Chapter 2

Therapeutic Potential of Seaweed Bioactive Compounds

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Abstract

Edible seaweeds are rich in bioactive compounds such as soluble dietary fibers, proteins, peptides, minerals, vitamins, polyunsaturated fatty acids and antioxidants. Previously, seaweeds were only used as gelling and thickening agents in the food or pharmaceutical industries, recent researches have revealed their potential as complementary medicine. The red, brown and green seaweeds have been shown to have therapeutic properties for health and disease management, such as anticancer, antiobesity, antidiabetic, antihypertensive, antihyperlipidemic, antioxidant, anticoagulant, anti-inflammatory, immunomodulatory, antiestrogenic, thyroid stimulating, neuroprotective, antiviral, antifungal, antibacterial and tissue healing properties. In proposed chapter, we discussed various active compounds include sulphated polysaccharides, phlorotannins, carotenoids (e.g. fucoxanthin), minerals, peptides and sulfolipids, with proven benefits against degenerative metabolic diseases. Moreover, therapeutic modes of action of these bioactive components and their reports are summarized in this chapter.

Keywords: seaweeds, marine, antioxidant, polysaccharides, bioactives

1. Introduction

Consumer interest has been increased from previous decades towards the health food and nutrition is the prime focus in formulating the food products. Algae are the organisms capable of providing bioactive compounds for producing novel medicinal and pharmaceutical substances. Algae are widely studied for human nutritional purpose and correspondingly utilized as functional foods [1]. Natural abundance, diverse origin and universal availability of

algae makes it an essential source of biologically functional ingredients [2]. The term marine algae are generally referred as marine macroalgae or seaweeds [3]. Seaweeds are living resources found notably in littoral habitats or attached to rocks. They grow in shallow coastal waters as well as in deep sea areas up to a depth of 180 m. These macroscopic algae relatively occur in river mouth and saline waters. Seaweeds constitute the basis of the marine food chain and are subdivided in to three divisions, namely, brown algae, red algae and green algae [4].

Seaweeds, sometimes referred as edible marine algae, are regarded as good reservoir of compounds with numerous biological and biomedical activities and are most remarkably abundant in sulfated polysaccharides [5]. These have been studied in recent years to develop novel pharmaceuticals and potent bioactive substances [6, 7]. Edible macro algae have become a good source of food and alternative medicine in Asian countries [8] and in the western countries they are extraction specific and used for many industrial applications in food [9], cosmetics and pharmaceuticals [10]. The algal biotechnology industry is growing with an aquaculture division that produces large quantities of seaweeds, such as Laminaria, Gracilaria, and Spirulina. Additionally, the utilization phycocolloids derived from algae such as algin, agar, and carrageenan has developed into a well-established industry [11]. Cultivation of macroalgae now contributes to over 90% of the global seaweed demand, with the remainder being naturally harvested. Despite the growing worth of algae as a source of food ingredients, the industry has developed with only varying amounts of success and its biotechnological application are still under-exploited [12].

1.1. Types of seaweeds

At present, algae are divided in to four domains: Bacteria, Plantae, Chromista and Protozoa. All these vary greatly in morphology and sizes, which ranges from unicellular to multicellular microalgae or colony forming marine organisms such as macrophytes and seaweeds. Macroalgae are traditionally classified based on their characteristic forms and sizes, however the most commonly use feature in algal classification is the presence of specific pigments.

Marine algae due to their richness in bioactive compounds may exhibit antioxidant, anti-inflammatory, anticoagulant, antimicrobial, antiviral, antitumour and hypocholesterolemic activity [13]. Since seventeenth century marine macroalgae have long been used for biomedical purposes because of their potential phytochemical constituents and highly diverse nature. Algae can be classified into two groups based on their size: phytoplankton (microalgae) having 5000 different species and seaweed (macroalgae) with 6000 species [14].

Natural pigments determine the inherence of marine algae to one of the three algal divisions referred to as brown algae (*Phaeophyceae*), red algae (*Rhodophyceae*), and green algae (*Chlorophyceae*), respectively [3]. Brown colour of Phaeophyceae is due to the presence of pigment fucoxanthin. Red color of Rhodophyceae is often due to the dominance of phycoerythrin and phycocyanin pigments over the other pigments such as chlorophyll, carotene and xanthophylls. Green color of Chlorophyceae is due the presence of chlorophyll and related compounds in the same concentration as in higher plants. Some specific commercially important cultivated seaweeds and seaweed products include the brown seaweed *L. japonica*, from the brown seaweed *Undaria pinnatifida*, and Hizikia from *Hizikia fusiforme*. Biotechnological advances regarding macro algae cultivation include establishment of cell and tissue cultures that can biologically synthesize desired compounds, such as eicosanoids, on a large scale under a controlled environment [12].

1.2. Nutritional profile

Seaweeds have been recently emerged as a potential source of bioactive compounds with unique nutritional value and therapeutic activities, and it has become an important field of research in food science and technology [15, 16]. One of the main dietary differences between Eastern and Western hemispheres is the higher seafood consumption such as fish and marine algae [17]. Seaweeds are characterized as distinguished sources of various bioactive compounds with abundance in many minerals and could be utilized as novel functional foods which provide health benefit activities. Seaweed tissues are abundant in mineral elements such as iron, potassium, sulfur and iodine [18]. Depending upon seasonal conditions and the geographic area, macroalgae differs in the content of biochemical elements such as proteins, lipids, carbohydrates, vitamins and minerals [19]. Cell surface polysaccharides are responsible for high level of minerals and trace elements due to the retention of inorganic marine substances in marine algae [20]. Marine microalgae are considered as potential source of high quality proteins. *S. platensis* is considered as a prime source of bioactive proteins in marine environment. Compositional analysis of microalgae proteins clearly indicates that this high quality protein can be effectively used as direct supplements or could be used for formulation of other health products such as nutraceuticals [21].

Peptides with therapeutic potentials are referred as bioactive peptides and these peptides have potential applications in functional foods and nutraceuticals [22] for health improvement and better disease control. *Chlorella vulgaris*, *Spirulina platensis*, *Navicula incerta* and *Pavalova lutheri* are few potential algal species that could be used to extract biologically active peptides with significant therapeutic potentials is a widely studied marine microalga for extraction of bioactive peptides [23]. Mineral content of some seaweeds may account for up to 50%. Seaweeds species of kelp such as *Alaria esculenta* and *Chondrus crispus* are important vegetable sources of calcium [24]. The percentage of calcium can be as high as 7% of the dry weight and may be up to 34% in *Halimeda* sp. J.V. Lamouroux having calcified green segments [25]. *Laminaria digitata* is extensively used as a supplement for treatment of hypothyroidism and goiter [26]. The content weightage of calcium may reach 3% of the dry weight in macroalgae such as Fucus and Ascophyllum and up to 33.6% in calcified macroalgae such as *Phymatolithon calcareum* [27]. Therefore, consumption of seaweed could be beneficial to those at risk of calcium deficiency like pregnant females, teenagers and the elderly [28].

