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Acknowledging Sulfated Polysaccharides from Marine Macroalgae Multi-Functional Properties

Farid Che Ghazali[1*], Abdul Qudus B Aroyehun[2], Shariza Abdul Razak[2]
[1]BioMedicine Program, School of Health Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan DN, Malaysia
[2]Nutrition Program, School of Health Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan DN, Malaysia

***Corresponding author**
Farid Che Ghazali

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Abstract: Marine macroalgae produce a great variety of biological active compounds which cannot be scientifically characterized with in other organism's biomass. These marine habitats have been scientifically reported for modern medicinal uses although rheteoratically associated to coastal communities' healthy eating and folk medicine practice. In tandem to this, these marine macroalgae have highly potentiate themselves as a tangible source of functional ingredients that is industrial applicable. Globally various division of geochemical marine macroalgae flora taxa (Chlorophyta, Phaeophyta, and Rhodophyta) flourish. However, despite substantial optimised yield and empirical evidence of their health potential benefits, these macroalgae remained largely pharmaceutical and medical related industries innovative unexploited. Of these leads compounds, sulfated polysaccharides offer a wide range of physiological and chemical-biological activities that include antioxidative, anticoagulant, antiviral, antitumor, anti-inflammatory, antihyperlipidemic and antihepatotoxic activities. *Per se*, the optimization of sulfated polysaccharides as functional food and *Vis a Vis*, as therapeutic agents is this millennium important research agenda. As such, this review extrapolates the bioprospect of sulfated polysaccharides (Sulfated galactans, Fucans, and Ulvans) from geochemical signature macroalgae potential context as functional food and as tangible source for drug discovery.
Keywords: Marine macroalgae, sulfated polysaccharides, bioactivity, functional food

INTRODUCTION

Marine biodiversity and its ecosystem, valuable sources of structurally diverse bioactive compounds

The marine eco-environment and its intertidal habitat is a creation of multi biodiverse, vastly unexplored communities with associated geochemical signatures. In tandem to this, at present the millennium industrial revolution agenda is focussed towards the outsourcing for natural product lead compounds that is of a biochemically tangible homogenous, biocompatible, excluded from zoonotic and gene mutation disease liability. The outsourcing of these natural product leads compounds is just not to ensure better management, a sustainable legacy of resources for future generation, but also to ensure cost effectively and uneconomic compliance of chronic systemic diseases affecting the present humankind communities. This industrial revolution has initiated soul searching exploration and the domestication of intertidal marine biodiversity. As such these activities on biodiverse world ocean ecosystem have untapped and transfer tangible knowledge for sustainable commercial optimisation. *Per se*, much attention is now focused to outsourcing for natural bioactive compounds as functional ingredients in neutraceuticals. Marine based organisms and invertebrates and algae are considered as valuable sources of structurally diverse bioactive compounds [1, 2]. Intertidal marine organisms and flora, macroalgae or seaweeds have a long well-documented history in folk medicine, fisheries industries and economic of coastal communities globally. As such, these marine floras have been an integral part of human civilization and the records of their utilization dates to 1300 years ago [late Pleistocene settlement] in Chile [3]. Most members of the genus Sargassum are perennial plants that are able to live through several rounds of growth cycles in its lifetime. [As such are submitted to extreme conditions such as changes in salinity, temperature, nutrients, UV-VIS irradiation and others. In order to survive, they must adapt rapidly to the new environmental conditions, producing a great variety of secondary metabolites which cannot be found in other organisms]. It has been reported that during periods of harsh environments, macroalgae would dieback and leave a short primary axis attached to its perennial holdfast [4]. When conditions are ideal, primary branches arise again from the surviving thallus until the onset of reproduction again. It could take several years before macroalgae genus senesce and die off. Thus, tagging each

individual plant by using a nondestructive method would ensure a more accurate representation of a typical macroalgae life history.

Current research revealed that seaweeds have potential medicinal uses against cancer, allergy, diabetes, oxidative stress, inflammation, thrombosis, obesity, lipidemia, hypertensive and other degenerative ailments. Moreover, their taxonomic diversity, and as a under exploited plant resource especially in the search of new biological active compounds, can be seen as an almost unlimited field. Scientific documentations have supported the presence of valuable sources of structurally diverse natural bioactive compounds with potential therapeutic applications in life sciences [5, 6]. Most of the members contain high concentration of macronutrients that serve as additives to fertilisers (Demir *et al.* 2006), polyunsaturated fatty acids that are useful in cosmetic products (Zubia *et al.* 2008), and many industrially important polysaccharides, namely alginate, fucoidans, mannitol, and phlorotannins (Zubia *et al.* 2008). As such the macroalgae biomass was purported enriched with sulfated polysaccharides, dietary fiber, lipids, PUFAs, proteins, essential amino acids, minerals and vitamins [7]. As such these marine macrophytic algae 'seaweeds' represent one of the important living renewable resources of the marine ecosystem. Globally there are various division existences of geochemical marine macroalgae flora taxa (Chlorophyta, Phaeophyta, and Rhodophyta). In tandem to this, these macroalgae are mainly classified into three categories based on their naked eye observed pigmentation. As such based on this pigmentation they are classified as red algae, brown algae, and green algae. Naturally, the demand for seaweed products has generated the impetus for increased knowledge; however, research on the biology, ecology, biochemistry and the life cycle of macroalgae seaweed species, which can be relatively complex, *vis a vis*, helped unlock the capacity to bring some of the world seaweed species, into culture thus optimised-able for humankind.

