - Sargassum	-The presence of sulfate ester groups imparts a negative charge on the macromolecule skeleton, responsible for the anionic characteristic of fucoidans. - Does not undergo spontaneous gelation due to its branched and highly charged structure.	[5]
Carrageenans 	-Chondrus -Eucheuma -Gracilaria	- An ester sulfate amount of iota-carrageenan (ι-CG) is about 28 to 30%, while kappa-(κ) and lambda-(λ) carrageenan have 33% and 41% of ester sulfate. - Gel formation with K+, Ca2+ and Na+ - Soluble in cold and hot water.	[6]
Ulvan 	-Ulva -Enteromorpha	- High content of ionic groups, high water solubility, and unique rheological properties. Displays weak or no self-gelation due to irregular sulfate distribution and side chains. Gelation can be induced via ionic crosslinking with multivalent cations (e.g., Ca^{2+}, Fe^{3+}).	[7]

SPs' unique combination of structural variability and biological activity has made them interesting candidates for the manufacture of hydrogels, films, inks for 3D printing, and scaffolds with applications in tissue engineering, drug delivery, and wound healing [8,9]. Despite their significant potential, the translation of SP-based systems from laboratory to clinical usage remains limited. This limitation is caused by variables such as heterogeneity in algal sources, limitations in structural characterization, challenges in batch-to-batch reproducibility, and difficulties in controlling mechanical properties and degradation profiles. As a result, fully employing SPs as next-generation biomaterials requires understanding the relationship between molecular structure, crosslinking behavior, and functional performance. Among the most popular SPs are fucoidan from the Phaeophyta family, carrageenan from the Rhodophyta family, and ulvan from the Chlorophyta family (Table 1).

All three have high potential and can be utilized as emulsifiers, stabilizers, or thickeners in various industries, including food, agriculture, and the chemical sector. Moreover, SPs have applications in pharmacological and medical areas, including antitumor, immunomodulatory, vaccine adjuvant, anti-inflammatory, anticoagulant, antiviral, antiprotozoal, antimicrobial, and antilipemic effects. They have been used as biomaterials for therapy in regenerative medicine, drug delivery, and tissue engineering applications [1,10,11]. Other reviews have addressed particular features of marine polysaccharides or their biological properties. Still, few have considered recent breakthroughs in processing technologies and biomaterial production, which characterize the current state of the art. In recent years, the introduction of innovative fabrication processes, including 3D bioprinting, electrospinning, and layer-by-layer assembly, has increased the design possibilities for SP-based systems. These methodologies enable precise control over porosity, microarchitecture, and bioactivity, enabling new potential to customize SPs for biological activities [12]. In this review, we bring together current advances in the design, modification, and production of biomaterials and hydrogels derived from macroalgal sulfated polysaccharides. The emphasis is on novel processing methods, structure-function interactions, and the physicochemical properties that influence their biological performance. In the final section, we examine present challenges and prospects for SP-based materials, aiming to provide an integrated perspective for researchers pursuing sustainable and biofunctional materials from marine resources.

2. Sulfated polysaccharides from macroalgae

Similar to some of the planet earliest life forms, marine algae are complex photosynthetic creatures with distinct taxonomy. They are often classified into two groups: Microalgae, frequently found as phytoplankton in marine ecosystems, and macroalgae, which are more numerous and diverse and reside in the intertidal zone [13]. The practical and potential uses of these polysaccharides as a basis for biological materials have significantly expanded due to enhanced technological capabilities for their isolation and purification [14]. They offer greater healing benefits than conventional natural alternatives due to their chemical and physical characteristics, such as mechanical strength, emulsification, adhesive capabilities, hydrocolloid formation potential, and non-toxicity [15–17].

SPs have emerged as a promising source of biomaterials for biological applications due to their unique physicochemical and biocompatibility properties. According to studies, SPs have advantageous anti-coagulant and anti-inflammatory properties that make them suitable for scaffolds for tissue engineering, drug delivery systems, and medical device coverings, etc. [18,19]. Because SPs can replicate the natural extracellular matrix, they are ideal for promoting cell adhesion and proliferation, which facilitates tissue regeneration and wound healing. Furthermore, the mechanical strength,

degradation kinetics, and presentation of bioactive ligands are among the physicochemical characteristics of SPs that can be altered to meet biomedical needs. The high negative charge density of sulfated polymers enables electrostatic interactions with positively charged proteins, affecting growth factor sequestration, cell adhesion, and expression [3].

Furthermore, polymer sulfation enhances their water solubility and swelling capability, which can be in drug delivery applications. This property increases the possibility of targeted drug delivery to particular tissues or cells, encapsulating and releasing the therapeutic biomolecules in a controlled manner [18,20]. The sulfate group in the polysaccharides is critical to the treatment's effectiveness because it can directly alter interactions with biological receptors and enzymes [14]. Furthermore, the position of these sulfate groups influences the stability and bioavailability of sulfated SPs, influencing their enzymatic breakdown rates and pharmacokinetics. Stronger interactions between sulfate groups and divalent cations improve gel strength and kinetics, which are impacted by specific places in the hydrogel material manufacturing process [3,21]. These characteristics are critical for tissue engineering applications, particularly in hydrogel-based treatments for wound healing, administering drugs, and tissue regeneration. Polysaccharides have hydrophilic functional groups that help in the stabilization of macromolecular assemblies. These groups include charged molecules as well as hydrogen bond donors and acceptors, which enable SPs to be assembled into biomaterials using a variety of mechanisms. These techniques include freezing-thawing cycles of polysaccharide-based mixtures, electrostatic crosslinking with metallic ions or small-molecule counterions, solvent evaporation, ionic gelation, and self-assembly techniques. Additionally, chemical changes and enzymatic crosslinking can be utilized to modify SP characteristics to specific applications [19,20].

2.1. Sulfated polysaccharides from red algae

SPs produced by red algae have caused significant attention due to their characteristics and prospective applications. Chemical methods for extracting SPs from red algae include enzymatic hydrolysis, ion exchange chromatography, and precipitation procedures [22]. These approaches enable the isolation of high-purity SPs, which is critical for biomedical applications. SPs are employed in the biomedical sector to produce anticoagulants, antivirals, and wound healing formulations. Their biocompatibility and distinct biological activity make them valuable components in medical and pharmaceutical products [23,24].

SPs from red algae species are composed of repeated sugar monomers such as galactose, xylose, and fucose, all with repeated sulfate groups in different positions, making these molecules complex polymers, and carrageenan is one of the most well-known polymers that is produced by red algae [25]. Carrageenan is derived from many species of red algae and is frequently used a thickening, gelling, and stabilizing agent in the food industry. Researchers focus on understanding their mechanisms of action, explaining the structure-functionality mechanism, developing new extraction and greener methodologies, and improving their use in various industries, such as pharmaceutical and biomedical, increasing their future applications. As multidisciplinary teams and technological breakthroughs progress, the potential to use the unique features of red algae SPs for a range of applications is projected to increase even further [26,27].

2.2. Sulfated polysaccharides from green algae

Green algae, or Chlorophyta, represent a considerable group of marine algae and are a source of polysaccharides [28]. Green seaweed SPs are highly diverse and complex in structure, with different glycosidic bonds between monomers, including sulfated galactans, ulvans, xylans, and mannans. The two primary SPs present in green algae are ulvans and sulfated galactans. The ulvan backbone is often composed of 1,4-linked monosaccharides (rhamnose, xylose, glucuronic, and iduronic acids) with distinctive repeating disaccharide units. Ulvans are water-soluble polyanionic heteropolysaccharides; their composition frequently includes additional monosaccharides, such as glucose, galactose, arabinose, and mannose [29]. Sulfation mostly takes place at locations C-4 and C-6 in sulfated galactans, which are highly branched sulfated-D-galactose molecules with 1,3 and 1,6 bonds.

Depending on the type of algae, the culture location, and the extraction technique, the structural patterns of the algae can change. Three categories have been identified in several investigations: (i) Sulfated xylorhamnoglycuronans, also known as ulvans, are polysaccharides made up of sulfate (16–19%), D-xylose (8–9%), and L-rhamnose (30–50%). Specific polysaccharides may contain residues of xylose or sulfated xylose (S-Xylose) in place of uronic acids. Here, ulvanobiose 3-sulfate type A (also known as U3S) and ulvanobiose-2,3-disulfate type B (also known as U2'S3S) comprise the disaccharides, respectively. (ii) the orders Cladophorales and Bryopsidales contain sulfated xyloarabinogalactans, also known as arabinoxylogalactans (15 to 20% sulfate), which are made up of D-galactopyranose, L-arabinofuranose, and D-xylopyranose units having a notable anticoagulant property. Finally, (iii) the glucuronoxylorhamnogalactans and the sulfated rhamnogalactogalacturonanes are isolated from some Ulvales and share structural similarities with the pectin acids of terrestrial plants. These qualities also demonstrate their capacity to produce novel therapeutic agents and functionally valuable materials, which could increase their effectiveness in biotechnological and medical applications [30,31].

2.3. Sulfated polysaccharides from brown algae

Unlike other SPs, such as carrageenan in red algae and ulvan in green algae, sulfated fucans are mostly found in the cell walls and gelatinous outer layers of brown algae [32]. Fucoidans are believed to be involved in osmoregulation, reactive oxygen metabolism, developmental biology, and other biological processes in brown algae [3,33]. Fucoidans, mostly made up of fucose and sulfate, are found in species of brown seaweed, including Fucus vesiculosus. However, most fucoidans have complex chemical compositions and contain uronic acids, proteins, acetyl groups, and other monosaccharides, such as mannose, galactose, glucose, and xylose [34,35].

3. Techniques and instruments for SP biomaterial production

A comparison of SPs shows that, depending on the particular biomedical application, each polymer has a unique function. κ-Carrageenan is characterized by its distinct coil-to-helix transitions, consistent thermally induced gelation, and rapid structural recovery following extrusion. Because of these features, it is frequently used in hot extrusion bioprinting. However, for soft-tissue regeneration, where flexibility is crucial, the brittleness and rigidity of their gels limit their performance. In contrast, the ion-responsive swelling behavior and higher elasticity of ulvan produce structures with mechanical characteristics closer

to those of the extracellular matrix. However, its variable composition among Ulva species poses challenges for reproducibility. Fucoidan does not form mechanically strong hydrogels and exhibits unique biofunctional properties, including anti-inflammatory activity, immune modulation, and pro-angiogenic effects. Consequently, rather than serving as a structural matrix, fucoidan is often utilized as a functional additive in hybrid scaffolds, enhancing the bioactivity of composite materials [36].