1.3. Bioactive compounds

Numerous metabolites extracted from marine algae possess biological activities. These bioactive compounds have been widely acknowledged because of their potential health benefits [3, 29]. Commercial bioactive compounds of algal origin include natural pigments (NPs), polyunsaturated fatty acids (PUFAs), lipids, proteins and polysaccharides [15, 16]. Some of these bioactive compounds with their sources are mentioned in **Table 1**. Natural variability in the content of bioactive molecules may be attributed to evolutionary relationships, ecological and chemical diversification but these should not be considered as limitations to commercialization [30]. Variation in the concentration of bioactive marine compounds of natural algal populations are influenced by environmental changes such as light, nutrients, contaminants, salinity, CO_2 availability, pH, temperature and biotic interactions [31].

Seaweeds	Bioactive compounds	References
Undaria pinnatifida	Fucoxanthin	[32]
Porphyra sp.	Phycoerythrobilin	[33]
Phaeophyceae	Sulfated fucoidans	[34]
Rhodophyceae	Sulfated galactans	[35]
Codium fragile	Xyloarabinogalactans	[36]
Codium cylindricum	Sulfated galactan	[37]
Sargassum thunbergii	Phlorotannins	[38]
Saccharina japonica	Fucoidans	[39]
Eisenia bicyclis	Phloroglucinol	[39]
Taonamaria atomaria	Stypoldione	[40]
Laurencia microcladia	Sesquiterpene elatol	[41]
Corallina pilulifera	Ethanolic extract	[41]
Schizymenia dubyi	Sulfated glucuronogalactan	[42]
Lobophora variegate	Fucans	[43]
Ecklonia cava	Phlorotannin 6,6′-bieckol	[44]
Porphyria dentate	Catechol, rutin and hesperidin	[45]

Table 1. Bioactive compounds from different seaweeds.

Functional materials of marine organisms occur in a wide variety and are enriched with polyunsaturated fatty acids, polysaccharides, pigments, minerals, vitamins, enzymes, phenolics and bioactive peptides [46]. Recently, the importance of algae as a source of structurally diverse bioactive compounds has been immensely emerged and research showed various biological activities of these compounds which are antioxidant, immunomodulation, anticoagulation and antiulcerogenic activities [47].

Seaweeds are the sole source of certain valuable phytochemicals, namely agar and carrageenan [48]. The richness of edible marine algae in sulfated polysaccharides (SPs) [49] as good sources of nutrients, span their uses from the food and pharmaceutical industries to biotechnology [5]. These anionic polysaccharide polymers are not only widespread in marine algae but also in mammals and invertebrates. Seaweeds are also the most significant sources of non-animal SPs and the chemical structure of these polymers vary according to the type of algae [50]. Major polysaccharides found in marine algae include fucoidan and laminarans found in brown algae, carrageenan in present red algae and ulvan in green algae [4].

Sulphated polysaccharides present in Rhodophyta are known as galactans which are composed of galactose or modified galactose units [51]. The class of Phaeophyta comprises of sulfated l-fucose units which are named as fucans. The polysaccharides found in Chlorophyta exhibit polydispersity among heteropolysaccharides together with traces of homopolysaccharides [50]. Carrageenan may also show anticoagulant activity [52], antiviral activity [53],

and antitumor activity [54]. Marine red algae primarily contain an agaran type polysaccharide, which was separated from *Grateloupia filicina* and was investigated for its antiangiogenic activity.

Fucoidan is a highly complex sulfated polysaccharide found in marine brown algae is also present in microorganisms, plants and animals [44]. Fucoidan have been shown to exhibit antiviral and anti-inflammatory affect. Anti-metastatic effects of fucoidan obtained from *Fucus vesiculosus*, have been described. Fucoidan could also be reflected as a potential therapeutic agent against the metastasized invasive human lung cancer cells. Phloroglucinol bioactives acquired from marine seaweeds have chemical diversity and are much studied for their remarkably beneficial biological actions.

Seaweeds have been majorly studied for their biologically active polyphenolic derivatives called phlorotannins [43]. Marine brown algae (*Phaeophyta*) accumulate a variety of phloroglucinol based polyphenols, as phlorotannins [47]. Among marine brown algae, *Ecklonia cava*, *Ecklonia stolonifera*, *Ecklonia kurome*, *Eisenia bicyclis*, *Sargassum thunbergii*, *Hizikia fusiformis*, *Undaria pinnatifida* and *Laminaria japonica* have been reported to exhibit health beneficial activities because phlorotannins. Due to the various biological activities of phlorotannins, marine brown algae are known to be a rich source of healthy food [55]. *Undaria pinnatifida* contain 5–10% fucoxanthin and it is one of the most well-known edible seaweed in Japan. Health benefits of fucoxanthin include anticancer effect and it is reported that neoxanthin and fucoxanthin cause a significant reduction in growth of prostate cancer cells. Anti-obesity activity and anti-inflammatory activity was also demonstrated [56]. Fucoxanthin is other major biofunctional pigment of brown seaweeds and has been found in high concentration in various edible seaweeds including *U. Pinnatifida* [57].

2. Remedial activities

2.1. Antioxidant activity

Antioxidants may affect the human health in a positive way as they can protect the human body against damage by Reactive oxygen species, which attack and impair macromolecules such as DNA, proteins and lipids lead to many health disorders such as diabetes, aging, cancer and other neurodegenerative diseases [58]. Recently, marine flora and fauna gain considerable interest as natural sources for the development of antioxidants in the food and pharmaceutical industry. Marine algae represent one of the richest sources of natural antioxidants among marine resources [59]. Antioxidant activity of marine derived bioactive peptides has been determined through radical scavenging activities which have been detected by electron spin resonance spectroscopy method as well as intra cellular free radical scavenging assays. The peptide chain contains hydrophobic amino acids which contribute towards their potential antioxidant activity [60, 61].

