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REVIEW



An overview on marine anti-allergic active substances for alleviating food-induced allergy

Kexin Wang^a, Siddanakoppalu Narayana Pramod^b, Tushar Ramesh Pavase^a, Ishfaq Ahmed^a, Hang Lin^c, Liangyu Liu^a, Shenglan Tian^a, Hong Lin^a, and Zhenxing Li^a

^aCollege of Food Science and Engineering, Food Safety Laboratory, Ocean University of China, Qingdao, P.R. China; ^bLaboratory for Immunomodulation and Inflammation Biology, Department of Studies and Research in Biochemistry, Sahyadri Science College (Autonomous), Kuvempu University, Shivamogga, Karnataka, India; ^cThe Affiliated Hospital of Qingdao University, Qingdao, P.R. China

ABSTRACT

Food provides energy and various nutrients and is the most important substance for the survival of living beings. However, for allergic people, certain foods cause strong reactions, and sometimes even cause shock or death. Food allergy has been recognized by the World Health Organization (WHO) as a major global food safety issue which affect the quality of life of nearly 5% of adults and 8% of children, and the incidence continues to rise but there is no effective cure. Drug alleviation methods for food allergies often have shortcomings such as side effects, poor safety, and high cost. At present, domestic and foreign scientists have turned to research and develop various new, safe and efficient natural sources of hypoallergenic or anti-allergic drugs or foods. There are many kinds of anti-allergic substances obtained from the plants and animals have been reported. Besides, probiotics and bifidobacteria also have certain anti-allergic effects. Of all the sources of anti-allergic substances, the ocean is rich in effective active substances due to its remarkable biodiversity and extremely complex living environment, and plays a huge role in the field of anti-food allergy. In this paper, the anti-food allergic bioactive substances isolated from marine organisms encompassing marine microbial, plant, animal sources and their mechanism were reviewed and the possible targets of anti-allergic substances exerting effects are illustrated by drawing. In addition, the development prospects of marine anti-allergic market are discussed and forecasted, which can provide reference for future research on anti-allergic substances.

KEYWORDS

Food allergy; anti-allergic active substances; marine microbial source; marine animal source; marine plant source

Introduction

Food allergy refers to the abnormal response of the immune system after exposure to certain foods. It can be divided into two types, IgE-mediated and non-IgE-mediated, and most common is IgE-mediated allergic reactions (Walker et al. 2018). The foods responsible for causing allergic reactions in adults and children include fish, shellfish, eggs, milk, peanuts, nuts, soy and wheat. Food allergies can cause a variety of symptoms, including discomfort in the digestive tract, respiratory tract, skin, and cardiovascular system (Andorf et al. 2017). Some common symptoms include itching in the mouth, throat or ear, itchy rash (hives or eczema), swelling around the face, eyes, lips, tongue and mouth (angioedema) and vomiting. Allergic reactions can be life-threatening when it affects the respiratory or cardiovascular systems, but most reactions are not serious (Pajno et al. 2018).

There is no proper treatment to eradicate food allergies now, however, the best way to prevent allergic reactions is to identify foods that cause allergies and avoid them in the diet. But this may affect the nutritional intake of the body, especially in children, and thus affect their growth

(Dhondalay et al. 2018). In general, three main medical treatments can be used to alleviate food allergies. One is antihistamines, which are suitable for mild to moderate allergic reactions. However, some antihistamines such as alimazine and promethazine are not suitable for children under two years old (Burks et al. 2018). The most common after antihistamines are steroid and non-steroid drugs to suppress immune cell activation involved in allergic reaction, but they have lots of side effects as they are known to effect various organs on long-term use in subjects. The third is adrenaline: in most cases of severe allergic reactions, intramuscular injection of epinephrine is the preferred route of administration. In the United States, the most widely used adrenaline product is the EpiPen auto-injector, but currently, this method is not available to adults and children in many countries. Moreover, there is no automatic syringe for infants in the world (Nowak-Węgrzyn and Groetch 2015). According to relevant surveys, the price of adrenaline auto-injectors ranges from \$30 to \$110. Prices in different places in the same country may vary by a factor of two. In some countries, the purchase cost is equivalent to the monthly salary of many patients (Sampson 2016). Care should also be

Table 1. Anti-food allergic ingredients in plants that have been reported.

Type	Main distribution	Name	Source	Reference
Flavonoids	Widely found in dicots and angiosperms	Luteolin, apigenin, diosmetin, fisetin and quercetin, etc.	<i>Chrysanthemum</i> , <i>Celery</i> , <i>Citrus limon</i> (L.) Burm. f., <i>mukdenia rossii</i> , etc.	(Kim et al. 2014; Kimata et al. 2000; Mlcek et al. 2016)
Terpenoids	Mainly distributed in gymnosperms and angiosperms	Paeoniflorin, tussilagone, tanshinone, etc.	<i>Paeonia lactiflora</i> , <i>Flos Farfarae</i> , the root of <i>Salvia miltiorrhiza</i> , etc.	(Lee et al. 2008; Li et al. 2015; Trinh et al. 2010)
Quinones	Mainly distributed in the family Polygonaceae, Leguminosae, Comfrey, Rubiaceae, etc. It is most common with anthraquinone and its derivatives.	Shikonin and aurantio-obtusin, etc.	<i>Lithospermum</i> , <i>Semen Cassiae</i> , etc.	(Kim et al. 2015; Wang et al. 2014)
Alkaloids	Generally distributed in plant populations with higher phylogeny, such as gymnosperms and angiosperms.	Oxymatrine, matrine and curine, etc.	<i>Sophora flavescens</i> , <i>Chondrodendron tomentosum</i> , etc.	(Kim et al. 2012; Ribeiro-Filho, Piuvezam, and Bozza 2015)
Phenylprop-anoids	Widely present in the wood and resins of plants	Lignans, fargesin, etc.	<i>Schisandra chinensis</i> , <i>flos magnoliae liliflorae</i> , etc.	(Li et al. 2006; Shen et al. 2008)

taken with the use of adrenaline, which can be life-saving if used properly and can be fatal if used improperly.

At present, a great attention has been paid to explore the anti-allergic substances from marine source to overcome the problems of food-induced allergies. A large number of literatures have reported the anti-food allergic activities of various plants, and the anti-food allergic ingredients in these plants include flavonoids, terpenes etc., as shown in Table 1. Small peptides such as wheat peptide, soybean peptide, black chicken peptide, collagen peptide, etc. all have good anti-allergic activity (Lozano-Ojalvo and López-Fandiño 2018). In recent times, research on plant based anti-food allergic substances are nearly saturated. What's more, due to its own complex composition and the constraints of drug developmental technicality such as separation and analysis, it encounters a series of difficulties in the extraction process (Cota, Bertollo, and de Oliveira 2013). In addition to plants, there are many resources such as marine resources that need to be rationally utilized.

The ocean is the birthplace of life, and its biodiversity far exceeds terrestrial organisms. Marine life includes marine animals, marine plants and marine microorganisms (Jaiganesh and Kumar 2012). The ocean accounts for about 71% of the Earth's surface area and is an open, versatile and complex ecosystem. The complexity of the special physical and chemical factors of the ocean is responsible for creating the complexity of life activities, the biodiversity of species resources and ecological functions. The ocean is extremely rich in biological resources, containing many kinds of biological active substances. It provides a large amount of food, a variety of materials and raw materials for human beings, and has the characteristics of being renewable. It has attracted the attention of all countries in the world and has great development potential (Kanani, Banerjee, and Rajendran 2014). At present, there are some progress in the research on marine anti-allergic substances by various research groups across the globe. This paper reviews the anti-food allergic bioactive substances isolated from marine resources (Figure 1) and its mechanism, aiming to provide some references for future research.

