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Review

Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae

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ABSTRACT

Recently, a great deal of interest has been developed to isolate novel bioactive compounds from marine resources because of their numerous health beneficial effects. Among marine resources, marine algae are valuable sources of structurally diverse bioactive compounds. The cell walls of marine algae are rich in sulfated polysaccharides (SPs) such as fucoidans in brown algae, carrageenans in red algae and ulvans in green algae. These SPs exhibit many beneficial biological activities such as anticoagulant, antiviral, antioxidative, anticancer and immunomodulating activities. Therefore, marine algae derived SPs have great potential for further development as products in nutraceutical, pharmaceutical and cosmeceutical areas. This contribution presents an overview of biological activities and potential health benefits of SPs derived from marine algae.

Contents

1. Introduction

As more than 70% of the world's surface is covered by oceans, the wide diversity of marine organisms offer a rich source of natural products. Marine environment contains a source of functional materials, including polyunsaturated fatty acids (PUFA), polysaccharides, essential minerals and vitamins, antioxidants, enzymes and bioactive peptides (Kim & Wijesekara, 2010; Pomponi, 1999). Among marine organisms, marine algae are rich sources of structurally diverse bioactive compounds with various biological activities. Recently, their importance as a source of novel bioactive substances is growing rapidly and researchers have revealed that marine algal originated compounds exhibit various biological activities (Barrow & Shahidi, 2008; Wijesekara & Kim, 2010; Wijesekara, Yoon, & Kim, 2010).

Edible marine algae, sometimes referred as seaweeds, have attracted a special interest as good sources of nutrients and one particular interesting feature is their richness in sulfated polysaccharides (SPs), the uses of which span from food, cosmetic and pharmaceutical industries to microbiology and biotechnology (Ren,

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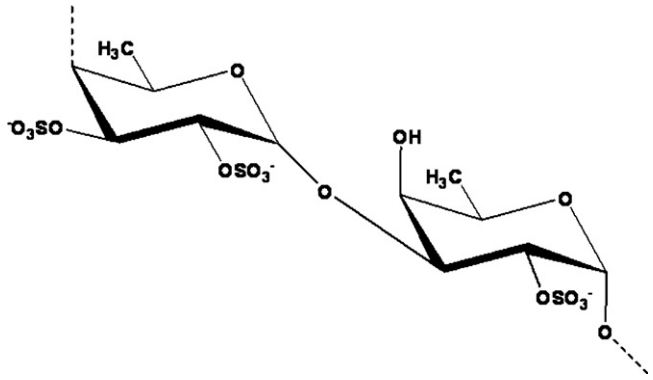

Fig. 1. Chemical structure of the repeating dimeric units of fucoidan.

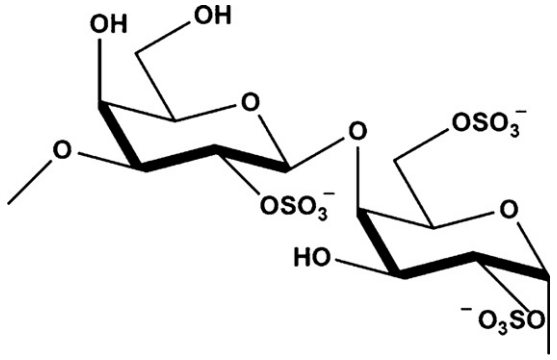

Fig. 2. Chemical structure of the repeating dimeric units of λ-carrageenan.

1997). These chemically anionic SPs polymers are widespread not only in marine algae but also occur in animals such as mammals and invertebrates (Mourao & Pereira, 1999; Mourao, 2007). Marine algae are the most important source of non-animal SPs and the chemical structure of these polymers varies according to the algal species (Costa et al., 2010). The amount of SPs present is found to be differ according to the three major divisions of marine algae, Chlorophyceae (green algae), Rhodophyceae (red algae) and Phaeophyceae (brown algae). The major SPs found in marine algae include fucoidan (Fig. 1) and laminarans of brown algae, carrageenan (Fig. 2) of red algae and ulvan (Fig. 3) of green algae. In recent years, various SPs isolated from marine algae have attracted much attention in the fields of food, cosmetic and pharmacology. Carrageenans, a family of SPs isolated from marine red algae, are widely used as food additives, such as emulsifiers, stabilizers, or thickeners (Campo, Kawano, da Silva, & Carvalho, 2009; Chen, Yan, Lin, Wang, & Xu, 2007). Ulvan displays several physiochemical and biological features of potential interest for food, pharmaceutical, agricultural and chemical applications (Lahaye & Robic, 2007). Compared with other SPs, fucoidans are widely available commercially from various cheap sources; hence, more and more fucoidans have been

