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*Review*

# Marine carbohydrate-based compounds with medicinal properties

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**Abstract:** The oceans harbor a great diversity of organisms, and have been recognized as an important source of new compounds with nutritional and therapeutic potential. Among these compounds, carbohydrate-based compounds are of particular interest because they exhibit numerous biological functions associated with their chemical diversity. This gives rise to new substances for the development of bioactive products. Many are the known applications of substances with glycosidic domains obtained from marine species. This review covers the structural properties and the current findings on the antioxidant, anti-inflammatory, anticoagulant, antitumor and antimicrobial activities of medium and high molecular-weight carbohydrates or glycosylated compounds extracted from various marine organisms.

**Keywords:** marine organisms; carbohydrate; glycoside; antioxidant; anticoagulant; anti-inflammatory; antitumor; antimicrobial.

## 1. Introduction

The oceans cover about 70% of the earth's surface, and harbor a great diversity of living beings, ranging from unicellular bacteria to large multicellular mammals [1]. The large biodiversity of the marine environment is also accompanied with great chemical variety, which makes this habitat a promising source of new biomedically active molecules [2, 3]. Currently some products obtained from marine sources are in the clinical trials phase for possible use as analgesics [4], anti-cancer drugs [5], and for treatments against viruses [6-8]. Despite these studies, marine potential remains largely unknown.

Among the promising but poorly explored marine molecules are carbohydrates, which stand out for their varied structural and chemical characteristics. Besides participating in energy storage and as structural component (especially in exoskeletons of invertebrates), carbohydrates play also many other key biological roles such as fertilization signaling [9-11], pathogen recognition [12], cellular interactions [13], tumor metastasis [14], in addition to important pharmacological activities such as antitumor [15, 16], antiviral [17, 18], anticoagulants [19], antioxidants [20] and anti-inflammatory [2, 21, 22].

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In this review we will discuss about the structural and biological aspects of the various carbohydrate-based compounds of marine origin endowed with potential biomedical and biotechnological applications. The main goal of this report is to reinforce to the scientific community the great value of marine-derived carbohydrates and glycosylated compounds of medium- and high molecular-weight (MW) to drug discovery and development. Although these molecules can present actions on multiple systems, attention is made more on their antioxidant, anti-inflammatory, anticoagulant, antitumor and antimicrobial properties.

## 2. Diversity of carbohydrates from marine sources

Carbohydrates are the most abundant biomolecules on Earth considering cellulose and chitin as the main representatives. These organic compounds act not only as the main energy source (as seen in starch and glycogen) but also as biologically functional structural players in events of cellular recognition, especially when present at the cell surface [23]. Carbohydrates are also the most complex biomolecules in terms of structure. The enhanced dynamic behavior, large conformational fluctuations, diversity of monomeric units accompanied by various enantiomers, multiple types of glycosidic bonds, and extensive post-polymerization modifications are factors that contribute to increase the structural complexity of these molecules. The carbohydrate classes are also vast. It can include both neutral and negatively charged saccharides with variable lengths. Famous examples are the N-linked or O-linked oligosaccharides in glycoproteins, glycosaminoglycan (GAG) in proteoglycans, glycolipids, sulfated fucans, sulfated galactans, among many other highly glycosylated products [24].

## 3. Structure and function

### *3.1. Alginic acid*

Alginic acid is a polysaccharide obtained from brown algae. It has linear structure and consists of β-D-manuronic acid (ManA) and α-L-guluronic acid (GulA) in repeating building blocks. These building blocks may be composed of consecutive GulA residues [GulA-GulA-GulA-GulA]$_n$, consecutive ManA residues [ManA-ManA-ManA-ManA]$_n$, or alternating ManA and GulA residues [GulA-ManA-GulA-ManA]$_n$ (Figure 1) [25]. This polysaccharide has a wide spectrum of application in medicine, in food industry, in biotechnology and in other industrial sectors [26].

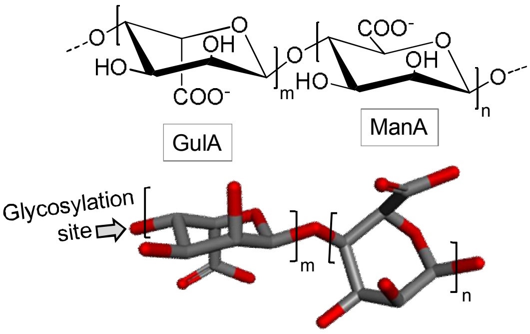

**Figure 1**: Chemical structure of alginate. It is composed of building blocks of α-L-guluronate (GulA) and β-D-mannuronate (ManA) units.

In the study of So and colleagues, alginic acid has been presented as a promising antioxidant agent against oxidative stress induced by free radicals [27]. In a work published five years later,

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Sarithakumari and coworkers investigated the antioxidant and the anti-inflammatory potential of alginic acid isolated from the brown algal species *Sargassum wightii* by *in vivo* assays using rats with induced arthritis [28]. Histopathological analysis of the animal paw tissue showed that treatment with alginic acid has the capacity to decrease the paw edema as well as the inflammatory infiltrates in the studied animal models. The polysaccharide was also able to reduce the activity of enzymes such as cyclooxygenase, lipoxygenase and myeloperoxidase, besides reducing the levels of C-reactive protein, ceruloplasmin and rheumatoid factor. Reduction of lipid peroxidation and increased antioxidant enzyme activity was also reported [28].

Supportively Endo and associates showed in a separate work two years later that alginic acid is able to eliminate free radicals and reduce the ferrous ion in stored pork [29]. The antioxidant activity of alginic acid was attributed to its capacity to chelate metal, to scavenge free radicals and to reduce ferric ions in the tissue. This last ability is quite useful in light of the elevated levels of Fe ions in pork meat. The literature also reports the antimicrobial activity of this polysaccharide [30]. For instance, in the work of Neettoo and collaborators, an alginate-based coating was tested in order to increase the microbiological safety in digestions of cold-smoked salmon. This study demonstrated the efficacy of alginate to control the growth of *Listeria monocytogenes*, a bacterium responsible for serious infections, mainly those caused by salmon uptake [30].

### *3.2. Sulfated polysaccarides*

#### 3.2.1. Fucoidan

Of complex structure fucoidans are obtained from brown algae. They generally consist of a backbone mostly 3-linked α-L-fucopyranose (Fuc) (Figure 2A) or alternating α-L-Fuc residues with 3- and 4-glycosidic linkages (Figure 2B). Either case can be replaced with sulfate or acetyl groups, and/or side branches containing Fuc or other glycosyl units [31]. In addition to Fuc residues, they may contain small amounts of several other monosaccharide types, such as glucose (Glc), galactose (Gal), xylose and/or mannose [32].

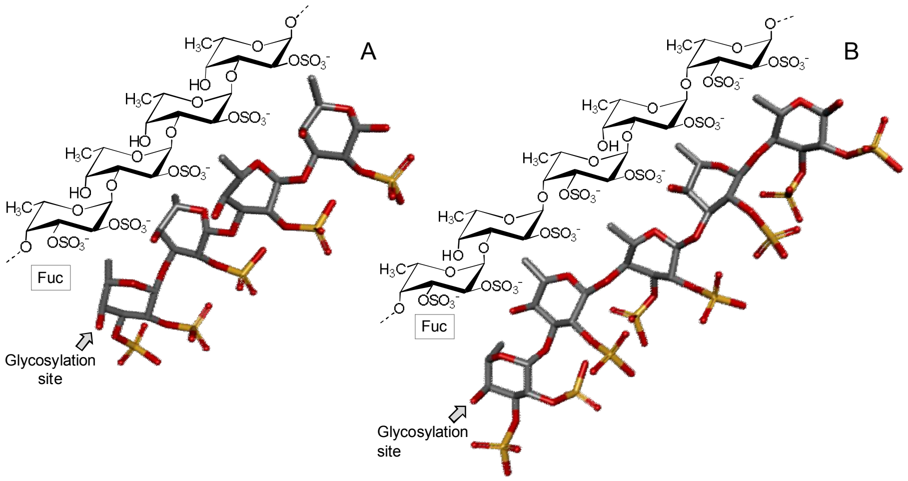

**Figure 2**. Fucoidans are polymers mostly composed of α-L-fucopyranose (Fuc) residues either (A) mostly 3-linked or (B) 3- and 4-linked.

One of the first attempts to propose the fucoidan structures was made in 1950 by Percival and Ross [33]. They analyzed the fucoidan-containg extracted from *Fucus vesiculosus*. In order to

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understand some of the fucoidan's biological action, Patankar and coworkers have revised the fucoidan structure four decades later and described it as a polysaccharide consisted mainly of 3-linked α-L-Fuc units (Figure 2A) [34]. More recent papers stated that Fuc units in fucoidan backbone can occur in the α-1,2 linkage type besides the α-1,3 and/or α-1,4 bonds [35]. It was also stated that sulfation can occur at positions 2, 3 and/or 4 as well [35]. Despite the many published works regarding fucoidan, the relationship between structure and biological activities is not clearly and easily established because of the obstacles in full structure determination [36, 37]. However, the scientific interest on fucoidans is so appealing because of the large spectrum of application - much research has annually been carried out in terms of both structure and biomedical function [38].

The highly cited review of Fitton covered potential applications of fucoidans in several types of therapies in which it was observed that the anti-inflammatory potential of fucoidan lies on its pleiotropic effects. These include selectin inhibition, complement inhibition and enzyme inhibitory activity [39]. In a comparative study of the anticoagulant property of fucoidans extracted from various species of algae, *Laminaria saccharina* was the one presenting the fucoidan with the highest level of activity [40, 41]. *In vitro* and *in vivo* assays are capable to evaluate the safety and clinical effects of fucoidan ingestion on hemostasis. Very strong *in vitro* anticoagulant activity has been presented as opposed to a modest effect on the *in vivo* assay [42]. Investigations on the antioxidant activity of fucoidans conclude that oral administration of fucoidan may lower serum parameters such as triacylglycerides, total cholesterol, low-density lipoprotein cholesterol and plasma Glc levels, and improve the anti-oxidation and innate immunity of catfish *Pelteobagrus fulvidraco* [43].

Other works have reported the anti-cancer activity of fucoidans extracts. An example is the well-cited paper from Cumashi and collaborators in which nine different fucoidans have been screened in terms of their multiple biomedical properties [40]. It has been shown that fucoidans from *L. saccharina*, *Laminaria digitata*, *Fucus serratus*, *Fucus distichus* and *F. vesiculosus* have the capacity to block adhesion of MDA-MB-231 breast carcinoma cells, resulting in potential beneficial therapeutics against tumor metastasis [40]. Following the same rational, other works have demonstrated that fucoidans of other seaweed species such as *Ecklonia cava*, *Sargassum hornery* and *Costaria costata* can present positive effects on human melanoma and colon cancer [44]. Fucoidans from other brown seaweeds like *Saccharina japonicus* and *Undaria pinnatifida* possess high antitumor activity and can inhibit proliferation and colony formation of breast cancer and melanoma cancer cell lines [45]. Fractions of native fucoidan and its derivatives have shown activity against the formation of colonies of two colorectal carcinoma cells, DLD-1 and HCT-116 [46].

The literature also mentions the antimicrobial properties of fucoidans [8, 47]. An example is the publication of Thuy and associates, where the anti-human immunodeficiency virus (HIV) activity of fucoidans extracted from three brown algae *Sargassum mcclurei*, *Sargassum polycystum* and *Turbinara ornata* is reported [47]. All these fucoidan types tested in this work exhibited anti-HIV effects. The mechanism of action has been attributed to the capacity of the fucoidan in blocking the first steps of HIV entry into the target cells [8, 47]. A very recent study illustrates the synthesis of silver nanoparticles (AgNPs) using fucoidan extracted from the alga *Padina tetrastromatica* as part of the coating material [48]. The focus of this work was on the increased antibacterial activity of antibiotics coated with AgNPs and fucoidan against antibiotic resistant bacteria. The synergistic effect of the combined antibiotics and fucoidan in nanoparticles resulted in a two-fold increase of the anti-bacterial activity as compared to these molecules in separate treatments.

### 3.2.2. Laminaran

The main chain of laminarans, also found in brown alga, is mostly consisted of 3-linked β-D- Glc residues (Figure 3) with a small proportion (usually less than 10%) of branches of single β-D-Glc residues attached to the C6 position of the Glc residues of the backbone [49]. According to the reducing terminal ends, laminarans may be of two types: one type with chains which are terminated by D-Glc residues (type G) (Figure 3A) and the second type with chains ending with D-mannitol (Man) residues (type M) (Figure 3B) [50]. The proportions of the two types of laminaran, and their consequent structures, vary according to the seaweed species. Environmental factors such as seasonal periods, salt concentration and frond age are additional influencing factors on chemical structures of laminaran [51]. Other environmental factors, including water temperature, salinity, waves, sea currents and depth of immersion (maybe pressure) have been also reported to influence on laminaran chemical composition [52]. Laminarans exist in either highly or poorly soluble forms. The first form is characterized by complete solubility in cold water, while the other is only soluble in hot water. The different solubility levels are influenced by the presence and number of branching residues. The higher the branching content, the greater the solubility in cold water [50].

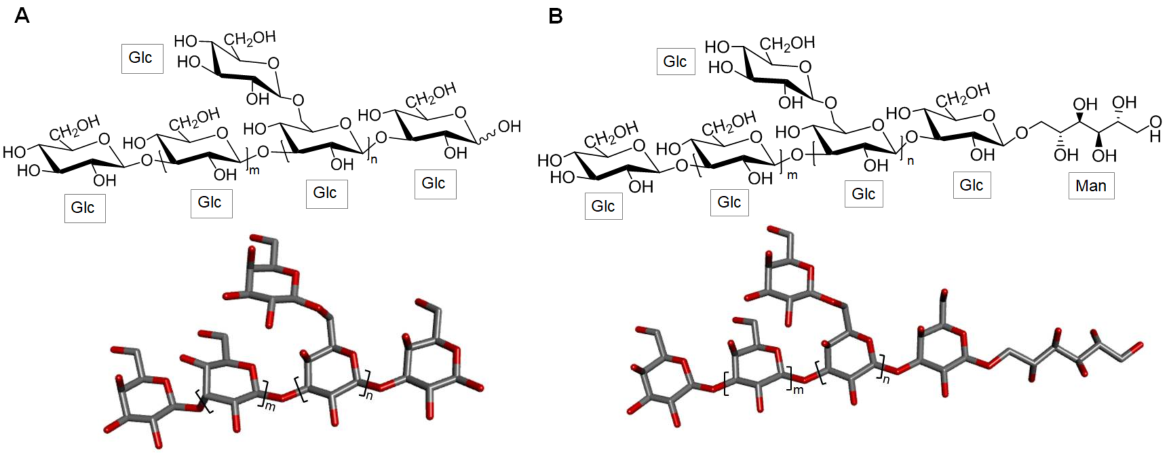

**Figure 3.** Representative chemical structure of laminaran which is composed of a backbone of 3-linked β-D-glucose (Glc) units with possible 6-linked branches of Glc residues and with reducing terminal ends with (A) Glc units (laminaran type G) or (B) D-mannitol (Man) residues (laminaran type M).

