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Review

Sulfated polysaccharides from marine diatoms: Insight into molecular characteristics and biological activity

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Abstract: Marine algae are a valuable source of sulfated polysaccharides presenting varied structural characteristics and biological activities. Regarding sulfated polysaccharides extracted from marine microalgae, molecular characteristics and bioactivity have yet to be fully explored, especially in diatoms. Sulfated polysaccharides from marine diatoms have great potential to produce numerous health benefits and lead to new biomedical materials. Nevertheless, these potential applications are based on the polysaccharide molecular characteristics, which define their functional properties. Therefore, a detailed understanding of sulfated polysaccharides from marine diatoms may represent the starting point for a broad development of innovative applications, especially in the biomedical area. In this context, the present manuscript aims to review marine diatom sulfated polysaccharides' molecular characteristics and biological activity, looking for a more profound knowledge of these macromolecules and their potential applications.

Keywords: diatoms; sulfated polysaccharides; macromolecular characteristics; bioactive properties

1. Introduction

The increasing search for novel substances for treating diseases such as cancer, microbial infections, and inflammatory processes has motivated the exploration of different sources for finding new natural products with biotechnological/biomedical properties [1]. Thousands of natural compounds are found in the literature being structurally diverse and biologically active, of which most are from a plant origin. However, many bioactive compounds in the marine environment, are still unexplored [2].

The ocean is considered the planet's richest source of natural products, and marine organisms are considered the best potential reservoir of such bioactive compounds. Due to the great diversity of species and the environmental conditions (sometimes extreme), numerous biologically active substances can be extracted from the sea [3]. Multiple marine compounds, such as peptides isolated from fish and polysaccharides recovered from algae, have been reported to present beneficial health properties [2].

Marine algae, especially macroalgae, are considered a valuable source of sulfated polysaccharides. These polysaccharides are mainly thickening, stabilizing, emulsifying, and gelling agents [4]. However, they have also been studied as bioactive compounds presenting antitumoral, anticoagulant, antioxidant, and antiviral properties, among others [5–7], with promising properties that could be related to their chemical components and structure. Moreover, there is a wide range of products and industry sectors to explore in which these macromolecules can enhance current and ongoing health-related needs. Regarding sulfated polysaccharides extracted from different microalgae, molecular characteristics and functional properties have yet to be fully explored, especially in diatoms.

To gain insight into the possible uses of marine algae sulfated polysaccharides, physicochemical and macromolecular characteristics must be considered since it has been reported they determine these molecules' functional properties [8]. A thorough investigation into these characteristics may serve as a starting point in developing innovative applications, bioactive compounds, and biomaterials, among others. In this context, the present manuscript aims to review marine diatom polysaccharides' molecular characteristics and bioactive properties, looking for a more profound knowledge of these macromolecules and their potential applications.

2. Polysaccharides molecular characteristics

Polysaccharides are biopolymers consisting of long chains made up of monosaccharide units. The tremendous structural variability they exhibit is due to the number of simple sugars available, primarily hexoses and pentoses, and the possibilities of glycosidic bonds. Several isomers can occur between the anomeric carbon in the α or β conformation bond and the five hydroxyls of the second monomer. The chain's flexibility also influences glycans' complexity, and given the nature of the sugars involved, the chains can be made up of homopolysaccharides and heteropolysaccharides. Finally, properties such as the molecular weight, the functional groups in the chains, and the presence of other covalently linked molecules, like proteins, contribute to a diverse structure-function relationship in these biopolymers [9].

The macromolecular characteristics of polysaccharides, such as molecular weight (*Mw*) and intrinsic viscosity ([η]), are crucial to understanding the conformation and behavior of polysaccharide chains in solution. Studying the *Mw* of polymers is essential since it represents the total atomic weights of the constituent atoms within a molecule. It signifies the typical length of polymer chains within the bulk [10]. Aside from the *Mw*, there are other characteristics to describe polysaccharides, such as [η], which measures the contribution of a polymer to the viscosity of a solution when its concentration

tends to zero and will depend on the conformation and *Mw* of the polymer in the solution [11]. Also, the polydispersity index (PDI) indicates the size distribution of the chains present in the polymer [12]. The PDI is 1 for monodisperse polymers, while PDI less than 1.2 and greater than 2 are generally considered narrow dispersion and broad dispersion, respectively [13].

The radius of gyration (Rg) and the hydrodynamic radius (Rh) are also essential parameters in polysaccharide characterization. Rg describes the distribution of mass center in the molecule, whereas Rh is defined as the radius of an equivalent hard-sphere diffusing at the same rate as the molecule [14,15]. In the Mark-Houwink-Sakurada equation, which is related to [η], the constants K and α allow for elucidating the conformation of polysaccharides. In this equation, the value of α is associated with the conformation of the polysaccharide chain, and values of 1.26 correspond to very rigid structures, while 0.50 indicates random coil structures. Furthermore, high K values represent an expanded coil conformation, and low K values correspond to a compact coil conformation [16].

