CHAPTER 22

Marine Macro- and Microalgae as Potential Agents for the Prevention of Asthma: Hyperresponsiveness and Inflammatory Subjects

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Abstract

Asthma is a variable disease and various factors are affected to increase the asthmatic symptoms and level of asthma control. It is believed that the cause for this disease is a combination of genetic and environmental factors. Numerous medications are available at present to treat this disease but it has been failed to control number of incidences successfully. Hence, recently many researchers have paid their interest to identify potential drugs from marine-based resources such as marine algae. *In vitro* and *in vivo*

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experiments have been conducted with extracts or compounds from algae and found that they showed significant activities against asthma. Accordingly, many marine macro- and microalgae have been reported to have potential to ameliorate the effect of asthma. However, detailed studies are needed in relation to identify the molecular mechanism of this disease to apply those marine resources against asthma effectively. In this chapter, an attempt has been taken to discuss the potential antiasthmatic activity of marine macro- and microalgae.

I. INTRODUCTION

Asthma is a common chronic disorder of the airways that is characterized by reversible airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation (NHLBI, 2007). The symptoms of this disease are wheezing, coughing, chest tightness, and short breathing. This interaction can be highly variable among patients and within patients over time. The interactions of these features determine the severity and the clinical manifestation of asthma. It is believed that the cause for this disease is the combination of genetic and environmental factors (Martinez, 2007). Asthma is clinically categorized depending on the frequency of the symptoms, forced expiratory volume in 1 s, and peak expiratory flow rate (Yawn, 2008). Further, asthma is classified as atopic or nonatopic based on whether symptoms are occurred allergens (atopic) or not (nonatopic) (Kumar *et al.*, 2010). Hundreds of thousands of people are suffering from asthma around the world. There is no age barrier for this and even school children are suffering at their very young ages. There are a number of chemopreventive methods available to control this problem but still there are new drugs needed to alleviate this disease as day by day patients are increasing.

Recently, huge interest has been paid to find natural drugs from marine-based resources to combat this menace. Both marine macroalgae and microalgae have been evaluated against asthma to find out a potential preventive drug. Many macroalgal species have reported to have significant activity *in vitro* and *in vivo* experiments. *Ecklonia cava* is an edible brown alga that widely distributes on the southern coast in Korea and Japan and widely evaluated against numerous activities including asthma. It has been reported that *Ecklonia* species have numerous biological and pharmaceutical activities, including antioxidative and anti-inflammatory activities (Senevirathne *et al.*, 2006; Shin *et al.*, 2006), antimutagenic activity (Han *et al.*, 2000; Lee *et al.*, 1998), bactericidal activities (Nagayama *et al.*, 2002), and inhibitory effects on HIV-1 reverse transcriptase, protease, and tyrosinase (Ahn *et al.*, 2004; Kang *et al.*, 2004).

Recently, it was shown that *E. cava* extract could block the release of histamine from anti-DNP IgE-sensitized rat basophile leukemia cells, RBL-2H3 cells, and it was suggested that *E. cava* extract may contain beneficial elements for human health and may be useful as a functional food (Sugiura *et al.*, 2006).

II. FACTORS AFFECTING ASTHMA

Several factors are affecting asthma including environmental and individual factors. There is seasonal variability in asthma; in autumn, it is increased, while in summer, it is minimum in the United States (Silverman *et al.*, 2003). The reasons for these variations include increased exposure to allergens such as pollen, house dust mites, and mould spores among younger generation and in adults it may be increased influenza or other respiratory tract infections (Riccioni *et al.*, 2001). Moreover, cigarette smoke is one of the most common asthmatic reasons. Both indoor and outdoor air pollutants may also increase asthma. Inhalation of toxic vapors from industrial fumes, bleach sulfur, or smoke from fire or tobacco may also affect asthma (Just *et al.*, 2002).

Several individual factors may also influence the variability of asthma. Poor inhaler technique for both metered-dose and dry powder inhalers is often observed in asthma patients and may be the cause for an increased risk of death. Further, personnel characteristics may also be the cause for the changes in lung functions. In healthy individuals, lung function exhibits a circadian rhythm. However, this will be changed in the individuals those who have nocturnal asthma. Moreover, obesity may also be a risk factor for asthma. Further, women may experience premenstrual and perimenstrual worsening of asthma symptoms. Asthma symptoms may be also triggered by exercise.

III. CHARACTERISTICS OF ASTHMA

The most important functional abnormality in asthma is increased resistance to airflow. This is the basis of most striking clinical manifestation of asthma, including breathlessness and wheezing. The mechanisms of increased airflow resistance include (1) decreased physical dimensions of the airways as a consequence of bronchoconstriction, (2) luminal narrowing due to airway wall edema, and (3) luminal obstruction resulting from hypersecretion of mucus (McFadden, 1998). Those changes induced by the various inflammatory mediators released by mast cells as part of hypersensitivity reactions are reversible. Another functional abnormality

in asthma is a heightened responsiveness of the airways to stimuli that might normally be expected to provoke airway narrowing.