The rapidly developing field involves complex procedures and advanced instruments to tailor these biomaterials for specific medical applications by exploiting their unique biological and physicochemical properties. It is crucial to understand the chemical synthesis and equipment used for fabrication to thoroughly investigate SP-based materials in the biomedical field. These materials include various processes, ranging from solution-based methodologies like solvent casting to gelation methods driven by temperature fluctuations and crosslinking agents. Additionally, advanced techniques such as 3D printing, layer-by-layer assembly, and electrospinning have emerged as innovative tools for precise, controlled SP structures and nanofiber morphologies (Figure 1) [37–39].

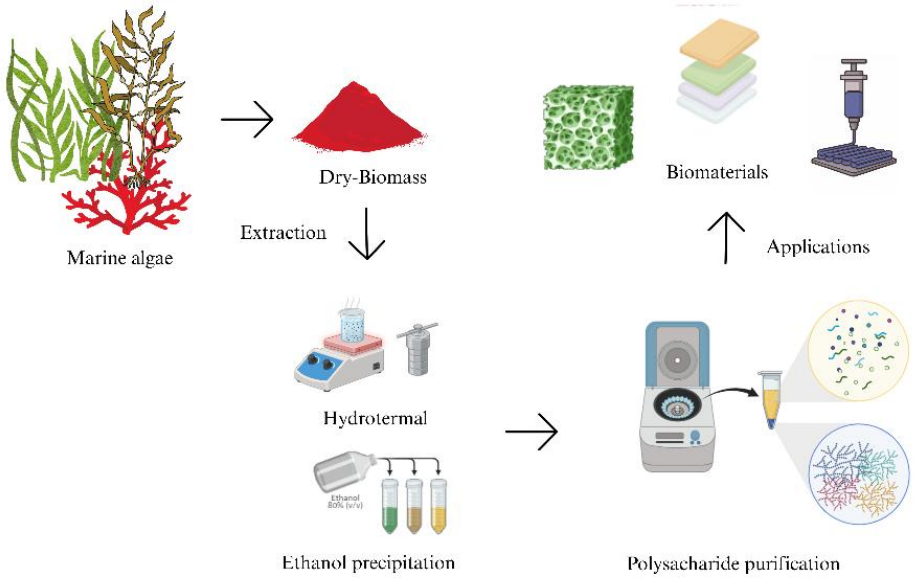


Figure 1. Extraction and applications of SPs from macroalgae.

3.1. Processing of hydrogel-forming algae polysaccharides

A family of materials known as hydrogels is composed of networks of crosslinked hydrophilic polymers that have been filtered using solvents, such as water or an organic solvent/water mixture. They have of applications in the fields of biomedicine, self-healing, sensory perception, energy, and water sustainability. In situ physical and/or chemical crosslinking may be utilized to create these hydrophilic polymer networks [40]. Due to their ability to provide bioactive functionalities and ionic crosslinking, SPs have been an essential part of synthesizing hydrogels. Sulfate groups, included in specific polysaccharides, such as carrageenan, provide bioactive functionality for ionic crosslinking that can interact strongly with divalent cations, like calcium ions, resulting in the formation of a gel-like structure. This property is often exploited in industrial, food, and health applications [41].

New possibilities for designing nanothin hydrogels with a structural hierarchy have been made possible by the recent development of thin multilayer hydrogels (less than 100 nm in dry thickness) based on the layer-by-layer (LbL) self-assembly of polymers [42]. LbL materials offer more control than randomly cross-linked hydrogels due to their hierarchical structure, which is established when a multilayer hydrogel consists of chemically distinct layer chains [3]. Their high-water content, adjustable physicochemical properties, compliant elasticity, in situ crosslinking ability, and simple diffusion of bioactive molecules make hydrogels, which possess 3D crosslinked networks, are attractive candidates for three-dimensional artificial extracellular matrices in tissue engineering, among others [43].

On the other hand, hydrogels can be synthesized through physical cross-linking, which relies on weak interactions such as hydrogen bonding, van der Waals forces, electrostatic interactions, and molecular chain transitions [44]. The coil-to-helix transition is a crucial stage in the polysaccharide gelling process, enabling the aggregation of molecules into a three-dimensional network structure that produces a double helix with specific mechanical properties (Figure 2). Hydrogels can also be developed through other mechanisms, such as thermal gelation, self-assembly of nanostructures, and physical cross-linking by regulating the environmental conditions of the polysaccharide (pH, ionic strength, and temperature). Researchers can engineer hydrogels with unique qualities for particular purposes by accurately controlling the polysaccharide gelation process and nanostructure development [45,46].

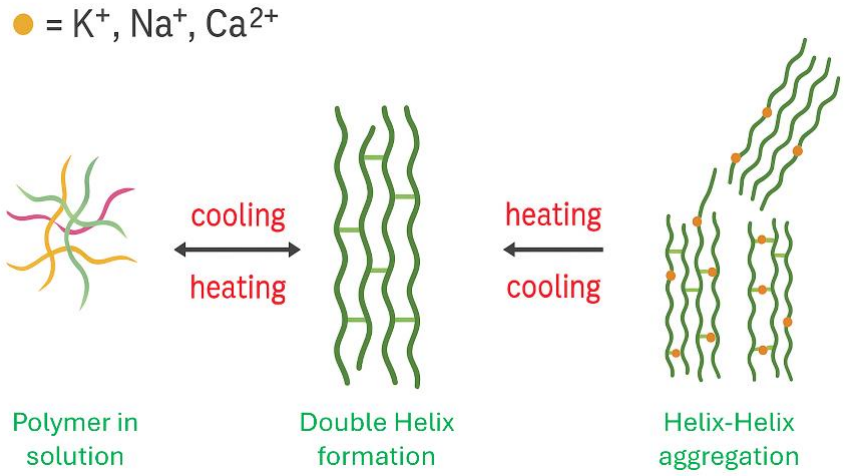


Figure 2. Thermal-induced structural transitions in polysaccharide solutions in the gelling mechanism of carrageenan with different cations.

SPs, such as fucoidan, carrageenan, or ulvan, can be converted into hydrogels in several ways once their physicochemical characteristics have been optimized (Figure 3). Pouring polymer solutions into specifically made molds is one of the easiest techniques. Researchers can then produce hydrogels with specific shapes and strengths by using heat, ionic reactions, or chemical procedures that enable these solutions to gel [47,48]. Extrusion-based 3D printing is quite fascinating as it enables the creation of complex, layer-by-layer structures filled with cells. To enhance the printing process, a biopolymer like κ-carrageenan often requires some modification or blending with other materials such as alginate, gelatin, or nanocellulose. This helps improve its ability to flow and maintain the details of the print. After printing, a gelation process that uses heat ensures that specific ions are present, stabilizing the final structure and holding it together well.

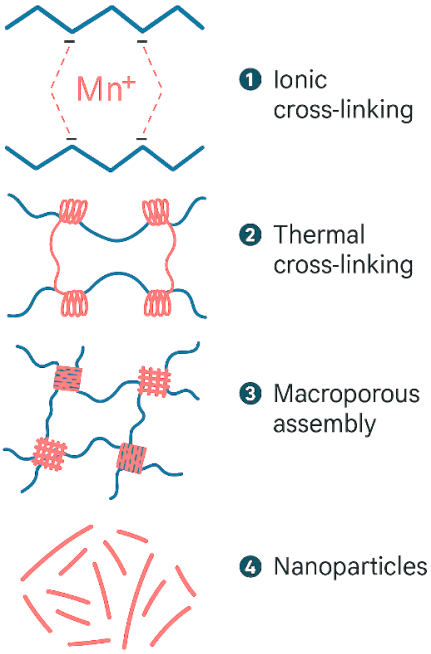


Figure 3. The four principal gelation mechanisms observed in SP-based hydrogels are each governed by distinct molecular interactions.

The first mechanism, ionic complexation, involves an interaction between negatively charged groups (like $–SO_3^-$ or $–COO^-$) found on specific polysaccharides (SP chains) and positively charged cations such as calcium (Ca^{2+}), iron (Fe^{3+}), or potassium (K^+). This electrostatic connection facilitates the rapid gelation of materials and is commonly observed in systems composed of carrageenan, alginate, and ulvan, which can be adjusted to achieve different stiffness levels [49,50]. κ- and ι-carrageenan polysaccharides are of particular interest because they follow the second mechanism of forming secondary structures in response to temperature changes. When the temperature drops, they transition from a coiled form to a helical structure, and as the temperature drops even further, these helices begin to unwind again. As the temperature decreases further, these helices begin to pack together, crosslinked in place by cations in organized networks.

This property is ideal for injectable formulations and bioink formulations for 3D printing because it is reversible by reheating the solution/gel, enabling it to adapt under stressful conditions while maintaining network integrity [51,52]. The third mechanism involves complexation through covalent or crystalline networks, which modify the SPs' chain with molecules or polymers, such as methacrylated fucoidan or ulvan [53]. Additionally, hydrogels used in applications requiring load-bearing capabilities, through processes such as photopolymerization or enzymatic crosslinking, yield a covalent hydrogel with enhanced mechanical strength [54].

One exciting technique for producing hydrogels is the use of colloidal or nanofibrillar assembly. This method leverages the inherent capacity of rod-like nanostructures, such as nanocellulose or SP-based nanoparticles, to self-assemble and form flexible networks without the need for additional crosslinkers [55,56]. SP-based nanoparticles can be produced via ionic complexation or controlled solvent exchange using techniques, such as nanoprecipitation and antisolvent approaches, holding particular promise for applications involving controlled and targeted drug delivery [57,58]. These

techniques are also excellent for creating injectable hydrogels, which maximize self-assembly and enable minimally invasive operations. All things considered, these gelation methods demonstrate the extraordinary adaptability of algal SPs, and they can be a motivation for researchers and designers to create hydrogels tailored to specific applications in biomedical domains, such as tissue engineering, drug delivery, and regenerative medicine.

Different from other carrageenan types, λ-carrageenan is not able to gel when exposed to monovalent or divalent cations, including calcium or sodium [59]. This is because it presents three sulfate groups linked to each disaccharide unit, resulting in stronger electrostatic forces from the higher sulfation degree, which maintains the molecules apart and gives them a coil-like flexible structure. Running, Falshaw, and Janaswamy [60] studied the behavior of trivalent iron (Fe^{3+}) with λ-carrageenan, observing that ions can balance the electrical charges of the SO4 group, helping it reorganize into a helical structure, forming a stable and robust gel. In another study, the resulting ferric gels of λ-carrageenan showed distinct Bragg reflections and polycrystalline diffraction patterns, which hint at a well-organized and compact structure at the molecular level [59].