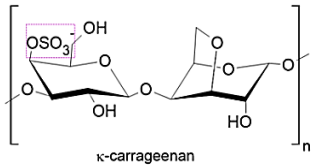
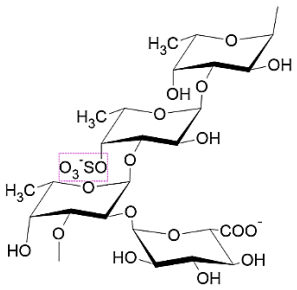
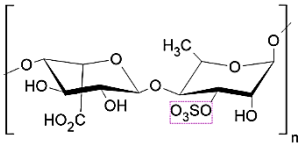
3. Marine algae sulfated polysaccharides

Algae are fundamentally valued for their content of high molecular weight polysaccharides denominated as hydrocolloids, which are associated with the cell wall and intercellular spaces of seaweeds. These macromolecules have numerous roles in algae; they are the main structural components of their cell walls and participate in the recognition mechanisms of pathogens [17]. Algae polysaccharides perform structural functions, provide rigidity, accumulate mucilage in their cell walls, and provide protection against desiccation or stress conditions [18]. Furthermore, because they can retain significant amounts of water, these phycocolloids form gels and chelate metals. These have also been used for various commercial purposes in pharmaceutical sciences, food technology, biotechnology, cosmetics, engineering, etc. [19].

Among the main polysaccharides in macroalgae are carrageenan, fucoidan, ulvan, laminarin, alginate, and agar [20,21]. The type of carbohydrate varies greatly among algae. For instance, soluble fibers like alginates, fucans, and lamellar are found in brown algae, while red algae, such as agars, carrageenans, xylans, and floridian starch, present soluble fibers with sulfated galactans [22]. For green algae, starch, xylans, mannans, and ionic polysaccharides containing sulfate groups have been reported [23]. Aside from non-ionic polysaccharides, sulfated polysaccharides have arisen industrially. The leading polysaccharides in research are from macroalgae sources and are classified as carrageenan, fucoidan, and ulvan (Table 1).

Unlike macroalgae, microalgae-extracted sulfated polysaccharides have not been fully characterized nor classified based on the main produced polysaccharides, such as macroalgae grouped by pigmentation. However, interest in microalgae is increasing due to their bioactive compounds and advantages, such as their ease of cultivation under controlled conditions. Most species are easy to grow, and the harvest does not depend on any climate or season, which enables the production of polysaccharides or any other compound throughout the year. Several microalgae species release polysaccharides and exopolysaccharides, and have been reported as antiviral, antioxidant, anti-inflammatory, immunoregulatory, and biomedical agents [27]. However, detailed information following specific microalgal species culture conditions and extraction techniques is still needed to understand the chain conformation nature, rheologic behavior, and bioactivity correlation.

Table 1. Sulfated polysaccharides from macroalgae.

Sulfated polysaccharide	Scheme	Structure	Reference
Carrageenan Extracted from red algae	 κ-carrageenan	Backbone of repeating galactose units and 3,6-anhydrogalactose, both sulfated and no sulfated linked by alternating α(1→3) and β(1→4) glycosidic linkages.	[24]
Fucoidan Extracted from brown algae		The backbone of α(1→3)-L-fucopyranose residues or of alternating α(1→3) and α(1→4)-linked L-fucopyranosyls, with sulfate substitutes, acetate, and side branches. It can also contain other monosaccharides (glucose, galactose, xylose, and mannose).	[25]
Ulvan Extracted from green algae		Commonly made up of α- and β-(1,4)-linked monosaccharides (rhamnose, xylose, glucuronic acid, and iduronic acid) with characteristic repeating disaccharide units denominated aldobiuronic acids and ulvanobiuronic acids.	[26]

The polysaccharide's structural variability results in extraordinarily diverse compositions and roles of carbohydrates in living beings. In microalgae, carbohydrates perform storage and structural functions, biological activations, adhesion supports, metabolism, and water content regulations [28]. The main monosaccharides reported in algae polysaccharides are glucose, galactose, mannose, rhamnose, arabinose, xylose, ribose, and fucose [29].

Due to their diverse biological features and low toxicity, high-molecular-weight polysaccharides and their degradation's low-molecular-weight products are economically significant. Most polysaccharides are utilized in the food sector as stabilizers, thickeners, and emulsifiers. Moreover, comprehending sulfated polysaccharides' chemical structure and physicochemical characteristics, such as their rheological characteristics and molecular weight, is essential for proposing their uses and future applications since they play a significant role in their biochemical behavior [27].

4. Marine diatoms sulfated polysaccharides

Diatoms (Bacillariophyta) are considered the most diverse group within oceanic phytoplankton, with an estimated 10^5 to 10^7 species. They are a group of great importance given that they contribute approximately 40% of primary productivity in marine ecosystems and 20% of global carbon fixation [30]. Diatoms belong to the Heterokontophyta division and are divided into two taxonomic groups based on cell shape, where central diatoms have radial symmetry, and pennate diatoms have bilateral symmetry.