The overall mechanism of allergic inflammation in type-I hypersensitivity reactions is shown in Figure 2. There are three main anti-allergic targets in marine antiallergic substances recently studied:

1. Compounds targetting the signal cascade of mast cell/basophil degranulation (Figure 3).
2. Compounds targetting the regulation of FcεRI receptor expression and calcium influx during allergic reactions (Figure 4).
3. Compounds targetted to reduce IgE induction by skewing the Th2 to Th1 by altering the interleukin IL-4, 10 and 5 expresion to IL-12, INF-γ which reduces the allergic sensitization (Figure 5).

Marine anti-food allergic natural active substance

Marine microbial source

Marine microorganisms have more than 1 million species, and the diversity of secondary metabolites is unparalleled by terrestrial microorganisms. However, only a few thousand kinds of marine microorganisms can be cultured artificially, less than 1% of the total; so far, marine microorganisms isolated and cultured for the purpose of isolating metabolites is very seldom. Because microorganisms can obtain a large number of fermentation products through fermentation engineering, thus the drug source is guaranteed. In addition, marine symbiotic microorganisms may be the real producers of natural active substances in their hosts, which has important research value (Chen, Wang, and Pei 2014).

Currently, many achievements have been made in the development and application of marine microbial natural active substances and it is mainly embodied in the development of marine drugs. To mention, a variety of substances with strong biological activity, including toxins, antibiotics, unsaturated fatty acids and carotenoids have been isolated from microorganisms which mainly include marine bacteria, actinomycetes and fungi (Jensen, Moore, and Fenical 2015). Xie et al. (2017) isolated nesterenkoniane, a novel cyclic

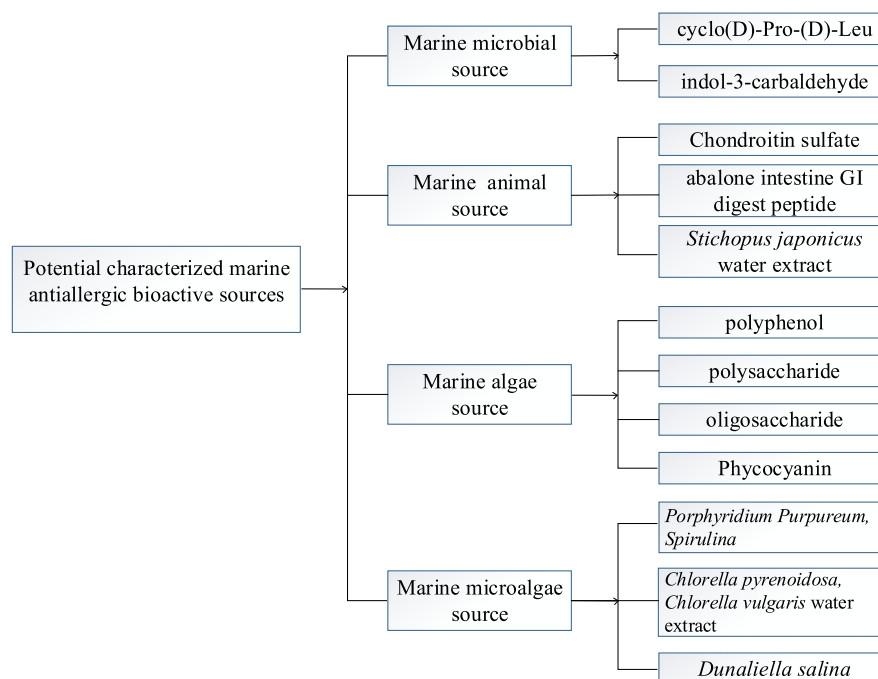


Figure 1. Potential characterized marine antiallergic bioactive compounds.

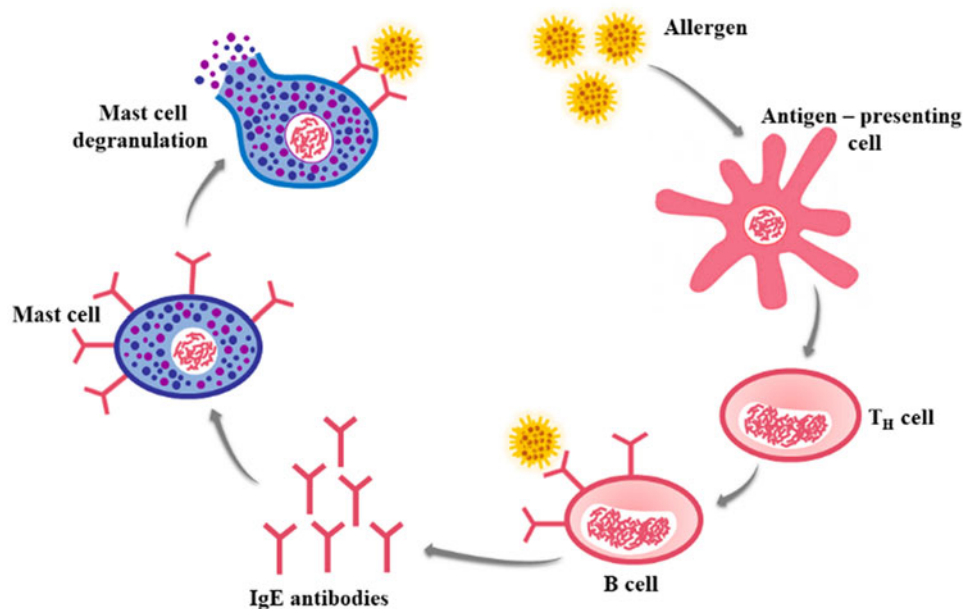


Figure 2. The mechanism of type-I hypersensitivity allergic reactions. After first contact, allergens are presented to Th cells through antigen presenting cells (APC), which helps regulate cellular immunity, promote isotype transformation and produce specific IgE antibodies from B cell. Subsequent antigen exposure induced the cross-linking of cell surface antigen-IgE complex with FcεRI, leading to the activation and degranulation of MCs.

ether (1) and twelve known compounds (2–13) from the deep-sea-derived actinomycete *Nesterenkonia flava* MCCC 1K00610 for the first time. The structure is shown in the Figure 6. Among these twelve known compounds are two macrolides (2, 3), two diketopiperazine compounds (4, 5), two nucleosides (6, 7), two indoles (8, 9), three phenolic compounds (10–12) and a butanol derivative (13). The authors compared the anti-allergic activity of these 13 compounds by measuring the amount of β -hexosaminidase released by the IgE-mediated rat RBL-2H3 cell model.

Among them, nine compounds (1, 4–10, and 13) showed positive effects, compound 4: cyclo(D)-Pro-(D)-Leu showed the strongest inhibitory effect, compound 8: indol-3-carbaldehyde took the second place, both higher than the positive anti-allergic drug loratadine, compound 1 showed moderate anti-allergic activity, the inhibition rate was about 9.86%, but lower than the positive control loratadine (37.41%). In this study, cyclo(D)-Pro-(D)-Leu (4) and indol-3-carbaldehyde (8) showed a significant anti-allergic effect on TM-specific IgE-mediated rat mast RBL-2H3 cells, indicating the