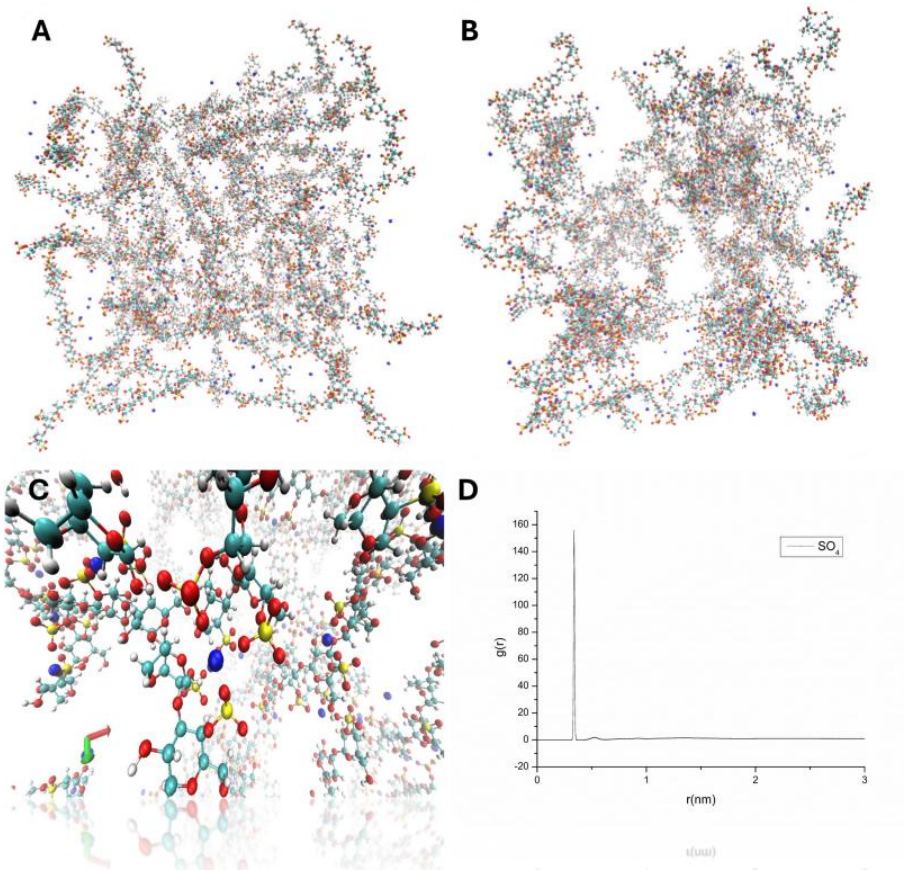


Figure 4. Molecular dynamics simulation of a highly sulfated carrageenan interacting with Fe^{3+} ions in aqueous solution. (A) Initial configuration at 0 ns shows dispersed polymer chains and free Fe^{3+} ions (blue). (B) After 100 ns, the system adopts a compact structure as a result of Fe^{3+} crosslinking. (C) Fe^{3+} coordination (blue) with multiple sulfate groups (red/yellow) across different polymer chains. (D) Radial distribution function (RDF) between Fe^{3+} and sulfate groups at 100 ns indicating strong local interactions at 0.35 nm.

Figure 4 shows the molecular dynamics simulation up to 100 ns of a highly sulfated carrageenan; it can be observed that a condensed network structure is formed between sulfate groups and trivalent iron ions. A very ordered structure can be observed in Figure 4C, conforming to an octahedral geometry, which is the more stable arrangement for these complexes. Figure 4D shows the radial distribution function, which exhibits a notable peak at approximately 0.35 nm, indicating intense interactions between groups. These results highlight the possibility of using Fe^{3+}-induced gelation as a structural approach to create sophisticated hydrogel structures for developing responsive wound dressings that can adjust to inflammatory settings where oxidative stress causes fluctuations in iron levels [61,62].

Fe^{3+} interaction with sulfate groups may be considered for innovative drug delivery systems due to its adaptability to changes in pH or redox conditions, in cases where iron levels are elevated, improving the control of drug absorption kinetics. This may be useful in cases involving drugs that bind to metals, enabling physical capture and chemical interactions [59]. Additionally, this study establishes a basis for the development of innovative materials utilizing rare-earth cations like La^{3+} or other transition metals like Al^{3+} and Cr^{3+}. With different gel formation points and mechanical characteristics, each of these metals has the potential to form distinct network topologies. By going beyond the traditional use of ions like Ca^{2+} or K^{+} in gelation, this method opens possibilities for customized hydrogel systems that are tuned to specific ions.

While Fe^{3+}-induced gelation demonstrates the potential of ion-specific crosslinking, alternative physicochemical approaches have also been explored to enhance the functional properties of κ-carrageenan. A NaOH/urea solvent combination, which creates a stable, hydrated complex between NaOH and κ-carrageenan (κ-CG) chains that facilitates the dissolution of κ-carrageenan, thereby avoiding the disadvantage of the traditional κCG-based hydrogel obtained from hot water, which can break easily under mechanical loading, has been employed. This new method enables κCG chains to dissolve in aqueous solutions, resulting in an extended, rigid chain shape. Conversely, urea facilitates the hydration of the polymer chains, which aids in the solubilization and dispersion of κCG. Furthermore, NaOH affects the conformation of the polymer chains, contributing to the solution's stability [63].

The freeze-thaw procedure using a NaOH/urea solvent combination induces structural modifications in the κCG chains adopted by the polymer chains improving its mechanical qualities. The NaOH/urea solvent system influences the interactions between polymer chains, crosslinking agents, and ionic species, determining the hydrogel's mechanical strength and stretchability.

In some polysaccharides, such as κ-carrageenan, thermal gelation is associated with the transition of polymer chains from a random coil conformation to a helical structure or a different conformation. This transition occurs as the temperature decreases, leading to the formation of double helices between polymer chains, as a result, the solution transforms into a gel network, where these new conformations serve as physical crosslinking that stabilizes the gel structure, in addition to the variable sulfate distribution and content on the same polymer, resulting in different gelation procedures and, in turn, other mechanical properties of the hydrogels that are produced [64]. Due to the formation of more rigid gel networks, particularly within the galactose units influenced by sulfate groups, κ-carrageenan gels tend to be solid and brittle [65].

The structural organization and characteristics of κ-carrageenan-based materials are influenced by the aforementioned transition, which is affected by several factors, including temperature, solvent effects, and mechanical forces. Researchers can customize the mechanical and functional properties of κCG-based materials by manipulating the helix-to-coil transition process. On the other hand, the gel

structure of γ-carrageenan is more flexible due to the presence of sulfate groups for both galactose and 3,6-anhydrogalactose units, which results in the softer gels [66]. In this sense, Makarova, Derkach, and Kadyirov et al. [67] studied the supramolecular architecture of κ-carrageenan, and gelatin explains the molecular interactions that result in thermal gelation. Figure 5 shows how κ-carrageenan chains engage with gelatin molecules through electrostatic and hydrogen bond interactions, resulting in stable polysaccharide-protein complexes. The resulting hybrid hydrogels demonstrate a 2- to 3-fold increase in compressive modulus (rising from roughly 45 kPa for pure gelatin to over 120 kPa in κ-carrageenan-gelatin composites) and better thermal stability, with the gel-sol transition temperature increasing from 37 to 52 °C. Thus, κ-carrageenan-gelatin systems are promising for biomedical and tissue engineering.

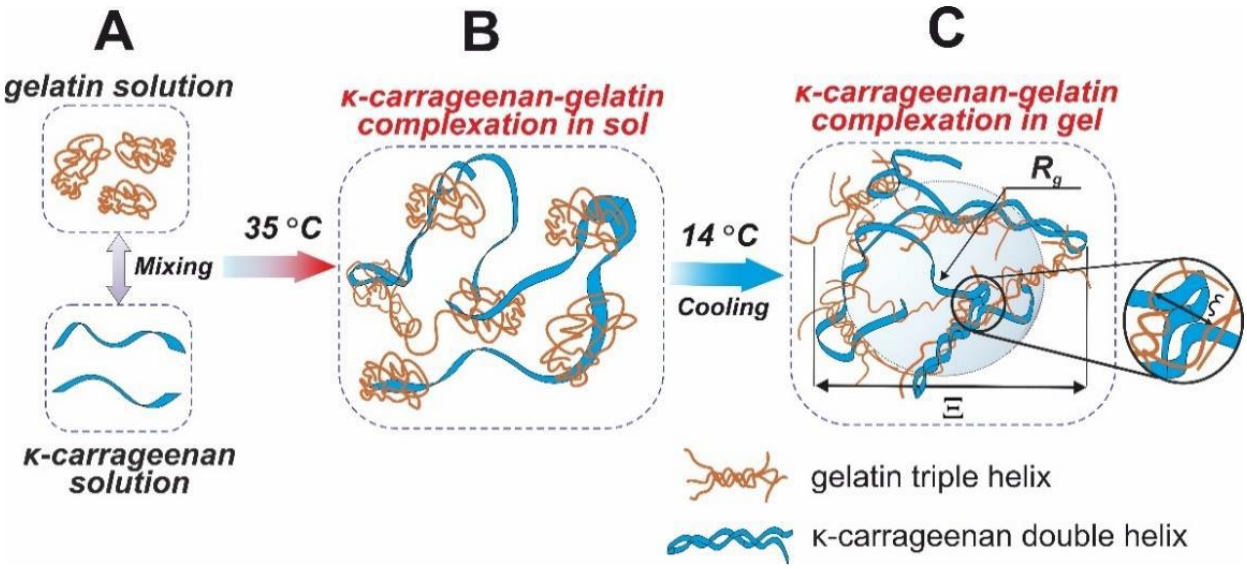


Figure 5. (A) Initial conformations of κ-carrageenan and gelatin molecules; (B) formation of polysaccharide–protein complexes through electrostatic and hydrogen-bond interactions; and (C) three-dimensional supramolecular κ-carrageenan–gelatin hydrogel network. Reproduced with permission from [67].

Fucoidan and ulvan can exhibit more complex and less predictable gelation behaviors compared to carrageenan, which present thermoreversible and ionically crosslinked gels due to their coil-helix transitions. These polysaccharides present irregular sulfation patterns, branched structures, and a heterogeneous monosaccharide composition, which limit their ability to form stable physical gels without modification or blending (Table 2).

Table 2. Gelation behavior, crosslinking ions, and rheological characteristics of SPs from macroalgae.