Central diatoms are predominantly planktonic, while pennate diatoms can be found attached to surfaces or growing and moving through the sediment [31].

In recent years, the potential of diatoms in nanotechnology and as a source of bioactive compounds, especially in the food industry, has been studied in parallel [30]. Depending on the mobility of the microalgae (benthic or planktonic) and the environmental conditions, these organisms produce different amounts of polymeric extracellular substances, mainly carbohydrates. Due to the thousands of species of the diatom group and the variety of shapes and symmetries available, monosaccharides' composition and glycoconjugates are usually particular. These organisms consist of a cell with a protoplast embedded in a frustule (name of the cell wall of diatoms) located between two overlapping valves or thecae, where the upper epitheca is larger than the lower hypotheca.

The frustule is made up of three successive layers:

(1) The innermost organic layer, the diatotepum, is in contact with the plasmalemma.

(2) A silicified mineral layer containing organic matter.

(3) An outer organic layer trapped in the secreted mucilage called "exopolysaccharide" is attached to the cell wall.

Cell wall polysaccharides, intracellular polysaccharides (storage food, generally denominated as chrysolaminarin), and the mucilage (attached exopolysaccharides, colloidal exopolysaccharides, and low molecular weight polysaccharides) produced in various diatoms have been investigated (Figure 1). These studies have revealed that these polysaccharides' content, composition, and characteristics vary with environmental conditions and extraction techniques [30,32].

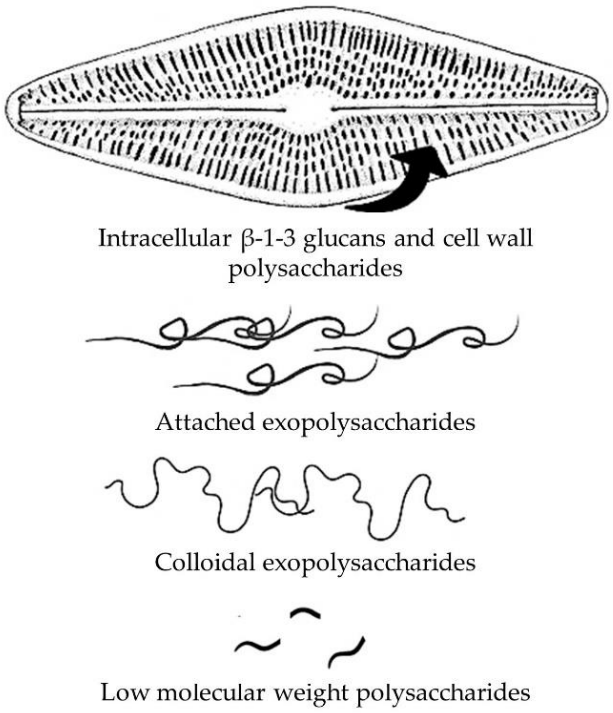


Figure 1. Conceptual model of the different polysaccharides in benthic diatoms [32].

The cell wall of diatoms is mainly composed of hydrated amorphous silica ($SiO_2 \cdot nH_2O$) and macromolecules, including proteins and polysaccharides. During synthesis, silicic acid polymerizes

into silica, forming the frustules of diatoms. A previous study [33] argues that hydrated silica possibly deposits on organic layers because amino acids such as serine and threonine have high percentages of OH groups. It has been proposed that dissolved $Si(OH)_4$ is deposited in protein layers through a dehydration reaction with OH-bearing amino acids. These layers exhibit a high Si–OH/Si–O–Si ratio and a low degree of polymerization Si-O.

According to these authors, the outer layer of polysaccharides consists of various sugars (glucose, mannose, fucose, and xylose), and outward-directed hydroxyl groups of sugars represent the hydrophilic zone. In addition, protein template residues are serine, glycine, threonine, and aspartic acid (Figure 2). More dehydrated and polymerized layers develop during the silica frustules' growth process and form thicker layers. However, the mechanisms responsible for these reactions are still unclear [32]. The polysaccharides reported in diatoms are mainly related to intracellular storage chrysolaminarin, followed by those found in the extracellular matrix called exopolysaccharides. Meanwhile, the polysaccharides associated with the frustule or cell wall are primarily sulfated [34].