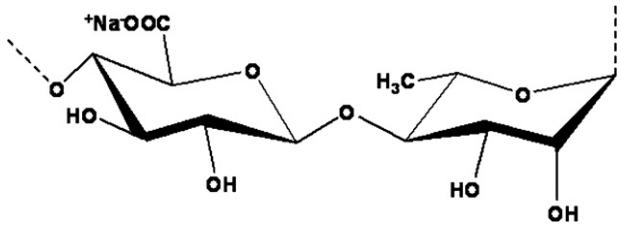

Fig. 3. Chemical structure of the repeating dimeric units of ulvan.

investigated in recent years to develop novel drugs and functional foods (Li, Lu, Wei, & Zhao, 2008).

Novel extraction and separation techniques, such as supercritical CO_2 extraction, ultrasonic-aided extraction and membrane separation technology have recently been applied in development of bioactive SPs from marine algae (Sheng et al., 2007; Ye, Wu, & Zhou, 2006). Biological activities of SPs depend on chemical structure, molecular weight and chain conformations (Ye, Wang, Zhou, Liu, & Zeng, 2008). Therefore, for the efficient recovery of bioactive SPs with desired molecular size and functional property, a suitable method is the use of an ultrafiltration membrane system.

The cell walls of seaweeds are rich in matrix SPs and they exhibited beneficial biological activities such as anticoagulant (Mao et al., 2009), antiviral (Ponce, Pujol, Damonte, Flores, & Stortz, 2003), antioxidative (Ruperez, Ahrazem, & Leal, 2002), anticancer (Synytsya et al., 2010) and anti-inflammation (Na et al., 2010). This review focuses on SPs derived from marine algae and presents an overview of their biological activities with potential health benefits.

2. Biological activities of SPs and potential health benefits

2.1. Anticoagulant activity

The blood coagulation system consists of intrinsic and extrinsic pathways, where a series of factors involve in the mechanism. Blood coagulation is proceeded by coagulation factors in order to stop the flow of blood though the injured vessel wall whenever, an abnormal vascular condition and exposure to non-endothelial surfaces at sites of vascular injury occurred. As endogenous or exogenous anticoagulants interfered with the coagulation factors by inactivate or restrict, the blood coagulation can be prolonged or stopped (Jung, Je, & Kim, 2001). These anticoagulants are used in therapeutic purposes, for example, as cure for hemophilia.

Heparin has been identified and used for more than fifty years as a commercial anticoagulant and it is widely used for the prevention of venous thromboembolic disorders. However, several side effects of heparin have been reported such as development of thrombocytopenia, hemorrhagic effect, and ineffectiveness in congenital or acquired antithrombin deficiencies, and incapacity to inhibit thrombin bound to fibrin (Pereira, Melo, & Mourao, 2002). Moreover, heparin is available in very low concentrations in pig intestine or bovine lungs from where it is primarily extracted. Therefore, the necessity of discovering alternative sources of anticoagulants has been arisen with interesting demand for safer anticoagulant therapy.

