REVIEW

The beneficial properties of marine polysaccharides in alleviation of allergic responses

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Marine polysaccharides have been found as the principle component in cell wall structures of seaweeds or exoskeletons of crustaceans. Due to numerous pharmaceutical properties of marine polysaccharides such as antioxidant, anti-inflammatory, antiallergic, antitumor, antiobesity, antidiabetes, anticoagulant, antiviral, immunomodulatory, cardioprotective, and antihepatopathy activities, they have been applied in many fields of biomaterials, food, cosmetic, and pharmacology. Recently, several marine polysaccharides such alginate, porphyran, fucoidan, and chitin and its derivatives have been evidenced as downregulators of allergic responses due to enhancement of innate immune system, alteration of Th1/Th2 balance forward to Th1 cells, inhibition of IgE production, and suppression of mast cell degranulation. This contribution, therefore, focuses on antiallergic properties of marine polysaccharides and emphasizes their potential application as bioactive food ingredients as well as nutraceuticals for prevention of allergic disorders.

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1 Introduction

Allergic diseases are one of the major public health problems in the developed world. The allergic rhinitis, asthma, and atopic eczema are among the commonest causes of chronic ill health. The prevalence, severity, and complexity of these diseases are rapidly rising and considerably adding to the burden of health-care costs [1]. Substantially, allergic reaction is characterized by the excessive activation of mast cells and basophils by IgE, resulting in an extreme inflammatory response [2, 3]. The allergic reaction is initiated by a specific immune reaction to antigen that induces the differentiation and activation of Th2 ($CD4^+$) lymphocytes [4]. Once activated, Th2 cells produce IL-4, IL-5, and IL-13, which cause the synthesis of allergen-specific IgE from B cells [5]. Subsequently, the allergen-specific IgE antibodies attach to the high-affinity IgE receptors (FcεRI) on the surface of mast cells and basophils. On subsequent exposure, the allergen binds the cell-associated IgE and triggers degranulation of the mast cells or basophils, causing the release of their allergy-producing mediators and also the sustained synthesis and release of cytokines, chemokines, and growth factors [6]. The preformed mediators of allergic reactions include histamine, acetylcholine, adenosine, chemotactic mediators, and neutral proteases. These preformed and synthesized mediators cause allergic inflammatory responses due to airway constriction, mucous production, increase of vascular permeability, and recruitment and accumulation of eosinophils, mast cells, lymphocytes, neutrophils, and basophils at local tissues [7, 8]. Recently, the role of marine natural products as antiallergic agents has been determined in vitro and in vivo by many researchers. Simultaneously, numerous marine compounds have been found to be efficient for antiallergic therapeutics [9].

The world's oceans, covering more than 70% of the earth's surface, represent an enormous resource for the discovery of promising therapeutic agents. Due to the unusual diversity of chemical structures, marine organisms have received

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Abbreviations: COS, chitooligosaccharides; **OVA**, ovalbumin; **TNF**, tumor necrosis factor

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much attention in screening marine natural products for their biomedical potential [10–13]. During the last decades, marine organisms such as algae, tunicates, sponges, soft corals, bryozoans, sea slugs, mollusks, echinoderms, fishes, microorganisms, etc. have been subjected for isolation of numerous novel compounds. They have significant amounts of lipid, protein, peptide, acid amine, neurotoxins, polysaccharides, chlorophyll, carotenoids, vitamins, minerals, and unique pigments [14–20]. Notably, marine polysaccharides have been known as potential promising materials for a variety of uses in food, medicine, pharmaceutical, and nutraceutical industries due to their health benefits and biological activities. In this review, we summarized the role of marine polysaccharides in regulation of allergic reaction and emphasize their potential application as functional food ingredients for prevention and/or treatment of allergic disorders.

2 Pharmaceutical properties of marine polysaccharides in regulation of allergic responses

Polysaccharides from marine sources offer diverse therapeutic functions due to their biocompatible, biodegradable to harmless products, nontoxic, and physiologically inert. Moreover, most of them are capable of forming hydrogels because of their remarkable hydrophilicity, which helps them to bind to proteins and other compounds. Several marine polysaccharides such as alginate, porphyran, fucoidan, and chitin and its derivatives have been found and extracted from various sources, especially seaweed and crustacean. In recent years, these marine polysaccharides have been determined as potential agents for downregulation of allergic reactions *via* enhancing innate immune system, altering Th1/Th2 balance forward to Th1 cells, inhibiting IgE production, and suppressing mast cell degranulation (Table 1).