Laminaran exerts many bioactivities such as anti-cancer, anti-inflammatory, anticoagulant and antioxidant effects [52]. A recent review was published discussing the anticancer effects of two brown algal polysaccharides - emphasis was given on laminaran [49]. In this review it was stated that laminaran can enhance the therapeutic effects of commercial anticancer drugs [49]. For instance, laminaran can exhibit *in vitro* inhibiting effect on the formation of colonies of colon cancer cells DLD-1. This polysaccharide also showed a synergistic effect with X-ray irradiation against this same cancer cell line by decreasing the amounts and size of the colonies [53]. In the study of Malyarenko et al., lamellar sulfates of *Fucus evanescens* showed the capacity to decrease the migration ability of cancer cells *in vitro* by inhibiting the activity of certain metalloproteinases such as MMP-2 and MMP-9 [54].

According to the publication of Lee and coworkers, laminaran shows also the capacity to enhance the release of some inflammatory mediators [55]. This makes laminaran a potential therapeutic with immunostimulatory and anti-inflammatory properties [55]. With respect to antimicrobial activity, this marine glycan shows also the inhibitory capacity on both gram-positive and gram-negative bacteria such as *Salmonella typhimurium*, *Listeria monocytogenes* and *Vibrio parahaemolyticus* to adhere on HT-29-Luc cells of human enterocytes, besides inhibiting the invasion of *S. typhimurium* in this cell line [56]. The literature survey has shown that laminaran is able to prevent HIV activity by decreasing (a) the adsorption of the HIV particle in human lymphocytes and (b) the efficiency of the HIV reverse transcriptase, which plays an important role in the proliferation of the virus during the infection cycle [57]. This study suggests that laminaran acts as an efficient inhibitor of HIV replication and proliferation [57].

### 3.2.3. Carrageenans

Carrageenans are sulfated galactans found in red seaweeds and composed of linear chains of alternating 3-linked D-Gal (conventionally ascribed as A units) and 4-linked α-D-Gal or D-3,6-anhydrogalactose (anGal) (B units), forming thus disaccharide repeating building blocks [58].

Carrageenans are classified according to the presence of the 3,6-anhydrous bridge at the 4-linked AnGal residues and the positions and numbers of sulfate groups (Figure 4). Carrageenans are traditionally identified by a Greek prefix accordingly to their structures. Structures vary in terms of sulfation pattens and the presence of AnGal units. The International Union of Pure and Applied Chemistry (IUPAC) establishes a nomenclature based on a code for the carrageenans: G = 3-linked β-D-Gal; D = 4-linked α-D-Gal; DA = 4-linked α-D-3,6-AnGal and S = sulfate ester ($SO_3^-$) [59, 60].

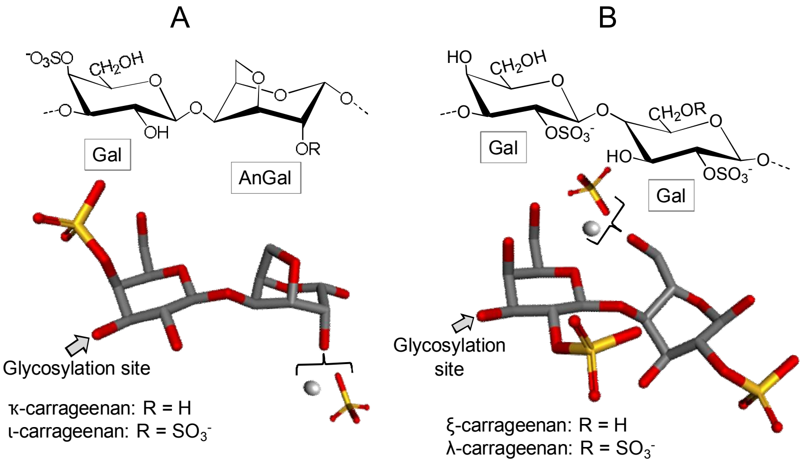

**Figure 4.** Representative chemical structures of carrageenans. These polymers are made up of alternating 3-linked galactose (Gal) units and (A) 4-linked anydrogalactose (AnGal) as seen in kappa (κ) and iota (ι) carrageenans or (B) Gal units as seen in zeta (ξ) and lambda (λ) carrageenans. These polymers also contain sulfation as their major substituent.

In Figure 4, four illustrative structures are shown: (A) one composed of AnGal units, and (B) other composed of Gal units, both either in their sulfated or non-sulfated forms of occurrence. The three most commercially exploited carrageenans are kappa (κ), iota (ι) and lambda (λ). Their corresponding names, based on the IUPAC nomenclature and on the letter codes are carrageenan 2,4-disulfate (DA2S-G4S), carrageenan 4-sulfate (DA-G4S), and carrageenan 2,6,2-trisulfate (D2S,6S-G2S), respectively [59, 60]. In addition to these three major types of carrageenan, two other types, called carrageenan ν and μ are frequently found in carrageenan commercial samples. They are the biological precursors of κ and ι-carrageenans, respectively [60].

In the food industry, carrageenans are widely explored because of their physicochemical properties like emulsifying, thickening, gelling and stabilizing effects. These additives give textural properties and protective effects to a wide range of food products [61]. Carrageenans are also widely used in the pharmaceutical and cosmetic industries [62].

Carrageenan-derived oligosaccharides produced by γ-irradiation exhibited antioxidant properties seen through multiple assays such as the hydroxyl radical scavenging, the power reduction and the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging ability [63]. The effect observed was dose-dependent and the carrageenan types were also observed to differently impact on the antioxidant activity, following the order of $\lambda < \iota < \kappa$ [63].

Talarico et al. analyzed the action of λ and ι carrageenans against dengue virus serotypes. In this study both carrageenans were shown to be potent inhibitors of the multiplication of dengue virus type 2 (DENV-2) and 3 (DENV-3) in Vero and HepG2 cells, with effective concentration values of 50% ($EC_{50}$) of 0.14 to 4.1 µg [18].

Still with respect to antiviral activity, Diogo and colleagues evaluated the action of λ-carrageenan against two viral pathogens of veterinary interest, bovine herpesvirus type 1 (BoHV-1) and herpesvirus suid type 1 (SuHV-1) viruses [64]. λ-carrageenan was able to reduce the infectivity of both types of virus. The concentration required to inactivate 50% of virus, virucidal concentration ($VC_{50}$) was 0.96 ± 0.08 µg/mL for BoHV-1 and 31.10 ± 2.28 µg/ml for SuHV-1. The antiviral activity of λ-carrageenan for BoHV-1 expressed in inhibitory concentration ($IC_{50}$) was 0.52 ± 0.01 µg/ml, whereas for SuHV-1 was 10.42 ± 0.88 µg/mL.

*In vitro* tests have shown that ι-carrageenan is a potent inhibitor of influenza A (H1N1) virus infection [65]. From this information Leibbrandt and coworkers decided to test a commercially available nasal spray containing ι-carrageenan in a model of influenza A infection in mice. Treatment of mice infected with a lethal dose of influenza A PR8/34 H1N1 virus and administered with ι-carrageenan at concentration of 60 µg/ml repeated twice daily starting within 48 hours post-infection resulted in strong protection of the mice, in a similar fashion as those treated with oseltamivir [65].

Studies on the cytotoxic effects of κ and λ-carrageenans on human cervical carcinoma cells (HeLa) and human umbilical vein endothelial cells (HUVEC) have shown that both carrageenans have no significant effect on HUVEC (normal cells). However, both carrageenans were cytotoxic to HeLa, although λ-carrageenan has stronger cytotoxicity properties compared to κ-carrageena. In addition, λ-carrageenan has been shown to have a stronger effect on suppression of tumor cell proliferation and cell division compared to κ-carrageenan [66].

### 3.2.4. Sulfated polymannuronate

Sulfated polymannuronate (SPM), also referred as polymannuroguluronate, is a sulfated polysaccharide extracted from brown algae, rich in 4-linked β-D-ManA with a mean MW of 10,000 Da (Figure 5) [67, 68]. Sulfation can occur at either C2 or C3 positions.

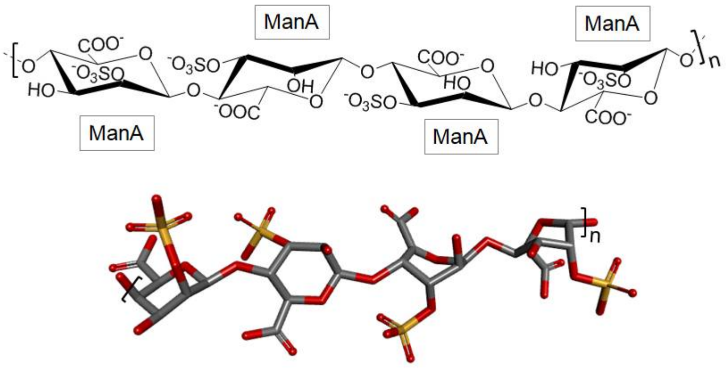

**Figure 5.** Structural representation of the brown algal sulfated polymannuronate (SPM). It is composed of 4-linked β-D-mannuronate (ManA) units in polymers with mean MW of 10 kDa. Sulfation can occur at either C2 or C3 positions.

SPM has presented anti-HIV properties [68]. SPM entered into the Phase II clinical trial in China, becoming the first marine sulfated polysaccharide with the potential to become a real anti-AIDS drug [69]. Several authors have focused on the elucidation of the molecular mechanism involved in the anti-HIV activity of SPM and their beneficial effects on the human cells of the immune system [69]. The particular study of Miao and coworkers has reported that CD4 is one of the possible targets for the specific binding of SPM on lymphocytes [69]. SPM-derived oligosaccharides have been shown the capacity to interact, in multiple ways, with gp120 and present therefore an anti-HIV outcome [68]. SPM can also inhibit the adhesion of the HIV Trans-activator of transcription (Tat) on SLK cells by direct binding to the KKR site (high-affinity heparin binding region) of Tat [67]. This structural information facilitates the elucidation of the structure-activity relationship of sulfated polysaccharides in the fight against HIV-1 infection.

### *3.2.5. GAGs*

GAGs are linear and heterogeneous sulfated glycans. Although structurally complex, the skeletons of these polysaccharides are simply constituted by repeated building blocks of disaccharides composed of alternating uronic acid (UroA) or Gal and hexosamine. The hexosamine may be glucosamine (GlcN) or N-acetylgalactosamine (GalNAc) and its differently substituted (mostly sulfated) derivatives. UroA can be either glucuronic acid (GlcA) or iduronic acid (IdoA) [70].

Heparin, heparan sulfate (HS), chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate (KS) and hyaluronan (HA) are the major classes of GAGs found in animals. Although GAGs are all composed of repeating disaccharide units, the patterns of sulfation and the alternating monosaccharides that make up these units within the polymers vary significantly. The GAG classification is conventionally set on these structural variations. Interestingly, GAGs of marine organisms can present distinct structures of those from terrestrial animals, even considering the same class of GAGs [71]. Structural variations and heterogeneities of GAG chains (from either marine or terrestrial sources) especially in terms of sequence domains and the common occurrence in the extracellular matrix or on the surface of cells are all relevant contributing factors to the diversity of their biological and medical functions.

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#### 3.2.5.1. Heparin

Heparin is mostly composed of alternating N-sulfated 6-sulfated α-D-GlcN (GlcNS6S) and 2-sulfated α-L-IdoA units (IodA2S), both 4-linked (Figure 6). Among its occurrence in marine invertebrates, heparin is found in several phyla such as mollusks, crustaceans, annelids, echinoderms, tunicates and other urochordates [72]. In some of these invertebrates the heparin-like structures have presented structural peculiarities which are unique and not commonly found in the commonest and well-known mammalian-derived heparins. These unique properties may comprise low-levels of N- and 6-sulfation content and high-levels of N-acetylation on the GlcN units together with consistent amounts of GlcA units [73]. Naturally occurring low MW heparins are also found in marine invertebrates [74]. Works have also suggested that marine heparin structures are related to the species of occurrence and the chemical differences lie mostly on the relative abundance of the various composing disaccharide units or different chains [75]. In addition to these structural variations, the marine invertebrate heparin-like compounds show also variable biological functions [72].

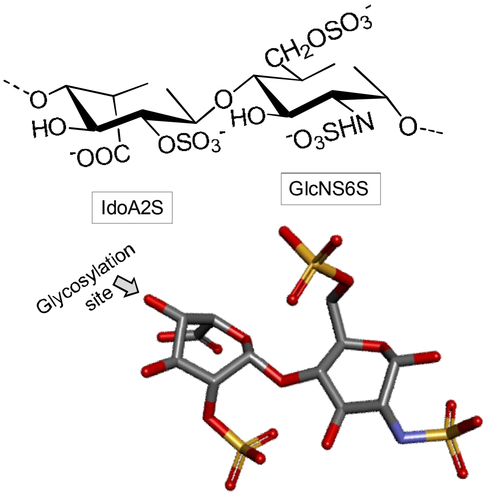


**Figure 6.** The heparin structure is mostly composed of alternating N-sulfated 6-sulfated α-D-glucosamine (GlcNS6S) and 2-sulfated α-L-IdoA (IdoA2S) units, both 4-linked.

Dietrich and coworkers reported the presence of a heparin in the crustacean *Penaeus brasiliensis* [74]. Of particular importance were the findings that this low MW heparin (LMWH) is enriched with non-sulfated UroA residues and exhibits potent antithrombotic activity. *In vitro* anticoagulant activities have shown that its effect is exerted on the inhibition of factor Xa and inhibition of thrombin (IIa) mediated mainly by cofactor heparin II (HCII) as opposed to mammalian heparins which exert their anticoagulant activity mainly through the inhibition of IIa and factor Xa mediated by antithrombin (AT). This shrimp-derived heparin has also presented potent *in vivo* antithrombotic activity as compared to the mammalian LMWH. Oppositely to the shrimp heparin, another heparin isolated from the crab *Goniopsis cruentata* has showed insignificant *in vitro* anticoagulant activity and low bleeding potency [72].

The heparin-like compound extracted from the shrimp *Litopenaeus vannamei* has shown capacity to reduce the influx of inflammatory cells in the lesion sites of a model of acute inflammation because this marine GAG is able to reduce the activity of the MMP in the peritoneal lavage of inflamed animals [73]. This molecule has been reported to reduce almost 90% the activity of MMP-9 secreted by activated human leukocytes besides presenting low hemorrhagic potential [73]. Another study has shown that this shrimp “heparinoid” is capable of suppressing neovascularization process [76].