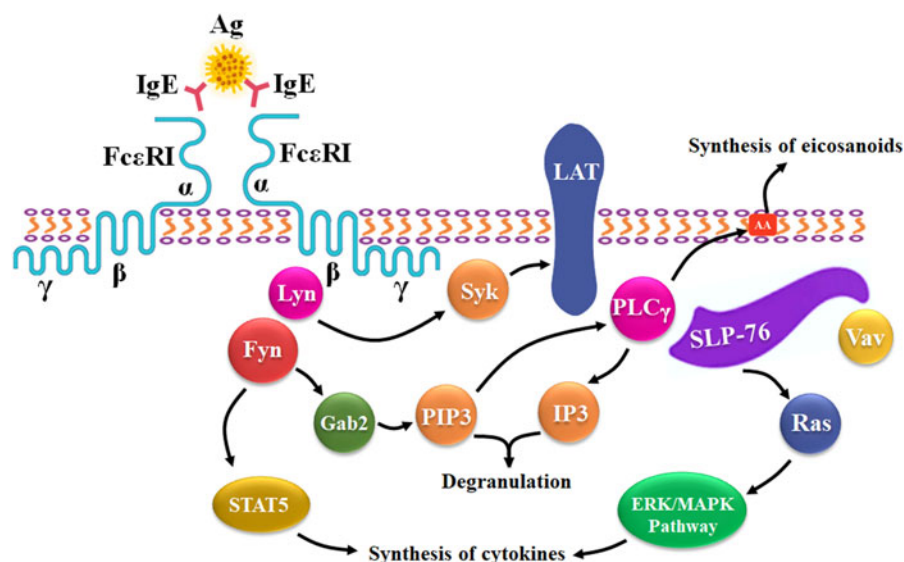


Figure 3. IgE-mediated downstream signal events after FcεRI activation. Ag, antigen; FcεRI, high affinity IgE receptor; PIP3, phosphatidylinositol triphosphate; IP3, inositol triphosphate; LAT, linker for activation of T cells; STAT5, signal transducers and activators of transcription-5; PLCγ, phospholipase Cγ; Ras, rat sarcoma; AA, arachidonic acid; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase.

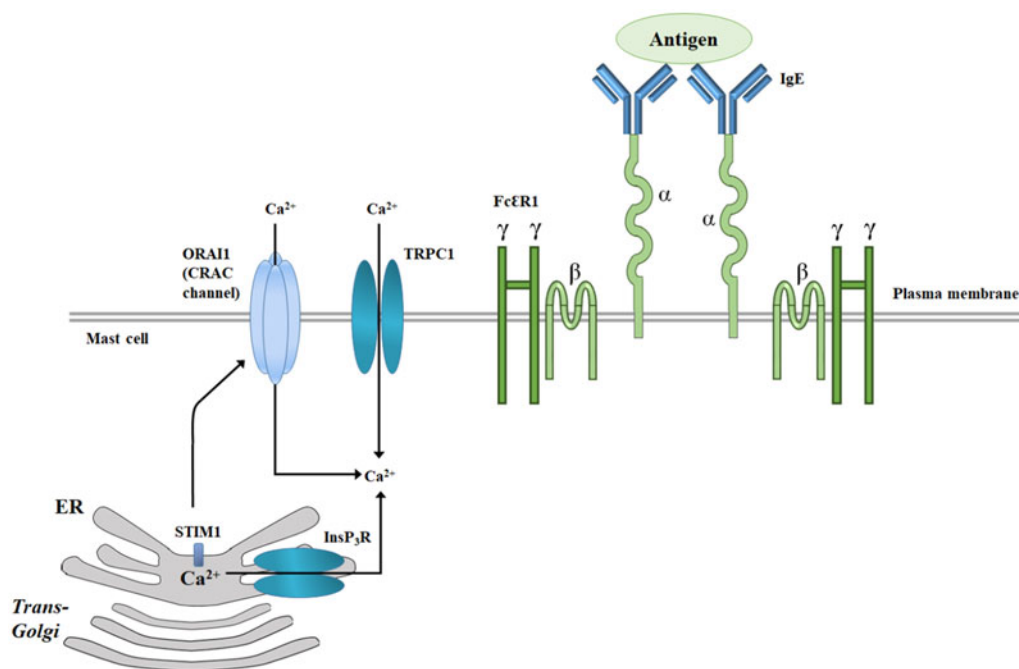


Figure 4. Compounds targetting the regulation of FcεRI receptor expression and calcium influx during allergic reactions. ER, Endoplasmic reticulum; CRAC (Ca²⁺ release-activated Ca²⁺ channel), is the main channel for extracellular Ca²⁺ to flow into cells in non-excitable cells discovered so far; TRPC1 (transient receptor potential canonical1), it is the main channel for store-operated Ca²⁺ entry (SOCE) in vascular endothelial cells and smooth muscle cells; InsP3R (inositol triphosphate receptor), is a membrane glycoprotein complex acting as a Ca²⁺ channel activated by inositol triphosphate (InsP3); STIM1 (stromal interaction molecule 1) and ORAI1, STIM1 and orai1 are the major components of SOCE. ORAI1 is a four-time transmembrane Ca²⁺ channel protein localized on the plasma membrane. STIM1 is a Ca²⁺ 'receptor' on the ER. The interaction between the two activates calcium channels (CRAC).

potential application of these two compounds as anti-allergic medicines. It is worth mentioning that this is the first report on secondary metabolites from the genus of *Nesterenkonia*.

Marine animal source

Table 2 summarizes the main outcomes of the studies evaluating marine animal source substances that exert allergic effects.

After extracting and purifying Chondroitin sulfate (ChS) from sturgeon, Huang et al. (2012) evaluated the anti-allergic effect of ChS by studying the degree of allergic swelling of the mouse induced by xylene and the effect of egg white on foot padding inflammation and comparing with ChS of shark at the same time. ChS is a kind of acidic mucopolysaccharide with different isomers in animal cartilage tissue. It has anti-inflammatory, anti-thrombotic, anti-tumor cell proliferation and immune regulation effects. The main source is animal cartilage such as poultry, livestock and

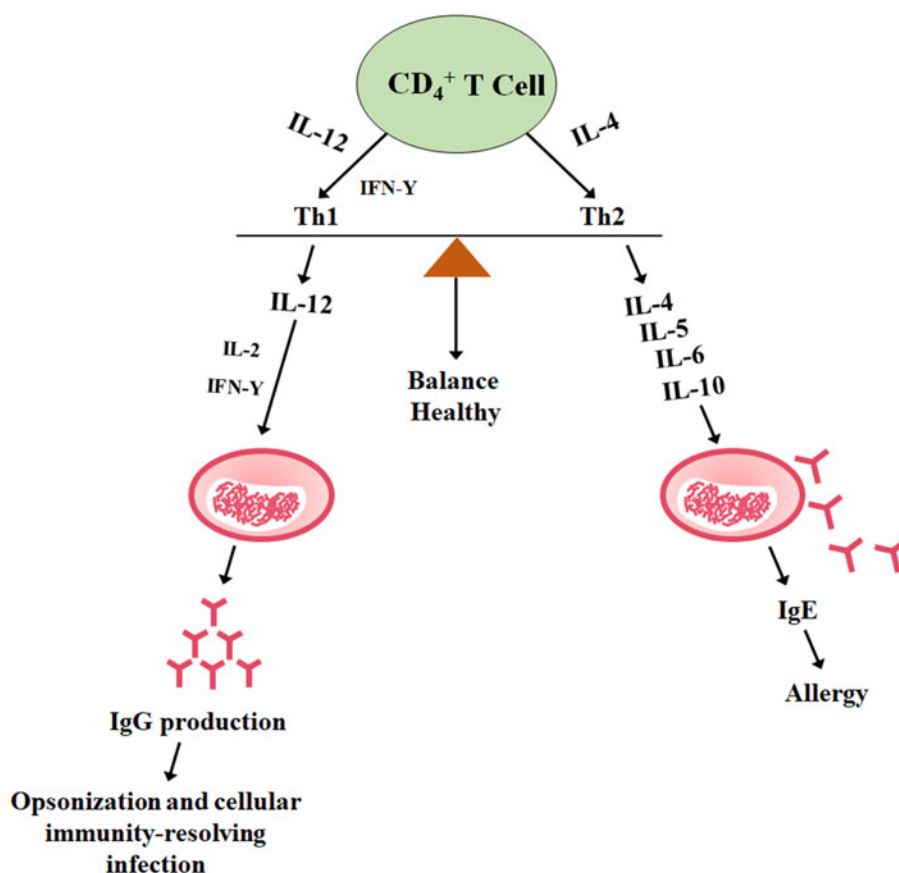


Figure 5. Th1/Th2 balance and allergic reaction. In a healthy state, Th1 and Th2 are balanced and regulated by Treg. When Treg is inadequate in regulation or when the body is exposed to certain proteins or small molecules (dust mites, pollen or seafood, etc.), the excessive activation of Th2 will lead to the excessive secretion of Th2 cytokines, which will help B cells to produce more allergic antibodies IgE, thus causing allergic symptoms. We can regulate the activity balance of immune cells by regulating the secretion of Th2 cytokines which are overreacted due to allergy, or by enhancing the immune response of Th1 type. The pathophysiological characteristics suggest that anaphylaxis is closely related to the balance of Th1/Th2.