Marine algae have various classes of natural polysaccharides including fucoxanthin, phycoerythrobilin, chlorophyll-a and their derivatives show potent antioxidant activity. Cho et al. [62] suggested that strong antioxidant activity of the *Enteromorpha prolifera* was caused by

chlorophyll-a derivatives, pheophorbidea, rather than phenolic compounds. The antioxidant activity is due to the specific scavenging of oxygen or radicals [63] formed during peroxidation or metal-chelating ability [64]. Yan et al. [32] discovered that fucoxanthin show strong radical scavenging activity [65] which isolated fucoxanthin from *Undaria pinnatifida* and prepared two fucoxanthin metabolites, fucoxanthinol and halocyn-thiaxanthin. Hence, fucoxanthin serves as substitute for synthetic antioxidants in nutraceuticals and pharmaceuticals. Cytoprotective effect of fucoxanthin has been observed in vitro against ROS formation induced by H_2O_2. Two hydroxyl groups are present in the ring structure of fucoxanthin, which are responsible for the inhibition of ROS formation. Several studies supported the fact that number of hydroxyl groups on the ring structure of fucoxanthin causes the effects of ROS suppression [66]. Recently, Yabuta et al. [33] demonstrated antioxidant activity of phycoerythrobilin derived from *Porphyra* sp.

NPs are useful effective bioactive substances in search for effective, non-toxic substances with potential antioxidant activity. NPs are distributed in large quantities in marine algae and could be used as a rich source of natural antioxidants with potential application in the food industry as well as cosmetic and pharmaceutical areas [3].

2.2. Anti-coagulant activity

Whenever an abnormal vascular condition occurs, blood coagulation begins to stop the flow of blood though the injured vessel wall and exposure to non-endothelial surfaces at sites of vascular injury occur. Blood coagulation is processed by coagulation factors. The blood coagulation can be prolonged or stopped when endogenous or exogenous anticoagulants interfere with these coagulation factors [67]. The anticoagulants derived from marine bioactive peptides have been extensively reported, but they have also been isolated from marine organisms such as marine echiuroid worm [68]. The anticoagulant activity of the bioactive peptides has been determined by prolongation of prothrombin time, thrombin time and activated partial thromboplastin time assays and the activity was compared with the standard commercial anticoagulant heparin. The normal clotting time of anticoagulant peptide isolated from marine echiuroid worm have been significantly prolonged [69].

Sulphated polysaccharides derived from marine brown algae are alternate sources for manufacturing of novel anticoagulants [37]. Anticoagulant activity is the most extensively studied property of sulphated polysaccharides and have been reviewed previously [70]. Two types of SPs have been recognized with high anticoagulant activity. Marine red algae produce sulfated galactans also known as carrageenan, [35] and marine brown algae produce sulfated fucoidans [34]. There are very few reports of anticoagulant SPs reported from marine green algae. Jurd et al. [36] found that the anticoagulant active SPs from *Codium fragile* contain xyloarabinogalactans. *Codium cylindricum* also contain a sulfated galactan with anticoagulant activity. Additionally, Maeda et al. [71] have revealed that the anticoagulant SPs from *Monostroma nitidum* yield a six fold higher activity as compared to heparin. Marine brown algae extracts demonstrate higher anticoagulant activity than red and green algae extracts [34]. The presence of sulfate functional groups in SPs can increase both the specific as well as nonspecific binding to a wide-range of biologically active proteins. Anticoagulant activity of sulfated galactans depends on the sulfate content, the sulfation position of the structure, and nature of the sugar

residue in SPs [72]. High molecular weight carrageenans having high sulfate content show higher anticoagulant activity in comparison to low molecular weight carrageenans having low sulfate content of SPs [73].

Low molecular weight and unfractionated heparins are the only sulfated polysaccharides currently used as anticoagulant drugs. Seaweed derived SPs possess anticoagulant activity similar to or higher than the heparin [50]. In the pharmaceutical industry, SPs derived from seaweeds are the promising bioactive agents to be used as anticoagulant agents. Phlorotannins derived from *Sargassum thunbergii* are potential anticoagulants in vitro and in vivo. These phlorotannins from *S. thunbergii* had a significant effect on the prolongation of prothrombin time, thrombin time and activated partial thromboplastin time. In addition, phloroglucinol can be established as a novel anticoagulant in pharmaceutical industry [38].

2.3. Anti-cancer activity

Marine algae produce a range of diverse anti-cancer phytochemicals. Based on epidemiological data, the protective effect of edible seaweeds has been established against mammary, skin and intestinal carcinogenesis [74]. The bioactive substances can kill cancerous cells by inducing apoptosis or they may affect cell signaling by the activation of cell signaling enzymes of protein kinase-c family of brown algae seaweeds [75]. *Laminaria*, *Gelidiumamansii* and *Porphyratenera* exhibit dose-dependent inhibition of growth in mutated human gastric and colon cells [76] and also cancer cells of mammary glands. Brown seaweeds such as *Laminaria* are edible as a functional food, and it is well known for reducing the incidence of breast cancer in Japan to about one sixth as that of the rate reported for American women. *Laminaria japonica* and *Sargassum muticum* species are widely used as components of conventional herbal medicines for the treatment of cancer in china [77].

Most remarkable compounds found naturally in the brown seaweeds are the fucoidans, glucans and some other secondary [75] metabolites. Most of these compounds are listed in (**Table 2**). These compounds are capable of producing anticancer activity. Fucoidans from *Saccharina japonica* and *Undaria pinnatifida* dose-dependently inhibit proliferation and colony formation in both breast cancer and melanoma cell. This proves that the use of sulfated polysaccharides from both above mentioned brown seaweeds are potential ingredients for cancer treatment. Low molecular weight fucoidan isolated from *Ascophyllumnodosum* selectively inhibits the invasion of breast cancer cells by a mechanism of blocking the accession of these cancerous cells in the extracellular matrix and it also inhibits the invasive colon adenocarcinoma cells [78].

Phloroglucinol and its essential polymers which are eckol, dieckol, phlorofucofuroeckol A, and 8,8′-bieckol isolated from the brown alga *Eisenia bicyclis* show significant anticancer activity [39]. The extract of the brown alga *Taonamaria atomaria* contains a compound stypoldione, an in-vitro inhibitor of microtubule polymerization, exhibits anticancer activity [40]. Red algae contain abundant concentration of secondary metabolites and their halogenated derivatives. *Laurencia microcladia* produces a sesquiterpene elatol exhibit antitumour activity. Elatol exhibits cytotoxicity by inducing cell cycle arrest leading cells to apoptosis. *Corallina pilulifera* is a calcareous red alga whose ethanolic extract show anti-proliferative activity on human cervical adenocarcinoma cells. *Acanthospora spicifer*, another red seaweed, exhibits tumouricidal activity against Ehrlich's ascites carcinoma cells. This is due to decrease in tumour volume