Marine Macroalgae Sulfated Polysaccharides

Seaweeds (marine macroalgae) are extensively used as functional foods and medicinal herbs, and have a long history of use and optimised in Asian countries folk-medicine. These macroalgae have long been used for the treatment of cancer, many crude or partially purified polysaccharides from various brown, green, and red macroalgae have been tested for their antitumor activities. These studies have indicated that marine algae constitute a promising source of novel compounds with potential as human therapeutic agents. Bioactive compounds extracted from synthetic or natural sources have shown potential in health therapeutic management [8]. As such these natural product have the capacity to alter the genetic expression of a host of cellular events, thereby influencing or impacting numerous biological activities [9] ranging from antioxidant or enzyme inhibitory activities, anti-inflammatory, antimicrobial and anti-cancer potentials [10, 11]. The cell wall structure of the marine algae consists mainly of polysaccharides and mucopolysaccharides [12-14]. These polysaccharides are polymers of simple sugars (monosaccharides) linked together by glycosidic bonds which physically support the thallus in water, though they are less rigid/strong compared to terrestrial plants and trees. Sulfated polysaccharides optimized from marine macroalgae, are non-toxic but sadly have varying presence among the macroalgae species. Sulfated polysaccharides protect the human anatomy pathophysiologically against detrimental tissue damage by reactive oxygen species (ROS), which attack macromolecules such as membrane lipids, proteins, and DNA, leading to many health disorders such as cancer, diabetes mellitus, aging and neurodegenerative diseases [15]. The *in vitro* antioxidant activity of marine algae-derived sulfated polysaccharides can be determined by various bioassay which includes total antioxidant power assay, metal-ion chelating ability, ferric reducing antioxidant power (FRAP) assay, 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, 2,2' -azino-bis (3-ethylbenzothizoline-6-sulphonic acid) (ABTS) radical scavenging assay, singlet oxygen quenching activity, lipid peroxide inhibition, superoxide and hydroxyl radical scavenging assays [15-19]. While, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG) and tert-butylhydroxytoluene (TBHQ) are the most commonly used synthetic antioxidants, they are now considered a risk factor for liver damage and carcinogenesis (Grice, 1988), thus it is essential to develop and utilize effective natural antioxidants that they can prevent or inhibit free radicals in the human body thereby retarding the progress of many chronic diseases (Nandita *et al.*, 2004). The development of a standardized marine macroalgal sulfated polysaccharide based product is a challenge, as their structure and properties are influenced by seasonal and climatic variations. Their high molecular weight and low bioavailability also form hurdles [20]. Despite these difficulties, scientists have succeeded in elucidating several biological significances for macroalgal derived sulfated polysaccharides in key therapeutic areas. Thus the writeup of this review aims to enumerate the relationship between structural characterization and bioactivities relations of sulfated polysaccharides from these marine macroalgae as a reflection of its potentials to be a source for drugs discovery, functional food and neutraceuticals exploitables, expecially those potentials ascribed to the edible marine macroalgae.

Chemical Properties, Structure and Bioactivity Relationship of Sulfated Polysaccharides

The bioactive mechanisms of crude sulfated polysaccharides extracted from marine macroalgae can be attributed to the relationship between sulphate content, physio-chemical properties and functional groups. The structural elucidation of sulfated

polysaccharides can be achieved using the Fourier Transform Infrared (FT-IR) Spectra Analysis and C-NMR spectroscopy, they reveal bands the characteristics of each functional groups present and details of attached sulfate esters along their backbones and glycosidic linkage types, as well as anomeric configurations and positions of branching or sulfation on the galactose residue responsible for their biological activity. Mass spectrometry (MS) structural analysis of sulfated polysaccharide provides precise and accurate molecular mass data of oligosaccharides components. The difficulty to identify the relationship between the chemical structure of algal sulfated polysaccharides and its biological activities, has also resulted in the application of several protocols which may include extraction and purification technique, source of macroalgae, structural characterisation, physio-chemical properties, oligosaccharides composition, reductive hydrolysis, acetylation of sulfated and desulfated polysaccharides, and sometimes comparison of information with the sulfated polysaccharides of marine invertebrates (sea cucumber and sea urchins) of regular structure and extensive research [21, 22].