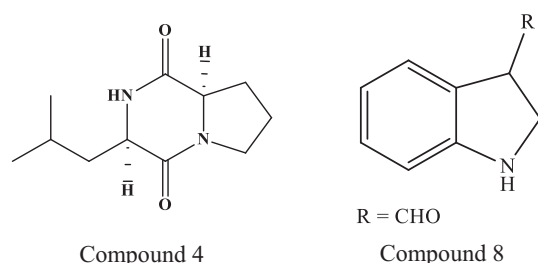


Figure 6. Compounds (4) and (8) isolated from *Nesterenkonia flava* MCCC 1K00610.

shark, but the cartilage content of poultry and livestock is low. Shark is a relatively scarce National Wildlife Conservation animal. At present, the sturgeon farming industry in China is developing well, and the cartilage content of sturgeon is quite high, the extraction rate is about 31.56% (He et al. 2014). In addition, the extraction technology of ChS from sturgeon is relatively mature. Moreover, studies have shown that the chemical structure of ChS in sturgeon is different from that of ChS in poultry, livestock and sharks (Mizumoto et al. 2013; Takeda, Horai, and Tamura 2016). The results showed that chondroitin sulfate of sturgeon could significantly reduce the ear swelling caused by xylene and footpad swelling caused by egg white inflammation. Compared with shark ChS, sturgeon ChS may

have better anti-inflammatory activity and enhance cellular immune function.

Song et al. (2013) evaluated the anti-allergic properties of the *Stichopus japonicus* extracts (a species of sea cucumber, is acylinder-shaped invertebrate that is mainly consumed in Asian countries as both food and traditional medicine) from Jeju Island (extracted with hexane, chloroform, ethyl acetate, butanol and water, respectively) and found that the *S. japonicus* water fraction (SJW) has the strongest anti-inflammatory properties compared with other extracts. Further anti-allergic activity was studied based on SJW. The effect of SJW on the release of β -hexosaminidase was determined by antigen-stimulated RBL-2H3 cells. The results showed that the SJW significantly inhibits the β -hexosaminidase secretion in IgE-sensitized RBL-2H3 cells in a dose-dependent manner. Meanwhile the survival rate of RBL-2H3 cells cultured with SJW was not affected. IL-4 can produced in IgE-activated RBL-2H3 mast cells which induces allergic reactions and the addition of SJW significantly reduced IL-4 mRNA levels.

In a word, SJW exerts anti-allergic effect by inhibiting antigen-induced degranulation of mast cells. This study also did some anti-inflammatory experimental designs and finally demonstrated the potential of *Stichopus japonicus* extracts as a therapeutic agent for the prevention or treatment of allergic inflammatory diseases.

Table 2. Anti-food allergic substance from marine animals.

Marine animal source	Main experimental methods	Main outcomes	Reference
Sturgeon chondroitin sulfate	Determination: the mouse immune organ weight, delayed hypersensitivity reaction, serum hemolysin, xylene induced ear swelling and inflammation of footpad caused by egg white	↑ The weight and index of the thymus gland and spleen of the mouse ↑ The number of peripheral blood leucocyte ↑ Delayed hypersensitivity intensity ↑ Specific antibody production capacity ↓ Xylene-induced mouse ear swelling and egg white-sensitized footpad swelling	(Huang et al. 2012)
Sea cucumber extracts	Extracted with hexane, chloroform, ethyl acetate, butanol and water, respectively Cell model: RBL-2H3 mast cells and RAW 264.7 macrophages Determination: 1) the release of β -hexosaminidase 2) the NO production, IL-6 and TNF- α mRNA expression in LPS-stimulated RAW 264.7 cell	The water extract of sea cucumber has strong anti-allergic activity ↓ the release of β -hexosaminidase ↓ mRNA expression of IL-6 and TNF- α	(Song et al. 2013)
Abalone intestinal digestive peptides	Ultrafiltration Animal model: ICR mice Cell model: HMC-1 cells PCA reaction in mice Histamine assay Determination: the histamine release from mast cells induced by PMACI	Three components obtained: I (>10 kDa), II (5–10 kDa), III (<5 kDa) Component III: ↓ PCA reaction AIGIDP: ↓ histamine release ↓ pro-inflammatory cytokines (TNF- α , IL-1 β and IL-6) AIGIDP: the Molecular Weight and amino acid sequence were 1175.2Da and PFNQGTFAS. Mechanism: inhibition of PMACI-induced nuclear factor- κ B (NF- κ B) activation by inhibiting I κ B α phosphorylation and inhibition of cytokine production by decreasing phosphorylation of JNK.	(Ko et al. 2016)

Main outcomes: ↑, increased or high levels; ↓, decreased or low levels; AIGIDP, abalone intestine GI digest peptide (a bioactive peptide isolated from fraction III).

Ko et al. (2016) studied the anti-allergic effect of abalone intestine gastrointestinal (GI) digests and tried to illustrate the related mechanisms. By simulating the gastrointestinal digestion environment *in vivo*, three components I (>10 kDa), II (5–10 kDa) and III (<5 kDa) were obtained after *in vitro* enzymatic digestion and ultrafiltration. Then the *in vitro* (PMACI-induced release of histamine from mast cells) and *in vivo* experiments (IgE-mediated passive cutaneous anaphylaxis reaction in mice) were carried out to verify the anti-allergic activity of the three components. It was found that I and III could inhibit the release of histamine. III had the strongest effect on inhibiting the passive cutaneous anaphylaxis (PCA) reaction in mice. Subsequently, an anti-allergic peptide AIGIDP (abalone intestine GI digest peptide) with molecular weight of 1175.2 Da was isolated and purified from component III. It can inhibit PMACI-induced histamine release and the expression of pro-inflammatory cytokines such as TNF- α , interleukin (IL)-1 β and IL-6 in human mast cells (HMC-1 cells). The results are also consistent with the known molecular weight of the anti-allergic active peptide and it is known that low molecular weight bioactive peptides are more likely to cross the intestinal barrier (Dong et al. 2015; Ko et al. 2012). The amino acid sequence was identified as PFNQGTFAS. It consists of a mixture of essential and non-essential amino acids with high concentration of branched-chain amino acids (proline) and low concentration of methionine which had been specifically used to produce nutritional supplements that enhance tolerance to inflammatory diseases (McCauley et al. 2015; Nebolsin et al. 2008).

In addition, in order to elucidate the anti-allergic mechanism, whether AIGIDP affects the activation of MAPKs pathway was studied. The MAPK (JNK, ERK1/2 and p38 MAPK) cascades are important signaling pathways for immune responses that play key roles in mast cell activation, survival and differentiation, and cytokine production (Oliver et al. 1988). Therefore, the MAPK pathway is a suitable target for the treatment of allergic diseases (Kim 2014; Xiong et al. 2015; Min et al. 2007). It was found that AIGIDP inhibits the activation of nuclear factor- κ B (NF- κ B) induced by PMACI by inhibiting the phosphorylation of I κ B α , and inhibits the production of cytokines by reducing the phosphorylation of JNK. After PMACI stimulated HMC-1 cells, phosphorylation of JNK, p38 and ERK 1/2 MAPKs increased. AIGIDP only inhibited PMACI-induced JNK phosphorylation, but did not affect ERK 1/2 and p38 MAPK phosphorylation.