After the investigation of blood anticoagulant properties from marine brown algae (Killing, 1913) it has been reported that SPs derived from marine algae are alternative sources for manufacture of novel anticoagulant drugs (Church, Meade, Treanor, & Whinna, 1989; Matsubara, 2004; Nishino, Yamauchi, Horie, Nagumo, & Suzuki, 2000). Anticoagulant activity is among the most widely studied properties of SPs (Costa et al., 2010) and anticoagulants from marine algae have previously been reviewed (McLellan & Jurd, 1992; Mestechkina & Shcherbukhin, 2010). Various anticoagulant SPs, from marine algae have been isolated and characterized (Table 1). Two types of SPs are identified with high anticoagulant activity including sulphated galactans or also known as carrageenan from marine red algae (Carlucci et al., 1997; Kolender, Pujol, Damonte, Matulewicz, & Cerezo, 1997; Sen et al., 1994) and sulfated fucoidans from marine brown algae (Chevolot et al., 1999; Colliec et al., 1991; Dobashi, Nishino, Fujihara, & Nagumo, 1989). However, there are fewer reports of anticoagulant SPs reported from marine green algae compared to brown and red algae (Mao et al., 2009; Zhang et al., 2008). Jurd, Rogers, Blunden, and McLellan

Table 1
Some anticoagulant sulfated polysaccharides (SPs) from marine algae: major sugar and source.

Major sugar of SPs	Source	Reference
Chlorophyceae		
Rhamnose	*Monostroma latissimum*	Mao et al. (2009)
Rhamnose	*Monostroma nitidum*	Maeda et al. (1991)
Rhamnose	*Ulva conglobata*	Mao, Zhang, Li, and Zhang (2006)
Arabinose	*Codium fragile*	Hayakawa et al. (2000)
Glucose	*Codium pugniformis*	Matsubara, Matsuura, Hori, and Miyazawa (2000)
Galactose	*Codium cylindricum*	Matsubara et al. (2001)
Phaeophyceae		
Fucose	*Ecklonia cava*	Athukorala, Jung, Vasanthan, and Jeon (2006)
Fucose	*Ecklonia kurome*	Nishino, Aizu, and Nagumo (1991)
Fucose	*Laminaria japonica*	Wang, Zhang, Zhang, Song, and Li (2010)
Fucose	*Ascophyllum nodosum*	Nardella et al. (1996)
Fucose	*Lessonia vadosa*	Chandia and Matsuhiro (2008)
Rhodophyceae		
Galactose	*Lomentaria catenata*	Pushpamali et al. (2008)
Galactose	*Gigartina skottsbergii*	Carlucci et al. (1997)
Galactose	*Schizymenia binderi*	Zuniga, Matsuhiro, and Mejias (2006)
Galactose	*Grateloupia indica*	Sen et al. (1994)
Galactose	*Porphyra haitanensis*	Zhang et al. (2010)
Mannose	*Nothogenia fastigiata*	Kolender et al. (1997)

(1995) found that the anticoagulant-active SPs from *Codium fragile* subspecies *atlanticum* (Chlorophyceae) contain xyloarabinogalactans. A sulfated galactan with anticoagulant activity has also reported from *Codium cylindricum* (Matsubara et al., 2001). In addition, Maeda, Uehara, Harada, Sekiguchi, and Hiraoka (1991) have revealed that the anticoagulant SPs from *Monostroma nitidum* (Chlorophyceae) yielded a six fold higher activity than that of heparin. In comparison, marine brown algae extracts exhibit higher anticoagulant activity than red and green algae extracts (Chevolot et al., 1999; Patankar, Oehninger, Barnett, Williams, & Clerk,1993).

The anticoagulant activity of the above SPs has been determined by prolongation of activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) assays. Most of studies reported that the anticoagulant activity of marine SPs based on APTT and TT pathways. The prolongation of APTT suggests inhibition of the intrinsic factors and is the measure of the intrinsic pathway-dependent clotting time. The TT revealed the inhibition of thrombin activity or fibrin polymerization as thrombin inhibition-dependent clotting time. PT is the extrinsic pathway-dependent clotting time. Since a few studies reported the prolongation of PT by marine SPs, it suggests that marine SPs interfered a little or may not inhibit the extrinsic pathway of coagulation. The relationship between structure and anticoagulant activity of some SPs has been reported (Colliec et al., 1991; Hayakawa et al., 2000). The presence of sulfate groups in SPs can increase both their specific and non-specific binding to a wide range of biologically active proteins. Anticoagulant activity of sulfated galactans depends on the nature of the sugar residue, the sulfation position of the structure and the sulfate content in the SPs (Melo, Pereira, Foguel, & Mourao, 2004; Silva et al., 2010). Moreover, the O-sulfated 3-linked α-galactans enhanced the inhibition of thrombin and factor Xa by antithrombin and/or heparin cofactor II in the intrinsic pathway of blood coagulation (Pereira et al., 2002). Furthermore, high molecular weight carrageenans with high sulfate content have shown higher anticoagulant activity than low molecular weight and low sulfate content SPs (Shanmugam & Mody, 2000).