2.1 Alginate

Alginates are quite abundant in nature as structural component in marine brown algae (Phaeophyceae) and as capsular polysaccharides in soil bacteria [21]. The function of alginates in algae is primarily skeletal, with the gel located in the cell wall and intercellular matrix conferring the strength and flexibility necessary to withstand the force of water in which the seaweed grows [22]. Alginate is a linear, anionic block copolymer heteropolysaccharide consisting of β-D-mannuronic acid (M) and α-L-guluronic acid (G) (Fig. 1). The relative amount and sequential distribution of homogeneous M-M segments (M-blocks), homogeneous G-G segments (G-blocks), and alternating M-G segments (MG-blocks), which represent the primary structure of alginate, depend on the producing species, and for marine sources, on seasonal and geographical variations [22, 23]. According to Asada et al. [24], alginate exhibited different effects against hyaluronidase activity and histamine release from mast cells. In the in vivo conditions, alginate inhibited compound 48/80-induced systemic anaphylaxis with doses of 0.25–1 g/kg and inhibited passive cutaneous anaphylaxis by 54.8% at 1 g/kg for 1 h pretreatment [25]. Moreover, alginate was found to have a maximum suppression rate (60.8%) on histamine release from rat peritoneal mast cells at concentration of 0.01 μg/mL. On the other hand, the antiallergic activities of alginate were also observed due to its suppressive effects on activity and expression of histidine decarboxylase, production of IL-1β and tumor necrosis factor (TNF) α, and protein level of nuclear factor κB/*Rel A* in phorbol myristate acetate plus calcium ionophore (A23187) stimulated HMC-1 cells [25]. Noticeably, alginate oligosaccharide (ALGO), a lyase lysate of alginate, has been revealed to be able to reduce IgE production in the serum of BALB/c mice immunized with beta-lactoglobulin [26, 27]. Moreover, antigen-induced Th2 development was blocked by ALGO treatment *via* enhancing the production of IFN-γ and IL-12, and downregulating IL-4 production in splenocytes of mice [26].

2.2 Porphyran

Porphyran is a sulfated polysaccharide isolated from seaweeds of order Bangiales especially from the genera Porphyra. It is obtained from red algae of Kingdom Rhodophyta. Chemically porphyran is related to agarose, consists of linear backbone of alternating 3-linked β-D-galactose and 4-linked 3,6-anhydro-α-L-galactose units. The L residues are mainly composed of α-L-galactosyl 6-sulfate units, and the 3,6-anhydrogalactosyl units are minor (Fig. 2). Porphyran has been reported to possess various pharmaceutical properties such as antioxidant, antitumor, immunostimulant, hypotensive, antifatigue, antibacterial, anticoagulant, anticancer, antiviral, antihyperlipidemic, and hepatoprotective activity [28, 29]. Related to antiallergic activity, porphyran has been found to be effective against different allergic responses. According to Ishihara et al. [30], oral administration of porphyran (2% in drinking water) from red algae *Porphyra tenera* and *P. yezoensis* were found to be capable to inhibit the contact hypersensitivity reaction induced by 2,4,6-trinitrochlorobenzene *via* decreasing the serum level of IgE in BALB/c mice. Moreover, Yoshizawa and colleagues have revealed that polysaccharide fractions from *P. yezoensis* possessed the ability to activate macrophages in vitro and in vivo *via* enhancing glucose consumption, the production of nitrite and tumor necrosis factor, secretion of IL-1 from macrophages, and carbon clearance activity of phagocytes from mice injected intraperitoneally. It has been indicated that porphyran is responsible for these effects and its sulfate group contributes to the macrophage-stimulating activities [31, 32]. In addition, oral administration of porphyran from *P. vietnamensis* evoked a significant increase in weight of the thymus, spleen, and lymphoid organ cellularity, and total leucocyte and lymphocyte [33].