The biochemical and molecular mechanism understanding of sulfated polysaccharides is thus important to maximize its therapeutic agent potentials. The monomeric components, molecular size, sulfate content, structural characterization and its degree of branching are important for its reproducibility and mechanisms of activity as a potential drug. The anticoagulant mechanism of sulfated polysaccharides lies in its ability to inhibit plasma proteases via allosteric changes as reported by [23]. The stereo specificities of some complexes are a factor of the number of residues in the repeating units, spatial patterns of sulfate groups, anomeric configuration, and glycosidic linkage position, molecular mass and esteric hindrances [24, 25] while heterogeneities such as methylation, acetylation, and pyruvilation are responsible in eliciting variations in functionality [26]. Studies have reveal oligosaccharides with well-defined chemical structures from sulfated fucan extrapolate carbohydrate–protein interactions [27]. The sulfated galactans of algae procoagulant effect along with the serpin-dependent anticoagulant activity is a factor for the sulfation pattern [28]. Thus sulfated polysaccharides structural attributes are very important for their biological activities however their present heterogeneous structure is a limiting factor. To resolve the problem pertaining to the algal sulfated polysaccharides heterogeneity, further informative approaches may be needed to deduce the functionality of these algal sulfated polysaccharides [25]. A low molecular weight sulfated polysaccharides can readily be incorporated into cells to reveal potent radical scavenging capabilities [29-32] than the high molecular weight. Till date, there seems to be no clear effect of the molecular weight of polysaccharides observed with any contradictory results [24, 33, 34], suggesting that composition and sequence of monosaccharides, configuration and position of glycosidic linkages, position of branching points could be the determinant thus requiring further studies [35, 36].

Bioprospect of Sulfated Polysaccharides representative; Alginic acid, Laminarins and Fucoidan from Marine Macroalgae

Marine macroalgae have been considered as a potential source of new bioactive compounds. Sulfated polysaccharides can be found in marine environment, in different macroalgae taxonomy. These polysaccharides don't have equivalent in the terrestrial plants and resembles the chemical and biological properties of mammalian glycosaminoglycans. In this perspective, are receiving growing interest for application on health-related fields. These sulfated polysaccharides have been optimized as fucoidan, alginate and laminarins (β-1, 3 glucan) of brown macroalgae, sulfated galactan/ carrageenans from red algae while ulvan/heteropolysaccharides in the green macroalgae [37-39]. These said polysaccharides are purported to contained polyanions that are majorly substituted by sulfate, thus differentiating it from those polysaccharides extracted from terrestrial plants sources [40]. The cell wall matrix of the brown macroalgae is mainly composed of fucoidan, alginate, and laminarin (3:1:1) and their derivatives. These reserve polysaccharides provide strength and flexibility, prevent desiccation and maintain ionic equilibrium. They are suitably used as thickeners and gelation agents. Alginate, a linear anionic polysaccharide with 1, 4-linked b-D-mannuronic acid and a-L-glucuronic acid residues, is commercially used as a gelling agent in biotechnology products while Laminarin, contains (1, 3)-b-D-glucopyranose residues, with relatively low molecular weight with structural features which are species and seasonal dependent [41]. Fucoidans are complex sulfated polysaccharides found in the extracellular matrix of the brown algae. They account for 10–20% dw, consisting mainly of sulfated L-fucose and small proportions of galactose, mannose, xylose, glucose, rhamnose and uronic acids [26, 27, 42]. Fucoidans are not found in other divisions of algae nor in land plants, but predominantly the Phaeophyceae and they show more complex and heterogeneous composition and structure than the related polymers found in marine invertebrates (homofucan sulfate), which contain only fucose and sulfate groups [5]. Fucans are very soluble, slightly viscous solutions and the technologies inputs include; extraction of low molecular weight compounds, extraction with water, acid or calcium chloride, or aided by hydrolytic enzymes, ultrasound, and microwave, precipitation and purification. The depolymerisation of crude fucoidans can be attained by chemical, physical, enzymatic process [33, 44] and the radical induced [45, 46].

Bioprospect of Sulfated Polysaccharides representative; Agar and Carrageenans from Marine Macroalgae