Health claims	Bioactive compounds	References
Antioxidant activity	• Fucoxanthin • Phycoerythrobilin • Chlorophyll-a and derivatives	[76]
Anti-coagulant activity	• Sulphated polysaccharides ○ Galactans/Carrageenan ○ Fucoidans ○ Heparins ○ Phlorotannins ○ Phloroglucinol	[37]
Anti-cancer activity	• Fucoidans • Glucans • Phloroglucinol • Stypoldione • Sesquiterpene elatol • Carotene • Lutien	[39]
Anti-viral/Anti-HIV activity	• Sulfated Glucuronogalactan • Sulphated galactans • Sulphated fucans • Carrageenan	[54]
Cardiovascular protection	• Carotenoids • Sterols • Cardiac glycosides • Eicosapentaenoic acid • Docosa-hexaenoic acid	[81]
Anti-inflammatory activity	• Marine terpenes • Bioactive peptides • Sulfated Polysaccharides • Fucoidan • Ascophyllan • Algal polyphenols • Phlorotannins • Terpenes and steroids • Alkaloids • Commercially produced microalgal PUFAs	[82]

Table 2. Bioactive compounds from seaweeds with their health promoting functions.

and viable cell counts and increase in the mean survival time [41]. *Porphyratenera*, a red alga, has been extensively reported for its high anti-carcinogenic effect [79]. Chlorophyll-related compounds, carotene and lutien isolated from algae exhibit strong anti-mutagenic activity in vitro as well as in vivo [80].

Various anticancer pathways are involved to accomplish the process of tumour cell death. Major pathways are anti-oxidation and immune stimulation, and apoptosis of cancerous cells. Tumors are in a 'pro-oxidant' state generating more free radicals. These free radicals usually accompanied by lack of DNA repair mechanisms. Reactive oxygen species are main sources of oxidative stress in cells, damaging DNA, proteins and lipids. Anti-oxidants cause inhibition of the growth of cancer cells through varied mechanisms. The most common is activation of apoptosis by antioxidant species and inhibition the process of tumour progression [64].

Apoptosis is a process of programmed cell death triggered by various extrinsic or intrinsic stimuli in unfavourable situations. The protein p53 and caspase-cascade signaling system are prime factors for promoting apoptosis [83]. Caspases belong to the interleukin 1β converting enzyme family of proteases. The process of apoptosis has three stages, namely activation, execution and cell deletion. All these stages are interlinked by caspases [84]. Tumour suppressor protein p53 triggers the apoptosis and induces cell growth arrest. The prevention of cancer is highly dependent on p53 for controlling the proliferation of cells with damaged DNA or with a potential for neoplastic transformation. Algae is a source of many phytochemicals which cause apoptosis. *Spirulina* and *Aphanizomenon fos-aquae* are two most common edible cyanobacteria [85]. Both contain phycocyanin, which is capable of showing apoptosis in the chronic myeloid leukaemia cells. Enzymatic extraction of alga, *Ecklonia cava* together with its polysaccharides and polyphenolics, displays tremendous anti-proliferative activity against cancer cell line [75].

The apoptosis is executed immunostimulation with two pathways, the NK cell and Fas receptor mediated pathways. The Fas receptor molecule plays an important role in the immune system, which allows the removal of auto-antibodies and the elimination of virally infected tumourigenic cells. Immune defence mechanisms do kill any abnormal cells including cancer. Polysaccharides are associated with biological activities of several microalgal species. Polysaccharide complexes from *Chlorella pyrenoidosa* contain glucose and any combination of mannose, galactose, arabinose, and rhamnose. The complexes *N*-acetylglucosamide and *N*-acetylgalactosamine have immune stimulating properties and can inhibit the proliferation of pathogenic microbes such as *Listeria monocytogene s*and *Candida albicans* [75] *Enteromorpha compressa*, produces a range of bioactive compounds which are proved to be useful in the treatment of cancer and inflammation [86]. Malyngamides isolated from *Lyngbya majuscule* have immunosuppressant properties and is also cytotoxic [87].

2.4. Anti-viral/Anti- HIV activity

Acquired immunodeficiency syndrome AIDS is a disease caused by human immunodeficiency virus (HIV-1) [88]. Marine algae derived SPs can inhibit replication of enveloped viruses such as herpes virus, togavirus, arenavirus, rhabdovirus, and orthopoxvirus families.

These sulaphated polysaccharides have great potential for the development of novel anti-HIV therapeutics. Marine algae possess significant quantities of complex structural SPs that inhibit the HIV. The chemical structure, constituent sugars, stereochemistry, degree of sulfation, molecular weight and conformation are affected the antiviral activity of algal SPs [89].

SPs from red algae also exhibit significant HIV-1 inhibitory activity. Anti-HIV activity of *Schizymenia dubyi* is due to sulfated glucuronogalactan. This polysaccharide causes inhibition of virus-host cell attachment in vitro. A mechanism which occur mainly during initial step of HIV infection [42]. Additionally, antiretroviral activity of sulfated galactans from *Grateloupia filicina* and *Grateloupia longifolia* was examined with a primary isolate of HIV-1 and human peripheral blood mononuclear cells [54]. Sulfated fucans from the brown seaweed *F. vesiculosus, Lobophora variegata, Dictyota mertensiian* and *Spatoglossum schroederi* were reported to inhibit HIV reverse transcriptase [90]. Human papilloma virus is the cause of cervical cancer due to infection in female genital tract. Therefore, HPV Infection control has acquired great attention from scientific studies [91]. Natural bioactive compounds and their derivatives are potential source for the manufacture of functional foods as novel anti-HPV therapeutics with fewer side effects, more effective and cost effective. Marine algae contain substantial quantities of complex structural SPs which are potent inhibitors of wide variety of viruses, such as papilloma virus [92].

Carrageenan has been shown to demonstrate anti-HPV activity in vitro [92]. Carrageenan inhibits HPV 3-fold higher in magnitude than heparin, a highly effective model for HPV. Carrageenan acts mainly by preventing the binding of HPV virions to cells and blocks HPV infection through a post attachment heparin sulfate-independent effect. This mechanism is consistent by the fact that carrageenan closely resembles heparin sulfate, which is recognized as HPV-cell attachment factor. Moreover, antigen-specific immune responses and antitumor effects of carrageenan were remarkable [93]. Carrageenan are the promising candidates for production of new therapeutic agents for HPV by being a part of food additives. There are numerous advantages of carrageenan over other classes of antiviral agents, such as reasonably low production costs, novel modes of action, broad spectrum, low cytotoxicity and safety [92].

2.5. Anti-cardiovascular disease activity

Dyslipidemia is a main cardiovascular risk factor for coronary heart disease incidence and mortality. Lipid disorders can accelerate the atherosclerosis process and result could be chronic heart failure. Nutraceuticals are effectively able to reduce the atherosclerosis process and coronary heart disease progression. Carotenoids are produced by seaweeds, plants and microorganisms. These fat soluble are the fundamental component of Mediterranean foods, are well known to reduce the incidence and frequency of cardiovascular events, perhaps by means of their antioxidant action on free radicals or by anti-inflammatory action on lipoxygenase enzyme activity [94].