Unfractionated heparins and low molecular weight heparins are the only sulfated polysaccharides currently used as anticoagulant drugs. Seaweed-derived SPs have been described to possess anticoagulant activity similar to or higher than heparin (Costa et al., 2010). Collectively, these evidences suggest that SPs derived from seaweeds have a promising potential to be used as anticoagulant agents in the pharmaceutical industry.

2.2. Antiviral activity

The potential antiviral activity of marine algal polysaccharides was first shown by Gerber, Dutcher, Adams, and Sherman (1958), who observed that the polysaccharides extracted from *Gelidium cartilagenium* (Rhodophyceae) protected the embryonic eggs against Influenza B or mump virus. The polysaccharides with antiviral activity were shown to be highly sulfated (Huheihel, Ishanu, Tal, & Arad, 2002). Many species of marine algae contain significant quantities of complex structural SPs that have been shown to inhibit the replication of enveloped viruses including members of the flavivirus, togavirus, arenavirus, rhabdovirus, orthopoxvirus, and herpesvirus families (Witvrouw & De Clercq, 1997). The chemical structure including the degree of sulfation, molecular weight, constituent sugars, conformation and dynamic stereochemistry are caused to determine the antiviral activity of algal sulphated polysaccharides (Adhikari et al., 2006; Damonte, Matulewicz, & Cerezo, 2004; Luscher-Mattil, 2000). In addition, both the degree of sulfation and the distribution of sulfate groups on the constituent polysaccharides play an important role in the antiviral activity of these SPs. Algal polysaccharides with low degrees of sulfation are generally inactive against viruses (Damonte et al., 2004).

Human immunodeficiency virus type-1 (HIV-1) is identified as the causative agent of acquired immunodeficiency syndrome (AIDS) which is one of the most crucial diseases with about 33.2 million people infected worldwide up to 2008 (Artan et al., 2008). The first generation anti-HIV drugs have been developed to treat AIDS patients after the introduction of AIDS in early 1980. However, failure in anti-AIDS treatment is observed in more than 50% of the patients infected with HIV as a result of drug-resistant strains of virus (Stoddart & Reyes, 2006). Therefore, the search for potential drug candidates containing higher inhibitory activity against various HIV strains is increasing in pharmaceutical industry. In this regard, natural bioactive compounds and their derivatives are great sources for the development of new generation of anti-HIV therapeutics which are more effective with less side-effects (Schaeffer & Krylov, 2000; Singh, Bharate, & Bhutani, 2005; Tziveleka, Vagias, & Roussis, 2003). Hence, marine algae derived SPs are an alternative source for searching novel therapeutic candidates for HIV. Moreover, several researchers have investigated the inhibitory effects of SPs on the herpes simplex virus strains (HSV-1 and HSV-2) (Table 2). Fucoidans are SPs extracted from marine brown seaweeds that possess some biological activities and fucoidans show the antiviral activity against infectious diseases, such as HIV, herpes simplex virus types (HSV-1 and HSV-2) and cytomegalovirus (Witvrouw & De Clercq, 1997). In addition, seaweed-derived SPs such as carrageenans, fucoidans and sulfated rhamnogalactans have inhibitory effects on the entry of enveloped viruses including herpes and HIV into cells. Some other algal fractions have virucidal and enzyme inhibitory activity or the ability to inhibit syncytium formation (Thompson & Dragar, 2004; Ponce et al., 2003; Pujol et al., 2002; Schaeffer & Krylov, 2000). Furthermore, the presence of sulfate group is necessary for the anti-HIV activity and potency increases with the degree of sulfation (Witvrouw & De Clercq, 1997). This leads to a hypothesis that anionic charges on the sulfate groups may be effective in inhibiting reverse transcriptase enzyme

Table 2
Anti-Herpes simplex virus (HSV) activity of SPs from marine algae: major sugar, source, virus strain and EC_{50} value.