An analogous of heparin isolated from the ascidian *Styela plicata* was investigated in a model of colitis in rats [77]. The result observed was a decrease in the production of TNF-α, TGF-β and VEGF, as well as reduced activation of NF-β and MAPK kinase. At the cellular level, this tunicate heparin analogue can attenuate the recruitment of lymphocytes and macrophages and reduce apoptosis levels on epithelial cells. A drastic reduction in collagen-mediated fibrosis has also been observed [77].

### 3. 2.5.2. HS

Heparin and HS are structurally related GAGs since both are composed of GlcN units in their backbones, although with different occurring concentrations [78]. HS is typically considered a less-modified heparin version. Among the sulfated GAGs, HS is the one with the greatest structural variability. Depending on the tissue and species of origin, such polysaccharide may be composed of several distinct disaccharide units, containing either GlcA or IdoA and GlcN with different extents of N- and/or 6-O-sulfation besides N-acetylation and 3-O-sulfation [78].

For example, the HS isolated from shrimp *Artemia franciscana* includes a high degree of N-sulfation and a relatively low degree of 6-O-sulfation of the GlcN residues. This compound exhibited high anticoagulant activity mediated by HCII [79]. In a study by Gomes and associates, a novel HS structure with unique characteristics was isolated from the bivalve mollusk *Nodipecten nodosus* (Figure 7). This HS was reported to be formed by GlcA and GlcN units and rare types of sulfation which can occur on carbons 2 or 3 of the GlcA units [80]. This mollusk HS can inhibit thrombus growth without inducing the provoking hemorrhage. The same group reported later the action of this HS in inhibiting P-selectin mediated events such as metastasis and recruitment of inflammatory cells [81].

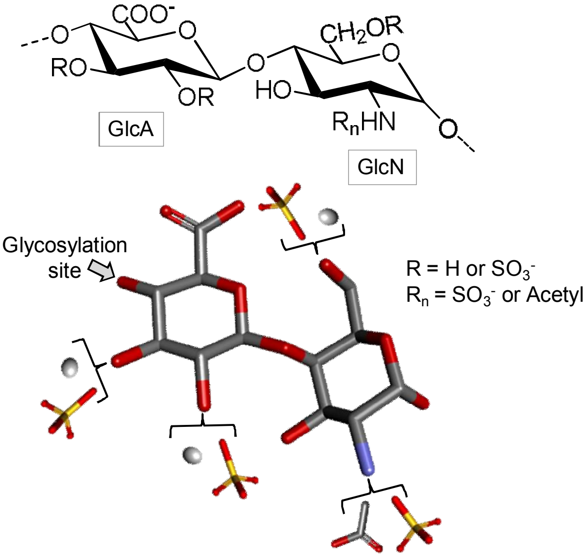
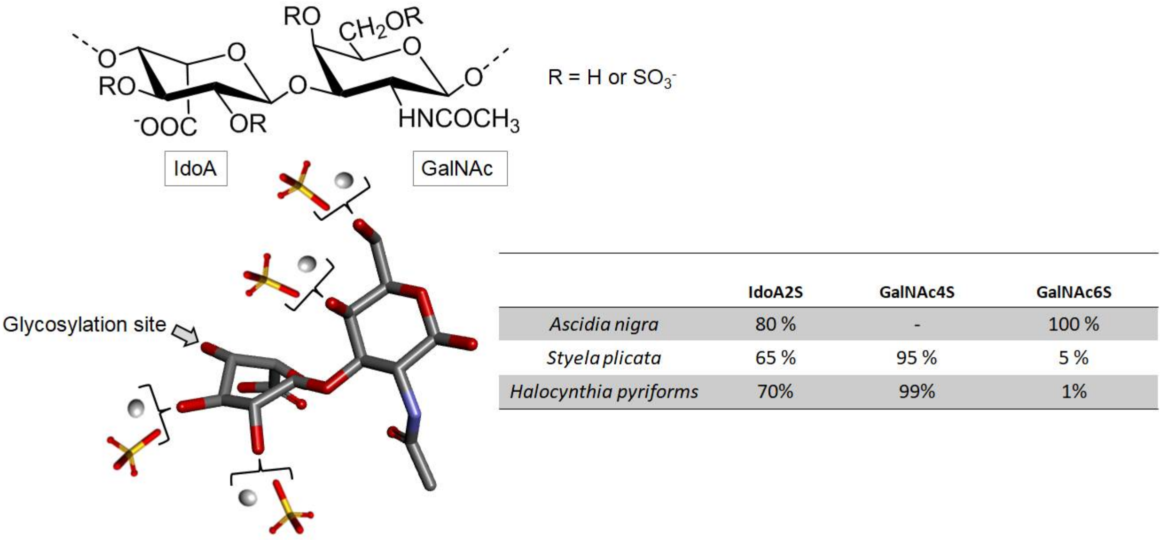


**Figure 7.** The heparan sulfate structure from the bivalve mollusk *Nodipecten nodosum* composed of alternating glucuronic acid (GlcA) and glucosamine (GlcN), both 4-linked. This molecule has a rare sulfation pattern on carbons 2 or 3 of the GlcA units. The C6 position of GlcN can also be sulfated. The substituents of $R_n$ can be either acetyl or sulfate.

#### 3.2.5.3. DS

DS is a linear variable-length polysaccharide composed of alternating disaccharide building blocks of 4-linked α-L-IdoA and 3-linked β-D-GalNAc units. These alternating disaccharide units can be variably sulfated at position C2 position of IdoA (IdoA2S) and/or C4 (GalNAc4S) and/or C6 (GalNAc6S) or both carbons (GalNAc4S6S) in the GalNAc unit, giving rise to different sulfated disaccharides [70].

In addition of being present in mammalian tissues, DS with high sulfation content was also found in different species of clam and tunicates [82-84]. The work of Pavão et al. [84] raises an interesting discussion about the structure-function relationship of DS extracted from different species of ascidians (Figure 8). For example, DS isolated from *Ascidia nigra* is fully sulfated at the C6 position of the GalNAc unit (100%) and at the C2 position of IdoA (80%) (Figure 8). The DS from *S. plicata* however is less sulfated at the C2 position (65%) and widely sulfated at the C4 position of GalNAc (Figure 8). The DS isolated from *Halocynthia pyriforms* is similar to that one seen in *S. plicata* (Figure 8).



| | IdoA2S | GalNAc4S | GalNAc6S |
|---|---|---|---|
| *Ascidia nigra* | 80 % | - | 100 % |
| *Styela plicata* | 65 % | 95 % | 5 % |
| *Halocynthia pyriforms* | 70% | 99% | 1% |

**Figure 8.** Representative chemical structure of dermatan sulfate (DS) which is composed of a backbone of 4-linked α-L-Idorunate (IdoA) and 3-linked β-D-N-acetylgalactosamine (GalNAc) units. The different radicals represent different patterns of sulfate substitutions. Ascidian DS are highly sulfated at the 2-position of IdoA, but differ in the sulfation pattern at GalNAc. The insert table displays the sulfation rates of the ascidian species *Ascidia nigra*, *Styela plicata* and *Halocynthia pyriforms*.

In terms of biological activities, the different sulfation patterns in ascidian DS seem to collaborate differently to the outcome. In terms of anticoagulation, the DS molecules from *S. plicata*, *H. pyriforms* which bear more GalNAc4S units have presented significant HCII-mediated IIa inhibition as opposed to *A. nigra* DS which did not present considerable anticoagulant activity [84, 85]. With the exception of *A. nigra*, the two ascidian DSs presented 10- and 6-fold more activity for HCII-related inhibition than the mammalian-derived native and oversulfated DS, respectively [84].

DS from *S. plicata* was also investigated regarding its anti-inflammatory activity in a model of colitis in rats [77]. This GAG exhibited a superior anti-inflammatory effect to that of mammalian heparin. This DS can decrease recruitment of lymphocytes and macrophages and apoptosis of epithelial cells. It is important to note that no hemorrhagic propensity has been pointed out after treatment with the ascidian glycan [77].

Kozlowski and colleagues investigated the effect of two DS isolated from *S. plicata* and *Phallusia nigra* in events of thrombosis, inflammation and metastasis [86]. The study showed that both GAGs can reduce thrombus size in a model of arterial thrombosis induced by $FeCl_3$. In addition, they can also attenuate metastasis of MC-38 colon carcinoma, B16-BL6 melanoma cells and the infiltration of inflammatory cells in a mouse model of thioglycollate-induced peritonitis. The authors suggested that the observed effects are related to the inhibition of P-selectin [86].

#### 3.2.5.4. Fucosylated chondroitin sulfate

Fucosylated chondroitin sulfate (fCS) is a distinct marine GAG found exclusively in sea cucumber (Echinodermata, Holothuroidea). This GAG is composed of the regular CS backbone with branches of α-L-Fuc units attached to the 3-position of the GlcA residues (Figure 9). The lateral units of Fuc can show different patterns of sulfation according to the holoturian species [87, 71].

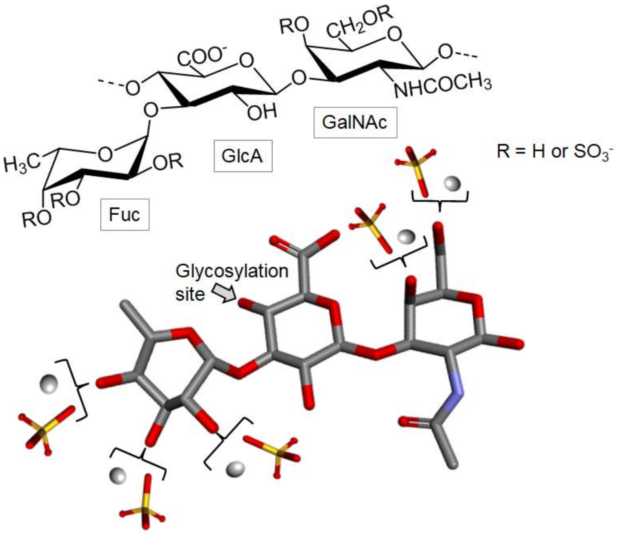


**Figure 9.** Structural representation of the holoturian fucosylated chondroitin sulfate (fCS). The structure is composed of α-L-fucose (Fuc), β-D-glucuronic acid (GlcA) and N-acetyl β-D-galactosamine (GalNAc).

With regard to the fCS' therapeutic properties, this glycan exhibits a wide range of applications: anticoagulant [88], anti-metastasis [89] anti-inflammatory [90] and antiviral activities [91]. For this reason several papers have focused on the study of fCS. One of the works investigated samples of fCS extracted from three species of sea cucumbers: *Apostichopus japonicus*, *Stichopus chloronotus* and *Acaudina molpadioidea* in order to carry out a structural comparison between the three molecules and their antioxidant and anti-inflammatory properties. Analysis of $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) of the polysaccharide identified three patterns of sulfation of the fucose branches: 4-O-, 2,4-di-O and 3,4-di-O-sulfation. In addition, their activities were affected by the sulfation patterns of the Fuc branches, revealing that sulfation in O4 is particularly important [92].

In the work of Ustyzhanina and colleagues, the fCS isolated from sea cucumber *Cucumaria japonica* inhibited platelet aggregation *in vitro*, and demonstrated significant anticoagulant activity. This latter activity was associated with the ability of fCS to increase inhibition of IIa and factor Xa by

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AT as well to influence von Willebrand factor activity. This latter property significantly distinguishes fCS from the LMWH [93]. fCS isolated from sea cucumber *Holothuria Mexicana* exhibited high affinity with fibroblast growth factors 1 and 2. These factors are important in the neovascularization event. In addition, it presented intrinsic anticoagulant activity and inhibited the activation of IIa and factor Xa by AT [94]. Still regarding anticoagulant properties, a new fCS isolated from the sea cucumber *Holothuria scabra*, was tested in comparison to heparin, and was shown to prolong activated partial thromboplastin time [95].

As mentioned above, the fucosylated sulfated polysaccharide also presents some antiviral properties, including against HIV. The anti-HIV action of holothurians fCS has generated a patent filed in the European patent bank [96]. Recent studies have reported the anti-HIV activity of the fCS obtained from the sea cucumber *Thelenota ananas*, which inhibited several strains of HIV-1 replication with different potencies. This study also reported that *T. ananas* fCS can bind potently to the recombinant HIV-1 gp120 protein, but did not inhibit recombinant HIV-1 reverse transcriptase [91].

### *3.3. N-acetylated sugars*

#### 3.3.1. Chitin and chitosan

Chitin is an important constituent of the exoskeleton of many organisms such as crustaceans and insects. In the marine environment chitin is certainly the most abundant biopolymer, being structurally composed GlcNAc and GlcN bound by β1,4 glycosidic bonds (Figure 10). In chitin, the GlcNAc content is higher than 70% of the total monosaccharide, making this polysaccharide highly N-acetylated. This, in turn, significantly decreases its water solubility property [97, 98].

Chitosan is a cationic polysaccharide composed of the same units and the glycosidic linkage of chitin (Figure 10). However, low amounts of GlcNAc are found in chitosan, usually less than 50%. Physicochemical characteristics such as hydrophobicity and inter-chain interactions depend on the amount and distribution of the acetylated groups [97, 98].

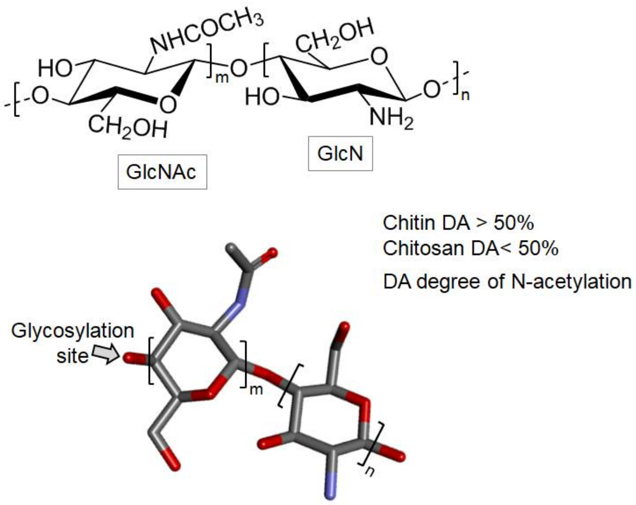


**Figure 10.** The chemical structures of chitin and chitosan. Chitin is consisting mainly of 2-acetamido-2-deoxy-D-β-glucopyranose (GlcNAc) units and partially of 2-amino-2-deoxy-β-D-glucopyranose (GlcN) units, both 4-linked. When the degree of N-acetylation

(DA) is less than 50% (GlcNAc content), the polymer is then named chitosan, otherwise, it is named chitin. DA is defined as the average number of N-acetylation per 100 monomers expressed as a percentage.