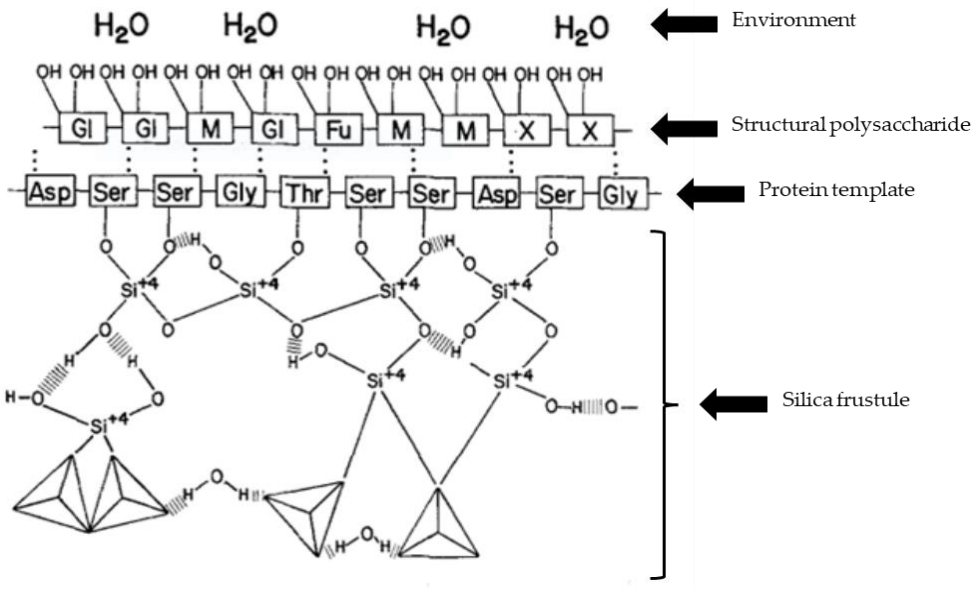


Figure 2. An organic layer arrangement is proposed in the diatom cell wall. Hatched lines show hydrogen bonds. Tetrahedra highlight the three-dimensionality of silicic acid (and the resultant silica) because, at its points, Si is in four-fold coordination with oxygen atoms [33].

Exopolysaccharides are produced in diatoms due to the photosynthetic fixation of inorganic carbon [35]. These polymers perform several functions; among them, they can form mucilage envelopes and covers that form a microenvironment around the cells and protect them from sudden and adverse environmental changes. The presence of carboxyl and sulfate groups in these exopolysaccharides ensures the detoxification caused by heavy metals and the immobilization of toxic substances, in addition to preventing the cells from drying out during low tide [36,37].

The typical sulfate concentration in seawater is approximately 28 mmol/L, serving as a readily available sulfur source for synthesizing various sulfur-containing compounds. Algae absorb sulfate to produce sulfur-rich metabolites like methionine, glutathione, phytoalexins, and others, all ultimately

derived from cysteine [38]. Many microorganisms, including microalgae, can secrete enzymes capable of releasing inorganic sulfur from organic compounds, thus making them accessible [39]. These enzymes, known as sulfatases, are categorized into aryl- and alkyl-sulfatases. Both types produce sulfur compounds but differ in their residual byproducts, yielding phenol and aldehyde. Upon uptake into the cytoplasm, sulfate is transported to plastids or stored in vacuoles when in excess [40].

Glycoconjugates, including glycans and polysaccharides, undergo assembly and modification within the endomembrane system. This process involves several steps, beginning with the formation of activated nucleotide sugars like nucleoside diphosphate (NDP) sugars or nucleoside monophosphate (NMP) sugars in the cytosol. Subsequently, these nucleotide sugars are transported to the endoplasmic reticulum (ER) and Golgi apparatus, where glycosyltransferases (GT) utilize them as donor substrates to extend glycoconjugates by transferring specific sugars from their activated nucleotide forms to specific acceptors [30].

The extracellular mucilage produced by diatoms comprises a high content of carbohydrates, and such a matrix can include other biopolymers. Sulfated polysaccharides are found in the cell walls of these microalgae. Sulfur compounds form the frustule, and the quantity and configuration vary according to environmental conditions. It has been reported that under stress conditions, the content of uronic acid, sulfates, and fucose increases to help the diatom adapt to sudden changes [34].

One of the reasons why benthic diatoms dominate over other algae is the ability to move thanks to the secretion of a mucilaginous substance that binds to the substrate and allows it to slide through it. This movement is characteristic of pennate diatoms with raphe and apical porous fields that would enable an association with the substrate. However, some centric diatoms can also secrete mucilage from valve processes less frequently [41,42]. These benthic diatom polysaccharides are incorporated into the marine food chain as a source of organic matter for planktonic and benthic marine animals [35,37].

5. Diatoms sulfated polysaccharides bioactive properties

Several studies highlight how polysaccharides' bioactive properties may be related to their molecular weight, sulfate group presence, and negative charge. Research on sulfated polysaccharides produced by various diatoms is complex since they are diverse and highly varied in structural characteristics. Unlike macroalgae, diatoms microalgae can be cultivated under controlled conditions (light intensity, wavelength, temperature, salinity, nutrients, pH, etc.), which makes its polysaccharides' chemical composition, structure, and functional behavior more stable regardless of the collection period [27].

Despite the recognized importance of algae and their bioactive products' potential, diatoms' polysaccharide structure, compared to macroalgae, has yet to be explored. Due to the difficulties involved in polysaccharide extraction and purification, and the complexity of their chemical structure, only a few polysaccharide structures have been resolved. To date, there is scarce information on sulfated polysaccharides for diatoms. Some studies on the bioactive properties of sulfated and non-sulfated polysaccharides from diatoms are summarized in Table 2.