Polysaccharide	Gelation Behavior	Crosslinking Ions	Rheological Data (G′, G″, viscosity)
κ-Carrageenan	Thermoreversible gel via coil-to-helix transition; enhanced with K^+ or Ca^{2+}.	K^+, Ca^{2+}	G′ > G″; G′ =10^3–10^4 Pa in the presence of phosphate salts; temperature- and ion-sensitive gelation [68].
ι-Carrageenan	Forms thermoreversible soft gels in the presence of Ca^{2+}; less rigid than κ-carrageenan.	Ca^{2+}, Ba^{2+}	G′ = 200–1000 Pa at 1–3 wt%; weak but thermoreversible gels enhanced by Ca^{2+}; mixed gels with κ-carrageenan increase rigidity [69]
λ-Carrageenan	Does not gel with mono-/divalent ions; gels with Fe^{3+}.	Fe^{3+}	G′ > G″ with Fe^{3+}; G′ = 1000 Pa [60].
Fucoidan	Does not self-gel; viscous solutions; gels only when blended or photo-crosslinked.	None alone; blends with Ca^{2+}, chitosan, or uses methacrylation	Viscous: η = 0.2–3 Pa·s; weak or no G′, more liquid-like or viscous behavior rather than a solid-like or elastic behavior [70].
Ulvan	Weak or no gelation alone; forms hydrogels when blended with other polymers.	Ca^{2+}, Fe^{3+}, or aldehyde-based crosslinkers in blends	G′ = 10–100 Pa in blends; highly shear-thinning [54].

Fucoidan tends to create a viscous solution rather than a gelation process under physiological conditions. Unlike other polysaccharides from marine algae, it lacks a regular backbone and repeating structural unit, which prevents it from forming a helical structure. To overcome this problem, fucoidan is frequently found blended with different polymers such as chitosan, gelatin, or synthetic ones. Additionally, it may go into chemical modifications, such as metacrylation, to facilitate photocrosslinking [71]. Moreover, research on the ionic interactions between fucoidan and divalent or trivalent cations has shown that the structures exhibit weaker and more porous characteristics compared to those ofhydrogels made from carrageenan [72].

On the other hand, ulvan presents anionic characteristics, enabling it to interact with multivalent cations such as iron and calcium; however, the gels formed are very weak. To overcome this, ulvan is combined with other polymers like alginate and gelatin, or it may be modified with aldehyde groups. These groups can react with different functional groups on ulvan or other polymers to form more robust cross-links, thereby strengthening the gel network [73,74]. The ionic responsiveness of these polysaccharides is a strength that must be strategically utilized with complementary polymers or tailored crosslinking methods.

3.2. Advancing hydrogel manufacturing with sulfated polysaccharide-based 3D bioprinting

Innovative 3D bioprinting is a revolutionary technology that using biomolecules such as polysaccharides and living cells. It offers benefits like reducing waste, fast prototyping, and creating complex structures. Its benefits include reducing waste, fast prototyping, and creating complex structures without specialized equipment (Figure 6) [75,76]. The general steps involved in bio-printing typically include three major stages: Pre-bio-printing, bio-printing, and post-bio-printing. In the pre-bio-printing stage, the first step involves selecting an appropriate bio-ink, a crucial component consisting of cells and biomaterials that provide structural support. Next, the desired biomaterial structure design is created using computer-aided design (CAD) software. The ink is loaded into the bio-printer syringe, a special device for precisely depositing layers one by one. During the bio-printing stage, the ink is deposited according to the predetermined design, creating a three-dimensional structure with spatial control over cell placement and biomaterial distribution. Finally, in the post-bio-printing stage, the printed construct undergoes maturation and differentiation to promote cell viability, tissue development, and functionality [77,78].

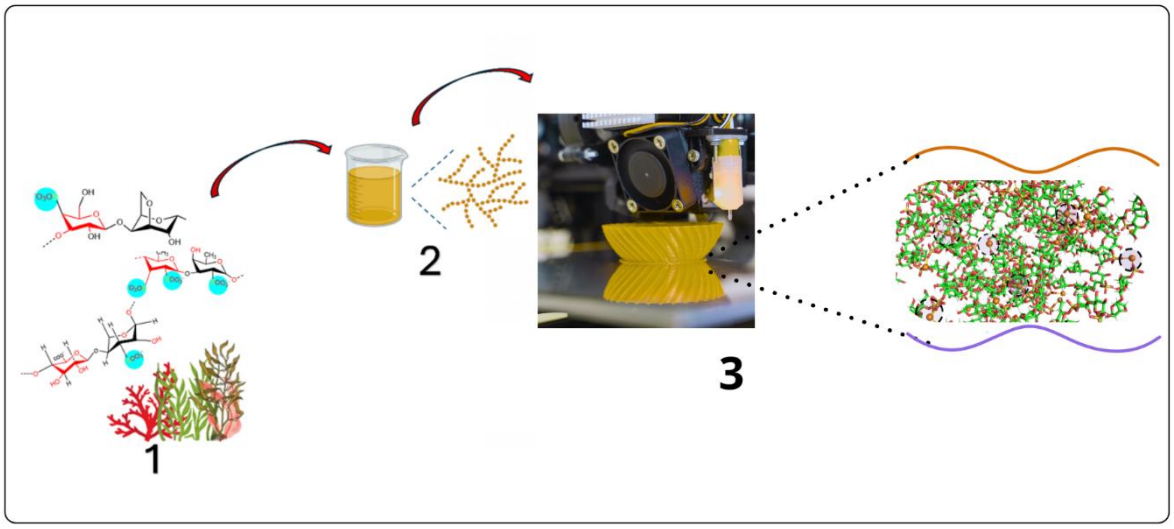


Figure 6. Representation of the production and application of marine-derived SPs as bioinks. (1) SPs such as fucoidan, κ-carrageenan, and ulvan are extracted from red and green macroalgae, with representative sulfate-rich structures. (2) The extracted polymers are processed into printable bioinks through solubilization and optional chemical or physical modifications. (3) Fabrication of 3D-printed constructs using extrusion-based bioprinting, resulting in tunable hydrogel networks with controlled structural and functional properties for biomedical applications. The black circles denote Fe(III) ions, which act as crosslinking points by coordinating with oxygen groups of the polysaccharide chains, thereby connecting multiple polymers and forming the hydrogel network.

Finding the ideal balance between biological and mechanical aspects when choosing biomaterials for 3D bioprinting is one of the major challenges in this field. The resulting 3D-printed structures may not effectively promote tissue regeneration, cell differentiation, and proliferation unless the right balance is achieved. As a result, scientists continually search for biomaterials that offer the ideal blend

of suitable physical properties, customizable dimensions, and biodegradability. These materials include synthetic polymers such as polycaprolactone, poly(lactic-co-glycolic acid), and polyethylene glycol, as well as natural polymers like collagen, alginate, and gelatin.

Marine-derived biomaterials for 3D bioprinting are naturally derived 'bioinks' that exhibit the necessary properties and advantages for biomedical applications. Furthermore, compared to synthetic hydrogels, marine-derived natural hydrogels offer several benefits, including a low immune response and excellent biocompatibility, making them suitable for various applications, such as tissue engineering, drug delivery systems, and wound healing. Marine-derived compounds have potential applications due to their suitable chemical structures and functionalities. Among marine-origin macromolecules, alginate, carrageenan, chitosan, hyaluronic acid, collagen, and gelatin have emerged as widely used biomaterials for 3D bioprinting of regenerative medicine in recent years [79]. Through various manufacturing and prototype approaches, 3D bioprinting has demonstrated broad applicability in tissue engineering and regenerative medicine by using biomaterials extracted from the marine environment to create tissues with intricate three-dimensional geometries (Table 3). Smooth printing and successful tissue reproduction depend on mechanical robustness, elasticity, and appropriate rheological properties. Sterile 3D printing is also essential for biological and medical applications to guarantee safe integration [80,81].

Table 3. 3D printing processes and applications of sulfated polysaccharide-based biomaterials.

Biomaterial	3D printing process	Crosslink mechanism	Advantage	Ref.
Pectin–fucoidan scaffold	Extrusion-based 3D printing	Dual crosslinking with citric acid and Ca^{2+} ions	Porous scaffold (pore size around 1.1 mm) with high swelling (278%) and controlled degradation (39% after 7 days); sustained sildenafil release (94.7% in 11 days) enhanced angiogenesis and wound closure (95% after 14 days).	[82]
Degraded and methacrylated fucoidan (dFuGMA) bioink	Digital Light Processing (DLP) printing	Photopolymerization via methacrylate groups	Viscosity reduced by 99.9%, enabling precise printing. The printed hydrogel showed a compressive modulus of 311 kPa and strong antioxidant and antibacterial properties.	[83]
Sodium alginate, agarose, ι-carrageenan	Multichannel extrusion printing	Ionically mediated using calcium chloride ($CaCl_2$)	The addition of carrageenan enhanced the printability of the magnetic resonance imaging-active inks and was crucial for generating open macroporous structures	[84]

Continued on next page

Biomaterial	3D printing process	Crosslink mechanism	Advantage	Ref.
κ-carrageenan	Hot extrusion	Temperature-induced gelification	The self-sustaining capability and rheological response are comparable to a reference conventionally prepared gel. Gel strength increases linearly as printing speed decreases, while layer height increases linearly as both printing speed and layer height decrease.	[85]
Sodium alginate and κ-carrageenan	Hot extrusion	Calcium sulfate	Excellent structural strength and printability of the carrageenan. The composite has no significant adverse effects on stem cell viability.	[86]
Ulvan	3D bioextrusion printer	Calcium chloride ($CaCl_2$)	The ulvan fibers exhibit significant improvements in mechanical properties compared to wet-spun alginate fibers, including a 211% increase in elongation at break and a 350% increase in Young's modulus.	[87]
Methacrylamide-modified gelatin (GelMA) and methacrylated κ-carrageenan	Extrusion	Chemical crosslinking by UV-A irradiation.	The hydrogel blends exhibited mechanical properties comparable to native breast tissue, providing structural support and stability for tissue regeneration.	[88]

Although there have been significant developments in the use of carrageenan in hydrogels, scaffolds, and medical device 3D printing, it is essential to highlight that other SPs have not been employed in these applications. Carrageenan has emerged as a viable alternative due to its unique rheological properties, biocompatibility, and ease of manipulation. However, other SPs, such as fucoidan and ulvan, present considerable untapped potential that could revolutionize the field. Exploring these alternative SPs may pave the way for creating scaffolds and medical devices with enhanced biomechanical properties and targeted bioactivity. The finding could lead to more complex clinical applications and substantial advancements in the field of biomedical 3D printing, perhaps enhancing patient outcomes and expanding treatment options.

