CHAPTER 30

# Medicinal Benefits of Sulfated Polysaccharides from Sea Vegetables

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Contents



Abstract

The cell walls of sea vegetables or 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 various biological activities such as anticoagulant, antiviral, antioxidative, and anticancer activities with potential health benefits. Therefore, SPs derived from sea vegetables have great potential

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in further development as nutraceuticals and medicinal foods. This chapter presents an overview of biological activities and potential medicinal benefits of SPs derived from sea vegetables.

## I. INTRODUCTION

Edible marine algae, sometimes referred to sea vegetables, have attracted a special interest as potential sources of nutrients and one particular interesting feature is their richness in sulfated polysaccharides (SPs), the uses of which span from food, cosmetic, and pharmaceuticals industries to microbiology and biotechnology (Ren, 1997). These chemically anionic SP polymers are not only widespread in sea vegetables but also occur in animals such as mammals and invertebrates (Mourao, 2007; Mourao and Pereira, 1999). Sea vegetables 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 major SPs (Fig. 30.1) found in sea vegetables include fucoidan of brown algae, carrageenan of red algae, and ulvan of green algae. In recent years, various SPs isolated from sea

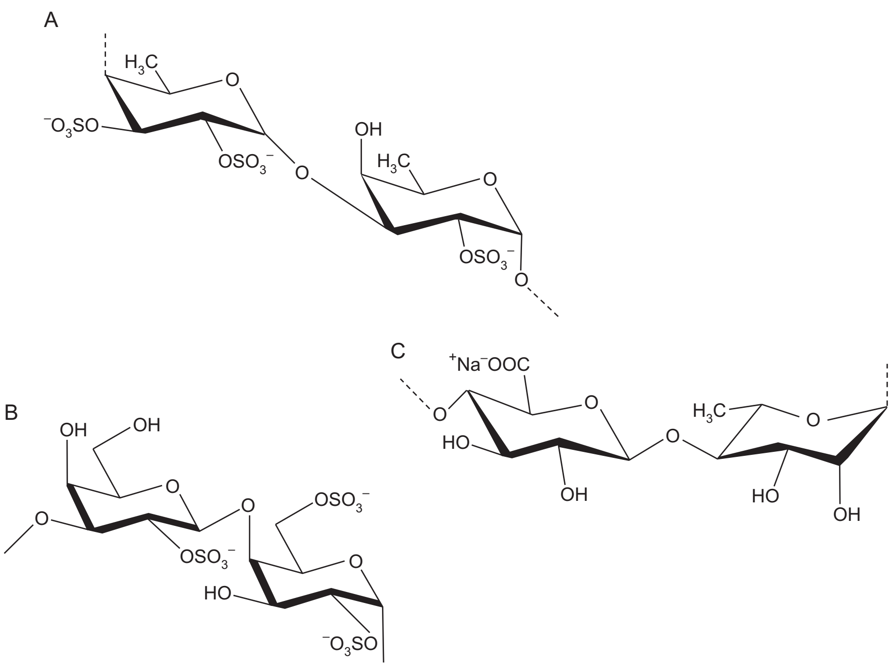


**FIGURE 30.1** Sulfated polysaccharides derived from sea vegetables, (A) fucoidan, (B) carrageenan, and (C) ulvan.

vegetables 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 *et al.*, 2009; Chen *et al.*, 2007). Ulvan displays several physiochemical and biological features of potential interest for food, pharmaceutical, agricultural, and chemical applications (Lahaye and Robic, 2007). Compared with other SPs, fucoidans are widely available commercially important compounds from various cheap sources; hence, more and more fucoidans have been investigated in recent years to develop novel drugs and functional foods (Li *et al.*, 2008).

Novel extraction and separation techniques, such as supercritical $CO_2$ extraction, ultrasonic-aided extraction, and membrane separation technology have recently been applied in the development of bioactive SPs from marine algae (Sheng *et al.*, 2007; Ye *et al.*, 2006). Biological activities of SPs depend on chemical structure, molecular weight, and chain conformations (Ye *et al.*, 2008). 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 *et al.*, 2003), antioxidative (Ruperez *et al.*, 2002), anticancer (Synytsya *et al.*, 2010), and anti-inflammation (Na *et al.*, 2010). This chapter focuses on SPs derived from sea vegetables and presents an overview of their biological activities with potential medicinal benefits.

## II. TYPES OF SPS DERIVED FROM SEA VEGETABLES

### A. Fucoidan

Fucoidan consists of fucose and sulfate groups, but the chemical composition of most fucoidans derived from brown sea vegetables is more complex. Besides fucose and sulfates, they also contain some other monosaccharides (mannose, galactose, glucose, xylose, etc.) and uronic acids, even acetyl groups and protein. Further, the structures of fucoidans from different brown sea vegetables vary from species to species (Li *et al.*, 2008).

### B. Carrageenan

Carrageenan is a generic name for a family of linear, sulfated galactans, obtained from red sea vegetables. The back bone of carrageenan is composed of -galactose units linked alternatively to $\alpha$-(1→4) linkages. In the food industry, carrageenans are widely utilized due to their excellent physical properties, such as thickening, gelling, and stabilizing abilities (Campo *et al.*, 2009).

## C. Ulvan

Ulvan is the main SPs in the green sea vegetables, especially the members of the Ulvales (*Ulva* sp. and *Enteromorpha* sp.). Ulvan contains rhamnose, xylose, and glucuronic acid with sulfate groups. One particular interesting feature of ulvan in the food industry is its ability to form gels.

