CHAPTER 21

Antiallergic Benefit of Marine Algae in Medicinal Foods

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Contents

Abstract

The prevalence of allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis has increased during the past two decades and contributed a great deal to morbidity and an appreciable mortality in the world. Until now, few novel efficacious drugs have been discovered to treat, control, or even cure these disorders with a low adverse-effect profile. Meanwhile, glucocorticoids are still the mainstay for the treatment of allergic disease. Therefore, it is essential to isolate novel antiallergic therapeutics from natural resources. Recently, marine algae have received much attention as they are a valuable source of chemically diverse bioactive compounds with numerous health benefit effects.

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This contribution focuses on antiallergic agents derived from marine algae and presents an overview of their potential application in medicinal foods for the treatment of allergic disorders.

I. INTRODUCTION

Allergy, also referred to atopy, is caused by an exaggerated reaction of the immune system to harmless environmental substances, such as animal dander, house dust mites, foods, pollen, insects, and chemical agents (Milián and Díaz, 2004). The prevalence, severity, and complexity of these allergic diseases in the population are rapidly rising and considerably adding to the burden of health-care costs. Therefore, the knowledge about the pathophysiology of allergic diseases has increased, offering new opportunities for therapeutic intervention. Substantially, allergic reactions or type I hypersensitivity reactions are induced upon binding of allergen to the IgE, which is tethered to the high affinity IgE receptor on the surface of mast cells and basophils. Following the aggregation of cell surface receptors is a cascade of intracellular events, including the increase of intracellular Ca^{2+} level; the release of preformed inflammatory mediators from secretory granules such as histamine and β-hexosaminidase; the synthesis and release of the newly synthesized mediators such as lipid mediators and cytokines. These mediators cause allergic inflammatory responses with airway constriction, mucous production, and recruitment of inflammatory cells (Galli *et al.*, 2008). According to this mechanism, the control of the downstream signaling molecules is especially important for the regulation of type I allergic reaction; thus allergic diseases may be managed. The current drugs that are used to treat allergies, such as antihistamines or corticosteroids, ameliorate symptoms but do not stop progression. There are also concerns regarding the side effects from chronic use of current drugs, particularly by children. Thus, the search for potential drug candidates containing higher antiallergy activity is increasing in the pharmaceutical industry. In this regard, natural bioactive compounds and their derivatives are great sources for the development of new generation antiallergic therapeutics which are more effective with fewer side effects.

The world's oceans, covering more than 70% of the earth's surface, represent an enormous resource for the discovery of potential therapeutic agents. During the past decades, numerous novel compounds have been isolated from marine organisms and many of these substances possess interesting biological activities. Notably, marine algae have been known as a promising group to provide not only novel biologically active substances but also essential compounds for human nutrition (El Gamal, 2010). In recent years, biological activities, nutritional value, and potential

health benefits of marine algae have been intensively investigated and reviewed. This contribution, however, focuses specifically on the antiallergic effects of marine algae and emphasizes their potential application as pharmaceutical candidates to prevent allergic disorders.

II. MARINE ALGAE AS THERAPEUTIC INHIBITORS AGAINST ALLERGIC DISORDERS

A. Marine macroalgae as crude materials with antiallergic activities

Although marine algae have been believed to be safe and efficient agents for antiallergic treatment, they have not been as extensively studied as terrestrial plants. Recently, a number of marine macroalgae have been studied for their capability against allergic reactions (Kimiya *et al.*, 2008; Sugiura *et al.*, 2006b). Among them, *Petalonia binghamiae*, *Eisenia arborea*, and *Sargassum thunbergii* were found to be effective inhibitors of histamine and β-hexosaminidase release from mast cells. Moreover, *Sargassum hemiphyllum* and *Carpopeltis affinis*, which are used in Korean folk medicine for the therapeutic treatment of various allergic diseases, have been determined to suppress atopic allergic reaction by attenuating the release of histamine, β-hexosaminidase, IL-8, and TNF-α from the activated mast cells (Na *et al.*, 2005a,b). Notably, brown alga *Ecklonia cava* has been identified as a suppressor of FcεRI, a high-affinity receptor for IgE on the cell surface of mast cell and basophils (Shim *et al.*, 2009b). The methanol extract of *E. cava* exhibited inhibitory effect on degranulation of KU812F cells due to reducing the cell surface expression of FcεRI and blocking the binding of IgE with its receptor. In another sense, the administration of ethanol extract of *E. cava* and *Laurencia undulate* caused a significant suppression of all asthmatic reactions induced by ovalbumin (OVA) in a mouse asthma model (Jung *et al.*, 2009; Kim *et al.*, 2008). The rats were fed with *E. arborea*, and this resulted in the decrease of IgE and histamine level in the serum, the reduction of Th2 cytokines release, and enhancement of Th1 cytokine expression from the spleen and mesenteric lymph nodes (Sugiura *et al.*, 2008a). The intraperitoneal administration of *Sargassum tenerrimum*, *Sargassum cervicorne*, and *Sargassum graminifolium* in turn induced the inhibition of both passive cutaneous anaphylaxis (PCA) and active cutaneous anaphylaxis (ACA) in mice triggered by OVA and shrimp allergen (Samee *et al.*, 2009). Herein, the extract of *S. tenerrimum* exhibited the most active suppression of PCA and ACA, which is comparable to antiallergic drug disodiumcromoglycate. According to these results, algae extracts could be useful crude materials for the treatment of allergic diseases.