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Table 1. Marine polysaccharides for downregulation of allergic responses

Polysaccharides	Components	Source	Activities	Ref.
Alginate	50% D-mannuronic acid and 50% L-guluronic acid	*Lessonia nigrescens*	Attenuate histamine release Inactivate hyaluronidase	[24]
Alginate	61% D-mannuronic acid and 39% L-guluronic acid	*Macrocystis pyrifera*	Inhibit systemic anaphylactic shock and passive cutaneous anaphylaxis Decrease histamine release in vitro and in vivo Inhibit histidine decarboxylase expression and cytokine production Suppress nuclear factor κB activation	[25]
Alginate oligosaccharide	Average degree of polymerization (DP) = 4.4 and the average molecular weight = 713		Suppress Th2 development and IgE production Enhance IL-12 production	[26]
Porphyran	Total sugar (78.2%), galactose (49.5%), 3,6-anhydrogalactose (17.5%) Bound type of sulfate (5.6%)	*Porphyra tenera* and *P. yezoensis*	Inhibit the contact hypersensitivity reaction Decrease the serum level of IgE	[30]
Fucoidans	Sulfated L-fucose	*Undaria pinnatifida*	Enhance Th1 cell response and suppress Th2 cell response Suppress serum IgE production	[41]
Chitin	β-(1-4)-*N*-acetyl D-glucosamine	Exoskeleton of crustaceans	Activate alveolar macrophages Modulate Th1/Th2 cell response forward to Th1 cell Suppress IgE production	[51, 54]
Chitosan	β-(1-4)-D-glucosamine	Exoskeleton of crustaceans	Enhance IgG, IgG1, IgG2a, and IgG2b antibody Promote IL-2 and IFN-γ cytokine productions Increase killing activities of natural killer cells	[60]
COS	β-(1-4)-D-glucosamine	Exoskeleton of crustaceans	Inhibit mast cell degranulation and cytokine generation in vitro and in vivo	[61, 63]

2.3 Fucoidans

Fucoidans are a complex series of sulfated polysaccharides found widely in the cell walls of brown seaweeds. The seaweed fucoidans are heterogenic and represent the mixtures of structurally related polysaccharides with certain variations of the content of carbohydrate units and noncarbohydrate substituents [34]. Fucoidans are mainly composed of fucose and sulfate. Besides, they also contain other monosaccharides (mannose, galactose, glucose, xylose, etc.) and uronic acids, even acetyl groups and protein. The fucoidans of most algae consist of sulfated L-fucose with major fucose components.

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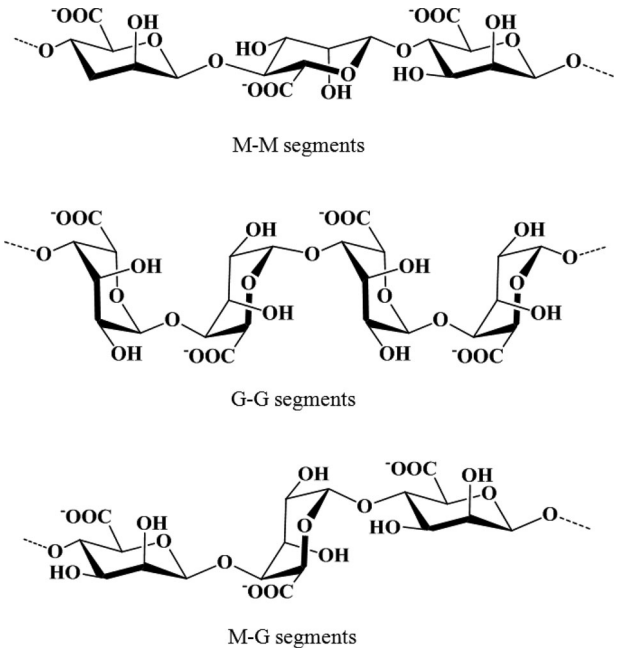

Figure 1. Three sections of alginate chain with two different monomers, β-D-mannuronic acid (M) and α-L-guluronic acid (G).