Developments have focused on utilizing chemical modification to enhance the mechanical performance and printability of bioinks based on sulfated polysaccharides. A degraded and methacrylated fucoidan (dFuGMA) bioink was developed; it reduced viscosity by 99.9%, making it suitable for digital light processing (DLP) 3D printing. The printed scaffolds demonstrated superior cell viability and cartilage regeneration capacity, as well as a compressive modulus of 311 kPa,

significant antioxidant (94.7% ROS inhibition), and antibacterial (>95%) activity [83]. These findings demonstrate the promise of derivatives of fucoidan as adaptable and useful materials for tissue engineering and high-resolution bioprinting applications.

3.3. Exploring electrospinning technique with sulfated polysaccharides from macroalgae

Electrospinning is an efficient and cost-effective technology for producing nanofibers with diameters ranging from 5 to 100 nm, which are significantly smaller than those generated using older methods. A uniaxial electrospinning system includes a syringe, a polymer solution, a flow rate controller, a voltage unit, and a grounded collector. Co-axial electrospinning uses two concentric capillaries to feed two solutions independently. When an electric field is applied, the polymer solution assumes a conical shape known as the "Taylor cone", leading to the development of a pattern. When the electric field directs thread development toward the collector, nanofibers form due to solvent evaporation. These approaches created biomaterials with higher mechanical strength, controlled drug release, and antibacterial properties. Furthermore, the addition of SPs to advanced dressings has shown promise in terms of wound healing, reducing inflammation, and preventing infection [89]. Researchers are also exploring their use in biomaterial applications, exploiting their unique properties for enhanced biocompatibility and bioactivity. They are enhancing their anti-inflammatory and antimicrobial properties to improve their appeal for wound dressings and hydrogels, thereby effectively reducing infection and inflammation [90,91].

The resulting material can be collected to form non-woven mats, which can be further processed into various forms such as hydrogels, scaffolds, and patches. One of the key advantages of electrospinning is the ability to control the morphology and diameter of the fibers by adjusting parameters, such as the solution viscosity, applied voltage, and collector configuration. This technique produces biomaterials with specific mechanical and biological properties, making them suitable for tissue engineering and drug delivery applications (Figure 7).

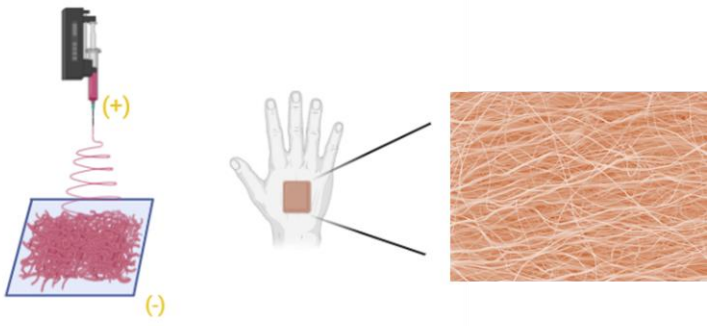


Figure 7. Electrospinning process for producing a fibrous wound dressing and its application on the skin. On the right, an enlarged image shows the intertwined structure of the fibers.

These polysaccharides are ideal for this application due to the presence of SO_3 groups along the polymer chain, which introduce electrostatic interactions and hydrogen bonding. This contributes to elasticity and toughness, improving specific interactions with surface receptors like integrins, leading

to enhanced functionality. These factors contribute to elasticity and toughness, improving specific interactions with surface receptors like integrins, leading to enhanced functionality. These groups introduce electrostatic interactions and hydrogen bonding, contributing to elasticity and toughness. They also improve specific interactions with surface receptors like integrins, leading to enhanced adhesion under hydration conditions [92]. Additionally, sulfate groups can stimulate cell proliferation by interacting with growth factors and cytokines, promoting their binding to cell surface receptors and initiating intracellular signaling pathways. Furthermore, polysaccharides can influence cell differentiation through regulating the expression of specific genes and signaling pathways involved in the differentiation process, hence enhancing wound dressings [3,93]. The combination of electrospinning and SPs is promising for developing advanced biomaterials with tailored properties for biomedical applications, including tissue engineering, regenerative medicine, drug delivery, and wound healing. Table 4 lists some of the most recent articles that utilize the electrospinning technique in combination with SPs from macroalgae sources.

Table 4. Applications and characteristics of SP-based biomaterials produced via electrospinning.

Sulfated Polysaccharide	Application	Biomaterial characteristics	Ref.
Ulvan	Thermally crosslinked to produce a water-stable biomaterial	Due to its biocompatibility and nanofibrous structure, the nanofibrous mat can be utilized in biomedical applications, including tissue engineering, wound healing, drug delivery systems, and scaffolds for cell growth.	[94]
Ulvan	Tissue regeneration	Patches composed of ulvan and marine gelatin in an appropriate ratio promoted faster wound contraction during the early stages of the burn wound healing process.	[73]
Ulvan	Wound dressing applications	Uniform nanofibrous structures with 200 to 700 nm diameters closely resemble the native extracellular matrix.	[95]
Carrageenan	Tissue regeneration	All membranes showed adequate stability for up to 28 days of incubation at 37°C in a simulated saliva solution, exhibiting a sustained release of Ca^{2+} for at least three weeks, which promotes the growth of osteoblasts and bone regeneration.	[96]
k-carrageenan and fucoidan	Bone tissue engineering	The incorporation of the anionic polysaccharides carrageenan or fucoidan in electrospun blend fibers led to a significantly improved cell viability.	[97]
Fucoidan	skin wound healing and tissue regeneration	produced homogeneous ribbon-shaped nanofibers (234–276 nm) with enhanced amorphous structure, hydrophilicity, and viscosity. The electrospun nets demonstrated possibilities for tissue regeneration and wound healing since they were non-cytotoxic and biocompatible.	[98]

Figure 8 demonstrates the incorporation of κ-carrageenan into a poly(L-glutamic acid)/PCL nanofibrous membrane for periodontal regeneration. In comparison to pure PCL (2.3 ± 0.2 MPa), the electrospun fibers showed consistent diameters of 180–240 nm and increased tensile strength (3.5 ± 0.3 MPa). The addition of κ-carrageenan strengthens the mechanical and biological performance of electrospun membranes for tissue engineering, as evidenced by the hybrid scaffolds increased fibroblast adhesion and surface roughness (Ra = 3.8 μm). The multi-layered arrangement offered mechanical strength and flexibility appropriate for clinical usage, while the enhanced surface roughness and hydrophilicity promoted cell contact. Overall, the study revealed that bioactive and mechanically reinforced membranes for periodontal tissue regeneration may be successfully created using electrospun fibers based on κ-carrageenan [96].

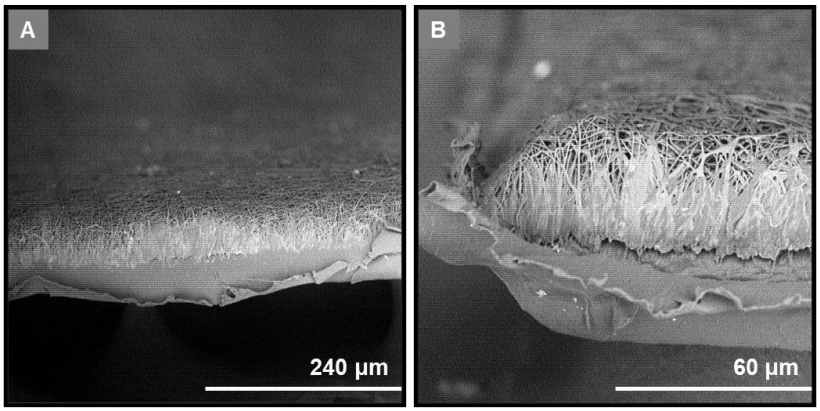


Figure 8. Scanning electron microscopy (SEM) images of the electrospun fibers deposited on the surface of the cast PCL outer layer of the bi-layer GTR3 membrane. (A) Side view at 500× magnification; (B) edge view at 2000× magnification. Reproduced with permission from [96].

Similarly, other sulfated polysaccharides such as ulvan have also been successfully applied in electrospinning to develop bioactive wound dressings. Terezaki et al. [73] used high-voltage electric fields to produce ulvan nanofibrous wound dressings that can incorporate various active ingredients for biopatch production. The skin of SKH-1 male hairless mice was treated with wound dressings made of electrospun nanofibrous matrices based on ulvan. The study's findings demonstrate that patches made of a proper blend of ulvan and gelatin accelerate wound contraction in the early phases of the healing process for burn wounds, thereby reducing inflammation and promoting uniform wound closure. As such, these patches can potentially be effective treatments for burn wounds [73].

The concentration of these bioactive compounds increases with the increased ulvan content in the composite material, potentially enhancing therapeutic benefits for wound healing. Furthermore, a higher ulvan content may improve the composite material's ability to gel, enhancing its adhesion to the wound site, retention of bioactive compounds, and overall wound coverage. Ulvan can interact with cell surface receptors and initiate signaling pathways involved in cell proliferation and migration, promoting cell proliferation and migration during wound healing through its ability to modulate cell signaling pathways, interact with the extracellular matrix, regulate growth factors, such as epidermal growth factor and fibroblast growth factor, exhibit anti-inflammatory effects, stimulate angiogenesis, and enhance cell adhesion and migration [74,99].

4. Novel biomedical applications with sulfated polysaccharides

Additionally, to enhance the processability and biological activity of electrospun scaffolds, researchers have focused on incorporating sulfated polysaccharides, such as fucoidan. Specifically, the fiber characteristics and electrospinning performance were significantly improved by the addition of fucoidan to zein-based matrices, according to [98], adding 5 to 10% fucoidan improved chain entanglement and fiber formation by increasing solution viscosity from 0.18 to 0.41 Pa.s. In comparison to pure zein fibers (74°), the resultant ribbon-shaped nanofibers (234–276 nm) demonstrated greater hydrophilicity (contact angle 56°) and negative effects on fibroblast cells after 48 hours highlighting the need for incorporating PS like fucoidan is a desirable component for wound healing and tissue regeneration applications.

4.1. Sulfated polysaccharide-based bioinks for 3D bioprinting

Cells, signaling molecules, and biocompatible biomaterials are bioinks in 3D printing technology to create tissue structures. Bioinks are fluid-like materials packed with cells that can have one or more matrix components. These materials are fed into 3D printers to create constructions that resemble real tissue. The enormous potential and positive effects of 3D printing have led to its widespread endorsement in various research fields, including regenerative medicine, prosthetics, and constructive therapy [100,101]. Due to their structural similarity to glycosaminoglycans (GAGs), innate bioactivity, and capacity for chemical or physical modification to achieve printability, SPs derived from marine macroalgae have attracted interest in the field of 3D bioprinting. They are excellent options for creating soft and hard, complex tissue scaffolds due to their adjustable rheological and mechanical properties.