The sulfated polysaccharides representative obtained from different species of Rhodophyta: *Gigartina, Chondrus crispus, Eucheuma,* and Hypnea [that occur as matrix material] are classified as agarans and carrageenans [47]. According to their stereochemistry and specificity, [that can be extracted with water or aqueous alkali methods]; galactans with 4-linked-galactose residues of the L-series are termed agarans while those of the D-series are termed carrageenans [48, 49]. These polysaccharides are represented by the Greek prefix: Iota (i)-, Kappa (j)-, Lambda (k)-, Mu (l)-, Nu (m) - and Theta (h) - carrageenans. This nomenclature is relevant for their chemical classification and commercial production since the different carrageenans subtypes are extracted from distinct weed sources [50, 51]. Carrageenans belong to the family of hydrophilic linear sulfated galactans. They mainly consist of alternating 3-linked β-D-galactopyranose (G-units) and 4-linked-D-galactopyranose (D-units) or 4-linked 3, 6-anhydro-D-galactopyranose (DA-units), forming the disaccharide repeating unit of carrageenans. Sulfated galactans are classified according to the presence of the 3, 6-anhydro-bridge on the 4-linked-galactose residue and the position and number of sulfate groups. Commercial carrageenans have an average molecular mass ranging between 100 and 1000 kDa, besides galactose and sulfate, other carbohydrate residues can be present in carrageenans preparations, such as xylose, glucose and uronic acids, as well as some substituent's, for example, methyl ethers and pyruvate groups [52, 53]. However, each natural carrageenan is a complex galactose-based polysaccharide with different quantities of sulfate esters at different positions and distributions, the term disaccharide repeating unit refers to the idealized structure [53]. Carrageenans demonstrate potential *in-vitro* antiviral activity. Carlucci *et al*. (1997, 1999) noted that λ-carrageenan and partially cyclized μ/ι-carrageenan from *Gigartina skottsbergii* have potent antiviral effects against different strains of HSV types 1 and 2 during the virus adsorption stage.

Bioprospect of Sulfated Polysaccharides representative; Ulvans from Marine Macroalgae

The cell wall polysaccharide from Ulva is a natural source of dietary fibers and contains a category of polysaccharides called ulvan, comprising of rhamnose, sulfate, xylose, iduronic acid, galactose, and glucose [54]. Ulvan can elicit responses and induce defense mechanisms in cultivated plants [55]. These indigestible polysaccharides are composed of water-soluble polysaccharides, amorphous cellulose, alkali-soluble glucuronan, and xyloglucan. The polysaccharides derived from various Ulva species are generally obtained by hot water solutions at 80-90ºC. The yield ranges from 10 percent to 30 percent of the algal dry weight depending on the process of extraction and purification. The investigation of pertinent to the water-soluble polysaccharide chemical properties from Ulva was initially reported by [56]. *Per se*, research on extraction, chemical compositions, and structures of polysaccharide from Ulva species have thus been increased considerably as innovative applications.

Table 1: A tabulated representation to highlight sulfated polysaccharides representatives from various different geographical origin

Geochemical signature/ Source	Algae Species	Sulfated polysaccharide	References
West Coast India Okha (22.28◦N, 69.04◦E) Gujarat and Diu (20.42◦N, 70.58◦E)	*Champia indica Champia parvula*	Sulfated Galactans	Kumar *et al.*, [12]
South East Coast of Tamil Nadu, India Latitude 10°3′0″N and Longitude 79°14′0″E	*Gracilaria edulis*	Agaran	Sakthivel and Pandima Devi, [57]
Vizhinjam coast of Kerala (Lat. 8°22′N; Long. 76°59′E on the West Coast of India)	*Padina tetrastromatica*	Heterofucans	Jose *et al.*, [58]
Coast of Mandapam Island, India	*Turbinaria ornata*	Fucoidan	Guru *et al.*, [59]
Tamil Nadu, India	*Turbinaria ornata*	Fucoidan	Ananthi *et al.*, [60]
Dayang Foodstuff Company	*Gracilaria rubra*	Agarans	Di *et al.*, [61]
Atlantic coast of Brazil (03° 13′ 25″ S and 039° 16′ 65″ W)	*Gracilaria birdiae*	Agarans	Souza *et al.*, [62]
Atlantic coast of Brazil (03° 13′ 25″ S and 039° 16′ 65″ W)	*Gracilaria birdiae*	Agarans	Maciel *et al.*, [63]