However, some fucoidans have minor fucose components and major other monosaccharides such as galactose or uronic acids [35]. According to Cumashi et al. [34], the polysaccharide backbones in fucoidans are known as type I or type II chains. The type I chains are found to contain the repeating (1→3)-linked α-L-fucopyranose residues, whereas type II chains contain the alternating (1→3)- and (1→4)-linked α-L-fucopyranose residues (Fig. 3). During the last decades, numerous pharmaceutical properties of fucoidans have been revealed due to their antioxidant, anti-inflammatory, antiallergic, antitumor, antiobesity, antidiabetes, anticoagulant, antiviral, antihepatopathy, antiuropathy, and antirenalpathy effects [35, 36]. According to Saito and colleagues, fucoidans obtained from brown algae *Fucus vesiculosus* possesse modulatory activities *via* decreased proinflammatory cytokine production, including TNF-α and IFN-γ and increased IL-10 production in the liver and plasma of concanavalin A administrated mice as compared with that of vehicle pretreatment [37]. Evidently, IL-10 is a potent anti-inflammatory cytokine derived from macrophages, regulatory T cells, B cells, or dendritic cells [38]. This cytokine has been evidenced to play an important role in suppression of proinflammatory Th2 cytokine production in an antigen-specific fashion [39, 40]. Accordingly, the role of fucoidans in enhancement of IL-10 production may contribute to downregulation of allergic response, and thus alleviating allergy and asthma symptoms. Recently, algal fucoidans have been found to be effective in suppression of IgE and Th2 cytokine production in vitro and in vivo. Fucoidan from *Undaria pinnatifida* reduced the concentrations of both IL-4 and IL-13 in bronchoalveolar lavage fluid, and inhibited the increase of antigen-specific IgE in ovalbumin (OVA) induced mouse airway hypersensitivity [41]. In the recent study, Yanase et al. [42] have reported that the peritoneal injection of fucoidan caused an alleviative effect of plasma IgE level by suppressing a number of IgE-expressing and IgE-secreting B cells from OVA-sensitized mice. On the other hand, the inhibitory effect of fucoidan on IgE production was determined due to preventing Cε germline transcription and nuclear factor κB p52 translocation in B cells [43]. Yet, the inhibitory activity of fucoidan has been not observed if B cells were prestimulated with IL-4 and anti-CD40 antibody before the administration of fucoidan. Thus, it suggested that fucoidan may not prevent a further increase of IgE in patients who have already developed allergic diseases and high levels of serum IgE. However, Iwamoto et al. [44] have recently determined that fucoidan effectively reduced IgE production in both peripheral blood mononuclear cells from atopic dermatitis patients and healthy donors. These findings indicated that fucoidan suppresses IgE production by inhibiting Ig class switching to IgE in human B cells, even after the onset of atopic dermatitis.

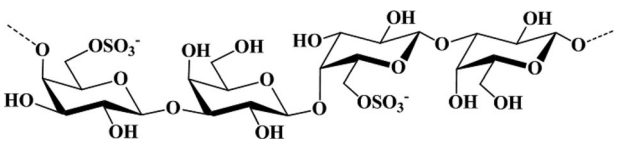

Figure 2. Chemical structure of porphyran polymer molecules.

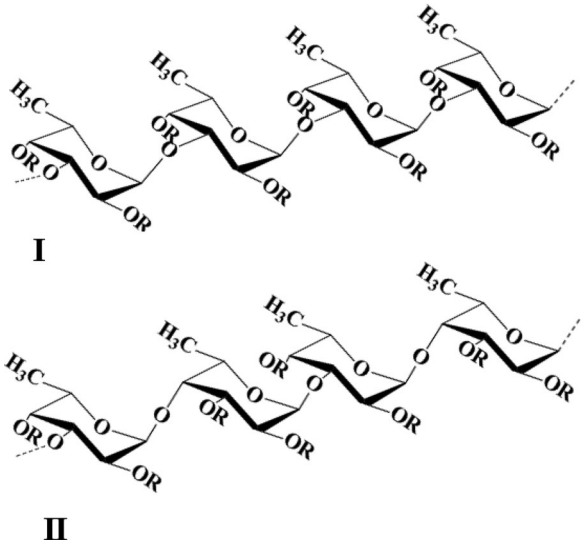

Figure 3. Two sections of brown seaweed fucoidans (Type I and II). R = fucopyranose or glucuronic acid or sulfate groups or acetyl groups.