Cell membranes contain sterols as important structural components, and some of them are cardiac glycosides used therapeutically in the treatment of cardiac failure and atrial arrhythmias. The positive effect of eicosapentaenoic acid and docosa-hexaenoic acid on human health has been reported as far as cardiovascular system. Enrichment of foods with EPA/DHA show

cardio protective effects. EPA and DHA may exert their cardio protective functions, namely influencing plasmatic triacylglycerol (TAG) and cholesterol levels, and modulation of the chronic inflammation in the vascular wall [95].

2.6. Anti-inflammatory activity

Inflammation underlies a mass of enormous malignancies such as asthma, myocardial ischemia, allergies, arthritis, atherosclerosis and cancer. Inflammation is a complex biological process and occurs in response to harmful stimuli such as presence of pathogens in vascular tissues or injury. Inflammation normally acts as a defense mechanism, and its deregulation is associated with a multitude of diseases. Chronic and acute inflammation is a physiological process mediated by the activation of immune cells such as mononuclear phagocytic cells and macrophages [96]. The mechanism of inflammation is controlled by endogenous chemical mediators such as vasoactive amines, platelet activating factor, cytokines, bradykinin, fibrin, complement component, eicosanoids, nitric oxide and reactive oxygen species. These inflammatory mediators play a pivotal role in controlling various steps of inflammation. Marine algae produce a diverse array of secondary metabolites which play a pivotal role as inhibitors of inflammation [97].

Marine algae produce a combination of metabolites which are implicated in large number of diseases because of anti-inflammatory and antioxidant properties, with high commercial utilization. These compounds include fatty acids, marine terpenes, bioactive peptides, polysaccharides and their structures ranges from aliphatic molecules with a linear chain to complex polycyclic entities. Marine sulfated PS exhibit anti-coagulant, anti-inflammatory, anti-viral and anti-tumor activities and are important in pharmaceutical industries [82].

These algal compounds usually possess immune-modulatory activities which potentially instigate the immune system activities to alleviate undesirable responses such as inflammation. Sulfated polysaccharides may target numerous pathways in the immune and inflammatory systems. They can affect disease pathophysiology and outcome, including tumour development and septic shock. Fucoidan possess extensive of biological activities which include anti-inflammatory and anti-oxidative effects. Research revealed that the mechanism behind anti-inflammatory effect of fucoidan is due to its capability to interact with an adhesion molecule selectin on the seaweed cell membrane [98]. Fucoidan show anti-oxidative effect by inhibiting the synthesis and release of reactive oxygen radicals as well as its clearance. Park et al. [43] studied the cellular and molecular mechanism underlying the anti-inflammatory properties of fucoidan.

According to research, ascophyllan is a discrete sulfated polysaccharide isolated from fucoidan with significant biological activity. *Lobophora variegate* is a brown marine alga, which possess a high content of fucans exhibit reduced anti-inflammatory process *in vivo*. Two sulfated PS from *Laminaria saccharina*, a brown seaweed, utilized for the treatment of inflammation. Sulfated polysaccharides of the seaweed *L. variegate* exhibit antioxidant power and anti-inflammatory activity against zymosan induced arthritis [99]. Sulfated PS 'sacran' is also of marine algal origin. A sulfated polysaccharide isolated from *Aphanothece sacrum* exerts an epicutaneous effect on 2,4,6-tncb (picryl chloride) induced allergic dermatitis *in vivo* by improving functions of skin barriers and by decreasing the pro-inflammatory cytokine production [100].

Algal polyphenols and phlorotannins have numerous biological properties besides their strong antioxidant properties. Phlorotannins are the main bioactive compounds found in marine algae. Yang *et al.* [44] proposed the underlying anti-inflammatory mechanism of the phlorotannin 6,6′-bieckol, an active component isolated from brown seaweed *Ecklonia cava.* These findings suggest that the anti-inflammatory properties of this compound are related to the inhibition of cyclooxygenase-2 and pro-inflammatory cytokines (TNF-$\alpha$and IL-6).

Porphyria dentate is a red edible seaweed and its use in treatment of inflammatory diseases was the long lasting tradition globally. Crude extract of *P. dentate* contain phenolic compounds such as catechol, rutin and hesperidin [45]. Researcher demonstrated that the therapeutic applications of c-phycocyanin obtained from blue-green algae Spirulina *platensis* that significantly suppress the activation of LPS-induced nitrite and iNOS protein expression, accompanied by an attenuation of TNF-α formation. Marine red algae are the source of anti-inflammatory cyclic dipeptides and diketopiperazine [101] Terpenes and steroids are the classes of anti-inflammatory compounds found ubiquitously in marine algae. Heo et al. [102] evaluated the potential of fucoxanthin to produce anti-inflammatory effect via inhibition of NO production and reduced Prostaglandin-E2 production. Further investigations indicated the suppression of iNOS and COX-2 mRNA expressions by fucoxanthin in LPS-stimulate macrophage cells. By the addition of fucoxanthin in a dose-dependent manner, the release of cytokines TNF-α, IL-1β and IL-6 were also reduced [102].

Alkaloids occur rarely in marine algae, alkaloids isolated from marine algae have been shown to possess anti-inflammatory properties [103]. Algal fatty acids are either saturated or unsaturated with reported bioactivity. Commercially produced microalgal PUFAs are of particular interest because they lead the human body to more anti-inflammatory environment. Various benefits accrued from docosahexaenoic acid and palmitoleic acid are the reduction in the incidence of certain heart diseases and oleic acid retain antioxidant capacity [16].

3. Conclusion

Seaweeds are a valuable source of bioactive compounds and could be introduced for the preparation of novel functional ingredients in food and also a good approach for the treatment or prevention of chronic diseases. Recently, much att`ention has been paid by the consumers toward natural bioactive compounds as functional ingredients in foods, and hence, it can be suggested that, seaweeds are an alternative source for synthetic ingredients that can contribute to consumer's well-being, by being a part of new functional foods and pharmaceuticals. Furthermore, the wide ranges of biological activities associated with marine algae-derived bioactive compounds have potential to expand its health beneficial value in food, and pharmaceutical industries.

Conflict of interest

Authors declare no potential conflict of interest.