5.1. Antioxidant

Oxidative stress induced by excessive production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) has been linked to pathophysiological events in a large number of diseases [6].

Diatom polysaccharides have been considered promising antioxidant sources for their free radical scavenging properties and for preventing oxidative damage [43]. The antioxidant activity of polysaccharides from diatoms has been determined by multiple tests, including ROS scavenging, superoxide anion radical, hydroxyl radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, and reducing power, among others [44]. Nevertheless, more information must be given regarding the molecular weight and the main functional groups that carry out this activity in the different sulfated polysaccharides and their oligosaccharides [45].

The main factors attributed to antioxidant activity are the molecular weight and the number of sulfate groups in polysaccharides. Some sources discuss the role of sulfate groups in attenuating the hydrogen bond's dissociation energy, which amplifies this polysaccharide's hydrogen ion donating capacity [46]. This property can also be attributed to the high molecular weight structure facilitating the capture of free radicals produced by lipid peroxidation and the formation of complexes with metal ions such as Fe^{3+} necessary to produce radicals. It can also be influenced by the degree of polymerization and the reduced sugar content [47]. Sulfated polysaccharides from *Chaetoceros muelleri*, *Navicula* sp., *Navicula inserta*, and *Odontella aurita*, registering molecular weight values of 17–108 kDa, 45, 4.13, and 7.72 kDa, respectively, exhibited antioxidant activity [43,48–50] (Table 2).

Lower molecular weight sulfated polysaccharides generally exhibit greater antioxidant activity. According to a study on degraded fucoidans from *Fucus vesiculosus*, the antioxidant assay, measured by the ferric-reducing antioxidant power (FRAP), increased with decreasing molecular weight [51]. This intensified antioxidant efficacy of lower molecular weight polysaccharides may result from their less compact structure, potentially allowing for more hydroxyl and amine groups to be accessible for neutralizing free radicals [52]. Furthermore, sulfate content plays a crucial role in determining the antioxidant potential of fucoidan. Research on fucoidan from *Laminaria japonica* suggests a positive correlation between sulfate content and the ability to scavenge superoxide radicals. It proposed the ratio of sulfate content to fucose as an effective indicator for evaluating the antioxidant activity of fucoidans [53].

5.2. Anticancer

Beyond the applications as gelling or emulsifying agents that algae polysaccharides are currently given in the food industry, in diatoms, these molecules have biological activity of high added value in biotechnological fields [60]. Multiple beneficial effects of different diatom polysaccharides on human health have been reported. Polysaccharides from diverse sources have emerged as promising molecules with good anticancer activity on various cancer cell lines. They could be considered alternative candidates for existing chemotherapeutic agents. In addition, they possess selective activity against tumor cells and present minimal side effects. Isolates from marine sources, among others, have reported an action mechanism mainly via apoptosis induction, Deoxyribonucleic Acid (DNA) damage, cell cycle arrest, mitochondrial membrane disruption, and nitric oxide production to kill cancer cells and prevent metastasis [5]. A 1→3;1→6-α-D-glucan corresponding to a chrysolaminarin chemical structure was isolated from the diatom *Synedra acus*. This polysaccharide presented a molecular weight of 8.5 kDa, was nontoxic, and inhibited the proliferation of human colon cancer [54]. Anticancer activity was also reported in a polysaccharide extracted from the diatom *Phaeodactylum tricornutum* using HepG2 (human hepatoma) cells, but the molecule's chemical structure needed to be elucidated in detail [55] (Table 2).

Table 2. Bioactive polysaccharides isolated from marine diatoms.

Source	Sugars	Yield (% w/w)	Sulfate content	*Mw* (kDa)	Bioactivity	Reference
Chaetoceros muelleri	n.d.	2.2	0.1 (mol/ disaccharide)	4.13	Antioxidant. DPPH radical scavenging of 23% at 20 mg/mL. Did not present cytotoxicity in CCD-841 colon cells	[43]
Navicula sp.	Glucose, galactose, rhamnose, xylose, mannose	4.4	0.33%	107	Antioxidant. DPPH radical scavenging 14–48% concentrations from 25–200 mg/mL	[48]
Navicula incerta	Glucose, galactose, mannose, xylose	4.8	0.46%	45	Antioxidant and antihemolytic. Ferric-reducing antioxidant power 1.47 µmol TE/g, 54% antiradical activity on ABTS+. 90% hemolysis inhibition	[49]
Odontella aurita	Glucose, mannose, ribose, arabinose, xylose, galactose	n.d.	n.d.	7.72	Antioxidant. DPPH radical scavenging activity 42% at 100 mg/mL. 83% hydroxyl radical scavenging activity at 10 mg/mL	[50]
Synedra acus	1→3;1→6-β-D-glucan	n.d.	n.d.	n.d.	Anticancer. Inhibition of human colon tumor cells IC50/72h of 54.5 and 47.7 µg/mL for HCT-116 and DLD-1 lines, respectively	[54]
Phaeodactylum tricornutum	Xylose, fucose, glucose, galactose	n.d.	20.36%	4810	Anticancer. Dose-dependent activity (up to 60.37% at 250 µg/mL). The effect occurs mainly through the induction of apoptosis of HepG2 cells	[55]
Navicula directa	Fucose, xylose, galactose, mannose, rhamnose	n.d.	8%	n.d.	Antiviral. Concentration-dependent inhibition of HSV-1, HSV-2, IFV-A infections, and cell-cell fusion caused by HIV	[56]
Gyrodinium impudicum	Galactose, uronic acid	n.d.	10.32%	18700	Antiviral effect against the encephalomyocarditis virus	[57]
Conticribra weissflogii	1→ 3-β-D-glucan	n.d.	n.d.	11.7	Immunomodulator. Enhanced the phagocytosis activity of macrophages RAW 264.7 at 0.5 µg/mL	[58]
Halamphora sp.	Galactose, fucose, glucose, uronic acid	n.d.	4.70%	n.d.	Immunomodulator. Phagocytosis rate 173% against *E. coli* for murine macrophage cells	[59]