# III. MEDICINAL BENEFITS AND BIOLOGICAL ACTIVITIES OF SPS FROM SEA VEGETABLES

## A. Antioxidant effect

Uncontrolled production of free radicals that attack macromolecules such as membrane lipids, proteins, and DNA is leading to many health disorders such as cancer, diabetes mellitus, and neurodegenerative and inflammatory diseases with severe tissue injuries (Butterfield *et al.*, 2002; Frlich and Riederer, 1995; Yang *et al.*, 2001). 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. 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 affects their safety and appearance. Therefore, in food and pharmaceutical industries, many synthetic commercial antioxidants such as butylated hydroxytoluene, butylated hydroxyanisole (BHA), *tert*-butylhydroquinone, and propyl gallate 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 *et al.*, 1996; Park *et al.*, 2001). Hence, the search for natural antioxidants as safe alternatives is important in the food industry (Penta-Ramos and 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 and 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 peroxidation inhibition, ferric reducing antioxidant power (FRAP), nitric oxide (NO) scavenging, ABTS radical scavenging, superoxide radical, and hydroxyl radical scavenging assays. In addition, Xue *et al.* (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 sulfation, 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 those of high molecular weight SPs (Sun *et al.*, 2009). 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 *et al.*, 2008). The SP 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 followed by the alkali- (2 M KOH, 37 °C) and water-soluble fractions (Ruperez *et al.*, 2002). Further, 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 aging 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, nontoxic 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.

## B. Antiviral effect

Many species of sea vegetables 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 and De Clercq, 1997). The potential antiviral activity of marine algal polysaccharides was first shown by Gerber *et al.* (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. The chemical structure including the degree of sulfation, molecular weight, constituent sugars, conformation, and dynamic stereochemistry is caused to determine the antiviral activity of algal sulfated polysaccharides (Adhikari *et al.*, 2006; Damonte *et al.*, 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).

SPs derived from sea vegetables 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). Fucoidans are SPs extracted from brown sea vegetables that possess some biological activities and they show the antiviral activity against infectious diseases, such as HIV, herpes simplex virus types (HSV-1 and HSV-2), and cytomegalovirus (Witvrouw and De Clercq, 1997). In addition, SPs such as carrageenans, fucoidans, and sulfated rhamnogalactans have inhibitory effects on the entry of enveloped viruses including herpes and HIV into cells. Further, the presence of sulfate group is necessary for the anti-HIV activity and potency increases with the degree of sulfation (Witvrouw and De Clercq, 1997). This leads to a hypothesis that anionic charges on the sulfate groups may be effective in inhibiting reverse transcriptase enzyme activity of the virus. In most of the studies, antiviral activity of SPs has been determined by plaque reduction and/or virus yield inhibition assays.

Moreover, it has been reported that SPs from red sea vegetables inhibit *in vitro* and *in vivo* infections 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) significantly 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. There are numerous advantages such as relatively low production costs, broad spectrum of antiviral properties, low cytotoxicity, safety, wide acceptability, and novel modes of action over other classes of antiviral drugs, and these suggest SPs from sea vegetables as promising drug candidates in the near future, but further studies are needed with clinical trials for these antiviral SPs.

## C. Immunomodulating effect

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 proinflammatory 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 *et al.*, 2008). However, the scientific analysis of anti-inflammatory activity of sea vegetable-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 *et al.*, 1993, 1995, 1996). Moreover, some types of carrageenans induce potent macrophage activation (Nacife *et al.*, 2000, 2004), while some carrageenans and fucoidan appear to inhibit macrophage functions (Van Rooijen and Sanders, 1997; Yang *et al.*, 2006). However, SPs may have potential biomedical applications in stimulating the immune system or in controlling macrophage activity to reduce associated negative effects (Leiro *et al.*, 2007).

## D. Anticancer effect

Several studies have reported that SPs derived from sea vegetables 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 *et al.* (1986) reported that the oral administration of several sea vegetables can cause a significant decrease in the incidence of carcinogenesis *in vivo*. Porphyran, the SPs of *P. yezoensis* (Rhodophyceae), can induce cancer cell death via apoptosis in a dose-dependent manner *in vitro* without affecting the growth of normal cells (Kwon and 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. Further, SPs from sea vegetables 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 SPs have potent capacities for new anticancer product developments in the pharmaceutical industry as novel chemopreventing agents for cancer therapy.

## E. Other medicinal benefits

Fucoidan extracted from the marine brown sea vegetable *Undaria pinnatifida* has significantly induced osteoblastic cell differentiation and has potential in use as a functional food ingredient in bone health supplements (Cho *et al.*, 2009). Moreover, fucoidan from *C. okamuranus* (Phaeophyceae) protects gastric mucosa against acid and pepsin. Therefore, fucoidan can be developed as a potential antiulcer ingredient in functional foods (Nagaoka *et al.*, 2000; Shibata *et al.*, 2000).

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 and Champ, 2000). Ulvan, which belongs to the SP group from *Ulva pertusa*, is a potential antihyperlipidemic 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), antihyperlipidemic activity of ulvan depends on the molecular weight of ulvan fractions; high molecular weight fraction is more effective on serum total and LDL-cholesterol, whereas low molecular weight fractions are more effective on TG and HDL-cholesterol. Ulvan contains uronic acid and sulfates, with potential capability of sequestering or binding bile acids (Lahaye, 1991).

# IV. CONCLUDING REMARKS

Recent studies have provided evidence that SPs from sea vegetables play a vital role in human health and nutrition. Further, 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 medicinal beneficial effects, sea vegetable-derived SPs have much potential as active ingredients for preparation of nutraceuticals and medicinal food products.

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