The chitosan molecule is non-toxic and has many biomedical applications, including bone tissue regeneration [99] and effects against a wide variety of pathogenic microorganisms [100-102]. Its proper use depends on many physicochemical factors and these factors can be managed accordingly to the levels of activity aimed for the chitosan. Examples of these factors are MW, degree of deacetylation, degree of substitution, length and position of a substituent in the GlcN units and pH [98].

The antineoplastic activity of chitin/chitosan and low MW chitin was evaluated using a human monocyte leukemia cell line, THP-1. Chitin and chitosan suppressed 100% growth of THP-1 tumor cells at concentrations equal to or greater than 1.5 mg/mL. The low MW chitin exhibited the same $EC_{50}$ of 250 μg/mL [103].

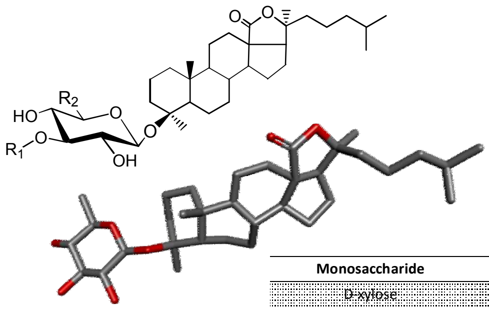
Antioxidant properties of chitosan were also investigated. Trung and Bao studied the molecule extracted from *L. vannamei* [104]. Their study suggested that the antioxidant effect observed was based on the free radical scavenging activity and the reduction of potency. Another study related to the antioxidant effect of this marine glycan was carried out by Sarbon et al. [105]. In their work the chitosan was extracted from the ladle shells species *Scylla olivacea*. The chitosan of *S. olivacea* exhibited a dose-dependent effect, where at the concentration of 10 mg/mL, the natural chitosan showed a greater reduction effect than the commercial chitosan.

Given the versatile applicability of this acetylated glycan, Divya and associates tested the antifungal and antioxidant activity of chitosan nanoparticles (ChNP) [106]. ChNP was tested in comparison to Amphotericin B, and showed good antifungal activity against all selected pathogens. The ChNP also exhibited significant antioxidant activity [106]. Previous work by the same group showed that chitosan nanoparticles inhibited the growth of clinically important microorganisms such as *Staphylococcus aureus*, *Pseudomona aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* besides exhibiting antibiofilm activity with an inhibition rate of up to 98% [102].

A recent study was conducted with chitin/chitosan obtained from the shrimp shell *Penaeus monodon* [107]. These polysaccharides showed inhibitory effects on the proliferation of the human ovarian cancer cell line, PA-1. Chitin and chitosan can suppress 100% growth of PA-1 tumor cells at the respective concentrations of 50 μg/mL and 10 μg/mL [107].

### *3.4. Triterpene glycosides*

The glycosides consist of amphiphilic compounds which contain a sugar bound to another functional group through a glycosidic bond (Figure 11). While the sugar can be a simple unit (monosaccharide) or various units (oligosaccharide) and the aglycone (functional group) may be a terpene, a flavonoid, or any other naturally occurring molecule [2, 108].



| Monosaccharide | $R_1$ | $R_2$ |
|---|---|---|
| D-xylose | H | H |
| D-quinovose | H | $CH_3$ |
| D-glucose | H | $CH_2OH$ |
| 3-O-methyl-D-xylose | Me | $CH_2OH$ |
| 6-O-acetyl-D-glucose | H | $CH_2OAc$ |
| 3-O-methyl-D-quinovose | Me | $CH_3$ |
| 3-O-methyl-D-xylose | Me | H |
| 3-O-methyl-D-glucuronic acid | Me | $CO_2H$ |

**Figure 11.** Chemical structures of glycoside with triterpenic backbone of holostane type bound to a sugar unit (glucose, Glc, in the case) and the possible substituents.

Glycosides of marine organisms can be isolated from sea cucumbers [109], starfish [110], sponge [111], algae [112] and corals [113]. Due to the great diversity of this class of molecule, many studies have focused on the investigation of their therapeutic properties. For example, glycosides isolated from the edible red seaweed *Laurencia undulata*, called Floridoside or D-isofloridoside, have their antioxidant properties investigated by Li and colleagues. The two compounds showed significant antioxidant activity and are presented as potential inhibitors of MMP-2 and MMP-9 [114].

Aurantoside K (a tetramic acid glycoside isolated from a sponge belonging to the genus *Melophlus*) exhibited a broad spectrum of antifungal activity against strains of *Candida albicans*, with the minimum inhibitory concentration (MIC) of 31.25 μg/mL for a strain resistant to amphotericin, and 1.95 μg/mL for a wild-type strain. It also showed a zone of inhibition of 14 mm of diameter in the concentration of 100 μg/disc for yeast *Cryptococcus neoformans*, 28 mm for *Aspergillus niger*, 31 mm *Penicillium* sp., 21 mm *Rhizopus sporangia* and 29 mm *Sordaria* sp. at the same concentration of 100 μg/disc [115]. Another study carried out with a class of triterpene glycosides, called variegatusides, isolated from the sea cucumber *Stichopus variegates* Semper (Holothuriidae), showed that these compounds have potent antifungal activities in biotestes *in vitro* [116].

Wang and collegues verified the cytotoxic effects of thirteen purified triterpenic glycosides of *Holothuria scabra* Jaeger and *Cucumaria frondosa* Gunnerus (Holothuroidea) against four human cell lines in order to advance the structure-activity relationship of these molecules [117]. The results showed that the number of glycosyl residues in the sugar chains and the aglycone side chain may affect their cytotoxicity to tumor cells and selective cytotoxicity in neoplastic versus normal cells. Works like this arouse interests in the use of these glycosides for the development of new antitumor drugs [105].

Given the vast number of actions that these compounds can present, it is worth also to understand the underlying mechanisms by which these molecules function. A good option to uncover their molecular mechanisms of action of marine glycosides is by identifying the relationships between their structures and activities. In a review of Park and co-authors the relationship between their effects and their structures were attempted on several molecular types.

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For example, Stichoposide C and Stichoposide D, both isolated from the holothurian *Stichopus chloronotus*, exert anticancer activity [118]. However, the activity of the compounds occurs by distinguished mechanisms due to differences in the sugar content. Stichoposide C has quinovose, and induces apoptosis through the generation of ceramide by the activation of acidic sphingomyelinase (SMase) and neutral SMase. While Stichoposide D possesses Glc as the second monosaccharide unit induces apoptosis by the activation of ceramide 6 synthase leading to the increase of cellular levels of ceramide.

Following the same thought, a recent study compared the effects of three frondosides (A, B and C) extracted from *Cucumaria frondosa* and its aglycone against pancreatic cancer cells. What can be observed was that frondoside A potentially inhibited the growth of pancreatic cancer cells with an EC 50 of ~ 1 μM. Frondoside B was less potent with an EC 50 of ~ 2.5 μM. Frondoside C and aglycone had no effect [119]. Frondoside A has potent antiproliferative, anti-invasive and antiangiogenic effects on a variety of cancers [120-122].

Cyclic steroid glycosides isolated from the starfish *Echinaster luzonicus*, identified as luzonicoside A (LuzA) and luzonicoside D (LuzD), were tested for their potential inhibitory capacity against RPMI-7951 and SK-Mel melanoma cell lines -28. LuzA inhibited proliferation, colony formation and migration of SK-Mel-28 cells more significantly than LuzD. The authors suggested that molecular mechanism of action is related to the regulation of the activity of cleaved caspase-3 and poly (ADP-ribose) polymerase (PARP), together with the levels of Survivin, Bcl-2, p21 and cyclin D1 [110].

### *3.5. Glycoproteins*

Glycoproteins are glycoconjugates in which various sugar monosaccharides are covalently attached to the protein backbone. Two major types of sugar chains (N and O-linked) are found in glycoproteins. N-linked sugar chains contain a GlcNAc residue at its reducing end which is, in turn, attached to the amide group of an asparagine (Asn) residue of the polypeptide backbone. The O-linked acid chains contain a residue of GalNAc at its reducing terminus which is, in turn, attached to a serine (Ser) or threonine (Thr) residue of a polypeptide backbone (Figure 12) [123].

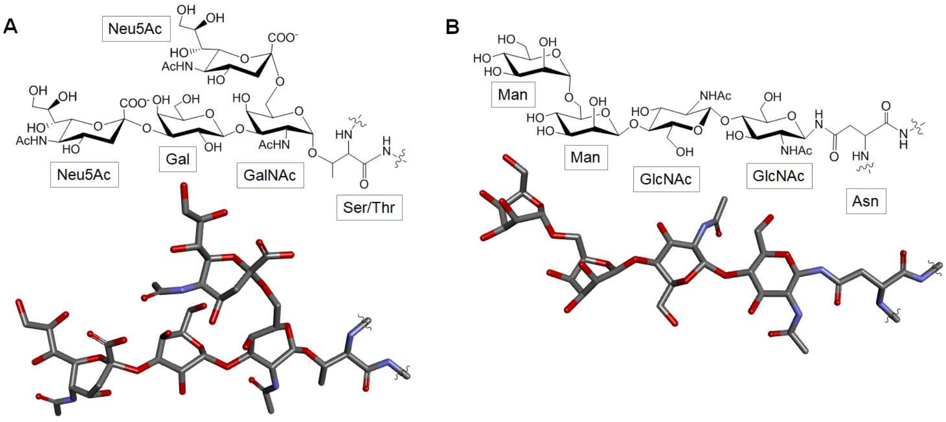

**Figure 12.** Chemical representatives of glycoproteins. (A) O-linked glycoprotein, which binds to the peptide by the amide group of a serine residue (Ser) or threonine (Thr). (B) N-linked glycoprotein, which binds asparagine (Asn) from a polypeptide backbone.

Glycoproteins represent a large class of biomolecules. Many of the proteins that are components of cell membranes are glycosylated (giving rise to glycoproteins). Glycoproteins may have essential functions as receptors that capture various ligands into the cell such as transport proteins that are involved in the ingestion of various compounds, or as structures that mediate molecular recognition, signaling and interactions between cells [124].

Among the glycoproteins of marine systems, it is important to consider the role of lectins. Lectins are recognition proteins of non-immune origin that bind to carbohydrates. They play many varied biological functions including regulation of cell adhesion, recognition of molecules in cell-cell and cell-molecule interactions, and are also known to have vital immune functions [125]. Lectins are isolated from a variety of marine organisms including algae [126, 127], sponges [128], mollusks [129] and echinoderms [130].

Many studies have reported the therapeutic effects of glycoproteins, especially lectins. For example, a study by Silva and collaborators has aimed on the potential anti-inflammatory action of the lectin extracted from the red alga *Pterocladiella capillacea* [131]. The authors have observed a reasonable anti-inflammatory effect through both the paw edema model and the neutrophil migration model, based on the injection of carrageenan as inflammation stimulus [131]. In a different work, the antinociceptive and anti-inflammatory effects of the lectin extracted from the red alga *Solieria filiformis* were evaluated [132]. In this work, the animals were pretreated with lectin by 30 min before receiving the nociceptive or inflammatory stimuli. The *S. filiformis* lectin significantly reduced the number of abdominal writhes and reduced the paw licking time in the formalin test. The lectin of *S. filiformis* also reduced neutrophil migration in a peritonitis model, in addition to reducing paw edema induced by carrageenan, dextran and serotonin [132]. In a recent work, Fontenelle and colleagues investigated the lectin extracted from the red seaweed *Bryothamnion triquetrum*, and reported its anti-inflammatory effect in mice [133].

Reports of anticancer activity of lectins have also been found in the literature. In one of the collected works, besides investigating the biological activity the authors also dealt with structural aspects of a lectin of the sea mollusk *Crenomytilus grayanus*. Cell viability assays have shown that *C. grayanus* lectin recognizes Gb3 globotriose on the surface of breast cancer cells, leading to cell death [134]. Also regarding anticancer activity, Liu et al. investigated the *in vivo* antitumor activity of hemocyanin (multifunctional glycoprotein) of the shrimp *L. vannamei* in Sarcoma-180 (S180) model of tumor-bearing mice [135]. After 8 days of treatment, the dose of 4mg/kg significantly inhibited the growth of S180 to 49% compared to untreated animals [135].

In terms of antimicrobial activity a new lectin was isolated from the green algae *Halimeda renschii*. The mannose-specificity lectin showed potent activity against influenza virus in NCI-H292 cells at half maximal effective dose ($ED_{50}$) of 2.45 nM. Antiviral action occurred through high affinity binding to hemagglutinin from the viral envelope [127].

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### *3.6. Glycolipids*

Glycolipids comprise a large and diverse group of lipids that serve numerous cellular functions [136]. They are amphipathic lipids, containing a hydrophilic portion, which is composed of units of carbohydrates, from which gives its name (the prefix "glyco"). Its lipid moiety is referred to as the hydrophobic tail, generally constituted of aliphatic fatty acid chains [137].

Among the classes of glycolipids are glycosphingolipids that are constituents of cell membranes in a wide variety of organisms (fungi, plants, animals and marine organisms) [138]. These compounds have biotechnological potential and play important physiological role due to variations in their sugar chains. They are classified into cerebrosides, ceramide oligohexosides, globosides and gangliosides based on the constituent sugars (Table 1). In recent years, some glycosphingolipids have been isolated from marine invertebrates such as echinoderms, porifera and mollusks [139].

Table 1. Classification of sphingolipids according to their sugar content.

| **Sugar moiety** | **Glycosphingolipid** |
|---|---|
| monosaccharide | cerebrosídeo |
| disaccharide | ceramide dihexoside |
| oligosaccharide | ceramide oligohexoside |
| oligosaccharide + amino sugar | globoside |
| oligosaccharide + sulfate | sulfatide |
| oligosaccharide + sialic acid | ganglioside |

Marine algae synthesize three major types of glycolipids, they are monogalactosylcyglycerides (MGDGs), digalactosyldecylglycerides (DGDGs) and sulfoquinovosylcyglycerides (SQDGs) (Figure 13). These glycoglycerolipids are present in the chloroplasts of any eukaryotic algae. MGDGs and DGDGs are the most abundant lipids of the thylakoid membrane and appear to play a crucial role in photosynthesis [140].