B. Potential antiallergic compounds derived from marine macroalgae

1. Phlorotannins

Brown algae have been recognized as a rich source of phlorotannins, which are formed by the polymerization of phloroglucinol (1,3,5-trihydroxybenzene) monomer units and biosynthesized through the acetate–malonate pathway. Notably, phlorotannins exhibited versatile beneficial bioactivities such as antioxidant, anticancer, antidiabetic, antihuman immunodeficiency virus, matrix metalloproteinase enzyme inhibition, and antihypertensive (Vo and Kim, 2010). In relation to antiallergic properties, many phlorotannins from brown algae were considered as potential natural inhibitors of allergic reactions. Phlorotannins of fucodiphloroethol G, eckol, dieckol, 6,6′-bieckol, and phlorofucofuroeckol A (PFF-A) purified from *E. cava* were evidenced to be efficient against A23187- or FcεRI-mediated histamine release from KU812 and RBL-2H3 cells. The inhibitory mechanism was known due to the blockade of these compounds on binding activity between IgE and FcεRI (Le *et al.*, 2009; Li *et al.*, 2008). Similarly, phlorotannins of dioxinodehydroeckol (DHE) and PFF-A obtained from *Ecklonia stolonifera* showed a suppressive effect on cell surface expression of FcεRI, and total cellular protein and mRNA levels of the FcεRI α chain in KU812 cells (Shim *et al.*, 2009a). Further, both of these compounds exerted inhibitory effects against the elevation of intracellular calcium level and histamine release from anti-FcεRI α chain antibody (CRA-1)-stimulated cells. On the other hand, several phlorotannins of eckol, dieckol, 6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, PFF-A, and PFF-B from *Eisenia bicyclis* and *E. arborea* have been recognized as strong inhibitors of hyaluronidase, phospholipase A_2, cyclooxygenase, and lipoxygenases (Shibata *et al.*, 2002, 2003; Sugiura *et al.*, 2008b, 2009), which correlated to suppression of eicosanoid synthesis and release (leukotriene and prostaglandin) from RBL cells (Sugiura *et al.*, 2009). Among these phlorotannins, PFF-B exposed the strongest activity against histamine and β-hexosaminidase release from RBL cells with IC_{50} value of 7.8 μM (Sugiura *et al.*, 2006a, 2007). Accordingly, these bioactive phloroglucinol derivatives may be promising candidates for the design of novel inhibitors of FcεRI-mediated allergic reaction and enzymes in allergic inflammation.

2. Polysaccharides

Marine algae are the most important source of polysaccharides and the chemical structure of the polymers varies according to the alga species. In recent years, various polysaccharides isolated from marine algae have been used in the fields of food, cosmetic, and pharmacology due to their beneficial biological activities, such as antivirus, anticoagulant,

anticancer, and anti-inflammation (Vo and Kim, 2010). A role of polysaccharides from marine macroalgae as antiallergic agents has been suggested. Alginic acid, a naturally occurring hydrophilic colloidal polysaccharide obtained from the several species of brown seaweeds, exhibited inhibitory effects on hyaluronidase activity and histamine release from mast cells (Asada *et al.*, 1997). Further, the antiallergic activities of alginic acid have also been found due to its suppressive effects on the activity and expression of histidine decarboxylase, the production of IL-1β and TNF-α, protein level of nuclear factor (NF)-κB/*Rel A* in the nucleus, luciferase activity, and DNA-binding activity in PMA plus A23187-stimulated HMC-1 cells (Jeong *et al.*, 2006). Noticeably, alginic acid oligosaccharide (ALGO), a lyase lysate of alginic acid, was able to reduce IgE production in the serum of mice immunized with beta-lactoglobulin (Uno *et al.*, 2006; Yoshida *et al.*, 2004). 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 (Yoshida *et al.*, 2004).