2.4 Chitin

Chitin is a linear polysaccharide consisting of β-(1-4)-*N*-acetyl D-glucosamine residues (Fig. 4). It is widely distributed in nature and is the second most abundant polysaccharide in

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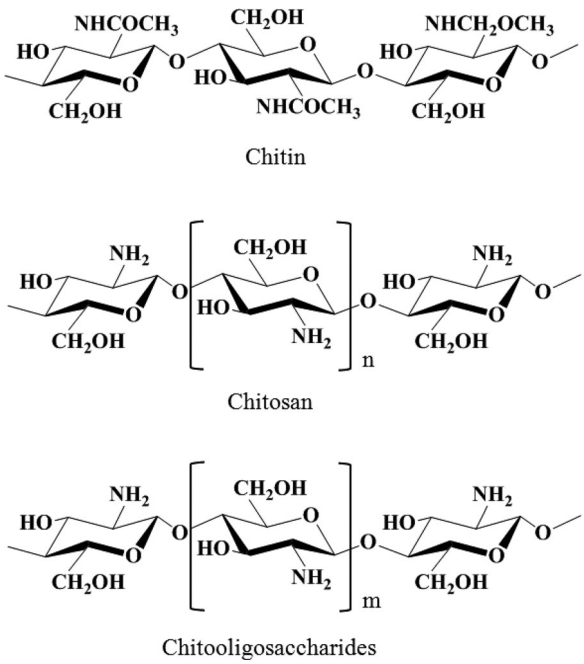

Figure 4. Chemical structure of chitin, chitosan, and chitooligosaccharides ($n >> m$).

nature after cellulose. It may be regarded as cellulose with hydroxyl at position C-2 replaced by an acetamino group. Chitin is a white, hard, inelastic, nitrogenous polysaccharide found in the cell walls of bacteria and fungi, mushrooms, exoskeleton of crustaceans and insects, the microfilarial sheath of parasitic nematodes, and the lining of the digestive tracts of many insect [45]. Chitin exists mainly in two forms including α-chitin and β-chitin. α-Chitin consists of sheets of tightly packed alternating parallel and antiparallel chains [46]. Meanwhile, β-chitin is arranged in parallel [47], which occurs less frequently in nature than α-chitin. Being nontoxic and environmentally safe, chitin has become of great interest not only as a utilized resource but also a new functional biomaterial of high potential in many fields such as medical, agricultural, and cosmetic applications [48–50]. Chitin has been evidenced as a potent innate immune stimulator of macrophages and other innate immune cells, and thus chitin is able to suppress allergen-induced type 2 allergic responses. Indeed, Shibata and colleagues have determined the immunological effects of chitin in vivo and in vitro using phagocytosable small-sized chitin particles. It has shown that intravenous administration of fractionated chitin particles into the lung activated alveolar macrophages to express cytokines such as IL-12, TNF-α, and IL-18, leading to IFN-γ production mainly by natural killer cells [51]. The production of cytokines induced by chitin is identified to be mediated by a mannose receptor [52]. In another study, it has determined that chitin stimulates macrophages by interacting with different cell surface receptors such as macrophage mannose receptor, Toll-like receptor-2, C-type lectin receptor dectin-1, and leukotriene 134 receptor (BLT1) [53]. These studies have shown the direct interactions between chitin and its cell surface receptors and thus chitin regulates the specific signaling pathways in immune responses.

In the further study of Shibata and colleagues, the suppressive effect of Th2 responses has been confirmed when chitin was given orally in BALB/c and C57BL/6 mice [54]. It was observed that chitin treatment resulted in decreases of serum IgE levels and lung eosinophil numbers in both strains. The inhibitory mechanisms of Th2 responses by chitin was found due to decrease of Th2 cytokines including IL-4, IL-5, and IL-10 levels and increase of the production of Th1 cytokine IFN-γ in spleen cells isolated from the ragweed-immunized mice. These results indicated that the immune responses were redirected toward a Th1 response by chitin treatment, and thus downregulating Th2-facilitated IgE production and lung eosinophilia in the allergic mouse. Moreover, the Th1 adjuvant role of chitin has been determined *via* upregulating Th1 immunity induced by heat-killed *Mycobacterium bovis* and downregulating Th2 immunity induced by mycobacterial protein [55]. Likewise, Hamajima et al. [56] has also reported the Th1 adjuvant effect of chitin microparticles in inducing viral-specific immunity.