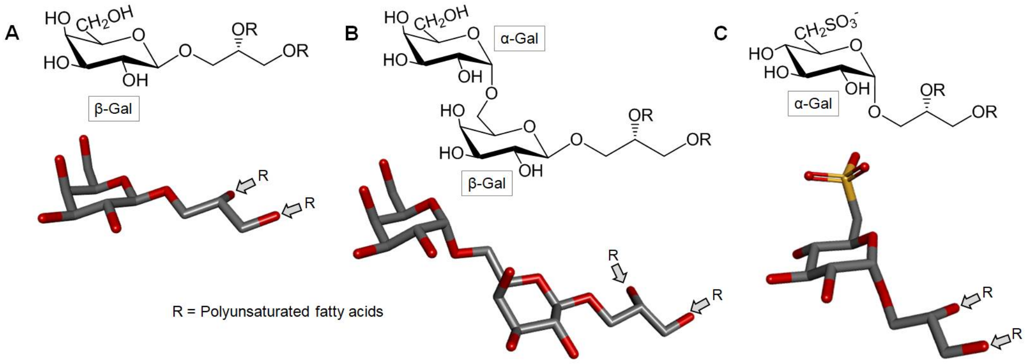

**Figure 13.** Representation of the general structure of the three main types of seaweed glycolipids. (A) Monogalactosylcyclic glycerides (MGDGs), (B) digalactosyldecylglycerides (DGDGs) and (C) sulfoquinovsylcyclic glycerides (SQDGs). R represents the acyl substituent chain.

Many papers have sought biologically active glycolipids from marine organisms to elucidate the structure-function relationships of glycolipids and to develop new medicinal resources. A good example of this was the study where eight new cerebrosides named Renierosides were isolated from an extract of the marine sponge *Haliclona* (*Reniera*) sp. The isolated compounds exhibited cytotoxicity of five human tumor cell lines, including human lung cancer (A549), human ovarian cancer (SK-OV-3), human skin cancer (SK-MEL-2), cancer cell line of the human central nervous system (XF498) and human colon cancer (HCT15) [141].

Plouguerné et al. identified SGDGs in fractions obtained after the purification of the organic extract of the *Sargassum vulgare* brown alga [142]. These metabolites exhibited antiviral activity against the herpes simplex virus type 1 (HSV1) and 2 (HSV2) viruses. The main SQDG responsible for anti-HSV1 and anti-HSV2 activities was characterized as 1,2-di-O-palmitoyl-3-O-(6-sulfo-α-D-quinovopyranosyl) glycerol [142]. Two SQDGs isolated from the red alga *Palmaria palmata* showed potent anti-inflammatory activity. Bioactive compounds were identified as (2S) -1-O-eicosapentaenoyl-2-O-myristoyl-3-O-(6-sulfo-α-D-quinazopyranosyl)-glycerol and (2S) -1-O-eicosapentaenoyl- 2-O-palmitoyl-3-O-(6-sulfo-α-D-quinovopyranosyl-glycerol and demonstrated nitric oxide inhibitory activity with $IC_{50}$ values of 36.5 and 11.0 μM, respectively [143].

In the paper by Reyes and coworkers the first characterization of the MGDGs, DGDGs and glycosylceramides of *Isochrysis galbana* (Haptophyte) was described together with a study of their anti-inflammatory properties as inhibitors of tumor necrosis factor α (TNF-α), a protein of cell signaling involved in the inflammatory response of the acute systemic phase [144]. In a recent paper, Che and colleagues have described that sea cucumber cerebrosides have improved learning and memory deficits, protecting against oxidative stress *in vivo*, and increasing the survival rate of PC12 cells, a rat pheochromocytoma cell line [138].

Overall, the bioactivities of the glycoglycerides are directly related to the sugar moiety. The position of the glycerol binding to the sugar, the length and the location of the acyl chain and the anomeric sugar configuration are all key structural contributors [145].

### *3.7. Iminosugar*

Naturally occurring iminos or azasugars are monosaccharides with nitrogen-substituted heterocyclic oxygen. In 1960 the first member of this class of compounds was isolated and characterized, a 5-amino-5-deoxyglucose antibiotic called Nojirimycin. Subsequently, more than 25 additional Nojirimycin analogs were described from plant and microbial sources [146, 147].

Iminosugar is commonly obtained from terrestrial sources or through chemical synthesis [146]. However, the work of Segraves and Crews described at the first time iminosugars from the marine environment [147]. In this work, three compounds were extracted from the sea sponge *Batzella sp*. and presented as iminosugar nucleus with a long chain of alkyl linked, indicating to be alkylated imino sugars. They were identified as Batzellasides A, B and C (Figure 14). The identification of these compounds occurred by comparison with the known natural and synthetic iminosugars properties, which aided in the determination of structures.

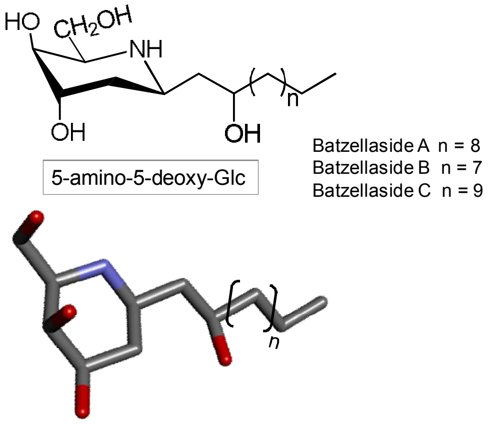

**Figure 14**. Representation of a nucleus of alkylated imino sugar. Batzellasides vary according to the size of the alkyl chain: Batzellasides **A** (8 carbon chain), Batzellasides **B** (7 carbon chain), Batzellasides **C** (9 carbon chain).

The iminosugars have shown important therapeutic importance such as antiviral [148], insecticides [149], and nematicidal activities [150]. These potentials are associated with the ability of these molecules to selectively inhibit enzymes that degrade carbohydrates (glycosidases). An example of the antiviral activity of iminosugars is seen from its capacity to interfere with the glycoprotein processing [151].

Regarding the investigation of these activities, the study by Segraves and Crews, evaluated the antimicrobial action of the three iminosugars studied therein (Batzellasides A, B and C) against the bacteria *Staphylococcus epidermidis* [147]. The three structures were able to inhibit the growth of the microorganism with lower MICs to 6.3 µg / mL [147].

The work of Sayce et al. has shown that the 1-deoxynojirimycin iminosugars bear Glc and inhibit the production of infectious virus *in vitro* including dengue virus (DENV), hepatitis B virus, virus hepatitis C virus, HIV and influenza A virus. Inhibition of endoplasmic reticulum α-glycosidases prevents virus release and is the main antiviral mechanism of action of iminosugars against DENV [151].

## 4. Concluding Remarks

It is not today that the marine environment arouses the interest of researchers in exploring their riches. The great diversity of this environment has led to the level of important source of obtaining novel molecules, especially with respect to molecules with biomedical potential such as those with glycosidic nature.

Throughout this work we have seen a miscellany of investigations into the effects of marine glycans or glycoconjugate on human health. However, it is still necessary to understand the molecular mechanisms behind these activities in order to understand the structural aspects of these molecules and what this diversity of structures may represent in the final effect.

Despite advances in study techniques that have allowed a reasonable understanding of the structure-activity relationship and some underlying mechanisms of action of these compounds, clinical trials using marine glycans are still scarce. It is necessary to evaluate the safety and efficacy of these molecules, aiming at a greater application of these compounds in the formulation of new drugs and for delivery of an end product.

## References

[1] Snelgrove, P. V. R. An Ocean of Discovery: Biodiversity Beyond the Census of Marine Life. *Planta Med*. **2016**, 82, 790-799. doi: 10.1055/s-0042-103934.

[2] Kang. H. K.; Seo, C. H.; Park, Y. The Effects of Marine Carbohydrates and Glycosylated Compounds on Human Health. *Int. J. Mol. Sci.* **2015**, *16*, 6018-6056. doi:10.3390/ijms16036018.

[3] Malve, H. Exploring the ocean for new drug developments: Marine pharmacology. *J. Pharm. Bioallied. Sci*. **2016**, *8*, 83-91. doi: 10.4103/0975-7406.171700.

[4] Molinski, T. F.; Dalisay, D. S.; Lievens, S. L.; Saludes, J. P. Drug development from marine natural products. *Nat. Ver. Drug Discov*. **2009**, 8, 69-85. doi: 10.1038/nrd2487.

[5] Schumacher, M.; Kelkel, M.; Dicato, M. Diederich, M. Gold from the sea: marine compounds as inhibitors of the hallmarks of cancer. *Biotechnol. Adv.* **2011**, 29, 531-547. doi: 10.1016/j.biotechadv.2011.02.002.

[6] Vo, T. S.; Ngo, D. H.; Ta,Q. V.; Kim, S. K. Marine organisms as a therapeutic source against herpes simplex virus infection. *Eur. J. Pharm. Sci*. **2011**, 44, 11-20. doi: 10.1016/j.ejps.2011.07.005.

[7] Pomin, V. H. Antimicrobial Sulfated Glycans: Structure and Function. *Curr. Top. Med. Chem*. **2017**, 17, 319-330. doi: 10.2174/1568026615666150605104444.

[8] Pomin, V. H.; Bezerra. F. F.; Soares, P. A. G. Sulfated Glycans in HIV Infection and Therapy. *Curr Pharm Des*. **2017**, 23, 3405-3414. doi: 10.2174/1381612823666170127113958.

[9] Vacquier, V. D. Evolution of gamete recognition proteins. *Science*, **1998**, 281, 1995-1998. doi: 10.1126/science.281.5385.1995.

[8] Vilela-Silva, A. C. E. S.; Alves, A. P.; Valente, A. P.; Vacquier, V. D.; Mourão, P. A. S. Structure of the sulfated α-L-fucan from the egg jelly coat of the sea urchin *Strongylocentrotus franciscanus*: patterns of preferential 2-O and 4-O-sulfation determine sperm cell recognition. *Glycobiology* . **1999**, 9, 927-933. doi: 10.1093/glycob/9.9.927.

[11] Pomin, V. H. Sulfated glycans in sea urchin fertilization. *Glycoconj J*. **2015**, 32, 9-15. doi: 10.1007/s10719-015-9573-y.

[12] Alpuchea, J.; Pereyrab, A.; Agundis, C.; Rosasa, C.; Pascuala, C. Slomiannyc, M. C.; Vázquez, L.; Zentenob, E. Purification and characterization of a lectin from the white shrimp *Litopenaeus setiferus* (*Crustacea decapoda*) hemolymph. *Biochim. Biophys. Acta*. **2005**, 1724, 86-93. doi: 10.1016/j.bbagen.2005.04.014.

[13] Chiu, P. C. N.; Tsang, H. Y.; Koistinen, H.; Seppala, M.; Lee, K. F.; Yeung, W. S. B. The Contribution of D-Mannose, L-Fucose, *N*-Acetylglucosamine, and Selectin Residues on the Binding of Glycodenlin Isoforms to Human Spermatozoa. *Biol. Reprod.* **2004**, 70, 1710-1719. doi: 10.1095/biolreprod.103.023259.

[14] Glavey, S. V.; Huynh, D.; Reagana, M. R.; Manier, S.; Moschetta, M. Kawano, Y.; Roccaro, A. M.; Ghobrial, I. M.; Joshi, L.; O'Dwyer, M. E. The cancer glycome: Carbohydrates as mediators of metastasis. *Blood Rev*. **2015**, 29, 269-279. doi: 10.1016/j.blre.2015.01.003.

[15] Kang, Y.; Wang, Z. J.; Xie, D.; Sun, X.; Yang, W.; Zhao, X.; Xu, N. Characterization and Potential Antitumor Activity of Polysaccharide from *Gracilariopsis lemaneiformis*. *Mar. Drugs*. **2017**, 15, 100. doi: 10.3390/md15040100.

[16] Zhou, G.; Sheng, W.; Yao, W.; Wang, C. Effect of low molecular λ-carrageenan from *Chondrus ocellatus* on antitumor H-22 activity of 5-Fu. *Pharmacol. Res*. **2006**, 53, 129-134. doi: 10.1016/j.phrs.2005.09.009.

[17] Hidari, K. I. P. J.; Takahashi, N.; Arihara, M.; Nagaoka, M.; Morita, K.; Suzuki, T. Structure and anti-dengue virus activity of sulfated polysaccharide from a marine alga. *Biochem. Biophys. Res. Commun.* **2008**, 376, 91-95. doi: 10.1016/j.bbrc.2008.08.100.

[18] Talarico, L. B.; Damonte, E. B. Interference in dengue virus adsorption and uncoating by carrageenans. *Virology*. **2007**, 363, 473-485. doi: 10.1016/j.virol.2007.01.043.

[19] Pomin, V. H. Structure-function relationship of anticoagulant and antithrombotic well-defined sulfated polysaccharides from marine invertebrates. *Adv. Food. Nutr. Res.* **2012**, 65, 195-209. doi: 10.1016/B978-0-12-416003-3.00012-3.

[20] Vinsová, J.; Vavríková, E. Chitosan Derivatives with Antimicrobial, Antitumour and Antioxidant Activities – a Review. *Curr. Pharm. Des.* **2011**, 17, 3596-3607. doi : 10.2174/138161211798194468.

[21] Lee, S. H.; Ko, C. I.; Ahn, G.; You, S.; Kim, J. S.; Heu, M. S.; Kim, J.; Jee, Y.; Jeon, Y.J. Molecular characteristics and anti-inflammatory activity of the fucoidan extracted from *Ecklonia cava*. *Carbohydr. Polym*. **2012**, 20, 599-606. doi: 10.1016/j.carbpol.2012.03.056.

[22] Pomin, V. H. Sulfated glycans in inflammation. *Eur J Med Chem*. **2015**, 6, 353-69. doi: 10.1016/j.ejmech.2015.01.002.

[23] Ernst, B.; Magnani, J. L. From carbohydrate leads to glycomimetic drugs. *Nat Rev Drug Discov*. **2009**, 8, 661-677. doi: 10.1038/nrd2852.

[24] Pomin, V. H. Marine medicinal glycomics. *Front. Cell. Infect. Microbiol.* **2014**, 4, 1-13. doi:10.3389/fcimb.2014.00005.

[25] Lee, K. Y.; Mooney, D. J. Alginate: properties and biomedical applications. *Prog Polym Sci.* **2012**, 37, 106-126. doi: 10.1016/j.progpolymsci.2011.06.003.

[26] Draget, K. I.; Moe, S. T.; Skjak-Braek, G.; Smidsrod, O. Alginates. In: *Food Polysaccharides and Their Applications*, 2nd ed.; Stephen, A. M.; Phillips, G. O.; Williams, P. A.; Taylor and Francis Group: *Press Boca Raton, USA*, **2006**, 289-334, ISBN 9780824759223.

[27] So, M. J.; Kim B. K.; Choi, M. J.; Park, K.Y.; Rhee, S. H.; Cho, E. J. Protective Activity of Fucoidan and Alginic Acid against Free Radical-Induced Oxidative Stress under in Vitro and Cellular System. *J. Food Sci. Nutr.* **2007**, 12, 191-196. doi: 10.3746/jfn.2007.12.4.191.