Shear-thinning behavior is a crucial property for SPs' printability, particularly in their use as bioinks in 3D printing for biomedical applications. It reduces viscosity under stress conditions, facilitating smooth bioink deposition and thereby enhancing the extrusion process through syringe nozzles [102]. Chemical or physical crosslinking after the printing process can stabilize structures, improving their mechanical properties. Optimizing 3D printer conditions, such as pressure, nozzle diameter, and print speed, can enhance extrudability and biomaterial resolution, leading to more accurate deposition [103]. To better understand the mechanical performance of bioinks derived from SPs, we compiled and compared representative compressive modulus values from studies. The stiffness properties of SP-based hydrogels, including those containing ulvan, fucoidan, and κ-carrageenan, are shown in Figure 9. These hydrogels can be employed individually or in combination with natural or synthetic polymers, such as GelMA, alginate, or PVA. To put things in perspective, we also evaluated the mechanical properties of these materials using a non-sulfated bioink formulation, which consists of hyaluronic acid and chitosan. The variety of compressive modulus demonstrates the adaptability of SP-based systems, from formulations intended for load-bearing applications to softer scaffolds that resemble skin tissue. This thorough examination serves as a guide for selecting SP-based bioinks designed to meet the requirements of various tissue engineering applications.

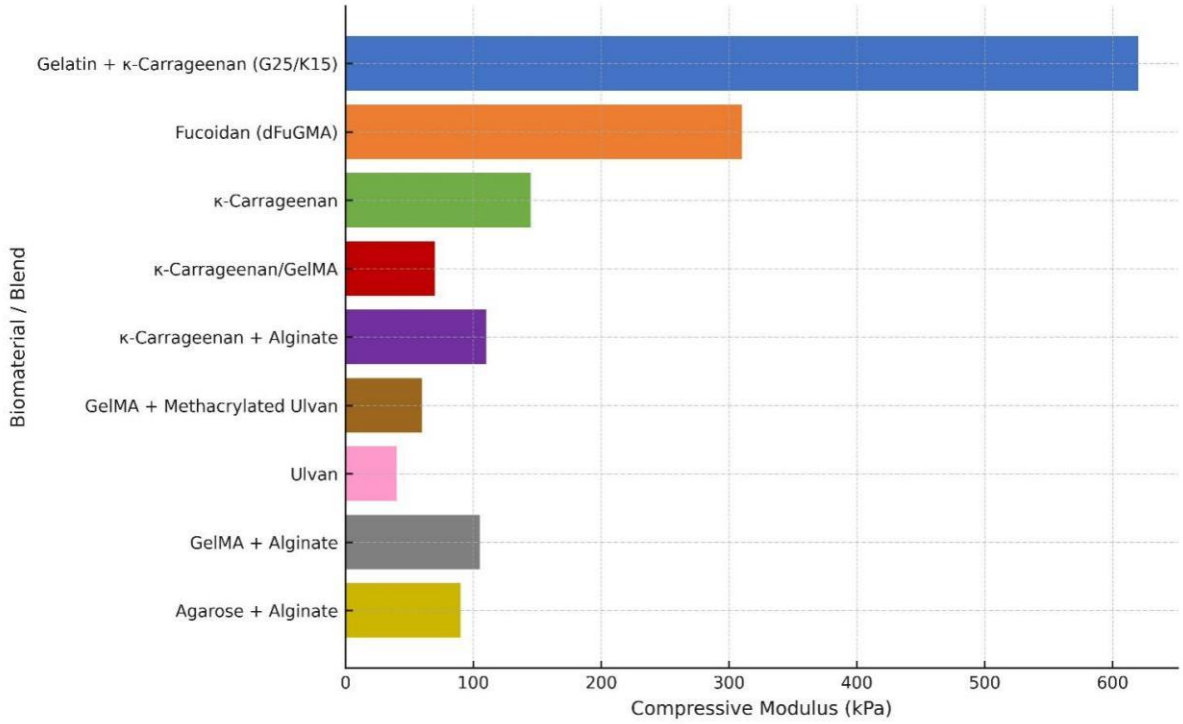


Figure 9. Compressive modulus of SP-based bioinks reported in recent studies. The Gelatin + κ-Carrageenan (G25/K15) [104], the fucoidan-based methacrylated hydrogel (dFuGMA) [83]. Ulvan combined with GelMA (UlMA) [54]. Pure κ-carrageenan formulations [85], while its combination with GelMA was reported by Tytgat et al. [88]. The alginate + GelMA blend was studied by AldanaValenteDilley et al. [105], and the agarose + alginate formulation by [106]. A hybrid of GelMA and methacrylated ulvan was presented by [54]. The κ-carrageenan + alginate system from [107].

The compressive modulus is a fundamental parameter when evaluating the performance of bioinks in 3D bioprinting applications [108,109]. A hydrogel's capacity to tolerate deformation under pressure and maintain structural integrity during and after the printing process depends on its compressive modulus. Shape fidelity, multi-layer printing, and scaffold stability as tissue matures are all ensured by a well-designed bioink with a suitable compressive modulus. Different stiffness levels are needed for different tissues, such as skin (5–50 kPa) and cartilage (300–800 kPa). Furthermore, through mechanotransduction, substrate stiffness affects adhesion, proliferation, and differentiation, hence influencing cellular activity. The creation of functional, tissue-specific bioinks thus depends on maximizing the compressive modulus of bioinks, which is essential for mechanical performance and directing biological responses.

The information shown in Figure 9 demonstrates the mechanical adaptability of bioinks based on SPs, indicating their potential for use in biomedical applications. The remarkable compressive modulus of around 620 kPa is attained by the dual-network hydrogel of gelatin and κ-carrageenan (G25/K15), which is substantially greater than the usual 20 to 60 kPa found in conventional GelMA-based bioinks. Systems based on fucoidan also function better than conventional collagen-only bioinks, which typically have moduli lower than 50 kPa. With moduli between 65 and 80 kPa, ulvan-based hydrogels fall within the soft tissue range but also function effectively by mimicking

glycosaminoglycan activity. These comparisons demonstrate that SP-based bioinks are suitable for use in load-bearing tissues, such as skin, cartilage, and vascular structures, as they offer greater mechanical integrity while maintaining biological performance. Due to their capacity to adjust stiffness, SP-based bioinks are likely to remain a versatile and competitive platform in the industry.

Carvalho, Dani, and Sotelo et al. [110] created a bioink made of chitosan from squid pens, fucoidan from brown algae, and collagen from shark skin that was successfully blended to create a sufficient biomaterial ink that enabled the production of reticulated, printable material with a high degree of shape fidelity. The printability of the ink was enhanced by viscosity control and shear-thinning behavior. Fucoidan supported the accurate deposition of material layers, resulting in precise and well-defined structures by ensuring appropriate flow and extrusion characteristics and by improving printability, which impacted the shape fidelity of the printed scaffolds. Managing pore size is crucial for achieving the desired mechanical properties and cellular behavior in the scaffolds, ultimately influencing shape fidelity. Accordingly, fucoidan influence on ink formulation probably impacted the printed scaffolds' microporosity. The relationship between pore size and fucoidan content indicates that fucoidan influenced the porosity of the constructs. Additionally, more than 90% of the immortalized human mesenchymal stem cells seeded directly onto the 3D-printed constructs were viable, as shown by live/dead assays used to assess cell viability.

Advances have demonstrated the potential of κ-carrageenan for the fabrication of printable and mechanically robust hydrogels via ionic and thermal gelation mechanisms. BonoSträssle Zuniga and Amstad [111] developed double network granular hydrogels using κ-carrageenan microgels embedded in a secondary polymeric network (e.g., PAM or PHEMA), achieving printable inks suitable for direct ink writing at room temperature. Reinforcement with Zr^{4+} ions and glucose enhanced both the Young's modulus (up to 0.9 MPa in tension) and strain at break (up to 250%), offering an algae-derived alternative to animal gelatin for applications in tissue engineering and food-grade products. These results highlight the potential of SP-based hydrogels to serve as load-bearing biomaterials with tunable viscoelastic and mechanical performance, expanding their biomedical applicability.

In another study, carrageenan addition resulted in improved shear-thinning behavior, fast recovery, and form integrity, demonstrating its significance as a structural enhancer for protein–polysaccharide hybrid gels used in biomedical applications and customized drug delivery by optimizing the rheological behavior and mechanical stability of a gelatin–carrageenan composite ink (12% gelatin + 0.65% κ-carrageenan) for semi-solid extrusion 3D printing [112]. When compared to other formulations printed between 36 °C and 42 °C, the ink printed at 40 °C (F6) showed the lowest weight variation (±3.5%), excellent layer definition, and smooth top and bottom surfaces (Figure 10). The 3D-printed tablets satisfied the pharmacopeial requirements for immediate-release dosage forms due to their fast and comprehensive drug release, which reached over 85% in 30 minutes.