Atlantic coast at North East of Brazil	*Gracilaria caudata (J Agardh)*	Agarans	Barros *et al.,* [64]
Coast of Putian, China	*Porphyra haitanensis*	Carrageenans	Zhang *et al.,* [65]
Southeast coast of India (Lat. 08°29'N; Long. 78°07'E)	*Codium tomentosum*	Sulfated galactans	Seedevi *et al.,* [66]
Atlantic coast of South America (42◦30′S and 64◦30′W)	*Codium decorticatum*	Sulfated galactans	Fernández *et al.,* [67]
Possjet Bay of (the Sea of Japan)	*Chordaria flagelliformis*	Fucoidan	Bilan *et al*., [68]
North-west Scotland	*Saccharina latissima*	Fucoidan	Bilan *et al*., [26]
Trinity Bay (the Sea of Japan)	*Saccharina japonica Undaria pinnatifida*	Fucoidan	Vishchuk *et al*., [69]
Trinity Bay (the Sea of Japan) (May/June/July/ October)	*Laminaria cichorioides (Thalli)*	Fucoidan	Anastyuk *et al*., [70]
Cultured in Shazikou Qingdao, China	*Laminaria japonica*	Fucoidan	Wang *et al.,* [31]
Cultured in Shazikou Qingdao, China	*Laminaria japonica*	Fucoidan	Wang *et al.,* [46]
Coast of Qingdao, Shandong, China	*Laminaria japonica*	Fucoidan	Cui *et al.,* [71]
South-west of Madagascar	*Gracilaria corticata*	Sulfated Galactans	Andriamanantoanina *et al.,* [72]
Tamil Nadu, Southeast coast of India ((Lat. 8◦06′N; Long. 77◦34′E)	*Gracilaria corticata*	Sulfated Galactans	Seedevi *et al.,* [30]
Sea of Japan	*Fucus evanescens*	Fucoidan	Anastyuk *et al.,* [73]
May o2001 and Sep 2002 (Gaspe & Île-Verte Québec, Canada)	*Fucus vesiculosus*	Fucoidan	Rioux *et al.,* [74]
May of 2001 and Sep 2002 (Gaspe & Île-Verte Québec, Canada)	*Saccharina longicruris*	Fucoidan	Rioux *et al*., [74]
Percé (48°31′59″ North–64°12′59″ West),L'Anse-à-Beaufils (48°28′29″ North–64°18′30″ West) Québec, Canada	*Saccharina longicruris (fronds)*	Crude galactofucans	Rioux *et al.,* [75]; Rioux *et al*., [76]
Coast of Wando (Island) in the Jeonam province of Korea	*Enteromorpha prolifera*	Ulvans	Cho *et al*., [77]
Coast of Qingdao, China	*Enteromorpha prolifera*	Ulvans	Li *et al.,* [78]

Extrapolating Sulfated Polysaccharide *in-vitro* antioxidant mechanism

Crude sulfated polysaccharide have been documented potent with total antioxidant activity, FRAP value, DPPH radical scavenging activity and ABTS radical scavenging activities. These reported activities are compared to the standard synthetic antioxidants such as, BHT, BHA, Quercetin, Ascorbic acid and catechol. However, studies seem to indicate that no profound effect on superoxide radical was observed. The enhanced radical scavenging activity of sulphated polysaccharides over its neutral form may be due to the presence of sulphate group that act as an electrophile and promote the intramolecular hydrogen abstraction [79]. Superoxide scavenging activity of sulphated polysaccharides depends on the degree of sulphation [80], the electron free radicals abstract anomeric hydrogen from carbohydrate and combine with it to form neutral molecules [79], while the alkoxyl radical generated promotes intermolecular hydrogen abstraction reaction in carbohydrate, by spiro cyclisation reaction to terminate the radical chain reaction [81]. The reducing properties of polysaccharide are characterized mostly with the presence of reducing

groups such as aldehydes/ketone, which exert its antioxidant mechanism through alteration of the free-radical chain by donating a hydrogen atom [82]. As such the chemical structures of polysaccharides play a key role on the reduction of ABTS radical and they are mediated by hydroxyl group present in sugar [24]. The scavenging ability of DPPH radical can be used to test sulfated polysaccharide as anti-oxidative compounds either as proton radical scavengers or hydrogen donors. It is also well accepted that the DPPH free-radical scavenging action by antioxidants is due to their hydrogen-donating ability to form a stable DPPH molecule [83]. The free-radical scavenging mechanism of carbohydrate is due to the supply of hydrogen. Tables 2 reveal that sulfated polysaccharides have an appreciable antioxidant capacity which is largely attributed to the structural characterization of sulfated polysaccharide. The electron or hydrogen donating capacity of crude sulfated polysaccharide were evaluated by total antioxidant activity and the rate of electron or hydrogen transfer determined by the FRAP assay. The ABTS and DPPH were used as a free radical to investigate the free-radical scavenging activities [84]. The superoxide ions are initiators of other free radicals, like hydroxyl, hydrogen peroxide and lipid peroxide radicals. Thus, the superoxide scavenging assay helps determine the potential of crude sulfated polysaccharide to scavenge superoxide radical.