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References

[1] Holdt SLV, Kraan S. Bioactive compounds in seaweed: Functional food applications and legislation. Journal of Applied Phycology. 2011;**23**(3):543-597

[2] Domanguez H. Algae as a source of biologically active ingredients for the formulation of functional foods and nutraceuticals. In: Functional Ingredients from Algae for Foods and Nutraceuticals. Cambridge: WoodHead; 2013. pp. 1-19

[3] Pangestuti R, Kim SK. Biological activities and health benefit effects of natural pigments derived from marine algae. Journal of Functional Foods. 2011;**3**(4):255-266

[4] Mayakrishnan V, Kannappan P, et al. Cardioprotective activity of polysaccharides derived from marine algae: An overview. Trends in Food Science & Technology. 2013;**30**(2):98-104

[5] Renn D. Biotechnology and the red seaweed polysaccharide industry: Status, needs and prospects. Trends in Biotechnology. 1997;**15**(1):9-14

[6] Suleria HAR. Marine Processing Waste-In Search of Bioactive Molecules. Natural Products Chemistry and Research. 2016;**4**:e118

[7] Li B, Lu F, et al. Fucoidan: Structure and bioactivity. Molecules. 2008;**13**(8):1671-1695

[8] Muhammad SA, Muhammad J, et al. Metabolites of marine algae collected from Karachi-coasts of Arabian Sea. Natural Product Sciences. 2000;**6**(2):61-65

[9] Suleria HAR, Gobe G, Masci P, Osborne SA. Marine bioactive compounds and health promoting perspectives; innovation pathways for drug discovery. Trends in Food Science & Technology. 2016;**50**:44-55

[10] Gamez-Ordaaez E, Jimanez-Escrig A, et al. Dietary fibre and physicochemical properties of several edible seaweeds from the northwestern Spanish coast. Food Research International. 2010;**43**(9):2289-2294

[11] Tseng C. Algal biotechnology industries and research activities in China. Journal of Applied Phycology. 2001;**13**(4):375-380

[12] Rasmussen RS, Morrissey MT. Marine biotechnology for production of food ingredients. Advances in Food and Nutrition Research. 2007;**52**:237-292

[13] Frestedt JL, Kuskowski MA, et al. A natural seaweed derived mineral supplement (Aquamin F) for knee osteoarthritis: A randomised, placebo controlled pilot study. Nutrition Journal. 2009;**8**(1):7

[14] Ravikumar S, Kathiresan K. Influence of tannins, amino acids and sugars on fungi of marine halophytes. Mahasagar. 1993;**26**(1):21-25

[15] Plaza M, Cifuentes A, et al. In the search of new functional food ingredients from algae. Trends in Food Science & Technology. 2008;**19**(1):31-39

[16] Plaza M, Herrero M, et al. Innovative natural functional ingredients from microalgae. Journal of Agricultural and Food Chemistry. 2009;**57**(16):7159-7170

[17] Terry PD, Rohan TE, et al. Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: A review of the epidemiologic evidence. The American Journal of Clinical Nutrition. 2003;**77**(3):532-543

[18] Kraan S. Pigments and minor compounds in algae. In: Domanguez H, editor. Functional Ingredients from Algae for Foods and Nutraceuticals. Cambridge: WoodHead; 2013. pp. 205-251

[19] Zubia M, Payri C, et al. Alginate, mannitol, phenolic compounds and biological activities of two range-extending brown algae, *Sargassum mangarevense* and *Turbinaria ornata* (Phaeophyta: Fucales), from Tahiti (French Polynesia). Journal of Applied Phycology. 2008;**20**(6):1033-1043

[20] Mabeau S, Jl F. Seaweed in food products: Biochemical and nutritional aspects. Trends in Food Science & Technology. 1993;**4**(4):103-107

[21] Brown MR. Nutritional value and use of microalgae in aquaculture. In: Avances en Nutrician Acuacola VI. Memorias del VI Simposium Internacional de Nutrician Acuacola. 2002;**3**:281-292

[22] Suleria HAR, Masci P, Gobe G, Osborne S. Current and potential uses of bioactive molecules from marine processing waste. Journal of the Science of Food and Agriculture. 2016;**96**(4):1064-1067

[23] Dewapriya P, Kim SK. Marine microorganisms: An emerging avenue in modern nutraceuticals and functional foods. Food Research International. 2014;**56**:115-125

[24] Nisizawa K. Seaweeds Kaiso: Bountiful Harvest from the Seas. Japan Seaweed Association. Shimane; 2002. pp. 44-50

[25] Arasaki S, Arasaki T. Vegetables from the Sea. Vol. 96. Tokyo: Japan Publ. Inc.; 1983. pp. 251-223

[26] Massig K. Iodine-induced toxic effects due to seaweed consumption. In: Comprehensive Handbook of Iodine. Amsterdam: Elsevier; 2009. pp. 897-908

[27] Blunden G, Campbell SA, et al. Chemical and physical characterization of calcified red algal deposits known as maarl. Journal of Applied Phycology. 1997;**9**(1):11-17

[28] Burtin P. Nutritional value of seaweeds. Electronic Journal of Environmental, Agricultural and Food Chemistry. 2003;**2**(4):498-503

[29] Suleria HAR, Osborne S, Masci P, Gobe G. Marine-based nutraceuticals: An innovative trend in the food and supplement industries. Marine Drugs. 2015;**13**:6336-6351

[30] Suleria HR, Butt MS, Anjum FM, Arshad M, Khalid N. Aqueous garlic extract mitigate hypercholesterolemia and hyperglycemia; rabbit experimental modelling. Annals of Nutrition and Metabolism. 2013;**63**:271

[31] Stengel DB, Connan SN, et al. Algal chemodiversity and bioactivity: Sources of natural variability and implications for commercial application. Biotechnology Advances. 2011;**29**(5):483-501

[32] Yan X, Chuda Y, et al. Fucoxanthin as the major antioxidant in *Hijikia fusiformis*, a common edible seaweed. Bioscience, Biotechnology, and Biochemistry. 1999;**63**(3):605-607

[33] Yabuta Y, Fujimura H, et al. Antioxidant activity of the phycoerythrobilin compound formed from a dried Korean purple laver (*Porphyra* sp.) during in vitro digestion. Food Science and Technology Research. 2010;**16**(4):347-352

[34] Chevolot L, Foucault A, et al. Further data on the structure of brown seaweed fucans: Relationships with anticoagulant activity. Carbohydrate Research. 1999;**319**(1):154-165

[35] Kolender AA, Pujol CA, et al. The system of sulfated -linked D-mannans from the red seaweed *Nothogenia fastigiata*: Structures, antiherpetic and anticoagulant properties. Carbohydrate Research. 1997;**304**(1):53-60

[36] Jurd KM, Rogers DJ, et al. Anticoagulant properties of sulphated polysaccharides and a proteoglycan from *Codium fragile* ssp. atlanticum. Journal of Applied Phycology. 1995;**7**(4):339-345

[37] Matsubara K. Recent advances in marine algal anticoagulants. Current Medicinal Chemistry. Cardiovascular and Hematological Agents. 2004;**2**(1):13-19

[38] Bae JS. Antithrombotic and profibrinolytic activities of phloroglucinol. Food and Chemical Toxicology. 2011;**49**(7):1572-1577