In addition, porphyran, a sulphated polysaccharide isolated from red seaweeds, has been recognized to be effective against different allergic responses. According to Ishihara *et al.* (2005), porphyran of red algae *Porphyra tenera* and *Porphyra yezoensis* were capable to inhibit the contact hypersensitivity reaction induced by 2,4,6-trinitrochlorobenzene through decreasing the serum levels of IgE and IFN-γ in Balb/c mice. Meanwhile, 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 OVA-induced mouse airway hypersensitivity (Maruyama *et al.*, 2005). In the recent study, Yanase *et al.* (2009) have reported that the peritoneal injection of fucoidan inhibited the increase of plasma IgE via suppressing a number of IgE-expressing and IgE-secreting B cells from OVA-sensitized mice (Yanase *et al.*, 2009). On the other hand, the inhibitory effect of fucoidan on IgE production was proved due to preventing Cε germline transcription and NF-κB p52 translocation in B cells (Oomizu *et al.*, 2006). However, the effect of fucoidan was not observed if B cells were prestimulated with IL-4 and anti-CD40 antibody before the administration of fucoidan. These observations 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. Conversely, Iwamoto *et al.* (2010) have determined that fucoidan effectively reduced IgE production in both peripheral blood mononuclear cells from atopic dermatitis patients and healthy donors (Iwamoto *et al.*, 2010). These findings indicated that fucoidan suppresses IgE induction by inhibiting immunoglobulin class switching to IgE in human B cells, even after the onset of atopic dermatitis.

C. Marine microalgae and their antiallergic properties

Microalgae are considered as the actual producers of some highly bioactive macromolecules in marine resources, including carotenoids, long-chain polyunsaturated fatty acids, proteins, chlorophylls, vitamins, and unique pigments (Kay, 1991). Thus, they have been used as additives in a variety of human foods and animal feeds. Ingestion of various edible microalgae not only supplies protein and other nutrients but also modulates both adaptive and innate aspects of immunity (Price *et al.*, 2002). Indeed, *Spirulina* was determined to decrease IgE antibody level, and increased IgG1 and IgA antibody production in the serum of the mice immunized with crude shrimp extract as an antigen (Hayashi *et al.*, 1998). In a clinical trial, *Spirulina* consumption resulted in the significant amelioration in symptoms and physical findings of allergic rhinitis patients compared with placebo (Cingi *et al.*, 2008). The clinical effect of *Spirulina* on allergic rhinitis was determined due to inhibiting the production of IL-4 and thus may suppress the differentiation of Th2 cells (Mao *et al.*, 2005). In addition, it has been documented that *Spirulina* had a great inhibition on allergic reaction via suppressing anaphylactic shock, PCA, and serum histamine levels in rats activated by compound 48/80 or anti-DNP IgE. Also, the *in vitro* experiment revealed that *Spirulina* inhibited histamine release and TNF-α production from rat peritoneal mast cells (Kim *et al.*, 1998; Yang *et al.*, 1997). As a result, *Spirulina* can be a rich source of potential anti-allergic components. Indeed, phycocyanin, a biliprotein of *Spirulina*, has been revealed to be an inhibitor of allergic responses (Remirez *et al.*, 2002). Moreover, phycocyanin has been demonstrated to enhance biological defense activity against infectious diseases through sustaining functions of the mucosal immune system and reduce allergic inflammation by the suppression of antigen-specific IgE antibody (Nemoto-Kawamura *et al.*, 2004).

Besides *Spirulina*, several other microalgae appeared as promising new candidates for antiallergic agents. *Porphyridium purpureum* and *Dunaliella salina* displayed their appreciable inhibition on the activation of hyaluronidase with IC_{50} values of 180 and 150 μg/ml, respectively, which were almost the same as that of disodium cromoglycate (IC_{50} = 140 μg/ml) (Fujitani *et al.*, 2001). Further, oral administration of hot water extract of *Chlorella vulgaris* (CVE) in mice suppressed the production of IgE against casein antigen accompanied by increasing mRNA expression of Th1 cytokines, including IFN-γ and IL-12 (Hasegawa *et al.*, 1999). Likewise, *Chlorella pyrenoidosa* was found to inhibit the production of IL-5 and IgE-dependent cytokine GM-CSF from mast cells. *In vivo*, mice treated with *C. pyrenoidosa* during OVA sensitization process significantly reduced eosinophil and neutrophil infiltration in the airways (Kralovec *et al.*, 2005). Collectively, the above studies suggested a potential

beneficial role of microalgae against allergic responses and thus they may be used as functional food or medicinal food ingredient to prevent and treat allergic diseases.

III. CONCLUSION

Recent studies have provided evidence that marine algae play a vital role in human health and nutrition. Specially, marine algae possess the immune-modulating effects due to suppressing Th2 development and enhancing the immunological function toward Th1 activity. Simultaneously, marine algae are effective inhibitors of the immediate-type allergic reactions via inhibiting degranulation, cytokine production, and FcεRI expression in mast cells and basophils. Hence, marine algae can be used as functional food ingredients to prevent and reduce allergic reactions in human body. Collectively, the wide range of biological activities associated with the antiallergic ingredients which derived from marine algae has the potential to expand its health beneficial value not only in the food industry but also in the pharmaceutical and cosmeceutical industries.

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