ABTS+: 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid). HCT-116: colorectal cancer cell line. DLD-1: colorectal adenocarcinoma cell line. HepG2: human hepatoma. HSV-1 and HSV-2: Herpes simplex viruses (human herpesvirus types 1 and 2). IFV-A: influenza A virus. HIV: human immunodeficiency virus. RAW 264.7: macrophage cell line from a tumor induced with the Abelson murine leukemia virus.

Studies state how molecular modification could hold changes in the steric hindrance and electrostatic repulsion, while the flexion and the extension of polysaccharide chains and the water solubility impact the bioactivities [61]. Chemical modification methods on macroalgae polysaccharides

have demonstrated that the sulfation of these macromolecules can improve their immunostimulant effects and thereby enhance their antitumor activity [61].

5.3. Antiviral

Sulfated polysaccharides have described antiviral activity by blocking the entry of viruses into cells. The negative charge of these molecules performs their inhibitory action by interacting with the positive charges on the virus or the cell surface and stopping the virus from entering the host cells [7,62,63]. A higher molecular weight in fucoidan has been correlated to a higher affinity between the polysaccharide and the S-protein of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [63]. Another study reported that 3-O-sulfated octasaccharide could prevent membrane fusion by specifically saturating the Glycoprotein D (gD) subunit of the Herpes Simplex Virus-1 (HSV-1) envelope protein. This specificity implied the potential for tailoring the sulfation level of oligosaccharide modification to produce a particular inhibitor of viral infection [62]. A polysaccharide from *Navicula directa* containing fucose, xylose, galactose, mannose, and rhamnose showed antiviral activity against herpes simplex virus types 1 and 2 and influenza A [56]. This polysaccharide contained fucose, xylose, galactose, mannose, rhamnose, and sulfate, with a molecular weight of 220 kDa. The antiviral effect against the encephalomyocarditis virus (EMCV) was reported in a sulfated exopolysaccharide recovered from the diatom *Gyrodinium impudicum* [57]. It was indicated to be a homopolysaccharide of galactose with uronic acid (2.96% w/w) and sulfate groups (10.32% w/w) (Table 2).

A recent study by [64] exposed that *i*-carrageenan effectively impeded the cell entry of SARS-CoV-2 pseudotyped lentivirus in a manner dependent on dosage. It demonstrated remarkable efficacy, inhibiting 79% of the SARS-CoV-2 virus at 10 μg/mL, whereas, notably, *k*- and λ-carrageenan achieved an 80% inhibition rate at 100 μg/mL. Another study indicated that non-sulfated polysaccharides, such as carboxymethylcellulose and hydroxypropyl methylcellulose, and low molecular weight galactose-4-sulfate, exhibited no activity at 100 μg/mL. Similarly, chondroitin sulfate, containing one sulfate group per dimer, did not exhibit significant inhibition of SARS-CoV-2 [65]. These findings suggest that the observed polysaccharide activity may be linked to the number of sulfate groups and the chain length.

Previous investigations have also highlighted the necessity of a high level of structural flexibility for polysaccharide binding to the S glycoprotein. This flexibility is accentuated by the stronger binding observed between sulfated glycosaminoglycan and envelope protein [66]. Additionally, the presence of sulfates on a polysaccharide chain enhances solubility and activity by adopting a more extended conformation than non-sulfated polysaccharides [67].

5.4. Immunomodulatory

The immune system aims to protect the body from infections and maintain health. Several authors have discussed that the immunological activity of sulfated polysaccharides depends not only on the source, but also on the molecule's structural characteristics, such as molecular weight and degree of substitution. The sulfated polysaccharides have an immune regulator role in maintaining homeostasis and regulating macrophages, T/B lymphocytes, natural killer cells (NK cells), and complement systems [68].