Notably, the effectiveness of chitin microparticles when given intranasally as a treatment for the symptoms of respiratory allergy and allergy asthma has been tested in two different mouse models of allergy, namely to *Dermatophagoids pteronyssinus* and *Aspergillus fumigates* [57]. The intranasal application of microgram doses of chitin microparticles substantially reduced the allergen-induced serum IgE levels, peripheral eosinophilia, airway hyperresponsiveness, and lung inflammation in both allergy models. This effectiveness was found due to the increase in Th1 cytokines IL-12, IFN-γ, and TNF-α and decrease in IL-4 production during allergen challenge. The immunostimulatory properties of chitin microparticles could offer a novel and natural approach to treating allergic disease in humans.

2.5 Chitosan

Chitosan, a deacetylated polymer of *N*-acetylglucosamine, is produced commercially by deacetylation of chitin [58] (Fig. 4). During the past decades, chitosan has received considerable attention due to its biodegradable, nontoxic, and nonallergenic properties, which made it possible to be used in many fields including food, cosmetics, biomedicine, agriculture, and environmental protection [50, 59]. In the most recent study, chitosan nanoparticles have been determined as an adjuvant agent *via* promoting immune response in OVA-challenged mice [60]. Mice were immunized subcutaneously with 25 μg OVA alone or with 25 μg OVA dissolved in saline containing Quil A (10 μg), chitosan (50 μg), or chitosan nanoparticles (12.5, 50, or 200 μg) on days 1 and 15. It was found that the serum OVA-specific IgG, IgG1, IgG2a, and IgG2b antibody titers and Con A-, LPS-, and OVA-induced splenocyte proliferation were significantly enhanced by

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chitosan nanoparticles as compared with OVA and chitosan groups. Notably, chitosan nanoparticles also significantly promoted the production of IL-2 and IFN-γ cytokines and upregulated the mRNA expression of IL-2, IFN-γ cytokines in splenocytes from the immunized mice compared with OVA and chitosan groups. Besides, chitosan nanoparticles remarkably increased the killing activities of natural killer cells activity. The results suggested that chitosan nanoparticles had a strong potential to increase both cellular and humoral immune responses.

2.6 Chitooligosaccharides

Chitooligosaccharides (COS) are oligomers prepared *via* cleaving glycosidic linkages of chitosan either chemically or enzymatically (Fig. 4). Recent studies have focused on the conversion of chitosan to COS since COS are not only water soluble and possess higher oral absorption, but also have various biological effects, including antimicrobial, antitumor, anticancer, antioxidant, anti-inflammatory, and antiangiotensin-I-converting enzyme activities [59]. Especially, the role of COS as protective agents against mast cell degranulation has been evidenced by Vo and colleagues. They have investigated the inhibitory effect of COS on mast cell activation induced by calcium ionophore A23187 or antigen. The pretreatment of COS causes significant inhibition on mast cell degranulation *via* reducing histamine and β-hexosaminidase release and intracellular Ca^{2+} elevation in RBL-2H3 mast cells [61, 62]. Moreover, the inhibitory effects of COS on expression as well as production of various cytokines such as TNF-α, IL-1β, IL-4, and IL-6 were also evidenced. Notably, the protective effect of COS (<1 kDa) against OVA-induced lung in inflammation in asthma model mice was also examined [63]. Oral administration of COS (16 mg/kg body weight/day) resulted in a significant reduction in both mRNA and protein levels of IL-4, IL-5, IL-13, and TNF-α in the lung tissue and bronchoalveolar lavage fluid. The protein levels of IL-4, IL-13, and TNF-α in bronchoalveolar lavage fluid were decreased by 5.8-fold, 3.0-fold, and 9.9-fold, respectively, compared to those in the OVA-sensitized/challenged asthma control group. Collectively, these results indicate that COS can contribute to attenuation of allergic reactions and might be a promising candidate for novel inhibitor of allergic reaction.