Major sugar of SPs	Source	Virus strain	EC_{50} (μg/ml)	Reference
Chlorophyceae				
Galactose	*Codium fragile*	HSV-2	4.7	Ohta, Lee, Hayashi, and Hayashi (2009)
Galactose	*Caulerpa racemosa*	HSV-2	3.0	Ghosh et al. (2004)
Phaeophyceae				
Fucose	*Sargassum horneri*	HSV-1	1.0	Hoshino et al. (1998)
Fucose	*Sargassum patens*	HSV-1	1.5	Zhu, Chiu, Ooi, Chan, and Ang (2006)
Fucose	*Undaria pinnatifida*	HSV-2	0.5	Thompson and Dragar (2004)
Rhodophyceae				
Galactose	*Cryptonemia crenulata*	HSV-1	0.5	Talarico et al. (2004)
Mannose	*Nemalion helminthoides*	HSV-1	5.4	Recalde, Noseda, Pujol, Carlucci, and Matulewicz (2009)

activity of the virus. In most of studies, antiviral activity of SPs has been determined by plaque reduction and/or virus yield inhibition assays.

Harden, Falshaw, Carnachan, Kern, and Prichard (2009) have evaluated the antiviral activity of SPs containing seaweed extracts from *Undaria pinnatifida*, *Splachnidium rugosum*, *Gigartina atropurpurea* and *Plocamium cartilagineum* against HSV-I and HSV-II. These extracts exhibited potential antiviral activity when added during the first hour of viral infection, but were ineffective if added later. Moreover, it has reported that SPs from red seaweeds inhibit *in vitro* and *in vivo* infection of flaviviruses, such as dengue and yellow fever viruses (Ono et al., 2003; Talarico et al., 2005). Dengue virus belongs to the family Flaviviridae, the same family as Japanese encephalitis and yellow fever viruses, which are controlled by specific vaccinations. However, until now no licensed dengue vaccination or anti-dengue agents are clinically available. Fucoidan from the marine alga *Cladosiphon okamuranus* (Phaeophyceae) potently inhibits dengue virus type 2 infection (Hidari et al., 2008) and they have found that virus particles bound exclusively to fucoidan, indicating that fucoidan interacts directly with envelope glycoprotein on the virus. Hence, this could be developed as a potential inhibitory agent against the dengue virus.

Furthermore, recent studies demonstrated that seaweed-derived SPs could be used as vaginal antiviral formulations without disturbing essential functions of the vaginal epithelial cells and normal bacterial flora (Beress, Wassermannv, Bruhn, & Beress, 1993). It will be a continuous challenge to select the most promising drug candidates among the wide array of available SPs compounds. There are numerous advantages over other classes of antiviral drugs, such as relatively low production costs, broad spectrum of antiviral properties, low cytotoxicity, safety, wide acceptability and novel modes of action, suggest marine algal SPs as promising drug candidates in the near future and further studies are needed with clinical trials for these antiviral SPs.