Inflammation of the airway is the peculiar pathological abnormality in asthma (Hegele and Hogg, 1996). Inflammatory responses are associated with the accumulation of numerous cells including lymphocytes, macrophages, and plasma cells in the lamina propria (Laitinen *et al.*, 1993). Further, more of those cells are found in the adventitial connective tissues of outer wall of smaller airways (Haley *et al.*, 1998). Moreover, the airway epithelium is infiltrated by the numerous leukocytes; eosinophils are prominent among them.

Another characteristic feature in asthma is airway wall remodeling. This refers to a variety of structural changes in the airway wall. Most prominent is the accumulation of a band of type III and type V collagens (Hoshino *et al.*, 1998) and other matrix components in the subepithelial region of the airway wall. Airway wall thickening and shortening of airway smooth muscle may occur and these may cause airway resistance.

IV. BRIEF MECHANISM ABOUT ASTHMA

FcεRI is located on the surfaces of basophils and mast cells, which act as effector cells in IgE-mediated immune responses (Kinet, 1990). FcεRI is composed of four subunits: one β-chain, one α-chain, and two disulfide-linked γ-chains. Most of the α-chain extends into the extracellular region, where it binds directly and with high-affinity to the Fc portion of IgE antibodies; thus, the α-chain is the most important component of the FcεRI molecule (Hakimi *et al.*, 1990). The cross-linking of FcεRI with allergen-IgE complexes causes the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins from activated basophils and mast cells, which contributes to the allergic responses in asthma, atopic dermatitis, allergic rhinitis, and food allergies (Drombrowicz *et al.*, 1993; Gauchat *et al.*, 1993; Metzer, 1991; Yanagihara *et al.*, 1997).

The progression of airway inflammations involves several types of cells such as $CD4^+$, Th2 cells, eosinophils, and mast cells (Wills-Karp, 1999). The immunopathogenic role of Th2 cells is determined by the roles of their products, such as IL-4, IL-5, and IL-13 in the recruitment and activation of the primary effector cells of the allergic response, eosinophils, and mast cells. Activation of these cells results in the release of many inflammatory mediators that seem to induce AHR individually or coordinately (Drazen *et al.*, 1996; Galli, 1997), although the precise molecular mechanisms predisposing to the development of AHR in asthmatics are largely unknown.

V. EXISTING REMEDIES AND DISADVANTAGES/FAILURES

Since the identification of asthma, many remedies have been implemented for curing it. However, most methods have failed to control this problem successfully; they are able to control the symptoms up to some extent. Presently, a number of treatments are used to control asthma. Glucocorticoids are effective for the treatment of allergic inflammation in asthma and result in reduced airway hyperresponsiveness which is thought to be due to reduced inflammation (Djukanovic *et al.*, 1992). Moreover, it has been reported that long-term use of corticosteroids does not eliminate the airway hyperresponsiveness (Van Essen-Zandvliet *et al.*, 1992). Therefore, this suggests that there are limitations to the use of these remedies in airway remodeling changes. However, there are some evidences that inhaled corticosteroids may stop or reverse the structural changes in airway (Hoshino, 2004). Another drug used for the treatment of asthma is β-agonists. In many instances, it is used together with corticosteroids and shows synergistic effects. A leukotriene receptor antagonist has been successful to prevent the smooth muscle thickening around the airway in an investigation in an animal model of asthma (Wang *et al.*, 1993). Further, leukotriene receptor antagonist has also been shown to inhibit other aspects of airway remodeling as a result of suppression of cell infiltration into the airway wall (Henderson *et al.*, 2002). Mast cell tryptase inhibitors may have potential in addressing not only bronchoconstriction but also airway remodeling, in particular, fibrosis (Cairns, 2005).

VI. MACROALGAE AS POTENTIAL ANTIASTHMATIC AGENTS

Algae extracts and compounds are well known for variety of biological activities including antiasthmatic activity. In addition, some algal species are used in Asian menus from long time. In a study, Kim *et al.* (2008) have shown that extract from *E. cava* suppresses the cytokine signaling in an animal model. The treatment of animals with *E. cava* extracts significantly reduced the concentration of Th2 (IL-4 and IL-5) cytokine in the airway. Hence, in their studies, they have proved that *E. cava* extract reduced the airway inflammation and hyperresponsiveness via inhibition of SOCS-3 protein expression. Shim *et al.* (2009) have also shown that extracts from *E. cava* inhibited the expression of FcεRI in human basophilic KU812F cells. Moreover, active compounds that are responsible for some specific activity have been isolated from *E. cava*. Compounds isolated from *E. cava* including phloroglucinol, dieckol, 6,6′-bieckol, and 1-(3″,5″-dihydroxyphenoxy)-7-(2″,4″,6-trihydroxyphenoxy)-