Table 2: The Source for Marine Macroalgae Sulfated Polysaccharide

Macroalgae source	**Sulfated polysaccharides yield**	**References**
Fucus vesiculosus	Fucoidan	Rocha de Souza *et al*., [85]
Fucus vesiculosus	Fucoidan	Díaz-Rubio et al., [19]
Porphyra haitanensis	Sulfated-Galactans	Zhang et al., [65]
Gigartinaacicularis Gigartina pisillata	Sulfated-Galactans	Rocha de Souza *et al*., [85]
Laminaria japonica	Fucoidan	Wang *et al.*, [31]
Laminaria japonica	Fucoidan	Cui *et al.*, [71]
Laminaria japonica	Fucoidan	Lu *et al.*, [86]
Laminaria japonica	Fucoidan	Zhang *et al.*, [65]
Pterocladia capillacea	Sulfated-galactans	Fleita *et al*., [87]
Pterocladiella capillacea	Sulfated-galactans Carrageenans	Sebaaly *et al.*, [88]
Mastocarpus stellatus	Sulfated-galactans	Gómez-Ordóñez *et al*., [89]
Dictyopteris delicatula	Heterofucans	Costa *et al*., [33]; Magalhaes *et al.*, [90]
Padina gymnospora	Fucoidan	Rocha de Souza *et al*., [85]
Padina gymnospora	Fucoidan	Praveen and Chakraborty, [91]
Padina tetrastomatica	Fucoidan	Praveen and Chakraborty, [91]
Padina tetrastromatica	Ascophyllan	Mohsin *et al*., [92]
Padina tetrastromatica	Fucoidan	Jose *et al*., [58]
Gracilaria rubra	Sulfated galactan	Di *et al*., [61]
Sargassum myriocystum	Fucoidan	Badrinathan *et al.*, [93]
Sargassum swartzii	Fucoidan	Vijayabaskar *et al.*, [94]
Sargassum filipendula,	Fucoidan	Costa *et al*., [37]
Sargassum glaucescens	Fucoidian	Huang *et al.*, [95]
Sargassum binderi	Fucoidan	Lim *et al.*, [96]; Suresh et al., [97]
Sargassum plagiophyllum	Fucoidan	Suresh *et al*., [97]
Sargassum pallidum	Fucoidan	Ye *et al.*, [98]
Sargassum horneri	Fucoidan	Hifney *et al*., [99]; Shao *et al.*, [100]
Gracilaria caudata	Sulfated-Galactans	Costa *et al.*, [37]
Gracilaria corticata	Sulfated Galactan	Seedevi *et al.*, [30]
Laminaria japonica	Fucoidan	Wang *et al.*, [31]
Ulva fasciata	Ulvans	Shao *et al.*, [101]
Ulva pertusa	Ulvans	Qi *et al*., [102]; Qi *et al*., [103]
Ulva pertusa	Ulvans	Zhang *et al.*, [65]
Ulva Lactuca	Ulvans	He *et al*., [104]
Solieria filiformis	Sulfated galactan	Sousa *et al*., [105]
Grateloupia livida	Sulfated Galactans	Tang et al., [106]
Undaria pinnitafida	Fucoidan	Hu et al., [107]

Undaria pinnatifida	Fucoidan Frond sporophylls	Mak *et al.*, [108]
Undaria pinnatifida (*frond and stipe)*	Alginate Fucoidan Laminaran	Je *et al*., [109]
Ascophyllum nodosum	Ascophyllan	Abu *et al.*, [110]
Ascophyllum nodosum	Fucoidan	Yuan and Macquarrie, [111]
Turbinaria ornate	Fucoidan	Ananthi *et al*., [60]
Turbinaria ornate	Fucoidan	Arivuselvan *et al*., [16]
Turbinaria conoides	Fucoidan, Alginic acid	Chattopadhyay *et al.*, [17]

Extrapolating and Optimization of Anti-coagulant and Anti-thrombotic Activity Activity from Marine Macroalgae Sulfated Polysaccharides

Macromolecule recognition processes are common in cells. Whereby their specificity is their most important characteristic. Global research agendas exploit these recognition events and in focused areas of biology, chemistry, medicine and pharmacology research. Biological reactions that involve recognition events include processes such as cell agglutination and coagulation, the stimulation of cell migration and fertilization. Several bioassays for the assessment of anticoagulation properties of sulfated polysaccharides derived from seaweeds have been investigated in recent times which includes tests ranging from activated partial thromboplastin time (APTT), thrombin time (TT), prothrombin time (PT), antithrombin to anticoagulation factor FXa activities have been studied and compared with heparin [112-114]. The enzymatic extract of *Ecklonia cava* containing its crude polysaccharide and crude polyphenolic fractions evaluated *in vitro* displayed high anticoagulant activities and in vivo analysis in Wister rats also exhibited an increase in the coagulation time in a dose and time-dependent manner [115]. The extraction of low molecular weight sulfated galactan from *Mastocarpus stellatus* either with acid or alkali as reported [116] showed red seaweeds exhibited strong anticoagulant capacity *in vitro*. The evaluated *in vitro* anticoagulant activities of *Dictyota carvicornis* when compared with low molecular weight Clexane a commercial heparin prolonged the coagulation time by 1.4-fold lesser with the value 0.01mg/100µl of the plasma [33]. However, for the prothrombin time (PT) test, which measures the extrinsic coagulation pathway, *Caulerpa cupresoides* was aggressive while *Codium fragile* and *Codium vermilara* water-soluble sulfated arabinogalactans inhibited coagulation, but induced platelet aggregation. It was observed anticoagulant activity was higher in SP samples with higher sulfate content. This corroborated *Codmium vermilara* to be superior in its activity with a higher degree of sulfation and arabinose content [117]. A pyruvated galactan sulfate CP2-1 isolated from green alga *Codium divaricatum* possessed a high anticoagulant activity *in vitro* based on the backbone which is made of galactopyranose residues with a small degree of branching [118]. The secondary structure of the sulfated polysaccharides seems important to biological activities because modulation of molecular weights, substitution positions and substitution degrees results in the conformation changes, as investigated in agarose and carrageenans of the red seaweed polysaccharides and their sulfated derivatives showing anticoagulant potency on rabbit whole blood method, APTT and PT test [119]. The positions of the sulfate groups are often related to the level of the inherent biological activity. The naturally sulfated galactans, kappa-, iota- and theta-carrageenans, when further sulfated, *in vitro* anti-coagulant activities in activated partial thromboplastin time (aPTT), (aPPT) test increases suggesting that sulfation at C2 of 3, 6-anhydro-α-d-Gal*p* and C6 of β-d-Gal*p* increased the anticoagulant activity [120]. The anticoagulant capacity of the isolated polysaccharides in the marine green algae *Monostroma nitidum* extracted in hot water showed they were potent thrombin inhibitors mediated by heparin cofactor II and also hasten thrombin and coagulation factors Xa inhibition by potentiating antithrombin III [121]. *Monostroma latissimum* extracted in hot water, purified and fractionated to derive sulfated rhamnose fragments with different molecular weights showed that a decrease in the molecular size reduces dramatically anticoagulant activities [4]. The heterofucan of *Sargassum vulgare* prolonged activated partial thromboplastin time (APTT) and displayed in vivo antithrombotic capacity with a concentration ten times higher the heparin by direct inhibition of the thrombin enzymatic action and stimulation of Fxa [122]. Pyruvylated sulfated galactans isolated from Bryopsidales species as studied by [123] exhibited moderate anticoagulant activity by direct thrombin inhibition on the prothrombin time (PT), the activated partial thromboplastin time (APTT), and thrombin time (TT) tests.