Proteins and polypeptides from marine organisms have many biological activities, such as anticoagulants, antimicrobials and antihypertensives. According to the composition and molecular size of amino acids, bioactive peptides can participate in a variety of biological functions. During digestion, proteolytic enzymes cause the production of absorbable bioactive peptides in the gastrointestinal tract (Belović et al. 2011). Because of the changes in structure, composition, sequence properties and biological activity after hydrolysis, protein hydrolysate have certain physiological benefits and can be used as general raw materials for the production of human health products and medicines. Studies have shown that many proteins and peptides can prevent disease by

Table 3. Anti-allergic effect of phlorotannins in marine algae.

Source	Main experimental methods	Main outcomes	Reference
Crude extract of <i>Ecklonia cava</i> , an edible marine brown alga	Histamine release assay on KU812 and RBL-2H3 cultured cell lines, respectively RBL-2H3 cell stimulation and assay for β -hexosaminidase release Flow cytometry analysis of binding activity between human IgE and Fc ϵ RI receptor on KU812F cell	Phloroglucinol (1), dieckol (2) and two main bioactive phlorotannin derivatives (3,4) obtained. Compound 2, 3 showed the strongest inhibitory effects. Potential anti-allergic mechanism: the suppression of binding activity between IgE and Fc ϵ RI.	(Le et al. 2009)
<i>Ecklonia stolonifera</i> , an edible marine brown alga	Isolation of DHE and PFF-A Evaluated for effects on cell surface Fc ϵ RI expression in KU812F cells [Ca ²⁺] _i measurement Histamine assay Flow cytometric analysis	Two bioactive phloroglucinol derivatives (DHE, PFF-A) were obtained by isolation. Inhibitory ability: PFF-A > DHE ↓ Cell surface expression ↓ Total cellular protein and mRNA levels for the Fc ϵ RI α chain. ↓ Intracellular calcium concentration [Ca ²⁺] _i and histamine release from anti-Fc ϵ RI α chain antibody (CRA-1)-stimulated cells.	(Shim, Choi, and Byun 2009)
<i>Scytosiphon lomentarius</i>	Purification of polyphenols from <i>Scytosiphon lomentarius</i> Determination of hyaluronidase inhibitory activity	The inhibition rate of hyaluronidase activity was 73.50%, which was 1.94 times higher than that before purification.	(Chen et al. 2015)
Ethanol extracts of brown seaweeds from Pakistan and China	Optimized at 85% (v/v) ethanol for the maximum yield of phlorotannin Anti-hyaluronidase activity assay	ST has the lowest IC ₅₀ with 21 μ g/ml among all the brown seaweeds and also lower than DSCG (21 vs 39 μ g/ml) and catechin (21 vs 20 μ g/ml).	(Samee et al. 2009)

Main experimental methods: DHE, dioxinodehydroeckol; PFF-A, phlorofucofuroeckol A. **Main outcomes:** ST, *Sargassum tennerimum*; DSCG/catechin, two positive controls for antihyaluronidase activity; ↓, decreased or low levels.

regulating some signaling pathways (Chu et al. 2011; Guo et al. 2016; Vassilopoulos et al. 2005; Zhu et al. 2008). For example, some studies have found that the regulation of ERK/MAPK signaling pathway promotes the osteogenic activity of collagen peptide, thereby improving the therapeutic effect on osteoporosis (Kim, Kim, and Leem 2013), whereas the MAPK pathway is known to be associated with anti-allergy. There are also evidences that GI digests of marine organisms *in vitro* has the same biological activity as other natural antioxidants (Jung et al. 2007; Qian et al. 2008), which also reveals that the ocean is a treasury of hidden resources to be exploited such as develop anti-allergic substances.

Marine plant source (marine algae)

Seaweed is a kind of macroalgae growing in the intertidal zone and sub-intertidal zone, which usually includes green algae, brown algae and red algae. In ancient China and Japan, there were records of using seaweed as food. The ancient Pharmacopeia includes the use of seaweed for the treatment of various diseases, such as 'Compendium of Materia Medica', 'Variorum of Shennong's Classic of Materia Medica', 'Oversea Materia Medica' and 'A Supplement to Materia Medica'. Different seaweeds have different pharmacological effects and clinical uses depending on their chemical composition (Mhadhebia et al. 2014; Namvar et al. 2013). Recent studies have shown that seaweed plays a vital role in the field of anti-allergy.

Phlorotannins

Phlorotannins are a class of phenolic compounds extracted from brown algae and are phloroglucinol derivatives.

Phlorotannins, known as purifiers for body toxins, have a wide range of biological activities and are important for the development of marine drugs. In recent years, the anti-allergic activity of seaweed polyphenols has also played an important role (Table 3).

Le et al. (2009) isolated four anti-allergic phloroglucins and their derivatives from crude extracts of edible marine brown algae *Ecklonia cava* in Jeju Island, South Korea, and identified their structures. These are phloroglucinol (1), dieckol (2), 6,6'-bieckol (3), 1-(3',5'-dihydroxyphenoxy)-7-(2''',4''',6-Trihydroxyphenoxy)-2,4,9-trihydroxydibenzo-1,4-dioxin(4). The specific structures are shown in the Figure 7. The human leukemia cell line, KU812, and rat basophilic leukemia cell line, RBL-2H3 were used to evaluate whether the four compounds inhibited cell degranulation. At the same time, two different treatments of calcium ionophore (A23187) stimulation and antibody stimulation were used to stimulate cell degranulation. Calcium ionophore mediate histamine release by selectively increasing intracellular Ca²⁺ concentration, which leads to degranulation of mast cells and basophils (Parker and Martz 1982). This increase may be related to the increase of cell membrane permeability (Plaut et al. 1989; Verbsky, Mcallister, and Malone 1996). In this study, the isolated compounds inhibited histamine release stimulated by A23187 in two cell lines. It is also indicated that the compounds may reduce the increase of intracellular Ca²⁺ level by stabilizing the cell membrane (intracellular Ca²⁺ levels are known to be associated with reduced histamine release). Compound 2 and 3 showed the strongest dose-dependent inhibition of histamine release in two cell lines and two stimulants. Compound 2 had the highest inhibitory activity on KU812 cells, while compound 3 had the strongest inhibitory effect on the degranulation level of RBL-2H3 cells. In both cell lines, the active