[39] Shibata T, Fujimoto K, et al. Inhibitory activity of brown algal phlorotannins against hyaluronidase. International Journal of Food Science and Technology. 2002;**37**(6):703-709

[40] Mayer AM, Lehmann VK. Marine pharmacology in 1998: Marine compounds with antibacterial, anticoagulant, antifungal, antiinflammatory, anthelmintic, antiplatelet, antiprotozoal,

and antiviral activities; with actions on the cardiovascular, endocrine, immune, and nervous systems; and other miscellaneous mechanisms of action. The Pharmacologist. 2000;**42**(2):62-69

[41] Vasanthi H, Rajamanickam G, et al. Tumoricidal effect of the red algae *Acanthophora spicifera* on Ehrlich ascites carcinoma in mice. Seaweed Research and Utilization. 2004:217-224

[42] Bourgougnon N, Lahaye M, et al. Annual variation in composition and in vitro anti-HIV-1 activity of the sulfated glucuronogalactan from *Schizymenia dubyi* (Rhodophyta, Gigartinales). Journal of Applied Phycology. 1996;**8**(2):155-161

[43] Park HY, Han MH, et al. Anti-inflammatory effects of fucoidan through inhibition of NF-IB, MAPK and Akt activation in lipopolysaccharide-induced BV2 microglia cells. Food and Chemical Toxicology. 2011;**49**(8):1745-1752

[44] Yang L, Zhang LM. Chemical structural and chain conformational characterization of some bioactive polysaccharides isolated from natural sources. Carbohydrate Polymers. 2009;**76**(3):349-361

[45] Kaza-owska K, Hsu T, et al. Anti-inflammatory properties of phenolic compounds and crude extract from *Porphyra dentata*. Journal of Ethnopharmacology. 2010;**128**(1):123-130

[46] Shahidi F, Alasalvar C. Marine oils and other marine nutraceuticals. In: Handbook of Seafood Quality, Safety and Health Applications. Chichestar: Blackwell; 2011. pp. 444-454

[47] Barrow C, Shahidi F. Marine Nutraceuticals and Functional Foods. New York. CRC Press; 2007

[48] Ismail A, Hong TS. Antioxidant activity of selected commercial seaweeds. Malaysian Journal of Nutrition. 2002;**8**(2):167-177

[49] Suleria HAR, Masci PP, Zhao KN, Addepalli R, Chen W, Osborne SA, Gobe GC. Anticoagulant and anti-thrombotic properties of blacklip abalone (*Haliotis rubra*): In vitro and animal studies. Marine Drugs. 2017;**15**(8):240

[50] Costa L, Fidelis G, et al. Biological activities of sulfated polysaccharides from tropical seaweeds. Biomedicine & Pharmacotherapy. 2010;**64**(1):21-28

[51] Mayer AM, Rodraguez AD, et al. Marine pharmacology in 2007: Marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous system, and other miscellaneous mechanisms of action. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology. 2011;**153**(2):191-222

[52] Opoku G, Qiu X, et al. Effect of oversulfation on the chemical and biological properties of kappa carrageenan. Carbohydrate Polymers. 2006;**65**(2):134-138

[53] Chiu YH, Chan YL, et al. Prevention of human enterovirus 71 infection by kappa carrageenan. Antiviral Research. 2012;**95**(2):128-134

[54] Wang W, Zhang P, et al. Preparation and anti-influenza A virus activity of Î°-carrageenan oligosaccharide and its sulphated derivatives. Food Chemistry. 2012;**133**(3):880-888

[55] Li YX, Wijesekara I, et al. Phlorotannins as bioactive agents from brown algae. Process Biochemistry. 2011;**46**(12):2219-2224

[56] Miyashita K, Hosokawa M. 12 beneficial health effects of seaweed carotenoid, fucoxanthin. In: Marine Nutraceuticals and Functional Foods. New York: CRC; 2007. p. 297

[57] Hosakawa M, Bhaskar N, et al. Fucoxanthin as a bioactive and nutritionally beneficial marine carotenoid: A review. Carotenoid Science. 2006;**10**:15-28

[58] Ngo DH, Wijesekara I, et al. Marine food-derived functional ingredients as potential antioxidants in the food industry: An overview. Food Research International. 2011;**44**(2):523-529

[59] Cornish ML, Garbary DJ. Antioxidants from macroalgae: Potential applications in human health and nutrition. Algae. 2010;**25**(4):155-171

[60] Mendis E, Rajapakse N, et al. Investigation of jumbo squid (*Dosidicus gigas*) skin gelatin peptides for their in vitro antioxidant effects. Life Sciences. 2005;**77**(17):2166-2178

[61] Mendis E, Rajapakse N, et al. Antioxidant properties of a radical-scavenging peptide purified from enzymatically prepared fish skin gelatin hydrolysate. Journal of Agricultural and Food Chemistry. 2005;**53**(3):581-587

[62] Cho M, Lee HS, et al. Antioxidant properties of extract and fractions from *Enteromorpha prolifera*, a type of green seaweed. Food Chemistry. 2011;**127**(3):999-1006

[63] Raza A, Butt MS, Suleria HAR. Jamun (*Syzygium cumini*) seed and fruit extract attenuate hyperglycemia in diabetic rats. Asian Pacific Journal of Tropical Biomedicine. 2017;**7**(8):750-754

[64] Jun SY, Park PJ, et al. Purification and characterization of an antioxidative peptide from enzymatic hydrolysate of yellowfin sole (*Limanda aspera*) frame protein. European Food Research and Technology. 2004;**219**(1):20-26

[65] Sachindra NM, Sato E, et al. Radical scavenging and singlet oxygen quenching activity of marine carotenoid fucoxanthin and its metabolites. Journal of Agricultural and Food Chemistry. 2007;**55**(21):8516-8522

[66] Heo SJ, Ko SC, et al. Cytoprotective effect of fucoxanthin isolated from brown algae *Sargassum siliquastrum* against H_2O_2-induced cell damage. European Food Research and Technology. 2008;**228**(1):145-151

[67] Jung WK, Je JY, et al. A novel anticoagulant protein from *Scapharca broughtonii*. BMB Reports. 2002;**35**(2):199-205

[68] Jo HY, Jung WK, et al. Purification and characterization of a novel anticoagulant peptide from marine echiuroid worm, *Urechis unicinctus*. Process Biochemistry. 2008;**43**(2):179-184

[69] Kim SK, Pangestuti R. Potential role of marine algae on female health, beauty, and longevity. Advances in Food and Nutrition Research. 2011;**64**:41-55

[70] Mestechkina N, Shcherbukhin V. Sulfated polysaccharides and their anticoagulant activity: A review. Applied Biochemistry and Microbiology. 2010;**46**(3):267-273