2,4,9-trihydroxydibenzo-1,4-dioxin were assessed by histamine release by human basophilic and rat basophilic leukemia cells and showed increased activities against them (Le *et al.*, 2009). *Eisenia arborea*, edible brown seaweed, has been used as a folk medicine for allergic disease for centuries by Koreans and Japanese. In a study, several bioactive phlorotannin compounds have been isolated from *E. arborea* and evaluated for antiallergic activities (Sugiura *et al.*, 2007). Phlorotannin compounds inhibited β-hexosaminidase released from basophilic leukemia (RBL-2H3) cells in their study. Moreover, the compounds showed higher activity ($IC_{50} = 7.8$ μM) than that of Tranilast ($IC_{50} = 46.6$ μM), a pharmaceutical agent used for the treatment of inflammation disorders including asthma, allergic rhinitis, and atopic dermatitis in Japan and Korea. Results revealed that they are potential agents to prevent the effect through various modes of actions. Further, preliminary investigation with the dried powder from *E. arborea* possessed antiallergic effects on Brown Norway rats, a type of allergic model animals (Sugiura *et al.*, 2007). The amount of histamine in the blood of Brown Norway rats fed with a diet containing 5% of powdered *E. arborea* was significantly lower (144.9 nM) than that of the animals fed with a diet without *E. arborea* (311.8 nM).

The red algal genus Laurencia is known to produce a wide array of natural products exhibiting number of biological activities, due to produce natural bioactive materials of polysaccharides, polyphenols, terpenes, and the other halogenated secondary metabolites. The protective effect of red algae, *Laurencia undulate*, has been evaluated against OVA-induced murine allergic airway reactions (Jung *et al.*, 2009). *Porphyra dentata*, edible red seaweed, has long been used as folk medicine for the treatment of inflammatory diseases including, bronchitis, hypersensitivity, and lymphadentis. The macrophage-based assays revealed that the crude extract and phenolic compounds present in *P. dentata* significantly inhibit inflammatory mediators such as NO, iNOS, and NF-κB (Kazłowskaa *et al.*, 2010).

VII. MICROALGAE AS POTENTIAL ANTIASTHMATIC AGENTS

Blue-green algae known as cyanobacteria have shown antioxidant, neuroprotective, cytoprotective, antiviral, antifungal, antibacterial, and anti-inflammatory activities. Edible blue-green algae, such as *Spirulina* and *Aphanizomenon flos-aquae*, are currently marketed as dietary supplements with various health claims for immune function, inflammation, heart disease, and general well-being. *Nostoc commune*, a blue-green edible microalga, has been used as a food delicacy or herbal medicine in Asian, African, and South American countries for centuries (Cao, 1998).

It has been used as potential source to treat various diseases in Chinese medicine and has been suggested that it can be used to treat a variety of diseases including inflammation, night blindness, digestion, and burns (Qui *et al.*, 2002). Depending on the variety of usages of this important microalga, Park *et al.* (2008) have shown that the lipid extract from *N. commune* var. *sphaeroids* represses the expression of several genes involved in the proinflammatory responses to inflammatory stimuli. Fatty acid mixture significantly reduced RNA abundance of TNF-α and COX-2. Further, DNA binding activity was also evaluated as NF-κB is the major regulator of proinflammatory gene expression and revealed that DNA binding activity of NF-κB significantly reduced by the treatment with *N. commune* lipid extract. Evaluation of dialyzed *Chlorella pyrenoidosa* extract (DCPE) on mast cell mediator release *in vitro* and overalbumin-induced airway inflammation *in vivo* revealed that *in vitro* treatment of mouse bone marrow-derived mast cells with DCPE for 18 h significantly inhibited antigen (trinitrophenyl-BSA)-induced IL-5 production (Kralovec *et al.*, 2005). *In vivo*, treatment of mice with DCPE during ovalbumin sensitization and stimulation process significantly reduced eosinophil and neutrophil infiltration in the airways. Further, unicellular *Chlorella pyrenoidosa* is used as a food supplement (Kay, 1991). It is a valuable source of nutrients and low in cellulose and exhibits a remarkable diversity of physiological and biochemical properties. Further, the beneficial effects of *Chlorella* preparations include the enhancement of immune functions and control of ulcerative colitis and hypertension (Merchant and Andre, 2001; Merchant *et al.*, 2002).

VIII. CONCLUSIONS

This review regarding the antiasthma activity of micro- and macroalgae provides an insight about asthma using the information published up-to-date. It is very clear that macroalgae provide a variety of biological activities against numerous diseases and have been reported as potential sources to be used in human-related dietary supplement production. Further, various bioactive compounds have been isolated and identified in marine microalgae. Hence, marine micro- and macroalgae can be developed as health promoting nutritional foods for the prevention of anti-inflammatory-related diseases. However, more deep studies are needed to be done regarding the microalgae to identify their molecular basis of the mechanisms, and clinical trials should be recommended before using these valuable agents.

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