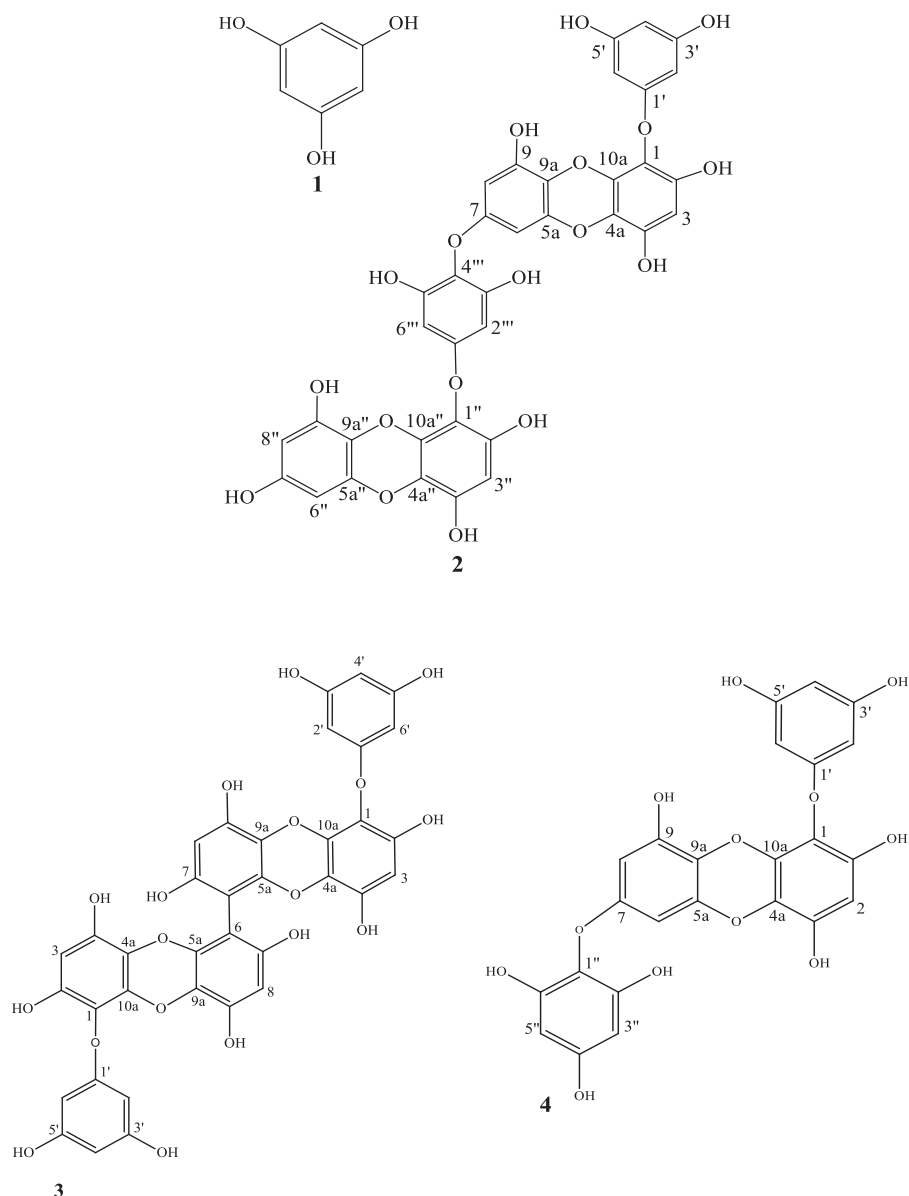


Figure 7. Chemical structures of phlorotannins isolated and identified from *Ecklonia cava*.

compounds showed stronger degranulation inhibition on antibody-stimulated cells compared to the A23187 stimulation. This also indicates that the active compounds may be more helpful in preventing allergic reactions caused by IgE.

In all cases, compound 1 with the lowest molecular weight had little inhibitory effect on histamine release from both cell lines. Compound 4 has a medium molecular weight and moderate inhibition compared to the other two active compounds. The larger the molecular weight of compound 2 and 3, the stronger the activity, indicating that the molecular size or the number of phenolic groups may be an important factor in exerting their activity (Sugiura et al. 2007). Apple polyphenols also have the same evidence (Kanada et al. 1998). At present, inhibition of IgE binding to FcεRI receptors has become a target for the development of anti-allergy drugs (Kon et al. 1996). In this experiment, compounds (2, 3 and 4) were demonstrated to inhibit the binding between IgE and FcεRI receptors in a dose-

dependent manner by using indirect fluorescent flow cytometry, which indicates that compounds 2, 3 and 4 can be used as anti-allergy substances in the pharmaceutical and food industries.

Shim, Choi, and Byun (2009) isolated two phloroglucin derivatives DHE and PFF-A from edible brown algae *Ecklonia stolonifera* and studied its effect on inhibiting the expression of FcεRI by human basophils KU812F. The Chemical structures is shown in Figure 8. Previous studies have shown that (-)-epigallocatechin-3-O-gallate (EGCG) of a green tea catechin and kaempferol of *Nelumbo nucifera* stamens have been proved to exert antiallergic activity by inhibiting the expression of FcεRI (Suzuki et al. 2000). The high affinity IgE receptor FcεRI expressed on the surface of mast cells and basophils participates in the regulation of IgE-mediated allergic reactions. The down-regulation of FcεRI expression may lead to the weakening of IgE-mediated allergic reactions (MacGlashan 2008). FcεRI molecule is

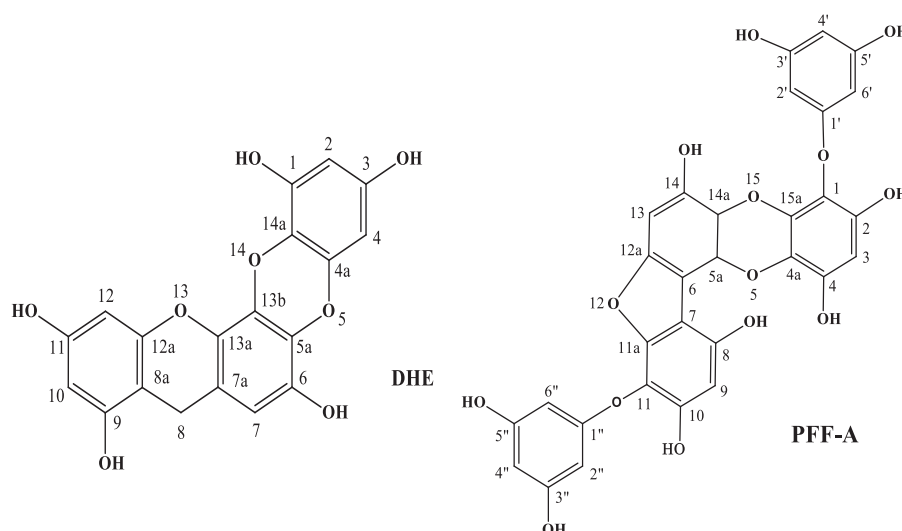


Figure 8. Chemical structures of DHE and PFF-A.

a tetramer receptor composed of one- α , one- β , and two disulfide-linked γ -chains. Among the three subunits of Fc ϵ RI, the γ -chain is expressed in Fc ϵ RI-positive cells and extends mostly to the extracellular region, where it binds directly to the Fc part of IgE antibody with high affinity (Dombrowicz et al. 1997). DHE and PFF-A were found to reduce cell surface expression and reduce total cellular protein and mRNA levels of the Fc ϵ RI α -chain. In addition, both compounds inhibited the increase of free calcium concentration and histamine release in CRA-1(anti-human Fc ϵ RI antibody) stimulated cells, and these inhibitory effects of PFF-A were stronger than DHE. The above results indicated that DHE and PFF-A can exert anti-food allergic effects by the down-regulation of Fc ϵ RI expression, calcium ion influx and degranulation in basophil cells.

Chen et al. (2015) found that the phlorotannins in the algae have good anti-allergic effects by using the inhibition rate of hyaluronidase activity as an evaluation index. The algae phlorotannin was purified and finally, a 45.27% purity of algae phlorotannin was obtained. The anti-hyaluronidase activity was determined, and the inhibition rate was 73.50%, while the specific activity was 1.94 times higher than the purified sample. Hyaluronidase is a specific lysase of hyaluronic acid. Hyaluronic acid plays an important role in many processes of human growth and regulation, such as cell adhesion, organogenesis, wound healing, tumorigenesis and angiogenesis. Inhibiting the activity of hyaluronidase can keep hyaluronic acid from being decomposed and maintain normal physiological functions. Studies have shown that hyaluronidase is a participant in type-I allergic reaction which is strongly correlated with inflammation and allergy. Kakegawa, Matsumoto, and Satoh (1985) have reported that various drugs that affect histamine release from mast cells can modulate the activity of hyaluronidase. There is a good correlation between inhibition of hyaluronidase activity and histamine release from mast cells. The determination of hyaluronidase inhibition rate has been widely adopted as an index for studying anti-allergic effects.