Extrapolating and Optimization of Anti-tumour Activity from Marine Macroalgae Sulfated Polysaccharides

A well-defined proliferation inhibition and induction of apoptosis process in tumorigenic cells is a strategic compliance in anti-tumor therapy. As such, the balance between proliferation and apoptosis signaling pathways controls tumor pathogenesis. Macroalgae seaweed has been shown to have several biological activities, including anti-tumour activity. 46 species of marine algae (four green, 21 brown and 21 red algae)

have been screened for antitumor activity. Significant activity against Ehrlich carcinoma was found in the brown algae *Scytosiphon lomentaria* (69.8% inhibition), *Lessonia nigrescens* (60.0%), *Laminaria japonica* (57.6%), *Sargassum ringgoldianum* (46.5%), the red algae *Porphyra yezoensis* (53.2%) and *Eucheuma gelatinae* (52.1%) and the green alga *Enteromorpha prolifera* (51.7%). Five brown and four red algae showed appreciable antitumor activity against Meth-A fibro sarcoma. These aqueous extracts contained sulfated polysaccharides [124]. Consumption of various types of seafood, including seaweed, has been suggested to be responsible for the low incidence of cancer in Japan and in other countries whose inhabitants traditionally consume high levels of marine organisms. Numerous studies have examined the effects of seaweeds on apoptotic pathways. The effects of laminarin, a storage glycans composed of β-glycans (β-1,3-β-1,6-glycan) found in brown algae, on colorectal cancer cells were investigated as well as the mechanisms through which laminarins induced apoptosis in these cells. In tandem to this, Sulfated polysaccharides with characteristics low molecular weight isolated from macroalgae seaweeds [60, 43, 125] have been obseved to exert potent antitumor activity by inducing cell cycle arrest and apoptosis in several tumor cell lines research [23, 126-128]. The polysaccharide fraction of *Sargassum horneri* demonstrated strong antitumor in inhibition of the DLD cells by influencing apoptosis-associated gene expressions of Bcl-2 and Bax [100]. In another study the sulfated polysaccharides from *Ulva fasciata*, *Gloiopeltis furcata* and *Sargassum henslouianum* reveal dose-dependent inhibitory features on growth rate of MKN45 gastric cancer cells and DLD intestinal cancer cells due the uronic acid content [101]. In pertinent to this, when *Sargassum plagiophyllum fraction* with a sulfate content yield of 21.9% was studied, higher anticancer activity against HepG2 and A549 cells lines with with IC_{50} values of 600µg/mL and 700 µg/mL, respectively using MTT assay was observed [97]. The sulfate position, molecular weight and the content of 2-linked disulfated rhamnose residues is essential for the sulfated heterorhamnans of *Gayralia oxysperma* to display the antitumor activity against U87MG cells [129]. The laminarans and their sulfated derivatives isolated from *Saccharina cichorioides*, *Saccharina japonica*, and *Fucus evanescens* inhibited proliferation, colony formation, and migration of human colorectal adenocarcinoma, melanoma, and breast adenocarcinoma cells by its action on the Matrix Metalloproteinase's based on the branching chain and sulfates position of β-(1→3)-D-glucopyranose and β-(1→6)-linked D-glucose residues [130]. The *invitro* investigation of the fractionated anionic polysaccharides obtained from *Sargassum vulgare* showed inhibition of VEGF secretion when incubated in RAEC cell line by MTT assay [131] indicating the antiangiogenic and antitumor potentials of sulfated polysaccharides. The inhibition activity displayed *in vitro* by fucoidan from the brown alga *Fucus evanescens* to the colony formation of SK-MEL-28 cell lines was attributed to the presence of sulphates and (1 → 4)-linked α-l-Fuc*p* residues in the main chain of oligosaccharides [43].