2.3. Antioxidant activity

Antioxidants may have a positive effect on human health as they can protect human body against damage by reactive oxygen species (ROS), which attack macromolecules such as membrane lipids, proteins and DNA, lead to many health disorders such as cancer, diabetes mellitus, neurodegenerative and inflammatory diseases with severe tissue injuries (Butterfield et al., 2002; Frlich & Riederer, 1995; Halliwell & Aruoma, 1991; Yang, Landau, Huang, & Newmark, 2001). Moreover, deterioration of some foods has been identified due to oxidation of lipids or rancidity and formation of undesirable secondary lipid peroxidation products. Lipid oxidation by ROS such as superoxide anion, hydroxyl radicals and H_2O_2 also causes a decrease in nutritional value of lipid foods, and affect their safety and appearance. Therefore, in food and pharmaceutical industries, many synthetic commercial antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tert-butylhydroquinone (TBHQ) and propyl gallate (PG) have been used to retard the oxidation and peroxidation processes. However, the use of these synthetic antioxidants must be under strict regulation due to potential health hazards (Hettiarachchy, Glenn, Gnanasambandan, & Johnson, 1996; Park, Jung, Nam, Shahidi, & Kim, 2001). Hence, the search for natural antioxidants as safe alternatives is important in the food industry (Penta-Ramos & Xiong, 2001). Recently, there is a considerable interest in the food industry as well as pharmaceutical industry for the development of antioxidants from natural sources, such as marine flora and fauna. Among them, marine algae represent one of the richest sources of natural antioxidants (Mayer & Hamann, 2002; Ruperez, 2001).

SPs not only function as dietary fiber, but they also contribute to the antioxidant activity of marine algae. It has been demonstrated that SPs have potential antioxidant activity and various classes of SPs including, fucoidan, laminaran and alginic acid have been shown as potent antioxidants (Rocha de Souza et al., 2007; Ruperez et al., 2002; Wang et al., 2008). Antioxidant activity of SPs have been determined by various methods such as 1,1-diphenyl-2-picryl hydrazil (DPPH) radical scavenging, lipid peroxide inhibition, ferric reducing antioxidant power (FRAP), nitric oxide (NO) scavenging, ABTS radical scavenging, superoxide radical and hydroxyl radical scavenging assays. In addition, Xue, Yu, Hirata, Terao, and Lin (1998) reported that several marine-derived SPs have antioxidative activities in phosphatidylcholine-liposomal suspension and organic solvents. According to Kim et al. (2007) the SPs of *Sargassum fulvellum* (Phaeophyceae), is more potent NO scavenger than commercial antioxidants such as BHA and α–tocophorol. Antioxidant activity of SPs depends on their structural features such as degree of sulfating, molecular weight, type of the major sugar and glycosidic branching (Qi et al., 2005; Zhang et al., 2003). For example, low molecular weight SPs have shown potent antioxidant activity than high molecular weight SPs (Sun, Wang, Shi, & Ma, 2009). In addition, Qi et al. (2005) have prepared different molecular weight ulvans from *Ulva pertusua* (Chlorophyceae) by H_2O_2 degradation and their antioxidant activities were investigated. Their results showed that low molecular weight ulvans have a strong antioxidant activity. The rationale for this is low molecular weight SPs may incorporate into the cells more efficiently and donate proton effectively compared to high molecular weight SPs. Moreover, a positive correlation has reported for sulfate content and superoxide radical scavenging activity in fucoidan fractions obtained from a brown alga *Laminaria japonica* (Wang, Zhang, Zhang, & Li, 2008). The SPs fraction obtained by acid hydrolysis (0.1 M HCl, 37 °C) of *Fucus vesiculosus* (Phaeophyceae) has shown the highest potential to be used as antioxidants by the FRAP assay, followed by the alkali- (2 M KOH, 37 °C) and water-soluble fractions (Ruperez et al., 2002). Furthermore, fucoidan has shown the highest antioxidant activity followed by alginate and laminaran from *Turbinaria conoides* (Phaeophyceae) according to FRAP and DPPH assays (Chattopadhyay et al., 2010). In

addition, *in vivo* antioxidant activity of SPs derived from marine red alga *Porphyra haitanensis* in ageing mice has been reported (Zhang et al., 2003).

These evidences suggest that among various naturally occurring substances, SPs prove to be one of the useful candidates in search for effective, non-toxic substances with potential antioxidant activity. SPs are by-products in the preparation of alginates from edible brown seaweeds 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.

2.4. Anticancer activity

The formation of cancer cells in human body can be directly induced by free radicals and natural anticancer drugs as chemopreventive agents have gained a positive popularity in treatment of cancer. Hence, radical scavenging compounds such as SPs from seaweeds can be used indirectly to reduce cancer formation in human body. During the cancer multi-stage cascade, normal cells undergo initiation, promotion and progression processes. Most natural anticancer compounds are able to manipulate the growth of cancer cells with no or minor side effects. Therefore, identification of novel effective cancer chemopreventive agents has become an important worldwide strategy in cancer prevention.