Samee et al. (2009) measured the anti-food allergic activity of five brown seaweeds from Pakistan and China by

hyaluronidase *in vitro* inhibition test and found that *Sargassum tenerrimum* had the best effect. Moreover, its ethanol extract is equivalent to catechin (a natural anti-allergic ingredients known at present) and is more effective than the clinically used antiallergic drug DSCG.

Seaweed polysaccharide

Seaweeds are rich in sulfated polysaccharides (SPs). In recent years, various SPs were isolated from seaweed that has attracted more attention in food or functional foods, cosmetic and pharmaceutical applications. SPs are commonly found in brown algae, red algae and green algae; for example, carrageenan in red algae, fucoidan in brown algae and polysaccharides in the green algae. SPs are complex macromolecules with a wide range of biological activities. Therefore, seaweed-derived SPs have great potential as food or nutritious foods in the food industry (Ngo and Kim 2013; Vo, Ngo, and Kim 2012a, 2012b). Some research results of anti-allergic activity are shown in Table 4.

Maruyama et al. (2005) found that mekabu fucoidan reduced the concentration of interleukin 4 (IL-4) and IL-13 in bronchoalveolar lavage fluid. Furthermore, an increase in IgE in the airway allergic reaction induced by ovalbumin (OVA) in mice was inhibited. Yanase et al. (2009) also found that intraperitoneal injection of fucoidan inhibited the increase of IgE in plasma by inhibiting IgE expression and secretion of IgE by B cells in OVA-sensitized mice. However, if B cells were pre-stimulated with IL-4 and anti-CD40 antibodies prior to the use of fucoidan, no effect of fucoidan was observed. These results indicated that fucoidan may not prevent further increases in IgE in patients with allergic disease and high levels of serum IgE. In addition, alginic acid (a natural polysaccharide) obtained from several brown seaweeds by Asada et al. (1997) has a certain effect on inhibiting hyaluronidase activity and histamine release from mast cells. It was found that alginic acid at a concentration of 0.01 g/ml inhibited the release of histamine from rat peritoneal mast cells by 60.8%.

Table 4. Anti-allergic effect of seaweed polysaccharide.

Name	Main experimental methods	Main outcomes	Reference
Mekabu fucoidan from <i>Undaria pinnatifida</i> sporophylls	Animal model: BALB / c mice Sensitization: OVA (50mg) + alum (1mg) (1 and 8 days later) IT: Mekabu fucoidan (50 mg/kg) in.p.(4days) T cell responses in BALF by measuring the amount of Th2 cytokines (IL-4, IL-5, IL-13) and gamma-interferon (IFN- γ) produced by Th1 cells.	↓ Th2 cytokines ($p < 0.05$) The amount of IFN- γ was not increased The experimental mice (ANTIOVA) < The control mice ($p < 0.05$)	(Maruyama et al. 2005)
Fucoidan	Animal model: female Balb/c (4 weeks) mice Sensitization: OVA (2 μ g/mouse)+ an alum adjuvant IT: Orally (10 mg/mouse) or intraperitoneally (100 μ g/mouse) (3 times every week) Measurement of IgE, IgG1, IgG2a, IL-4, and IFN- γ in plasma. Flow cytometric analysis	↓ Increase of plasma IgE (i.t.) WF < WOF Fucoidan inhibits the increase of plasma IgE through the suppression of IgE-producing B cell population. The effect of fucoidan <i>in vivo</i> is crucially dependent on the route and timing of its administration.	(Yanase et al. 2009)
Alginic acids	Three types of sodium alginate (types 0.6, 1.0 and 2.0 according to M/G ratio) Inhibitory effects of sodium alginates on the activity of hyaluronidase. Inhibitory effects of sodium alginates and their derivatives on mast cell degranulation.	Alginic acid with an M/G ratio of 1.0 exhibited the strongest inhibition of both activities, the higher molecular weight alginic acids of 150 to 370 kDa being preferable in both cases.	(Asada et al. 1997)

Main experimental methods: in.p., intraperitoneal; IT, immunotherapy; M/G, D-mannuronic acids (M) /guluronic acids (G). **Main outcomes:** ANTIOVA, anti-OVA IgE and IgE levels in serum determined after challenge with aerosolized OVA; WF, the production of IL-4 and IFN- γ with fucoidan; WOF, the production of IL-4 and IFN- γ without fucoidan.

Seaweed oligosaccharide

Uno and Hattori (2006) found that when oral alginic acid oligosaccharide (ALGO) was administered, the production of IgE was significantly inhibited in mice fed ALGO compared to the control mice. The results indicated that ALGO also has anti-food allergic activity in the case of oral administration.

Shi et al. (2016) explored the anti-food allergic effects of oligosaccharides obtained by co-culture of deep sea bacteria (*Flammeovirga pacifica*) and *Gracilaria lemaneiformis*. Th2 animal allergic model was established by intraperitoneal injection of TM in BALB/c mice to explore the regulation of oligosaccharides on serum TM specific antibodies IgE, IgG1 and IgG2a. IgE is a decisive index for evaluating the allergic status of the body. IgE binds to the surface receptors of mast cells and basophils, leading to the release of inflammatory mediators and cytokines such as IL-4, IL-5 and IL-13 (Yoshimoto et al. 1999). The detection of Th1-specific IgG2a and Th2-specific IgG1 can also well indicate the polarization of Th1/Th2, thus indicating the allergic condition of the body (Nonaka et al. 2008). The results showed that intraperitoneal injection of the oligosaccharides (100 μ g/mouse) did significantly reduce the serum specific IgE and IgG1 levels of allergic mice, increase the specific IgG2a level, and significantly reduce the level of histamine in feces of mice by intragastric administration (10 mg/mouse), effectively alleviating the allergic pathological phenomena of jejunal tissue. When the body is allergic, Th2 cells produce IL-4 and IL-13, which induce B cells to produce IgE. Therefore, the contents of IL-4 and IL-13 are important indicators for evaluating food allergy. Th1 cells are characterized by secretion of cytokines IFN- γ , which can alleviate inflammation and resist pathogen invasion (Hsu et al. 2003). At the transcriptional

and translational level, the regulation of related cytokines was studied by mouse spleen lymphocyte experiments, which proved that the oligosaccharide can significantly reduce the content of Th2 cytokines (IL-4, IL-5, IL-13) and promote the secretion of IFN- γ in Th1. It also showed that it could effectively regulate the transformation of immune function of helper T cells to Th1 cells, thereby inhibiting Th2 cell-dominated food allergic reactions.

Many natural polysaccharides are macromolecule compounds, which can not reach the cells through the body barrier and affect their biological functions. Degradation of polysaccharides to obtain appropriate molecular weight polysaccharide fragments or oligosaccharides can improve the biological activity of polysaccharides. At present, for the extraction of seaweed oligosaccharides, the seaweed polysaccharide is usually extracted first, and then the polysaccharide is degraded into oligosaccharides by strong acid or enzyme. The operation process has many steps and high cost, which greatly limits the application development of seaweed oligosaccharide, and the process requires the use of strong acid and organic solvent, which also causes pollution to the environment. In this study, *Flammeovirga pacifica*, a strain from deep-sea sediments in the western Pacific Ocean was used which can degrade to obtain oligosaccharides directly.