[71] Maeda M, Uehara T, et al. Heparinoid-active sulphated polysaccharides from *Monostroma nitidum* and their distribution in the chlorophyta. Phytochemistry. 1991;**30**(11):3611-3614

[72] Silva F, Dore C, et al. Anticoagulant activity, paw edema and pleurisy induced carrageenan: Action of major types of commercial carrageenans. Carbohydrate Polymers. 2010;**79**(1):26-33

[73] Shanmugam M, Mody K. Heparinoid-active sulphated polysaccharides from marine algae as potential blood anticoagulant agents. Current Science. 2000;**79**(12):1672-1683

[74] Yuan YV, Walsh NA. Antioxidant and antiproliferative activities of extracts from a variety of edible seaweeds. Food and Chemical Toxicology. 2006;**44**(7):1144-1150

[75] Sithranga Boopathy N, Kathiresan K. Anticancer drugs from marine flora: An overview. Journal of Oncology. 2010;1-18. http://dx.doi.org/10.1155/2010/214186

[76] Cho EJ, Rhee SH, et al. Antimutagenic and cancer cell growth inhibitory effects of seaweeds. Preventive Nutrition and Food Science. 1997;**2**(4):348-353

[77] Yubin J, Guangmei Z. Pharmacological Action and Application of Available Antitumor Composition of Traditional Chinese Medicine. Heilongjiang, China: Heilongjiang Science and Technology Press; 1998

[78] Haroun F, Lindenmeyer F, et al. In vitro effect of fucans on MDA-MB231 tumor cell adhesion and invasion. Anticancer Research. 2002;**22**:214-221

[79] Yamamoto I, Maruyama H, et al. The effect of dietary or intraperitoneally injected seaweed preparations on the growth of sarcoma-180 cells subcutaneously implanted into mice. Cancer Letters. 1986;**30**(2):125-131

[80] Okai Y, Higashi-Okai K, et al. Identification of antimutagenic substances in an extract of edible red alga, *Porphyra tenera* (Asadusa-nori). Cancer Letters. 1996;**100**(1-2):235-240

[81] Givens DI, Gibbs RA. Current intakes of EPA and DHA in European populations and the potential of animal-derived foods to increase them: Symposium on how can the n-3 content of the diet be improved? Proceedings of the Nutrition Society. 2008;**67**(3):273-280

[82] Jiao G, Yu G, et al. Chemical structures and bioactivities of sulfated polysaccharides from marine algae. Marine Drugs. 2011;**9**(2):196-223

[83] Launay S, Hermine O, et al. Vital functions for lethal caspases. Oncogene. 2005;**24**(33):5137

[84] Fan TJ, Han LH, et al. Caspase family proteases and apoptosis. Acta Biochimica et Biophysica Sinica. 2005;**37**(11):719-727

[85] Hart AN, Zaske LA, et al. Natural killer cell activation and modulation of chemokine receptor profile in vitro by an extract from the cyanophyta *Aphanizomenon flos-aquae*. Journal of Medicinal Food. 2007;**10**(3):435-441

[86] Hiqashi-Okaj K, Otani S, et al. Potent suppressive effect of a Japanese edible seaweed, *Enteromorpha prolifera* (Sujiao-nori) on initiation and promotion phases of chemically induced mouse skin tumorigenesis. Cancer Letters. 1999;**140**(1):21-25

[87] Burja AM, Banaigs B, et al. Marine cyanobacteriaaea prolific source of natural products. Tetrahedron. 2001;**57**(46):9347-9377

[88] Vo TS, Kim SK. Potential anti-HIV agents from marine resources: An overview. Marine Drugs. 2010;**8**(12):2871-2892

[89] Adhikari U, Mateu CG. Structure and antiviral activity of sulfated fucans from *Stoechospermum marginatum*. Phytochemistry. 2006;**67**(22):2474-2482

[90] Queiroz K, Medeiros V, et al. Inhibition of reverse transcriptase activity of HIV by polysaccharides of brown algae. Biomedicine & Pharmacotherapy. 2008;**62**(5):303-307

[91] Lehtinen M, Dillner J. Preventive Human Papillomavirus Vaccination. The Medical Society for the Study of Venereal Disease; London; 2002

[92] Campo VL, Kawano DFB, et al. Carrageenans: Biological properties, chemical modifications and structural analysis: A review. Carbohydrate Polymers. 2009;**77**(2):167-180

[93] Buck CB, Thompson CD, et al. Carrageenan is a potent inhibitor of papillomavirus infection. PLoS Pathogens. 2006;**2**(7):e69

[94] Scicchitano P, Cameli M, et al. Nutraceuticals and dyslipidaemia: Beyond the common therapeutics. Journal of Functional Foods. 2014, 2014;**6**:11-32

[95] Komprda TA. Eicosapentaenoic and docosahexaenoic acids as inflammation-modulating and lipid homeostasis influencing nutraceuticals: A review. Journal of Functional Foods. 2012;**4**(1):25-38

[96] Zedler S, Faist E. The impact of endogenous triggers on trauma-associated inflammation. Current Opinion in Critical Care. 2006;**12**(6):595-601

[97] Nguyen MHT, Jung WK, et al. Marine algae possess therapeutic potential for Ca-mineralization via osteoblastic differentiation. Advances in Food and Nutrition Research. 2011;**64**:429-441

[98] Cui Y, Luo D, et al. Fucoidan: Advances in the study of its anti-inflammatory and antioxidative effects. Yao Xue Xue Bao [Acta Pharmaceutica Sinica]. 2008;**43**(12):1186-1189

[99] Medeiros V, Queiroz K, et al. Sulfated galactofucan from *Lobophora variegata*: Anticoagulant and anti-inflammatory properties. Biochemistry (Moscow). 2008;**73**(9): 1018-1024

[100] Ngatu NR, Okajima MK, et al. Anti-inflammatory effects of sacran, a novel polysaccharide from *Aphanothece sacrum*, on 2,4,6-trinitrochlorobenzene-induced allergic dermatitis in vivo. Annals of Allergy, Asthma & Immunology. 2012;**108**(2):117-122. e2

[101] Huang R, Zhou X, et al. Diketopiperazines from marine organisms. Chemistry & Biodiversity. 2010;**7**(12):2809-2829

[102] Heo SJ, Yoon WJ, et al. Evaluation of anti-inflammatory effect of fucoxanthin isolated from brown algae in lipopolysaccharide-stimulated RAW 264.7 macrophages. Food and Chemical Toxicology. 2010;**48**(8):2045-2051

[103] Gaven KMC, Percot A, et al. Alkaloids in marine algae. Marine Drugs. 2010;**8**(2):269-284