[28] Sarithakumari, C. H.; Renju, G. L.; Kurup, G. M. Anti-inflammatory and antioxidant potential of alginic acid isolated from the marine algae, *Sargassum wightii* on adjuvant-induced arthritic rats. *Inflammopharmacol*. **2013**, 21, 261-268. doi: 10.1007/s10787-012-0159-z.

[29] Endo, Y.; Aota, T.; Tsukui, T. Antioxidant Activity of Alginic Acid in Minced Pork Meat. *Food Sci Technol Res*. **2015**, 21, 875-878. doi: 10.3136/fstr.21.875.

[30] Neetoo, H.; Ye, Mu.; Chen H. Bioactive alginate coatings to control *Listeria monocytogenes* on cold-smoked salmon slices and fillets. *Int. J. Food Microbiol*. **2010**, 136, 326-331. doi:10.1016/j.ijfoodmicro.2009.10.003.

[31] Karunanithi, P.; Murali, M. R.; Samuel, S.; Raghavendran, H. R. B.; Abbas, A. A.; Kamarul, T. Three Dimensional Alginate-Fucoidan Composite Hydrogel Augments the Chondrogenic Differentiation of Mesenchymal Stromal Cells. *Carbohydr. Polym*. **2016**, 147, 294-303. doi: 10.1016/j.carbpol.2016.03.102.

[32] Alea, M. T.; Meyer, A. S. Fucoidans from brown seaweeds: an update on structures, extraction techniques and use of enzymes as tools for structural elucidation. *RSC Adv.* **2013**, 3, 8131-8141. doi: 10.1039/C3RA23373A.

[33] Percival, E. G. V.; Ross, A. G. Fucoidin. Part 1. The isolation and purification of fucoidin from brown seaweeds. *J Chem Soc.* **1950**, 717-720.

Peer-reviewed version available at *Mar. Drugs* **2018**, *16*, 233; doi:10.3390/md16070233

[34] Patankar, M.S.; Oehninger, S.; Barnett, T.; Williams, R. L.; Clark, G. F. A Revised Structure for Fucoidan May Explain Some of Its Biological Activities. *J Biol Chem*. **1993**, 268, 21770-21776.

[35] Holtkamp, A. D.; Kelly, S. ; Ulber, R.; Lang, S. Fucoidans and fucoidanases—focus on techniques for molecular structure elucidation and modification of marine polysaccharides. *Appl Microbiol Biotechnol*. **2009**, 82, 1-11. doi: 10.1007/s00253-008-1790-x.

[36] Bilan, M. I.; Grachev, A. A.; Ustuzhanina, N. E.; Shashkov, A. S.; Nifantiev, N. E.; Usov, A. I. Structure of a fucoidan from the brown seaweed *Fucus evanescens* C.Ag. *Carbohydr. Res*. **2002**, 337, 719-730. doi: 10.1016/S0008-6215(02)00053-8.

[37] Pomin, V. H.; Mourão, P. A. Structure, biology, evolution, and medical importance of sulfated fucans and galactans. *Glycobiology*. **2008**, 18, 1016-27. doi: 10.1093/glycob/cwn085.

[38] Fitton, J. H.; Stringer, D. N.; Karpiniec, S. S. Therapies from Fucoidan: An Update. *Mar. Drugs.* **2015**, 13, 5920-5946. doi:10.3390/md13095920.

[39] Fitton, J. H. Therapies from Fucoidan; Multifunctional Marine Polymers. *Mar. Drugs.* **2011**, 9, 1731-1760. doi:10.3390/md9101731.

[40] Cumashi, A.; Ushakova, N. A.; Preobrazhenskaya, M. E.; D'Incecco, A.; Piccoli, A. Totani, L.; Tinari, N.; Morozevich, G. E.; Berman, A. E.; Bilan, M. I.; Usov, A. I.; Ustyuzhanina, N. E.; Grachev, A. A.; Sanderson, C. J.; Kelly, M.; Rabinovich, G. A.; Iacobelli, S.; Nifantiev, N. E. Consorzio Interuniversitario Nazionale per la Bio-Oncologia, Italy. A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds. *Glycobiology*. **2007**, 17, 541-552. doi:10.1093/glycob/cwm014.

[41] Ushakova, N. A.; Morozevich, G. E.; Ustyuzhanina, N. E.; Bilan, M. I.; Usov, A. I.; Nifantiev, N. E.; Preobrazhenskaya, M. E. Anticoagulant Activity of Fucoidans From Brown Algae. *Biochemistry (Moscow) Supplement Series B: Biomedical Chemistry*, **2009**, 3, 77-83. ISSN: 1990-7508.

[42] Irhimeh, M. R.; Fitton, J. H.; Lowenthala, R.M. Pilot clinical study to evaluate the anticoagulant activity of fucoidan. *Blood Coagul Fibrinolysis*. **2009**, 20, 607-610. doi:10.1097/MBC.0b013e32833135fe.

[43] Yang, Q.; Yang, R.; Li, M.; Zhou, Q.; Liang, X.; Elmada, Z. C. Effects of dietary fucoidan on the blood constituents, anti-oxidation and innate immunity of juvenile yellow catfish (*Pelteobagrus fulvidraco*). *Fish Shellfish Immunol.* **2014**, 41, 264-270. doi: 10.1016/j.fsi.2014.09.003.

[44] Ermakova, S.; Sokolova, R.; Kim, S. M.; Um, B. H.; Isakov, V.; Zvyagintseva, T. Fucoidans from brown seaweeds *Sargassum hornery*, *Ecklonia cava*, *Costaria costata*: structural characteristics and anticancer activity. *Appl. Biochem. Biotechnol.* **2011**, 164, 841-850. doi: 10.1007/s12010-011-9178-2.

[45] Vishchuk, O. S.; Ermakova, S. P.; Zvyagintseva, T. N. Sulfated polysaccharides from brown seaweeds *Saccharina japonica* and *Undaria pinnatifid*a: isolation, structural characteristics, and antitumor activity. *Carbohydr Res.* **2011**, 346, 2769-2776. doi: 10.1016/j.carres.2011.09.034.

[46] Usoltsevaa, R. V.; Anastyuka, S. D.; Ishinaa, I. A.;Isakova, V. V.; Zvyagintsevaa, T. N.; Thinhb, P. D.; Zadorozhnyc, P. A.; Dmitrenok, P. S.; Ermakovaa, S. P. Structural characteristics and anticancer activity *in vitro* of fucoidan from brown algae *Padina boryana. Carbohydr. Polym.* **2018**, 184, 260-268. doi: 10.1016/j.carbpol.2017.12.071.

[47] Thuy, T. T.; Ly, B. M.; Van, T. T.; Quang, N. V.; Tu, H. C.; Zheng, Y.; Seguin-Devaux C.; Mi, B.; Ai, U. Anti-HIV activity of fucoidans from three brown seaweed species. *Carbohydr. Polym*. **2015**, 115, 122-128. doi: 10.1016/j.carbpol.2014.08.068.

[48] Rajeshkumar, S. Phytochemical constituents of fucoidan (*Padina tetrastromatica*) and its assisted AgNPs for enhanced antibacterial activity. *IET Nanobiotechnol*. **2017**, 3, 292-299. doi: 10.1049/iet-nbt.2016.0099.

[49] Sanjeewa, K.K. A.; Lee, J. S.; Kim,W. S.; Jeon, Y. J. The potential of brown-algae polysaccharides for the development of anticancer agents: An update on anticancer effects reported for fucoidan and laminaran. *Carbohydr. Polym*. **2017**, 177, 451-459. doi. 10.1016/j.carbpol.2017.09.005.

[50] Rioux, L. E.; Turgeon, S. L.; Beaulieu, M. Structural characterization of laminaran and galactofucan extracted from the brown seaweed *Saccharina longicruris*. *Phytochemistry*. **2010**, 71, 1586-1595. doi: 10.1016/j.phytochem.2010.05.021.

[51] Rioux, L. E.; Turgeon, S.L.; Beaulieu, M. Effect of season on the composition of bioactive polysaccharides from the brown seaweed *Saccharina longicruris*. *Phytochemistry*. **2009**, 70, 1069-1075. doi: 10.1016/j.phytochem.2009.04.020.

[52] Kadam, S. U.; Tiwari, B. K.; O'Donnell, C. P. Extraction, structure and biofunctional activities of laminarin from brown algae. *In.t J. Food Sci. Technol*. **2015**, 50, 24-31. doi: 10.1111/ijfs.12692.

[53] Usoltseva,P. V.; Shevchenko, N. M.; Malyarenko, O. S.; Ishina, I. A.; Ivannikova, S. I.; Ermakova, S. P. Structure and anticancer activity of native and modified polysaccharides from brown alga *Dictyota dichotoma. Carbohydr. Polym*. **2018**, 180, 21-28. doi: 10.1016/j.carbpol.2017.10.006.

[54] Malyarenko, O. S.; Roza V. Usoltseva, R. V.; Shevchenko, N. M.; Isakov, V. V.; Zvyagintseva, T. N.; Ermakova, S. P. In vitro anticancer activity of the laminarans from Far Eastern brown seaweeds and their sulfated derivatives. *J. Appl. Phycol*. **2017a**, 29, 543-553. doi: 10.1007/s10811-016-0915-3.

[55] Lee, J. Y.; Kim, Y. J.; Kim H. J.; Kim, Y. S.; Park, W. Immunostimulatory Effect of Laminarin on RAW 264.7 Mouse Macrophages. *Molecules.* **2012**, 17, 5404-5411. doi: 10.3390/molecules17055404.

[56] Kuda, T.; Kosaka, M.; Hirano, S.; Kawahara, M.; Sato, M.; Kaneshima,T.; Nishizawa, M. Takahashi, H.; Kimura, B. Effect of sodium-alginate and laminaran on *Salmonella Typhimurium* infection in human enterocyte-like HT-29-Luc cells and BALB/c mice. *Carbohydr. Polym*. **2015**, 125, 113-119. doi: 10.1016/j.carbpol.2015.01.078.

[57] Ahmadi, A.; Zorofchian, S.; Moghadamtousi, S. Z.; Abubakar, S.; Zandi, K. Antiviral Potential of Algae Polysaccharides Isolated from Marine Sources: A Review. *Biomed Res Int*. **2015**, 2015, 1-10. doi:10.1155/2015/825203.

[58] Pomin, V. H. Structural and functional insights into sulfated galactans: a systematic review. *Glycoconj J*. **2010**, 1, 1-12. doi: 10.1007/s10719-009-9251-z.

[59] van de Velde, F.; Pereira, L.; Rollema, H. S. The revised NMR chemical shift data of carrageenans. *Carbohydr. Res*. **2004**, 339, 2309-2313. doi: 10.1016/j.carres.2004.07.015.

[60] Campo, V. L.; Kawano, D. F.; Silva Jr., D. B.; Carvalho, I. Carrageenans: Biological properties, chemical modifications and structural analysis–A review. *Carbohydr. Polym*. **2009**, 77, 167-180. doi:10.1016/j.carbpol.2009.01.020.

[61] Cash, M. J. New iota carrageenan allows gelatin replacement, simplified manufacturing, and new textures for confectionary applications. In Abstract of IFT Annual Meeting, Dallas, TX, 64-4, June 10-14, 2000.

[62] Sun, Y.; Yang, B.; Wu, Y.; Liu, Y.; Gu, X.; Zhang, H.; Wang, C.; Cao, H.; Huang, L.; Wang, Z. Structural characterization and antioxidant activities of κ-carrageenan oligosaccharides degraded by different methods. *Food Chem*. **2015**, 178, 311-318. doi: 10.1016/j.foodchem.2015.01.105.

[63] Lucille Abad, V.; Relleve, L. S.; Racadio, C. D. T.; Aranilla, C. T.; De la Rosa, A. M. Antioxidant activity potential of gamma irradiated carrageenan. *Appl. Radiat. Isot*. **2013**, 79, 73-79. doi:10.1016/j.apradiso.2013.04.035.

[64] Diogo, J. V.; Novo, S. G.; González, M. J.; Ciancia, M.; Bratanich, A. C. Antiviral activity of lambda-carrageenan prepared from red seaweed (*Gigartina skottsbergii*) against BoHV-1 and SuHV-1. *Res Vet Sci*., **2015**, 98, 142-144. doi:10.1016/j.rvsc.2014.11.010.

[65] Leibbrandt, A.; Meier, C.; König-Schuster, M.; Weinmüllner, R.; Kalthoff, D.; Pflugfelder, B.; Graf, P.; Frank-Gehrke, B.; Beer, M.; Fazekas, T.; Unger, H.; Prieschl-Grassauer, E.; Grassauer, A. Iota-carrageenan is a potent inhibitor of influenza A virus infection. *PloS one*. **2010**, 5, e14320. doi:10.1371/journal.pone.0014320.

[66] Prasedya, E. S.; Miyake, M.; Kobayashi, D.; Hazama, A. Carrageenan delays cell cycle progression in human cancer cells in vitro demonstrated by FUCCI imaging. *BMC Complement Altern Med*. **2016**, 16, 2-9.doi: 10.1186/s12906-016-1199-5.

[67] Lu, C. X.; Li, J.; Sun, Y. X.; Qi, X.; Wanga, Q. J.; Xin, X. L.; Geng, M. Y. Sulfated polymannuroguluronate, a novel anti-AIDS drug candidate, inhibits HIV-1 Tat-induced angiogenesis in Kaposi's sarcoma cells. *Biochem. Pharmacol*. **2007**, 74, 1330-1339. doi:10.1016/j.bcp.2007.06.012.

[68] Liu, H.; Geng, M.; Xin, X.; Li, F.; Zhang, Z.; Li, J.; Ding, J. Multiple and multivalent interactions of novel anti-AIDS drug candidates, sulfated polymannuronate (SPMG)-derived oligosaccharides, with gp120 and their anti-HIV activities. *Glycobiology*. **2005**, 15, 501-510. doi:10.1093/glycob/cwi031.

[69] Miao, B.; Geng, M.; Li, J.; Li, F.; Chen, H.; Guan, H.; Ding, J. Sulfated polymannuroguluronate, a novel anti-acquired immune deficiency syndrome (AIDS) drug candidate, targeting CD4 in lymphocytes. *Biochem Pharmacol*. **2004**, 68, 641-649. doi:10.1016/j.bcp.2004.04.009.

[70] Pomin, V. H.; Mulloy, B. Glycosaminoglycans and Proteoglycans. *Pharmaceuticals*. **2018**, 11, 27. doi: 10.3390/ph11010027.

[71] Vasconcelos, A. A.; Pomin, V. H. The Sea as a Rich Source of Structurally Unique Glycosaminoglycans and Mimetics. *Microorganisms*. **2017**, 5, 51. doi:10.3390/microorganisms5030051.