Phycocyanin

The phycocyanin is a dark blue powder isolated from spirulina and is mainly found in cyanobacteria, red algae and cryptophyta. The phycocyanin is usually also classified into C-phycocyanin and R-phycocyanin. The former is mainly present in cyanobacteria, the latter is mainly present in red algae, and both are in cryptophyta. It is both a protein and

an excellent natural food coloring, as well as a good healthy food. Remirez, Ledon, and González (2002) studied whether phycocyanin inhibited allergic inflammatory reactions by mouse experiments *in vivo*, and showed that it inhibited the release of histamine from ovalbumin-sensitized mouse mast cells. The inhibition is generally dose-dependent, and the mechanism by which phycocyanin inhibits allergic inflammatory responses is at least largely affected by inhibiting the release of histamine from mast cells. Romay et al. (2003) evaluated the immunomodulatory function of R-phycocyanin (R-PC) using mouse bone marrow-derived dendritic cells (BMDCs). The results showed that R-PC treatment resulted in decreased endocytosis, co-stimulatory molecule expression, and increased IL-12 in mouse BMDC. Furthermore, R-PC-treated dendritic cells are capable of promoting CD41⁺ T cells stimulating ability and increasing the expression of IFN- γ in CD41⁺ T cells.

Liu et al. (2015) also found that R-phycocyanin isolated from *Porphyra haitanensis* could effectively reduce the level of IgE and histamine in mice sensitized by tropomyosin (TM). These assist in alleviating allergic symptoms and jejunal inflammation, and inhibiting the expression and releasing of IL-4 and IL-13 in peritoneal lavage fluid. R-phycocyanin attenuates TM sensitivity by blocking the polarization of Th2 cells and inhibits the release of allergic mediators from antigen-stimulated mast cells. It has the potential to be employed as a functional food ingredient in patients with food allergy.

Marine microalgae

Microalgae are considered as the producers of some highly bioactive macromolecules in marine resources (Bule et al. 2018), including carotenoids, long-chain polyunsaturated fatty acids, proteins, chlorophyll, vitamins, etc. (Kay and Barton 1991).

Recent studies have found that *Spirulina* can reduce IgE levels in serum of mice sensitized by crude shrimp extract (Yang, Lee, and Kim 1997). In addition to spirulina, several other microalgae are also effective anti-food allergic agents. *Porphyridium purpureum* and *Dunaliella salina* have significant inhibitory effects on hyaluronidase activity, which are almost identical to the anti-allergic drug disodium cromoglycate (Fujitani et al. 2001). In addition, Oral Chlorella vulgaris Water Extract (CVE) inhibits the production of IgE for casein antigens, while increasing the mRNA expression of Th1 cytokines including IFN- γ and IL-12, indicating that CVE can inhibit allergic reactions caused by casein (Hasegawa et al. 1999). Similarly, we found that *Chlorella pyrenoidosa* inhibited the production of IL-5 and IgE-dependent cytokines GM-CSF by mast cells. *In vivo*, treatment of OVA-sensitized mice with *Chlorella pyrenoidosa* significantly reduced eosinophils and neutrophil infiltration in the airways (Kralovec et al. 2005). The above studies generally indicate that microalgae have a potential effect on allergic reactions and can be used as an ingredient of a functional food or medicinal food to prevent and treat allergic diseases.

Conclusion

Recent studies have shown that marine-derived active substances play an important role in alleviating allergies by the mechanisms of inhibiting the development of Th2, enhancing the immune function of Th1 activity, inhibiting the degranulation of mast cells and basophils, the production of cytokines and the expression of Fc ϵ RI, regulating the intracellular calcium concentration, etc. Therefore, bioactive substances from the ocean can be used as functional food raw materials to prevent and reduce allergic reactions in human body. Generally speaking, the anti-allergic active ingredients from marine sources have potential beneficial value not only in food industry, but also in medicine and cosmetics industry. After all, the ocean is a treasure that humans still have at their disposal.

Discussion and future prospect

Research concentrating on allergens focuses on the detection of allergens in food and the reduction of allergens, that is, prevention and control of allergens before the occurrence of allergic reactions; When the attention is removed from the allergen, that is, after the allergic reaction occurs, allergy alleviation has become a new concern. Hypoallergenic foods and anti-allergic drugs have emerged. Since common anti-allergic drugs cannot completely eliminate food allergy symptoms and have harmful side effects, it is particularly important to develop safe and stable natural anti-allergic active substances. The ocean is the most potential resource pool on the earth. It is rich in bioactive substances and is the best source for solving the three major problems of food, resources and environment faced by human beings. From a biodiversity perspective, few people know that marine biodiversity is far more rich than terrestrial organisms. Of the 34 animal Phylum Chordata currently found, the ocean actually accounts for 33 Phylum Chordata, and 15 of them can only live in the marine environment. In contrast, only 13 of the 34 Phylum Chordata can inhabit the land (Pereira et al. 2010). This disparity shows that the ocean is the place to preserve most of the biodiversity on Earth. The United States was the first country to conduct research on marine bioactive substances. Subsequently, countries also turned to the ocean to carry out related research. Over the past few decades, more than 6,000 marine natural products have been discovered, including more than 200 new compounds with important activities and patents. Compared with the 150,000 natural products derived from terrestrial plants, more than 10,000 marine natural products have been discovered so far, so marine natural products have great potential for research and development (Sala et al., 2000). Recent studies have shown that many natural active substances in the ocean have stable anti-food allergy effects. The current research on marine anti-allergic active substances mostly focuses on marine algae, and most of the studies were carried out in the late 20th century and early 21st century. If we can fully utilize the diverse marine resources, there will be broad prospects.

Anti-food allergy drugs on the market are constantly updated to minimize their defects and ensure their safety. How to obtain more natural, safe and stable anti-allergic matrix for the development of anti-allergic drugs is the most important thing. The mechanism of anti-food allergy drugs is to inhibit the release of allergy mediators or antagonize the food allergy mediators in every link of the occurrence of allergic reactions. Marine natural active substances exert the anti-food allergy effect through multi-target and multi-level actions. Many natural active substances play an anti-food allergy role by neutralizing allergens, inhibiting the presentation of antigen-presenting cells, down-regulating the secretion of Th2 cytokines, inhibiting the production of IgE, hindering the binding of IgE and FcεRI receptors, preventing degranulation and inhibiting the release of allergic mediators. In addition, some marine natural active substances exert an anti-food allergic activity by regulating the Th1/Th2 balance (inhibiting the Th2 cells and promoting the activity of Th1 cells).

At present, industrial fish production and processing will produce a large amount of fish waste which accounts for more than 60% of the total processed fish in the global aquatic product processing industry, including fish viscera, fish head, fins, fish skin, fish scales, fish bone, minced meat, etc. The traditional treatment of fish waste is processed into animal feed or surimi and fish meal, and some factories even directly discard (Chen et al. 2016; Nges, Mbatia, and Björnsson 2012). Thus, high-valued utilization is required. In addition, studies have shown that fish oil supplementation in pregnant and lactating women can reduce the risk of infant allergies, among which omega-3-polyunsaturated fatty acids (ω -3-PUFAs) play a vital role in affecting the incidence of infant allergic diseases (Furuhjelm et al. 2009; Palmer et al. 2012; Ikemoto 2013). Fish oil is rich in the polyunsaturated N-3 fatty acids, eicosapentaenoic (EPA) and docosahexaenoic acids (DCHA). Some studies have also reported the anti-food allergic effects of essential fatty acids in plants. For example, Kunisawa et al. (2015) found that omega-3 fatty acids play a role in alleviating food allergies by converting omega-3 fatty acids into 17,18-epoxyeicosapentaenoic acid, a metabolite in the intestine. Academics found that dietary supplementation with omega-3-PUFA-rich fish oil can reduce signs of food allergy in ovalbumin-sensitized mice (de Matos et al. 2016). At an early stage, Lee et al. (1991 and 1986) had discussed and prospected the anti-allergic effect of fish oil (the effects of dietary fish oil lipids on allergic and inflammatory diseases and the prospects for modifying the allergic response by fish oil diets). Deep-sea creatures, especially fish, are rich in unsaturated fatty acids and algae are rich in carotenoids. The main problem nowadays is how to convert these wastes into treasures, and efficient use of such resources is worth exploring.

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