Polysaccharides can interact directly or indirectly with the immune system, activating the immune system through numerous cellular/molecular events. Most investigations focused on macrophage activity when looking for poly-saccharide-reported immunostimulatory properties [69]. Numerous *in vivo* studies have demonstrated that immunostimulatory polysaccharide treatment enhances macrophage phagocytic function. These polysaccharides may improve not only phagocytosis, but also the production of reactive oxygen species (ROS), nitric oxide (NO), tumor necrosis factor (TNF-α), interleukin (IL)-1, IL-6, IL-8, IL-12, and interferon (IFN)-γ, as well as the secretion of these pro-inflammatory cytokines [69–73]. Additionally, it has been noted that these macromolecules influence macrophage proliferation and differentiation [74].

A recent study [58] identified a polysaccharide from the centric diatom *Conticribra weissflogii*. The chemical structure corresponds to a (1→3)-linked β-D-glucan with β-glucose substitutions at C-6. This polysaccharide registered a low molecular (11.7 kDa), no cytotoxic activity against glioblastoma cells, and possesses immunomodulatory properties. A polysaccharide from *Halamphora* sp. containing galactose, fucose, glucose, and uronic acid exhibited phagocytosis against *E. coli* [59] (Table 2).

6. Diatoms sulfated polysaccharides rheological properties

During their life cycle, diatoms release large amounts of adhesive polysaccharides, which are believed to play an essential role in carbon deposition. These polysaccharides assemble into non-covalently bound molecular networks [75], which aggregate into small exopolymer particles that aggregate diatom cells, minerals, and other larger marine particles [76]. It has been reported that fucose in diatoms possesses stability and adhesive properties, contributing to particle formation and potentially to carbon sequestration in the ocean [77]. A study found that *C. socialis* and two other *Chaetoceros* species produced a negatively charged polysaccharide rich in fucose, galactose, and sulfate, presenting adhesive properties [77].

When cultivated, microalgae secrete polysaccharides increase the viscosity of the culture medium. These polysaccharides are generally attributed to non-Newtonian rheological behavior [78]. At low concentrations, these secreted biopolymers usually form solutions with high viscosities. It has been reported that the chemical composition of polysaccharides influences their solution's rheological properties. This fact can be related to the forming of hydroxyl or amino hydrogen bonds in the chain structure [79].

Understanding the mechanical properties of microalgae culture is critical to optimizing bioreactors' design, expansion, and operation. This rheological behavior also influences the biomass recovery process. Rheology can help monitor and control microalgae production by studying how a material deforms and flows when subjected to applied stresses and shear speeds. [80]. This monitoring applied to the cultures could identify changes in exopolysaccharide properties and recover the most significant amount of the product synthesized with the best viscosity characteristics [81].

6.1. Hydrogel potential from diatom sulfated polysaccharides

Some marine sulfated polysaccharides can form hydrogels, three-dimensional networks of water-soluble polymers. They have drawn significant interest as drug delivery systems, mainly due to their very porous structure, which enables drug loading into the gel matrix and subsequent drug release at a rate that relies on the molecule's diffusion coefficient through the gel matrix. When exposed to

water or other biological fluids, hydrogels swell without dissolving and can be easily modified by adjusting the density of crosslinks in the gel matrix [82].

Polysaccharide hydrogels have shown attractive advantages in wound treatments due to their excellent biochemical and mechanical properties. For example, when used as dressings, hydrogels seek to fulfill the role of physical insulation and create a moist environment. Still, with increasing demands on the requirements for treating wounds and constant research, more hydrogel dressings with biological functions have been developed [83].

In sulfated polysaccharides extracted from *Navicula* sp. [48], the authors reported gelling capability in the presence of 0.4% (w/v) $FeCl_3$ (Figure 3a,b). The polysaccharide/$FeCl_3$ system registered an elastic modulus (G') higher than the viscous (G") modulus value from 20 to 40 °C. The predominance of G' over G" confirms the formation of a polymer network (Figure 3). This trivalent iron-induced gelation in sulfated polysaccharide from *Navicula* sp. was compared to that reported in λ-carrageenan from *Gigartina lanceata* [84]. Sulfated polysaccharides from *Navicula* sp. also present antioxidant capacity, increasing the macromolecule's potential for developing diverse biomaterials for biomedical or biotechnological applications.