Up to now, numerous bioactive polysaccharides have been discovered from bacteria, mushrooms, fungi, yeasts, algae, lichens, plants, and animals [64, 65]. The biological activities of polysaccharides have attracted more and more attention in biochemistry and medicine. Various beneficial properties of polysaccharides have been found and the mechanisms involved in these effects are thought due to the modulation of innate immunity [65]. Similarly, the antiallergic activities of marine polysaccharides were mainly observed to relate to activation of macrophages, stimulation of Th1 cells, and suppression of Th2 cells. Although the structure and composition of marine polysaccharides are significantly different from other polysaccharides, no consensus could be made that polysaccharides from marina products possess better antiallergic effect than others. However, an important difference observed when comparing marine polysaccharides and others is the presence of sulfated group such as porphyran and fucoidan and amid group such as chitin [64, 66]. The sulfated group is present in various type of algal polysaccharides including sulfated galactan (red algae) [67], sulfated fucans (brown algae) [68], sulfated glucans, sulfated galactans, and sulfated arabinogalactans (green algae) [69, 70]. Meanwhile, amid group is present in chitin polysaccharides found in numerous shellfish (including shrimp, crab, lobster, and krill), oyster, squid, clams, and marine diatoms [71]. Although the presence of sulfated group and amid group in marine polysaccharides has been extensively studied, their different function as compared with other polysaccharides in modulation of innate immunity remains unclear. In general, the immunomodulatory activities have been determined to be different due to their molecular mass, chain length, degree of branching, structure, conformations, and solubility of the polymer. Indeed, the immunomodulatory activities of polysaccharides from *Ganoderma lucidum* [72], Aloe [73], and *Chlorella pyrenoidosa* [74] importantly depend on their molecular masses. Moreover, the triple-helix structure contributes greatly to the immunomodulatory activities of glucans [75, 76]. Random coil polysaccharides from *Cordyceps militaris* could also strengthen the functional events *via* activating macrophages, such as nitric oxide production and cytokine (IL-1β and TNF-α) expression [77]. In addition, lower degree of polysaccharides were found to be desirable properties for immunomodulatory activities [61, 63]. Accordingly, polysaccharides offer the high capacity for carrying biological information such as immunomodulatory properties because of their great potential for structural variability.

The beneficial effects of marine polysaccharides in downregulation of allergic reactions have been determined in numerous studies using cell line and/or animal as experimental models. However, their dose effect is also important to decide whether these polysaccharides are possible to be applied as antiallergic medicine. Herein, alginate was found to be effective on suppression of the in vitro mast cell activation at very low concentration (0.01 μg/mL) [25]. Likewise, intraperitoneal administration of alginic acid oligosaccharide at low dose (200 μg/mice) also exhibited significant inhibition on IgE production and Th2 development [26]. Meanwhile, the suppressive effect of alginate on the in vivo systemic anaphylaxis in compound 48/80-injected mice was observed at very high dose of oral administration (1 g/kg body weight) [25]. Despite of high-dose effect, the suppressive activity of alginate was able to expose after short time of administration (1 h). It indicated that dose effect of alginate is dependent on its target as well as the time of administration. On the other hand, the intraperitoneal administration of fucoidan with dose of 50 mg/kg or 100 μg/mouse is capable to downregulate Th2 immune responses and decrease serum IgE

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production [41, 42]. Likewise, chitin with low dose of oral administration (8 mg/day) significantly attenuated serum IgE levels and altered Th1/Th2 balance toward to Th1 responses [54]. These dose effects of marine polysaccharides indicate a capable application of them in antiallergic medicines.