[72] Andrade, G. P. V.; Lima, M. A.; Souza Jr., A. A.; Fareed, J.; Hoppensteadt, D. A.; Santos, E. A.; Chavante, S. F.; Oliveira, F. W.; Rocha, H. A. O.; Nader, H. B. A heparin-like compound isolated from a marine crab rich in glucuronic acid 2-O-sulfate presents low anticoagulant activity. *Carbohydr. Polym*. **2013**, 94, 647-654. doi:10.1016/j.carbpol.2013.01.069.

[73] Brito, A. S.; Arimatéia, D. S.; Souza, L. R.; Lima, M. A.; Santos, V. O.; Medeiros, V. P.; Ferreira, P. A.; Silva, R. A.; Ferreira, C. V.; Justo, G. Z.; Leite, E. L.; Andrade, G. P.; Oliveira, F. W.; Nader, H. B.; Chavante, S. F. Anti-inflammatory properties of a heparin-like glycosaminoglycan with reduced anti-coagulant activity isolated from a marine shrimp. *Bioorg Med Chem*. **2008**, 16, 9588-9595. doi: 10.1016/j.bmc.2008.09.020.

[74] Dietrich, C. P.; Paiva, J. F.; Castro, R. A.; Chavante, S. F.; Jeske, W.; Fareed, J.; Gorin, P. A.; Mendes, A.; Nader, H. B. Structural features and anticoagulant activities of a novel natural low molecular weight heparin from the shrimp *Penaeus brasiliensis*. *Biochim Biophys Acta*. **1999**, 1428, 273-283. doi:10.1016/S0304-4165(99)00087-2.

[75] Nader, H.B.; Lopes, C. C.; Rocha, H. A.; Santos, E. A.; Dietrich, C. P. Heparins and heparinoids: occurrence, structure and mechanism of antithrombotic and hemorrhagic activities. *Curr. Pharm. Des*. **2004**, 10, 951-66. doi : 10.2174/1381612043452758.

[76] Dreyfuss, J. L.; Regatieri, C. V.; Lima, M. A.; Paredes-Gamero, E. J.; Brito, A. S.; Chavante, S. F.; Belfort, R. Jr.; Farah, M. E.; Nader, H. B. A heparin mimetic isolated from a marine shrimp suppresses neovascularization. *J Thromb Haemost*. **2010**, 8, 1828-1837. doi: 10.1111/j.1538-7836.2010.03916.x.

[77] Belmiro, C. L.; Castelo-Branco, M. T.; Melim, L. M.; Schanaider, A.; Elia, C.; Madi, K.; Pavão, M. S.; de Souza, H. S. Unfractionated heparin and new heparin analogues from ascidians (chordate-tunicate) ameliorate colitis in rats. *J Biol Chem*. **2009**, 284, 11267-11278. doi: 10.1074/jbc.M807211200.

[78] Pomin, V. H. $^1$H and (15)N NMR Analyses on Heparin, Heparan Sulfates and Related Monosaccharides Concerning the Chemical Exchange Regime of the N-Sulfo-Glucosamine Sulfamate Proton. *Pharmaceuticals*. **2016**, 9, 58. doi: 10.3390/ph9030058.

Peer-reviewed version available at *Mar. Drugs* **2018**, *16*, 233; doi:10.3390/md16070233

[79] Chavante,S. F.; Santos, E. A.; Oliveira, F. W.; Guerrini, M.; Torri, G.; Casu, B.; Dietrich, C. P.; Nader, H. B. A novel heparan sulphate with high degree of N-sulphation and high heparin cofactor-II activity from the brine shrimp *Artemia franciscana. Int J Biol Macromol*. **2000**, 27, 49-57. doi: 10.1016/S0141-8130(99)00114-2.

[80] Gomes, A. M.; Kozlowski, E. O.; Pomin, V. H.; de Barros, C. M.; Zaganeli, J. L.; Pavão, M. S. Unique extracellular matrix heparan sulfate from the bivalve *Nodipecten nodosus* (Linnaeus, 1758) safely inhibits arterial thrombosis after photochemically induced endothelial lesion. *J Biol Chem*. **2010**, 285, 7312-7323. doi: 10.1074/jbc.M109.091546.

[81] Gomes, A. M.; Kozlowski, E. O.; Borsig, L.; Teixeira, F. C.; Vlodavsky, I.; Pavão, M. S. Antitumor properties of a new non-anticoagulant heparin analog from the mollusk *Nodipecten nodosus*: Effect on P-selectin, heparanase, metastasis and cellular recruitment. *Glycobiology*. **2015**, 25, 386-393. doi: 10.1093/glycob/cwu119.

[82] Volpi. N.; Maccari, F. Structural characterization and antithrombin activity of dermatan sulfate purified from marine clam *Scapharca inaequivalvis*. *Glycobiology*. **2009**, 4, 356-367. doi: 10.1093/glycob/cwn140.

[83] Gandra, M.; Cavalcante, M. C. M.; Pavão, M. S. G. Anticoagulant sulfated glycosaminoglycans in the tissues of the primitive chordate *Styela plicata* (Tunicata). *Glycobiology*, **2000**, 10, 1333-1340. doi: 10.1093/glycob/10.12.1333.

[84] Pavão, M. S. G.; Mourão, P. A. S.; Mulloy, B.; Tollefsen, D. M. A Unique Dermatan Sulfate-like Glycosaminoglycan from Ascidian. Its structure and the effect of its unusual sulfation pattern on anticoagulant activity. *J. Biol. Chem*. **1995**, 270, 31027-31036. doi: 10.1074/jbc.270.52.31027.

[85] Pavão, M. S.; Aiello, K. R.; Werneck, C. C.; Silva, L. C.; Valente, A. P.; Mulloy, B.; Colwell, N. S.; Tollefsen, D. M.; Mourão, P. A. Highly sulfated dermatan sulfates from Ascidians. Structure versus anticoagulant activity of these glycosaminoglycans. *J Biol Chem*. **1998**, 273, 27848-27857. doi: 10.1074/jbc.273.43.27848.

[86] Kozlowski, E. O.; Pavão, M. S.; Borsig, L. Ascidian dermatan sulfates attenuate metastasis, inflammation and thrombosis by inhibition of P-selectin. *J Thromb Haemost*. **2011**, 9, 1807-1815. doi: 10.1111/j.1538-7836.2011.04401.x.

[87] Pomin, V. H. Holothurian Fucosylated Chondroitin Sulfate. *Mar. Drugs*. **2014**, 1, 232–254. doi: 10.3390/md12010232.

[88] Zhang, X.; Yao, W.; Xu, X.; Sun, H.; Zhao, J.; Meng, X.; Wu, M.; Li, Z. Synthesis of Fucosylated Chondroitin Sulfate Glycoclusters: A Robust Route to New Anticoagulant Agents. *Chemistry*. **2018**, 24, 1694-1700. doi: 10.1002/chem.201705177.

[89] Liu, X.; Liu, Y.; Hao, J.; Zhao, X.; Lang, Y.; Fan, F.; Cai, C.; Li, G.; Zhang, L.; Yu, G. In Vivo Anti-Cancer Mechanism of Low-Molecular-Weight Fucosylated Chondroitin Sulfate (LFCS) from Sea Cucumber *Cucumaria frondosa*. *Molecules*. **2016**, 21, pii: E625. doi: 10.3390/molecules21050625.

[90] Panagos, C. G.; Thomson, D. S.; Moss, C.; Hughes, A. D.; Kelly, M. S.; Liu, Y.; Chai, W.; Venkatasamy, R.; Spina, D.; Page, C. P.; Hogwood, J.; Woods, R. J.; Mulloy, B.; Bavington, C. D.; Uhrín, D. Fucosylated chondroitin sulfates from the body wall of the sea cucumber *Holothuria forskali*: conformation, selectin binding, and biological activity. *J Biol Chem*. **2014**, 289, 28284-28298. doi: 10.1074/jbc.M114.572297.

[91] Huang, N.; Wu, M. Y.; Zheng, C. B.; Zhu, L.; Zhao, J. H.; Zheng, Y. T. The depolymerized fucosylated chondroitin sulfate from sea cucumber potently inhibits HIV replication via interfering with virus entry. *Carbohydr. Res*. **2013**, 380, 64-69. doi: 10.1016/j.carres.2013.07.010.

[92] Mou, J.; Li, Q.; Qi, X.; Yang, J. Structural comparison, antioxidant and anti-inflammatory properties of fucosylated chondroitin sulfate of three edible sea cucumbers. *Carbohydr. Polym*. **2018**, 185, 41-47. doi: 10.1016/j.carbpol.2018.01.017.

[93] Ustyuzhanina, N.E.; Bilan, M. I.; Dmitrenok, A. S.; Shashkov, A. S.; Kusaykin, M. I.; Stonik, V. A.; Nifantiev, N. E.; Usov, A. I. Structure and biological activity of a fucosylated chondroitin sulfate from the sea cucumber *Cucumaria japonica*. *Glycobiology*. **2016**, 5, 449-459. doi: 10.1093/glycob/cwv119.

[94] Li, Q.; Cai, C.; Chang, Y.; Zhang, F.; Linhardt, R. J.; Xue, C.; Li, G.; Yu, G. A novel structural fucosylated chondroitin sulfate from *Holothuria Mexicana* and its effects on growth factors binding and anticoagulation. *Carbohydr. Polym*. **2018**, 181, 1160-1168. doi: 10.1016/j.carbpol.2017.10.100.

[95] Yang, L.; Wang, Y.; Yang, S.; Lv, Z. Separation, purification, structures and anticoagulant activities of fucosylated chondroitin sulfates from *Holothuria scabra*. *Int J Biol Macromol*. **2018**, 108, 710-718. doi: 10.1016/j.ijbiomac.2017.11.058.

[96] Hoshino, H.; Heiwamachi, M. Anti-HIV Drug. EP 0410002A1. European Patent. **1991**.

[97] Pomin, V. H. Marine medicinal glycomics. *Front Cell Infect Microbiol*. **2014**, 4, 5. doi: 10.3389/fcimb.2014.00005.

[98] Kumirska, J.; Czerwicka, M.; Kaczyński, Z.; Bychowska, A.; Brzozowski, K.; Thöming, J.; Stepnowski, P. Application of spectroscopic methods for structural analysis of chitin and chitosan. *Mar. Drugs*. **2010**, 8, 1567-636. doi: 10.3390/md8051567.

[99] Venkatesan, J.; Vinodhini, P. A.; Sudha, P. N.; Kim, S. K. Chitin and chitosan composites for bone tissue regeneration. *Adv Food Nutr Res*. **2014**, 73, 59-81. doi: 10.1016/B978-0-12-800268-1.00005-6.

[100] Liu, H.; Tian, W.; Li, B.; Wu, G.; Ibrahim, M.; Tao, Z.; Wang, Y.; Xie, G.; Li, H.; Sun, G. Antifungal effect and mechanism of chitosan against the rice sheath blight pathogen, *Rhizoctonia solani*. *Biotechnol Lett*. **2012**, 34, 2291-2298. doi: 10.1007/s10529-012-1035-z.

[101] Berger, L. R. R.; Stamford, N. P.; Willadino, L. G.; Laranjeira, D.; de Lima, M. A. B.; Malheiros, S. M. M.; de Oliveira, W. J.; Stamford, T. C. M. Cowpea resistance induced against *Fusarium oxysporum* f. sp. *tracheiphilum* by crustaceous chitosan and by biomass and chitosan obtained from *Cunninghamella elegans*. *Biol. Control*. **2016**, 92, 45-54. doi: 10.1016/j.biocontrol.2015.09.006.

[102] Divya, K.; Vijayan, S.; George, T.K.; Jisha, M. Antimicrobial properties of chitosan nanoparticles: Mode of action and factors affecting activity. *Fibers and Polymers*. **2017**, 18, 221-230. doi: 10.1007/s12221-017-6690-1.

[103] Salah, R.; Michaud, P.; Mati, F.; Harrat, Z.; Lounici, H.; Abdi, N.; Drouiche, N.; Mameri, N. Anticancer activity of chemically prepared shrimp low molecular weight chitin evaluation with the human monocyte leukaemia cell line, THP-1. *Int. J. Biol. Macromol*. **2013**, 52, 333-339. doi: 10.1016/j.ijbiomac.2012.10.009.

[104] Trung, T. S.; Bao, H. N. D. Physicochemical Properties and Antioxidant Activity of Chitin and Chitosan Prepared from Pacific White Shrimp Waste. *Inter. J. Carbohydr. Chem.* **2015**, 2015, 6. doi:10.1155/2015/706259.

[105] Sarbon, N. M.; Sandanamsamy, S.; Kamaruzaman, S. F.; Ahmad, F. Chitosan extracted from mud crab (*Scylla olivicea*) shells: physicochemical and antioxidant properties. *J. Food Sci. Technol*. **2015**, 7, 4266-75. doi: 10.1007/s13197-014-1522-4.

[106] Divya, K.; Smitha, V.; Jisha, M. S. Antifungal, antioxidant and cytotoxic activities of chitosan nanoparticles and its use as an edible coating on vegetables. *Int J Biol Macromol*. **2018**, 114, 572-577. doi: 10.1016/j.ijbiomac.2018.03.130.

[107] Srinivasan, H.; Kanayairam, V.; Ravichandran, R. Chitin and chitosan preparation from shrimp shells *Penaeus monodon* and its human ovarian cancer cell line, PA-1. *Int. J. Biol. Macromol*. **2018**, 107, 662-667. doi: 10.1016/j.ijbiomac.2017.09.035.

[108] Mondol, M. A. M., Shin, H. J., Rahman, M. A., & Islam, M. T. Sea Cucumber Glycosides: Chemical Structures, Producing Species and Important Biological Properties. *Mar. Drugs*. **2017**, 15, 317-352. doi: 10.3390/md15100317.

[109] Aminin, D. L.; Menchinskaya, E. S.; Pisliagin, E. A.; Silchenko, A. S.; Avilov, S. A.; Kalinin, V. I. Anticancer Activity of Sea Cucumber Triterpene Glycosides. *Mar. Drugs*. **2015**, 13, 1202-1223. doi: 10.3390/md13031202.

[110] Malyarenko, O. S.; Dyshlovoy, S. A.; Kicha, A. A.; Ivanchina, N. V.; Malyarenko, T. V.; Carsten, B.; Gunhild, V. A.; Stonik, V. A.; Ermakova, S. P. The Inhibitory Activity of Luzonicosides from the Starfish *Echinaster luzonicus* against Human Melanoma Cells. *Mar. Drugs*. **2017b**, 15, 227. doi: 10.3390/md15070227.

[111] Kalinin, V. I.; Ivanchina, N. V.; Krasokhin, V. B.; Makarieva, T. N.; Stonik, V. A. Glycosides from Marine Sponges (Porifera, Demospongiae): Structures, Taxonomical Distribution, Biological Activities and Biological Roles. *Mar. Drugs*. **2012**, 10, 1671-1710. doi: 10.3390/md10081671.