Several studies have reported that SPs have antiproliferative activity in cancer cell lines *in vitro*, as well as inhibitory activity of tumor growth in mice (Rocha de Souza et al., 2007; Ye et al., 2008). In addition, they have antimetastatic activity by blocking the interactions between cancer cells and the basement membrane (Rocha et al., 2005). SPs inhibit tumor cell proliferation and tumor cell adhesion to various substrates, but their exact mechanisms of action are not yet completely understood. Yamamoto, Maruyama, Takahashi, and Komiyama (1986) reported that the oral administration of several seaweeds can cause a significant decrease in the incidence of carcinogenesis *in vivo*. Porphyran, the SPs of *Porphyra yezoensis* (Rhodophyceae) can induce cancer cell death via apoptosis in a dose-dependent manner *in vitro* without affecting the growth of normal cells (Kwon & Nam, 2006). Moreover, the SPs purified from *Ecklonia cava* (Phaeophyceae) stimulate the induction of apoptosis *in vitro* (Athukorala et al., 2009) and have potential antiproliferative effect on human leukemic monocyte lymphoma cell line (U-937). Anticancer activity of fucoidans has been reported to be closely related to their sulfate content and molecular weight. When native fucoidans have hydrolyzed in boiling water with HCl acid for 5 min, it significantly increased anticancer activity. However, fucoidans hydrolyzed in a microwave oven showed little improvement of anticancer activity. This suggests that anticancer activity of fucoidans could be significantly enhanced by lowering their molecular weight only when they are depolymerized at mild conditions (Yang et al., 2008).

Furthermore, SPs from marine algae are known to be important free-radical scavengers and antioxidants for the prevention of oxidative damage, which is an important contributor in carcinogenesis. Therefore, it might be suggested that these marine algae derived SPs have potent capacities for new anticancer product developments in the pharmaceutical as well as the food industries as novel chemopreventing agents for cancer therapy.

2.5. Immunomodulating activity

The immunostimulating effect of SPs is mainly based on macrophages modulation. Macrophages are the residence of immune cells in the innate immune system which plays an important role in the maintenance of homeostasis by changing their function according to the tissue. As the residence of the immune system, macrophages are a predominant source of pro-inflammatory factors. It is hypothesized that the origin of cancer was at sites of chronic inflammation, in part based on the hypothesis that some classes of irritants, together with the tissue injury and ensuing inflammation they cause, enhance cell proliferation.

Marine algae derived water soluble compounds such as SPs are known to have promising anti-inflammatory activities (Abad, Bedoya, & Bermejo, 2008). However, the scientific analysis of anti-inflammatory activity of seaweed-derived SPs has been poorly carried out until now and a few studies were reported. For example, SPs isolated from two red algae *Porphyra yezoensis* and *Gracilaria verrucosa* stimulate phagocytosis and respiratory burst in mouse macrophages *in vitro* and *in vivo* (Yoshizawa, Enomoto, Todoh, Ametani, & Kaminogawa, 1993; Yoshizawa et al., 1995, 1996). Carrageenan from red marine algae is known to be a potent inflammatory agent in rodents, primes mice leucocytes to produce tumor necrosis factor-α (TNF-α) in response to bacterial lipopolysaccharide (Ogata, Matsui, Kita, & Shigematsu, 1999). Moreover, some types of carrageenans induce potent macrophage activation (Nacife, Soeiro, Araujo-Jorge, Neto, & Meirelles, 2000; Nacife et al., 2004), while some carrageenans and fucoidan appear to inhibit macrophage functions (Van Rooijen & Sanders, 1997; Yang, Yoon, Oh, Kim, & Kang, 2006). However, SPs may have potential biomedical applications in stimulating the immune system or in controlling macrophage activity to reduce associated negative effects (Leiro, Castro, Arranz, & Lamas, 2007).