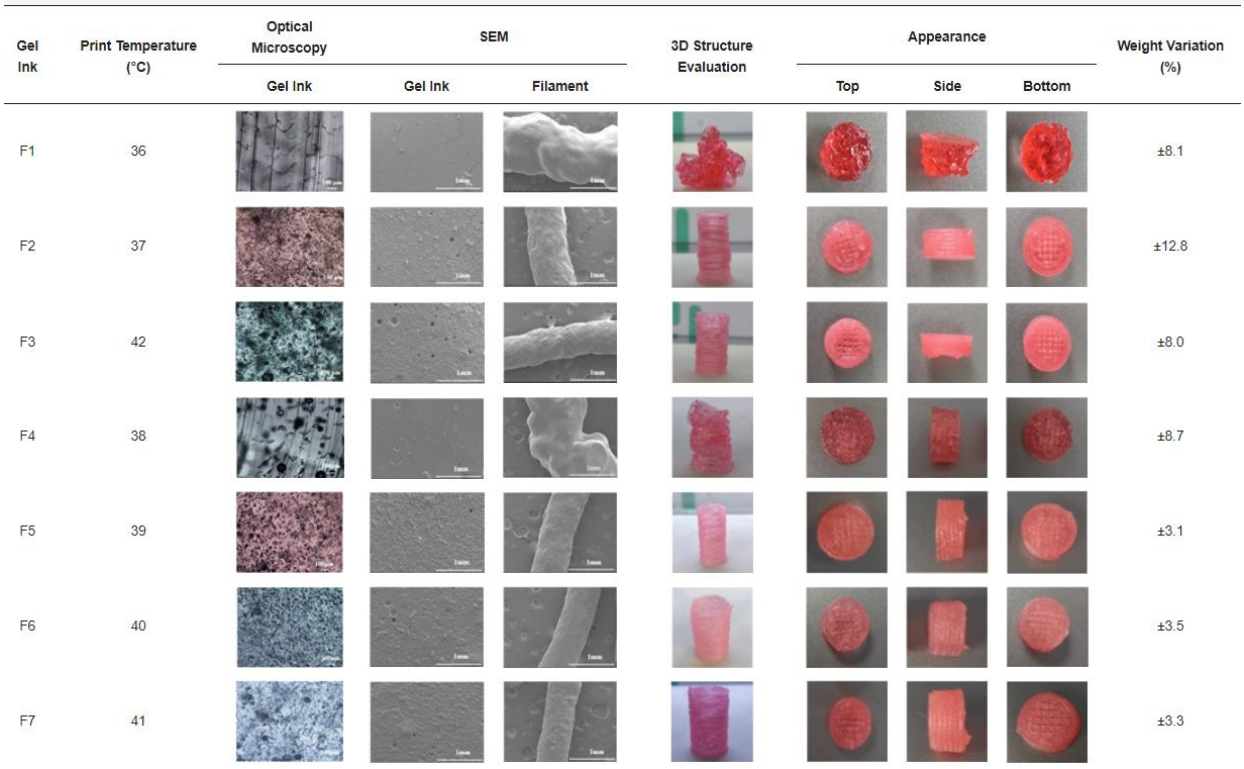


Figure 10. Gelatin–carrageenan gel inks (F1–F7) produced at various extrusion temperatures are compared. Print quality and layer definition are demonstrated by 3D structure evaluations (top, side, and bottom views), while optical microscopy and SEM imaging show morphological variations in the gel ink and fiber surfaces. Reproduced with permission from [112].

In addition to κ-carrageenan systems, fucoidan has been shown to significantly enhance the mechanical strength and structural stability of 3D-printed composite scaffolds. Muslim and colleagues [82] used extrusion-based printing to produce pectin-fucoidan scaffolds with sildenafil-loaded nanomicelles. The resulting uniform porous structures (1.1 mm) had a high swelling capacity (278%) and regulated degradation (39% after 7 days). During extended incubation, the constructs retained excellent mechanical integrity and shape fidelity, demonstrating that fucoidan not only improves biological performance but also reinforces pectin-based scaffolds mechanically and sustains their stability over time for wound-healing applications [82].

4.2. Sulfated polysaccharide-enhanced microneedles for advanced drug delivery

A transdermal drug delivery system (TDDS) provides an attractive and noninvasive administration route for drug delivery when compared to conventional oral administration and hypodermic injection. TDDS utilizes the skin as a portal to deliver biotherapeutics into systemic circulation, thereby avoiding potential metabolization and degradation due to the gastrointestinal tract and/or first-pass liver effect. To overcome these problems, microneedles (MNs) have been designed sufficiently long to bypass the stratum corneum but short enough to prevent skin injury and pain. MNs have emerged as a promising technology for transdermal drug delivery and tissue engineering

applications [113]. However, one of the challenges in microneedle production is finding suitable materials that are both biocompatible and biodegradable and easily accessible. SPs possess desirable characteristics such as biocompatibility, low toxicity, and the ability to enhance drug delivery due to their mucoadhesive properties (Figure 11).

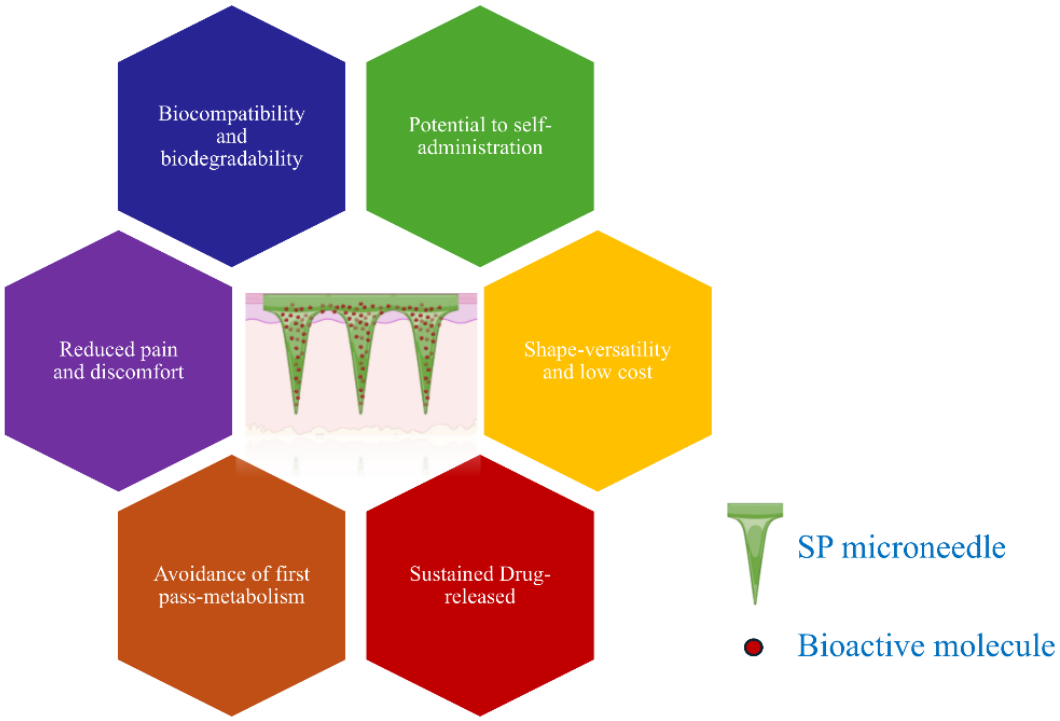


Figure 11. SP microneedles for bioactive molecule delivery: biocompatibility, self-administration, versatility, pain reduction, metabolism avoidance, and sustained release.

The microneedle delivery system delivers the drug topically, which temporarily disrupts the skin's surface layer following the diffusion mechanism. A small patch has hundreds of MNs arranged on it to help deliver a sufficient amount of drug to have a therapeutic effect [4,114].

Drug sustainability release is reached after a polysaccharide water-soluble microneedle is inserted into the skin, regulated by polymer hydrolysis under physiological conditions, different from other devices that require needles to be removed after insertion [115]. The skin's outermost layer is typically between 50 and 100 μm thick, so the length and diameter of these devices are significant, usually having dimensions of 150–1500 μm in length, 50–250 μm in width, and 1–25 μm in tip thickness, with a sharp tip [116,117]. For example, DonChenLee et al. [118] created ulvan-based dissolving microneedle, which is extracted from Ulva lactuca, and polydimethylsiloxane (PDMS) in two steps by inversely replicating a 3MTM microneedle patch that is sold commercially (3M Company). The ulvan microneedle effectively penetrated the porcine skin during the *in vitro* skin insertion procedure, yielding an estimated insertion ratio of 86.3 ± 3.5% showing enough mechanical strength to penetrate the pig skin's stratum corneum and dissolve to deposit the FITC-BSA even after the microneedle patch was peeled off. Since the researchers aimed to create a microneedle patch that would dissolve in the skin's interstitial fluid, it is critical to evaluate how quickly the patch dissolves after insertion.

In addition to ulvan SP, TangdilintinAchmadStephanie et al. [119] developed a fucoidan thermoresponsive gel combined with polymer-based solid microneedles to enhance skin penetration and anti-aging efficacy. The optimized formulation exhibited a gelation temperature of 36.3 ± 0.6 °C, a viscosity increase from 335 mPa·s (4 °C) to 27,200 mPa·s (37 °C), pseudoplastic flow, and suitable pH (5.5). *In vivo* tests confirmed that the fucoidan system restored epidermal thickness and reduced UV-induced skin damage, demonstrating fucoidan effectiveness in transdermal delivery for regenerative applications (Figure 12).

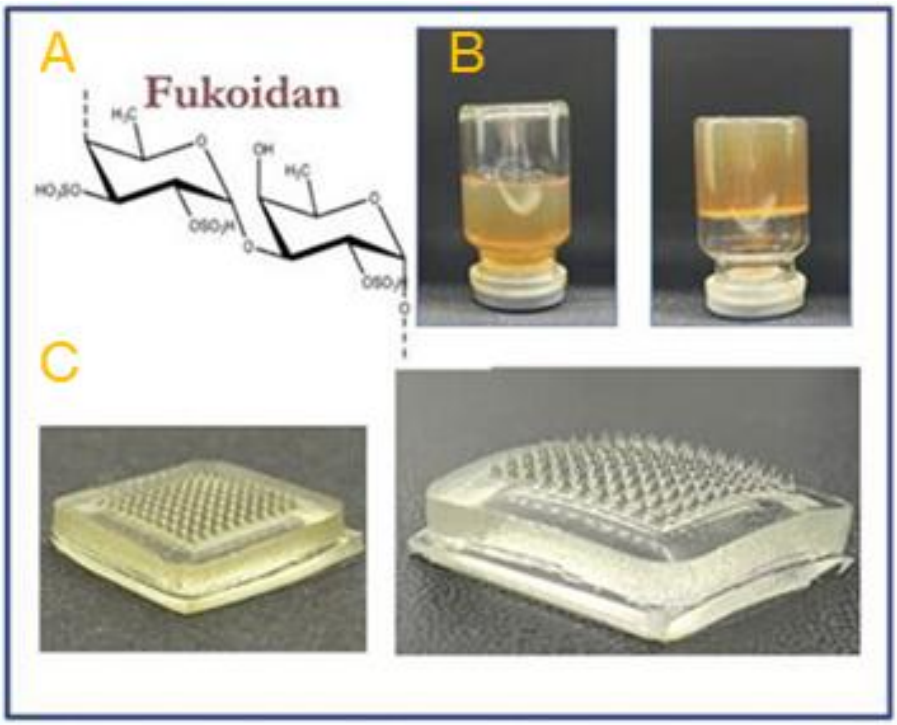


Figure 12. Fucoidan-based thermoresponsive microneedle system. (A) Chemical structure of fucoidan showing its sulfated α-L-fucopyranose backbone. Thermoresponsive behavior of the fucoidan-loaded gel (TRG-FUC) before and after gelation at 37 °C. (C) Polymer-based solid microneedle patch before and after swelling. Reproduced with permission from [119], Copyright 2025 American Chemical Society.