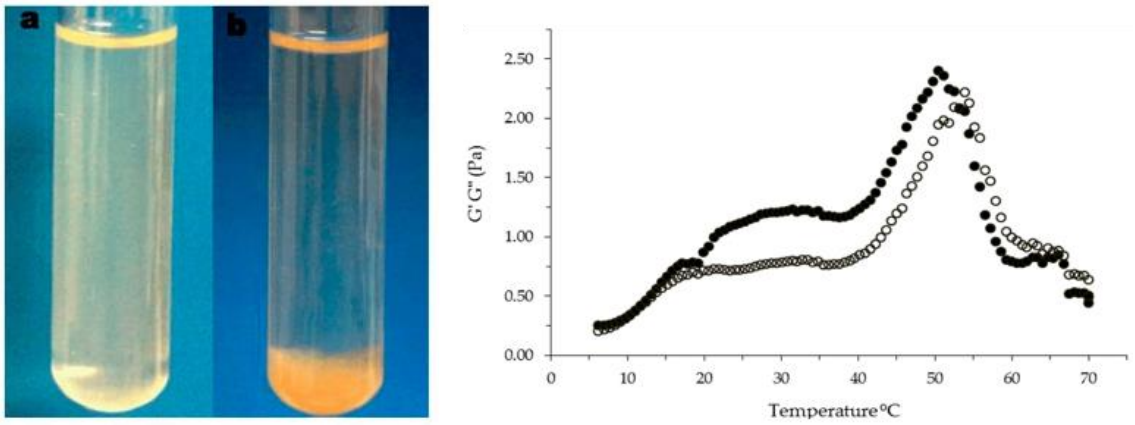


Figure 3. Sulfated exopolysaccharide recovered from *Navicula* sp. (a) before and (b) after $FeCl_3$ addition as a gelling agent; (c) elastic G' (●) and viscous G" (○) moduli changes in 1% (w/v) sulfated exopolysaccharide/0.4% (w/v) $FeCl_3$ during temperature ramp at 1 Hz and 2% strain [48].

Rheological characteristics of sulfated polysaccharides from diatoms help develop and tailor different biomaterials for diverse applications. However, innovative approaches are needed to devise cost-effective ways to isolate these bioactive compounds, streamline their productivity, and elucidate detailed mechanisms of action [85]. The heterogeneity and structural diversity of sulfated polysaccharides derived from diatoms pose challenges in their investigation. Consequently, gaining a deeper understanding of the molecular characteristics of these polysaccharides is essential, as they play a determining role in their behavior and potential applications. Additionally, there is a need for more comprehensive information on other components within the biology of these organisms for a thorough understanding of the therapeutic or biotechnological properties of these macromolecules. This lack of knowledge seems to delay progress in utilizing microalgae polysaccharides effectively for various applications.

7. Challenges and perspectives

One of the main limitations for the large-scale or commercialized application of these molecules could be the low biomass production compared to other organisms such as bacteria or macroalgae. These polysaccharides have been studied and characterized for several decades; however, new strategies are still necessary to increase the production of microalgae. The cultivation process presents specific challenges, such as operating costs, electrical energy consumption, and the bottleneck of biomass recovery.

Multiple parameters can influence the production of polysaccharides during the cultivation process. Generally, nutrient limitations are carried out to accumulate these macromolecules; however, there is evidence that they can decrease the growth rate of microalgae. Biorefineries could enhance utilization and balance the cost ratio with biomass recovery. In addition, they could investigate the conditions that promote higher yields and better viability to take advantage of these biomolecules for various commercial sectors [86].

On the other hand, the path towards its industrial application is challenging given the heterogeneous characteristics of these macromolecules. Currently, studies are focused on the structure and biological activity of sulfated polysaccharides from macroalgae, as well as the different harvesting stages and how these influence the structural characteristics. Heterogeneity and molecular weight are recognized as two of the main challenges limiting the therapeutic use of fucoidan, for example. Hence, there is also an increased interest in how low molecular weight polysaccharides with a certain degree of sulfation may improve the spectrum of bioactivities, as well as a vast investigation gap in methods for the obtention of specific and homogeneous fractions [87,88].

Further work is required to improve the ability to compare and establish connections between studies. Therefore, it is necessary to continue research on the modifications and adaptations of these macromolecules while examining their native structures. This involves considering factors such as extraction methods, harvesting, or cultivation conditions in microalgae. Additionally, conducting detailed analyses of macromolecular characteristics is necessary to enhance our understanding of their potential implications for biological activity.

8. Conclusions

Ongoing investigations into sulfated polysaccharides from diatoms yield new insights into their sources, chemical composition, functional attributes, and potential uses. Numerous studies have focused on sulfated polysaccharides sourced from macroalgae, but gap in knowledge concerning the extraction and detailed characterization of sulfated polysaccharides from microalgae remains. The growing interest in the obtention of these polysaccharides suggests potential benefits for future applications. Nevertheless, further research is required to address questions regarding the molecular characteristics, properties, and bioactivity of sulfated polysaccharides. Exploring the structural attributes of these macromolecules is essential to comprehend their structure-function relation and potential utility.

Use of AI tools declaration

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

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization, V. M.-A., E.C.-M. and D. F.-O.; software, V. M.-A., J. L.-M. and J. M.-E.; validation, V. M.-A., E.C.-M., D. F.-O., A.R.-C., A., M.-B., M.A.M.-E. and J. L.-M.; resources, V. M.-A., E.C.-M., D. F.-O., A.R.-C., A., M.-B, J. L.-M.; writing—original draft preparation, V. M.-A.; writing—review and editing, V. M.-A., E.C.-M., D. F.-O, A., M.-B., J. L.-M., A.R.-C., M.A.M.-E. and J. M.-E.; visualization, V. M.-A., E.C.-M., D. F.-O, A., M.-B.; supervision, E.C.-M.; project administration, E.C.-M.; funding acquisition, E.C.-M. All authors have read and agreed to the published version of the manuscript.

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