It is assumed that marine polysaccharides have gained the increased interest by medical and pharmacological industries as well as academic research institutions due to their wide potentiality and applications in several biological, biomedical, and nutritional fields. However, marine polysaccharides must satisfy certain safety criteria in order to protect the health of consumers. Majority of marine organisms with potential polysaccharides are seaweeds and shellfishes. Most of the Asian countries have used seaweeds as food for human consumption for several centuries. Recently, seaweeds have received approval as food ingredients in Europe. Processed eucheuma seaweed is now permitted as a food additive in all countries. Kelp, potential source of sulfated polysaccharides such as fucoidan, is classified by the Food and Drug Administration as a natural substance when prepared under Good Manufacturing Practices. Sulfated polysaccharides, one of the best examples of the seaweed polysaccharides, are nontoxic and possess tremendous antioxidative capacity. These properties of sulfated polysaccharides made them to be potential for application in food, pharmaceutical, and nutraceutical industries [78]. Although the major undesirable side effect of sulfated polysaccharides is their well-known anticoagulant activity, this adverse effect can be avoided by selecting sulfated polymers such as fucoidan that have no discernible anticoagulant activity at the therapeutically administrable doses [79,80]. In addition, alginate from seaweeds was also established as nontoxic nature. Food grade quality alginates comply with relevant international and national purity specification. Especially, alginate has been given number by International Numbering System for Food Additives [78]. With regard to shellfishes-derived polysaccharides, chitin and its derivatives have been evidenced as a bioactive material due to its biodegradable, nontoxic, and nonallergenic characteristics. The available literature on chitin and chitosan suggests a low order of toxicity, based on animal studies [49, 58]. The safety of chitooligomers prepared by the enzymatic depolymerization of chitosan has been reported in a short-term mice feeding study with a maximum of 10 g/kg body weight [81]. In the United States, Dietary Supplement Health and Education Act have permitted the use of chitin or chitosan as food supplements without premarket approval as long as no health claims are made [82]. In Japan, chitosan is added to foods such as noodles, potato, crisps, and biscuits. In Canada, chitin and chitosan are also approved for various food applications. Chitosan is sold in the form of dietary capsules to assist weight loss in the European market. Collectively, marine polysaccharides are useful potential to be used as safe ingredients in foods or pharmaceutical products, however, will require standardization of identity, purity, and stability.

Marine polysaccharides are the most abundant organic molecules in the oceans and present an enormous variety of structures. They are still underexploited and therefore be considered as an extraordinary source of chemical diversity for discovery of novel antiallergic drugs. Until now, a large number of antiallergic agents derived from marine polysaccharides have been identified based on the specific assay system or screening approaches. However, the experimental models are still limited in using cell lines and animals, which lack clinical trial investigations regarding beneficial properties of marine polysaccharides in allergic diseases. Substantially, the search for potential drug candidates containing efficient antiallergy activity from natural products is necessary and increasing in the pharmaceutical industry. Therefore, marine polysaccharides may gain much attention by pharmaceutical companies as well as research institutes for clinical trial investigations in the recent future. Moreover, the strong anticoagulant activity of some sulfated polysaccharides may restrict their use in human. Luckily, marine organisms such as macroalgae, microalgae, bacteria, cyanobacteria, invertebrates, and chordata offer a rich source of polysaccharides with original structures largely species specific. Furthermore, the possibility of chemical modification, blending, and addition of biodegradable additives allows tailoring the final properties of polysaccharides and opens the doors to wider applications in antiallergic therapeutics. On the other hand, the obstacle of drug development may be due to the large-scale production. It is not easy to isolate a large yield of desired polysaccharides. However, the combinatorial genetic and metabolic engineering will be the future solution for commercial production of marine polysaccharides. Moreover, the aquaculture and fermentation processes are also expected to gain the large-scale production.

3 Conclusion

Marine polysaccharides are potential biomaterials that are the focus of biomedical research today. Herein, marine polysaccharides including alginate, porphyran, fucoidan, and chitin and its derivatives have been determined as exciting agents for modulation of allergic responses. These polysaccharides have been determined to be effective in enhance of innate immune system, regulation of Th1/Th2 balance toward Th1 dominance, decrease in IgE production, and inhibition of mast cell degranulation. Accordingly, marine polysaccharides can be used as safety and efficacy biomaterials for the development of food, pharmaceutical, and nutraceutical industries in prevention and/or treatment of allergic disorders. The possibility of producing a variety of chemically modified derivatives makes these polysaccharides versatile biomaterials in almost all fields of biomedical interest.

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