4.3. Sulfated polysaccharides photoprotective effects against UV radiation

SPs from macroalgae have shown promise in biomaterial production and in providing photoprotective effects against UV radiation. Studies have highlighted the potential of these polysaccharides in serving as natural filters for UV radiation in skincare and cosmetic products (Table 5). The unique chemical composition of SPs enables them to absorb and scatter UV radiation, protecting the skin from the harmful effects of sun exposure. Incorporating these polysaccharides into sunscreen formulations enables the development of photoprotective products with enhanced efficacy and natural origin. Their potential as natural, sustainable alternatives to synthetic UV filters further aligns with the increasing consumer demand for eco-friendly and skin-friendly sun protection products.

Table 5. Bioactivity of SPs from various sources and their protective effects against UV radiation.

Source Polysaccharide	Bioactivity	Ref.
Enteromorpha sp. Ulvan	The incorporation of Enteromorpha polysaccharides into TiO_2–polyvinyl butyral nanohybrid films improved their water resistance, photostability, and UV-blocking effectiveness. The films demonstrated their promise as natural antioxidant sunscreen additions by shielding skin from UV-induced oxidative stress, preserving moisture, while remaining biocompatible and easily dissolved.	[120]
Padina boryana Fucoidan	Protect human epidermal keratinocytes (HaCaT cells) by reducing apoptosis and lowering intracellular reactive oxygen species levels following UVB exposure by mitigating oxidative damage, inhibiting collagen degradation, and suppressing inflammatory responses triggered by UVB irradiation.	[121]
Eucheuma denticulatum Eucheuma cottonii iota (ι), kappa (κ)-carrageenans	Carrageenans offer protection against UVB-induced ECM damage in keratinocytes by acting as antioxidants, reducing oxidative stress, inhibiting the activation of key mediators involved in photoaging, and enhancing the activities of antioxidant enzymes.	[122]
S. japonica Fucoidan	It significantly reduced the intracellular reactive oxygen species level, cell death, NO production, and lipid peroxidation in UVB-irradiated zebrafish in a dose-dependent manner in a zebrafish model.	[123]
Undaria pinnatifida Fucoidan	Polysaccharides can stimulate the activation of the AMPK/SIRT-1/PGC-1α pathway to increase mitochondrial biogenesis in HaCaT cells and HFF-1 cells. These findings suggest that UPF has great potential in the application of antiphotoaging.	[124]

Through various processes, natural-source polysaccharides derived from natural resources protect the skin against the effects of photoaging. These polysaccharides promote skin health by decreasing the proportion of old skin cells and enhancing the vitality of fibroblasts in human skin. Furthermore, they aid in lowering the concentrations of malondialdehyde, a persistent photoproduct that causes oxidative damage in photoaging, reducing oxidative stress and skin damage [125]. According to another study, polysaccharides increase the amount of hydroxyproline. This amino acid is present in collagen and is indicative of the metabolism of the extracellular matrix, helping to preserve the

flexibility and structure of the skin [126]. Additionally, polysaccharides function as antioxidants by regulating oxidative stress, thereby increasing the activity of antioxidant enzymes such as catalase and superoxide dismutase, which neutralize reactive oxygen species and reduce oxidative damage to the skin [127,128]. Through these mechanisms, they play a vital role in preventing photoaging, maintaining skin elasticity, and promoting overall skin health by preserving the structural integrity and function of the skin's extracellular matrix, as well as enhancing the skin's natural defense systems.

The trends associated with the relationship between the structure of polysaccharides and their anti-photoaging activity remain unknown and require continuous study to reveal their deeper connection. Further and systematic research is necessary to investigate the structure and functional groups of polysaccharides, which is crucial for them to achieve their maximum effects. Additionally, compared to chemicals and synthetic drugs, natural polysaccharides are considered more efficient, less toxic, and have fewer side effects.

5. Current challenges and future prospects

Extensive research has been conducted on SPs, such as fucoidan, carrageenan, and ulvan, yet several significant challenges continue to hinder their application in biomedical hydrogel systems. One of the major obstacles is the inherent variability of marine polysaccharides.

Factors such as the algal species, environmental conditions, and extraction methods result in considerable differences in molecular weight, degree of sulfation, and monosaccharide composition, which in turn affect essential properties, including gelation behavior, rheological consistency, and bioactivity. To enhance the reliability and consistency of biomedical formulations, it is crucial to develop and implement standardized protocols for extraction, purification, and structural characterization. Techniques such as Size Exclusion Chromatography with Multi-Angle Light Scattering (SEC-MALS), Fourier Transform Infrared Spectroscopy (FTIR), and Nuclear Magnetic Resonance (NMR) should be prioritized. By focusing on these areas, we can enhance reproducibility and ensure greater consistency across different production batches. Additionally, the increasing manufacturing of SP-based materials presents barriers due to high sterilization costs and batch variability. The complexity of their structures makes it difficult to standardize analytical procedures for characterization and quality control, and in the biomedical field, there is a lack of in vivo and clinical data to support the safety and efficacy of these materials; the regulatory procedure for natural polysaccharide-based material approval is uncertain. Addressing these issues is critical to increasing the clinical translation of SP-based hydrogels and biomaterials.

The mechanical properties of SP-based hydrogels, especially those derived from fucoidan and ulvan, are a significant limitation for further applications. To overcome this, it is necessary to combine and blend other polymers to enhance structural integrity. Nevertheless, κ-carrageenan tends to create brittle and less stable hydrogels in the long term, but with a relatively higher storage modulus (G' > 1000 Pa). Features in improving mechanical properties have been shown in studies using crosslinking with trivalent cations such as La^{3+}, incorporation of nanocomposites, and the incorporation of nanocelluose or silver NPs, showing promising results in improving elasticity, toughness, and biofunctionality of the hydrogels. However, a key challenge remains in finding the right balance between biodegradability, mechanical robustness, and controlled drug release, particularly in advanced applications such as 4D printing or injectable systems designed for tissue regeneration and targeted therapies. More sophisticated materials, like bioresorbable MNs, stimuli-

responsive hydrogels, and 4D-printed structures with shape-changing capabilities, are incorporating smart biopolymers. For example, hydrogels reinforced with cellulose nanofibers and composed of ulvan and alginate have shown outstanding swelling ratios of over 250% and elastic moduli of over 1000 Pa.

The development process of SP-based materials is expected to be significantly improved by combining computational design, in silico modeling, and machine learning techniques to investigate SP-ion interactions, network structures, and degradation behaviors. This will open opportunities for more creative solutions in the field, such as cancer treatments, soft tissue scaffolding, wound healing, and smart polymers technology implants. Despite the above disadvantages, many of these problems have been continuously addressed by innovations in extraction technology, structural characterization, and polymer modification. Mechanical strength and biological performance can be enhanced by combining sulfated polysaccharides with other natural or synthetic polymers and using production methods like electrospinning or 3D bioprinting. In order to transform these materials into effective therapeutic products, chemists, biologists, and engineers will need to work together. Overall, the successful transfer of SP-based hydrogels and biomaterials from the lab to actual biomedical applications will depend on continuing developments in the field.

6. Conclusion

Overall, κ-carrageenan, ulvan, and fucoidan each provide distinct structural and biological advantages that determine their specific suitability for different biomedical applications.

Sustainable SPs offer advantages and disadvantages that affect their competitiveness when compared to more well-known biomaterials. Synthetic polymers such as polyethylene glycol (PEG) and polycaprolactone (PCL) provide high mechanical stability and reproducibility but require external functionalization to achieve biological performance. On the other hand, SPs are multifunctional replacements for next-generation biomaterials because they naturally combine biological functionality, anticoagulant, anti-inflammatory, and antiviral activities with renewable marine source and adaptable gelation methods. In this context, SPs provide a unique value proposition: They combine intrinsic bioactivity (anticoagulant, anti-inflammatory, and antiviral) with renewable marine sources and variable gelation methods, positioning them as sustainable and multifunctional alternatives. To fully realize their potential in next-generation biomaterials, however, better standardization and hybrid techniques are required, given their lower mechanical strength compared to PCL or GelMA and the unpredictability of natural extraction procedures.

The processing of SPs has been transformed by advances in ionic crosslinking, electrospinning, and 3D/4D bioprinting. This has made it possible to create bioinks, fibrous scaffolds, and stimuli-responsive hydrogels with adjustable mechanical, rheological, and biological characteristics. These technologies have demonstrated the flexibility of SPs to biomedical situations by expanding their usage in tissue regeneration, wound healing, drug delivery, and microneedle manufacturing. Crucially, combining SPs with other polymers, nanoparticles, or reinforcing agents increases mechanical performance and opens possibilities for smart and hybrid materials that may react to physiological stimuli.

Using SPs' structural adaptability and bioactive properties, scientists have created cutting-edge materials that may effectively tackle intricate medical issues, improve treatment results, and advance overall wellness. There are unexplored industrial areas, such as the cosmetic and agricultural industries,

as well as new applications in the food industry for these SPs, including the incorporation of functional foods and nutraceuticals, or their antioxidant properties. SPs produced from macroalgae have demonstrated extraordinary adaptability in the production of advanced biomaterials. Overall, this review proposes a novel conceptual framework in which sulfated polysaccharides are active, adaptable, and ecologically safe building blocks for developing intelligent biomaterials. Their incorporation into new technologies represents a watershed moment in the development of long-lasting, high-performance biopolymers that have the potential to revolutionize the future of regenerative medicine and biofabrication.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of thisarticle.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization, Elizabeth Carvajal-Millán and David Encinas-Basurto; methodology, Elizabeth Carvajal-Millán and David Encinas-Basurto; software, David Encinas-Basurto; validation, Elizabeth Carvajal-Millán and Jorge Marquez-Escalante; formal analysis, Jorge Marquez-Escalante, Anselmo Miranda-Baeza, and David Encinas-Basurto; investigation, Elizabeth Carvajal-Millán and David Encinas-Basurto; resources, Elizabeth Carvajal-Millán; data curation, Jorge Marquez-Escalante, Anselmo Miranda-Baeza, and Elizabeth Carvajal-Millán; writing—original draft preparation, Elizabeth Carvajal-Millán and David Encinas-Basurto; writing—review and editing, David Encinas-Basurto and Jorge Marquez-Escalante; visualization, Elizabeth Carvajal-Millán and David Encinas-Basurto; supervision, Elizabeth Carvajal-Millán; project administration, Elizabeth Carvajal-Millán; funding acquisition, Elizabeth Carvajal-Millán. All authors have read and agreed to the published version of the manuscript.

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