SPs extracted from marine green alga *Ulva rigida* have induced a more than 2-fold increase in the expression of several chemokines and interleukins and also induced nitrite production. In addition, *U. rigida* SPs can stimulate macrophage secretion of prostaglandin E2 (PGE_2) and induce an increase in cyclooxygenase-2 (COX-2) and nitric oxide synthase-2 (NOS-2) expression, suggested that their potential in clinical applications for modifying certain macrophage activities in diseases where macrophage function is impaired or needs to be boosted (Leiro et al., 2007).

2.6. Other biological activities

Fucoidan contains large proportions of L-fucose and sulphate, together with minor amounts of other sugars like xylose, galactose, mannose and galaturonic acid (Duarte, Noseda, Noseda, Tulio, & Pujol, 2001). Fucoidan extracted from the marine brown alga *Undaria pinnatifida*, has significantly induced osteoblastic cell differentiation and has potential in use as a functional ingredient in bone health supplements (Cho, Jung, Kim, Choi, & Kim, 2009). Moreover, fucoidan from *Cladosiphon okamuranus* (Phaeophyceae) protects gastric mucousa against acid and pepsin. Therefore, fucoidan can be developed as a potential anti-ulcer ingredient in functional foods (Nagaoka et al., 2000; Shibata et al., 2000). In addition, fucoidan inhibits ultraviolet B (UV B) induced matrix metalloproteinase-1 (MMP-1) enzyme activity in human skin fibroblasts (Moon et al., 2008). Matrix metalloproteinases (MMPs) are responsible for the degradation or inhibition of synthesis of collagenous extracellular matrix in connective tissues. Moon et al. (2008) have demonstrated that fucoidan can mainly inhibit UV B induced MMP-1 expression by inhibiting the extra-cellular signal-regulated kinases (ERK) pathways. Hence, fucoidan might be used as a potential agent in skin cosmetics for the prevention of skin photoaging.

Dietary fibers support to reduce cholesterol levels and recent studies have shown that dietary fibers with ion-exchange capacity contain more potent effects on cholesterol lowering (Guillon & Champ, 2000). Ulvan, belongs to the SPs group from *Ulva pertusa* is a potential anti-hyperlipidemic agent and has significantly reduced serum triglyceride (TG), total and low density lipoprotein cholesterol (LDL-cholesterol) and elevated high density lipoprotein cholesterol (HDL-cholesterol) in mice (Yu et al., 2003a). According

to Yu et al. (2003b), anti-hyperlipidemic activity of ulvan depends on the molecular weight of ulvan fractions; high molecular weight fraction is more effective on serum total and LDL-cholesterol, where as low molecular weight fractions are more effective on TG and HDL-cholesterol. Ulvan contains uronic acid and sulphates, has a potential capability of sequestering or binding bile acids (Lahaye, 1991). Furthermore, porphyran from marine red alga *Porphyra yezoensis* can also be used as a potent anti-hyperlipidemic agent (Ren, Noda, Amano, Nishino, & Nishizawa, 1994; Tsuge et al., 2004). In addition, porphyran reduces apolipoprotein B100 (apoB100) secretion mainly through suppression of lipid synthesis in human liver derived cells (Inoue et al., 2009). This apoB100 is an essential component in very low density lipoprotein (VLDL) and its level in blood is positively correlated with cardiovascular diseases (Huff & Burnett, 1997). It has assumed that the sulphate groups in porphyran contribute to the hypolipidemic activity (Inoue et al., 2009).

3. Concluding remarks

Recent studies have provided evidence that marine algal derived SPs play a vital role in human health and nutrition. Furthermore, seaweed processing by-products with bioactive SPs can be easily utilized for producing functional ingredients. The possibilities of designing new functional foods and pharmaceuticals to support reducing or regulating the diet related chronic malfunctions are promising. Therefore, it can be suggested that due to valuable biological functions with health beneficial effects, marine algal derived SPs have much potential as active ingredients for preparation of nutraceutical, cosmeceutical and pharmaceutical products. Until now, most of the biological activities of marine derived SPs have been observed *in vitro* or in mouse model systems. Therefore, further research studies are needed in order to investigate their activity in human subjects.

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