Extrapolating and Optimization of Anti-inflammation/ Anti-nociception Activities from Marine Macroalgae Sulfated Polysaccharides

Macroalgae, especially red macroalgae, are rich in 20-carbon atom polyunsaturated fatty acids (PUFAs), chiefly eicosapentaenoic and docosahexanoic acids [132, 133]. Seaweeds are capable of metabolizing various C20-PUFAs via oxidative pathways [134] and in the Gracilariales; prostaglandins are one of the products. Sulfated polysaccharides derived from macroalgae *Solieria filiformis* showed strong antinociception properties on the pain sensitivity stimulus when investigated in Male Swiss mice pre-treated with sulfated polysaccharides [135]. Also, when sulfated polysaccharides from brown seaweed *Spatoglossum schroederi* was evaluated for its antinociceptive effect on Swiss mice, it was noted that purified fraction inhibited both phases of the formalin test which confirms similar mechanism to morphine suggesting it could be developed as a new source of analgesic drugs [136]. Hwang *et al*., [136] also explored the effect of sulfated polysaccharide from brown seaweed *Sargassum hemiphyllum* for possible anti-inflammatory effect against mouse macrophage cell line (RAW 264.7) activated by lipopolysaccharide (LPS), low secretions of proinflammatory cytokines, such as IL-1b, IL-6, TNF-a, and NO, were noted significantly in various dose ranges of treated groups. The sulfated polysaccharide galactan fraction isolated and purified from the red marine alga *Gelidium crinale* and tested by intravenous route in rodent experimental models induced different inflammatory stimuli by inhibition of both neurogenic and inflammatory phases of the formalin test and the treated animals [137]. The effects of SP from the *Gracilaria cornea* in nociceptive and inflammatory mice models at different dosage showed SP significantly reduced nociceptive responses, as measured by the number of writhes while in formalin test the SP significantly reduced licking time at dose dependent manner [126]. In the hot-plate test, the antinociceptive effect was observed only in animals treated with higher dosage of SP, suggesting its analgesic effect occurs through a central action mechanism. He also investigated anti-inflammatory mechanisms of the sulfated polysaccharides fraction obtained from red marine alga *Gracilaria cornea* using a paw edema model induced in rats by different inflammatory agents and Gc-FI administered subcutaneously at doses of 3, 9 or 27 mg/kg, significantly inhibited rat paw edema induced as confirmed by myeloperoxidase and Evans' blue assessments, respectively by down-regulation of IL-1β, TNF-α and COX-2 mRNA and protein levels [138]. The antinociceptive activity of non-

anticoagulant fraction *Caulerpa cupressoides* var. lycopodium (Chlorophyta) evaluated *in vivo* in male Swiss mice induced toxicity reveal reduction in the number of writhes induced by acetic acid by 44.21, 47.72 and 90.87%, respectively however with its analgesic action occurs through peripheral mechanisms [139]. The results indicate that analgesic and anti-inflammatory effects of sulfated polysaccharides from seaweed could be of biomedical applicability as a new, natural therapeutic in pain and acute inflammatory conditions [140]. The potential in vivo antinociceptive activity of a sulfated polysaccharide extracted from the green seaweed *Caulerpa racemosa* and the involvement of the hemoxigenase-1 (HO-1) pathway in its anti-inflammatory effect after treatment with acetic acid and formalin respectively showed decreased number of leukocytes in the peritoneal cavities of the rats and reduction in the amount of paw edema [141]. Ananthi *et al.,* [60] investigated the anti-inflammatory effect of crude sulfated polysaccharides from brown alga *Turbinaria ornata* against carrageenans-induced paw edema in rats and vascular permeability in mice and observed that oral administration of sulfated polysaccharides showed inhibitory effect on the vascular permeability and reduced paw edema purportedly in a dose-dependent manner. The sulfated fucan extracted from brown algae *Padina gymnospora* showed reduction of leukocyte cell influx into the peritoneal cavity in mice model when given at 10 mg/kg body weight. The component cause a decrease of 60 %, with no cytotoxicity features observed [142].

CONCLUSIONS

Global demand for marine macroalgal as functional foods is growing beyond their traditional application as local exotic soup and tangible fertilizers. Marine macroalgae seaweed sulfated polysaccharides is thus a crucial global exploitable functional food for human health consumption and physiological activities needs. The optimization of well-taxonomised species with biotechnological approaches may present better perspectives applications.

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