[112] Garcia, M. M.; van der Maarel, M. J. E. C. Floridoside production by the red microalga *Galdieria sulphuraria* under different conditions of growth and osmotic stress. *AMB Express*. **2016**, 6, 71. doi: 10.1186/s13568-016-0244-6.

[113] Liu, C. Y.; Hwang, T. L.; Lin, M.-R.; Chen, Y. H.; Chang, Y. C.; Fang, L. S.; Wang, W. H.; Wu, Y. C.; Sung, P. J. Carijoside A, a Bioactive Sterol Glycoside from an Octocoral *Carijoa* sp. (Clavulariidae). *Mar. Drugs*. **2010**, 8, 2014-2020. doi: 10.3390/md8072014.

[114] Li, Y. X.; Li, Y.; Lee, S. H.; Qian, Z. J.; Kim, S. K. Inhibitors of oxidation and matrix metalloproteinases, floridoside, and D-isofloridoside from marine red alga *Laurencia undulata*. *J. Agric. Food Chem*. **2010**, 58, 578-586. doi: 10.1021/jf902811j.

[115] Kumar, R.; Subramani, R.; Feussner, K. D.; Aalbersberg, W. Aurantoside K, a new antifungal tetramic acid glycoside from a Fijian marine sponge of the genus *Melophlus*. *Mar. Drugs*. **2012**, 10, 200-208. doi: 10.3390/md10010200.

[116] Wang, X. H.; Zou, Z. R.; Yi, Y. H.; Han, H.; Li, L.; Pan, M. X. Variegatusides: new non-sulphated triterpene glycosides from the sea cucumber *Stichopus variegates* semper. *Mar. Drugs*. **2014**, 4, 2004-2018. doi: 10.3390/md12042004.

[117] Wang, J.; Han, H.; Chen, X.; Yi, Y.; Sun, H. Cytotoxic and Apoptosis-Inducing Activity of Triterpene Glycosides from *Holothuria scabra* and *Cucumaria frondosa* against HepG2 Cells. *Mar. Drugs*. **2014**, 12, 4274-4290. doi: 10.3390/md12084274.

[118] Park, J. I.; Bae, H. R.; Kim, C. G.; Stonik, V. A.; Kwak, J. Y. Relationships between chemical structures and functions of triterpene glycosides isolated from sea cucumbers. *Front Chem*. **2014**, 2, 77. doi: 10.3389/fchem.2014.00077.

[119] Al Shemaili, J.; Parekh, K. A.; Newman, R. A.; Hellman, B.; Woodward, C.; Adem, A.; Collin, P.; Adrian, T. E. Pharmacokinetics in Mouse and Comparative Effects of Frondosides in Pancreatic Cancer. *Mar. Drugs*. **2016**, 14, 115. doi: 10.3390/md14060115.

[120]. Al Marzouqi, N.; Iratni, R.; Nemmar, A.; Arafat, K.; Al Sultan, A. M.; Yasin, J.; Collin, P.; Mester, J.; Adrian, T.E.; Attoub, S. Frondoside A inhibits human breast cancer cell survival, migration, invasion and the growth of breast tumor xenografts. *Eur. J. Pharmacol*. **2011**, 668, 25-34. doi: 10.1016/j.ejphar.2011.06.023.

[121] Attoub, S.; Arafat, K.; Gélaude, A.; Al Sultan, M. A.; Bracke, M.; Collin, P. L.; Takahashi, T.; Adrian, T. E.; De Wever, O. Frondoside a suppressive effects on lung cancer survival, tumor growth, angiogenesis, invasion, and metastasis. *PLoS ONE*. **2013**, 8, 115. doi: 10.1371/journal.pone.0053087.

Peer-reviewed version available at *Mar. Drugs* **2018**, *16*, 233; doi:10.3390/md16070233

[122] Ma, X.; Kundu, N.; Collin, P. D.; Goloubeva, O.; Fulton, A. M. Frondoside A inhibits breast cancer metastasis and antagonizes prostaglandin E receptors EP4 and EP2. *Breast Cancer Res. Treat*. **2011**, 132, 1001-1008. doi: 10.1007/s10549-011-1675-z.

[123] Murray, R. K. Glycoproteins. In: *Harper's Illustrated Biochemistry*, 26th ed.; Murray, R. K.; Granner, D. K; Mayes, P. A; Rodwell, V. W. McGraw-Hill Companies: New York, USA, **2003**, 514-534, ISBN: 0-07-138901-6.

[124] Zanetta, J. P.; Kuchler, S.; Lehmann, S.; Badache, A.; Maschke, S.; Thomas, D.; Dufourcq, P.; Vincendon, G. Glycoproteins and lectins in cell adhesion and cell recognition processes. *Histochem J*. **1992**, 24, 791-804. doi:10.1007/BF01046351.

[125] Sharon, N.; Lis, H. History of lectins: from hemagglutinins to biological recognition molecules. *Glycobiology*. **2004**, 14, 53R-62R. doi: 10.1093/glycob/cwh122.

[126] Benevides, N. M. B.; Holanda, M. L.; Melo, F. R.; Freitas, A. L. P.; Sampaio, A. H. Purification and Partial Characterisation of the Lectin from the Marine Red Alga *Enantiocladia duperreyi* (C. Agardh) Falkenberg. *Bot. Mar*. **1998**, 41, 521-526. doi: 10.1515/botm.1998.41.1-6.521.

[127] Mu, J.; Hirayama, M.; Sato, Y.; Morimoto, K.; Hori, K. A Novel High-Mannose Specific Lectin from the Green Alga *Halimeda renschii* Exhibits a Potent Anti-Influenza Virus Activity through High-Affinity Binding to the Viral Hemagglutinin**.** *Mar. Drugs*. **2017**, 15, 255; doi: 10.3390/md15080255.

[128] Gundacker, D.; Leys, S. P.; Schröder, H. C.; Müller, I. M.; Müller, W. E. Isolation and cloning of a C-type lectin from the hexactinellid sponge *Aphrocallistes vastus*: a putative aggregation factor. *Glycobiology*. **2001**, 11, 21-29. doi: 10.1093/glycob/11.1.21.

[129] Bulgakov, A. A.; Park, K. I.; Choi, K. S.; Lim, H. K.; Cho, M. Purification and characterisation of a lectin isolated from the *Manila clam Ruditapes philippinarum* in Korea. *Fish Shellfish Immunol*. **2004**, 4, 487-99. doi: 10.1016/j.fsi.2003.08.006.

[130] Hatakeyama, T.; Kohzaki, H.; Nagatomo, H.; Yamasaki, N. Purification and characterization of four Ca(2+)-dependent lectins from the marine invertebrate, *Cucumaria echinata*. *J Biochem*. **1994**, 116, 209-214. doi: 10.1093/oxfordjournals.jbchem.a124495.

[131] Silva, L. M.; Lima, V.; Holanda, M. L.; Pinheiro, P. G.; Rodrigues, J. A.; Lima, M. E.; Benevides, N. M. Antinociceptive and anti-inflammatory activities of lectin from marine red alga *Pterocladiella capillacea*. *Biol. Pharm. Bull*. **2010**, 33, 830-835. doi: 10.1248/bpb.33.830.

[132] Abreu, T. M.; Ribeiro, N. A.; Chaves, H. V.; Jorge, R. J.; Bezerra, M. M.; Monteiro, H. S.; Vasconcelos, I. M.; Mota, É. F.; Benevides, N. M. Antinociceptive and Anti-inflammatory Activities of the Lectin from Marine Red Alga *Solieria filiformis*. *Planta Med*. **2016**, 7, 596-605. doi: 10.1055/s-0042-101762.

[133] Fontenelle, T. P. C.; Lima, G. C.; Mesquita, J. X.; Lopes, J. L. S.; de Brito, T. V.; Vieira Jr., F. D. C.; Sales, A. B.; Aragão, K. S.; Souza, M. H. L. P.; Barbosa, A. L. D. R.; Freitas, A. L. P. Lectin obtained from the red seaweed *Bryothamnion triquetrum*: Secondary structure and anti-inflammatory activity in mice. *Int. J. Biol. Macromol*. **2018**, 112, 1122-1130. doi: 10.1016/j.ijbiomac.2018.02.058.

[134] Liao, J. H.; Chien, C. T.; Wu, H. Y.; Huang, K. F.; Wang, I.; Ho, M. R.; Tu, I. F.; Lee, I. M.; Li, W.; Shih, Y. L.; Wu, C. Y.; Lukyanov, P. A.; Hsu, S. T.; Wu, S. H. A Multivalent Marine Lectin from *Crenomytilus grayanus* Possesses Anti-cancer Activity through Recognizing Globotriose Gb3. *J. Am. Chem. Soc*. **2016**, 138, 4787-95. doi: 10.1021/jacs.6b00111.

[135] Liu, S.; Zheng, L.; Aweya, J. J.; Zheng, Z.; Zhong, M.; Chen, J.; Wang, F.; Zhang, Y. *Litopenaeus vannamei* hemocyanin exhibits antitumor activity in S180 mouse model *in vivo*. *Plos one*. **2017**, 12, e0183783. doi: 10.1371/journal.pone.0183783.

[136] Róg, T.; Vattulainen, I. Cholesterol, sphingolipids, and glycolipids: what do we know about their role in raft-like membranes? *Chem Phys Lipids.* **2014**, 184, 82-104. doi: 10.1016/j.chemphyslip.2014.10.004.

[137] Ratnayake, W. M. N.; Galli, C. Fat and Fatty Acid Terminology, Methods of Analysis and Fat Digestion and Metabolism: A Background Review Paper. *Ann. Nutr. Metab.* **2009**, 55, 8-43. doi: 10.1159/000228994.

[138] Che, H.; Du, L.; Cong, P.; Tao, S.; Ding, N.; Wu, F.; Xue, C.; Xu, J.; Wang, Y. Cerebrosides from Sea Cucumber Protect Against Oxidative Stress in SAMP8 Mice and PC12 Cells. *J Med Food*. **2017**, 20, 392-402. doi: 10.1089/jmf.2016.3789.

[139] Yamada, K. Chemo-pharmaceutical studies on the glycosphingolipid constituents from echinoderm, sea cucumbers, as the medicinal materials. *Yakugaku Zasshi.* **2002**, 122, 1133-43. doi: 10.1248/yakushi.122.1133.

[140] Hölzl, G.; Dörmann, P. Structure and function of glycoglycerolipids in plants and bacteria. *Prog Lipid Res*. **2007**, 46, 225-43. doi: 10.1016/j.plipres.2007.05.001.

[141] Mansoor, T. A.; Shinde, P. B.; Luo, X.; Hong, J.; Lee, C. O.; Sim, C. J.; Son, B. W.; Jung, J. H. Renierosides, cerebrosides from a marine sponge *Haliclona* (Reniera) sp. *J Nat Prod.* **2007**, 70, 1481-1486. doi: 10.1021/np070078u.

[142] Plouguerné, E.; da Gama, B. A. P.; Pereira, R. C.; Barreto-Bergter, E. Glycolipids from seaweeds and their potential biotechnological applications. *Front Cell Infect Microbiol*. **2014**, 4, 174. doi: 10.3389/fcimb.2014.00174.

[143] Banskota, A. H.; Stefanova, R.; Sperker, S.; Lall, S. P.; Craigie, J. S.; Hafting, J.T.; Critchley, A. T. Polar lipids from the marine macroalga *Palmaria palmata* inhibit lipopolysaccharide-induced nitric oxide production in RAW264.7 macrophage cells. *Phytochemistry*. **2014**, 101, 101-108. doi: 10.1016/j.phytochem.2014.02.004.

[144] Reyes,C.; Ortega, M. J.; Rodríguez-Luna, A.; Talero, E.; Motilva, V.; Zubía, E. Molecular Characterization and Anti-inflammatory Activity of Galactosylglycerides and Galactosylceramides from the Microalga *Isochrysis galbana*. *J. Agric. Food Chem*. **2016**, *64*, 8783-8794. doi**:** 10.1021/acs.jafc.6b03931.

[145] Zhang, J.; Li, C.; Yu, G.; Guan, H. Total synthesis and structure-activity relationship of glycoglycerolipids from marine organisms. *Mar. Drugs*. **2014**, 12, 3634-3659. doi: 10.3390/md12063634 .

[146] Simmonds, M. S. J.; Klte, G. C.; Porter, E. A. Taxonomic Distribution of Iminosugars in Plants and Their Biological Activities. In: *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*. Stiitz, A. E. Wiley-VCH Verlag GmbH, **1999**, 8-30, ISBN: 3-527-29544-5.

[147] Segraves, N. L.; Crews, P. A Madagascar Sponge *Batzella* sp. as a Source of Alkylated Iminosugars. *J. Nat. Prod.* **2005,** 68, 118-121. doi: 10.1021/np049763g.

[148] Chang, J.; Wang, L.; Ma, D.; Qu, X.; Guo, H.; Xu, X.; Mason, P. M.; Bourne, N.; Moriarty, R.; Gu, B.; Guo, J. T.; Block, T. M. Novel imino sugar derivatives demonstrate potent antiviral activity against flaviviruses. *Antimicrob Agents Chemother*. **2009**, 53, 1501-1508. doi: 10.1128/AAC.01457-08.

[149] Jüttner, F.; Wessel, H. P. Isolation of di(hydroxymethyl)dihydroxypyrrolidine from the cyanobacterial genus *Cylindrospermum* that effectively inhibits digestive glucosidases of aquatic insects and crustacean grazers. *J. Phycology*. **2003**, 39, 26-32. doi:10.1046/j.1529-8817.2003.02029.x.

[150] Birch, A. N. E.; Robertson, W. M.; Geoghegan, I.E.; McGavin, W. J.; Alphey, T.J.W.; Phillips, M. S.; Fellows, L. E.; Watson, A. A.; Simmonds, M. S. J.; Porter, E. A. Dmdp - a Plant-Derived Sugar Analogue With Systemic Activity Against Plant Parasitic Nematodes. *Nematologica*. **1993**, 39, 521-535. doi: 10.1163/187529293X00466.

[151] Sayce, A. C.; Alonzi, D. S.; Killingbeck, S. S.; Tyrrell, B. E.; Hill, M. L.; Caputo, A. T.; Iwaki, R.; Kinami, K.; Ide, D.; Kiappes, J. L.; Beatty, P. R.; Kato, A.; Harris, E.; Dwek, R. A.; Miller, J. L.; Zitzmann, N.

Iminosugars Inhibit Dengue Virus Production via Inhibition of ER Alpha-Glucosidases-Not Glycolipid Processing Enzymes. *PLoS Negl Trop Dis.* **2016**, 10, e0004524. doi: 10.1371/journal.pntd.0004524.