Anti-Allergic Activities of Natural Products from Marine Organisms

Subjects: Biochemistry & Molecular Biology

Contributor: Na Chen , Shanshan Zhang , Ansar Javeed , Cuiqin Jian , Yi Liu , Jinlyu Sun , Shandong Wu , Peng Fu , Bingnan Han

It is essential to find alternative anti-allergic agents from natural products. The special environment of high salt and pressure, low temperature, oligotrophicity, hypoxia, and limited light determines that the secondary metabolites of marine organisms have very unique traits compared with secondary metabolites of terrestrial organisms. Secondary metabolites of marine natural products possess many biological effects like anti-tumor, anti-inflammatory, anti-allergic, antiviral, antibacterial, etc.

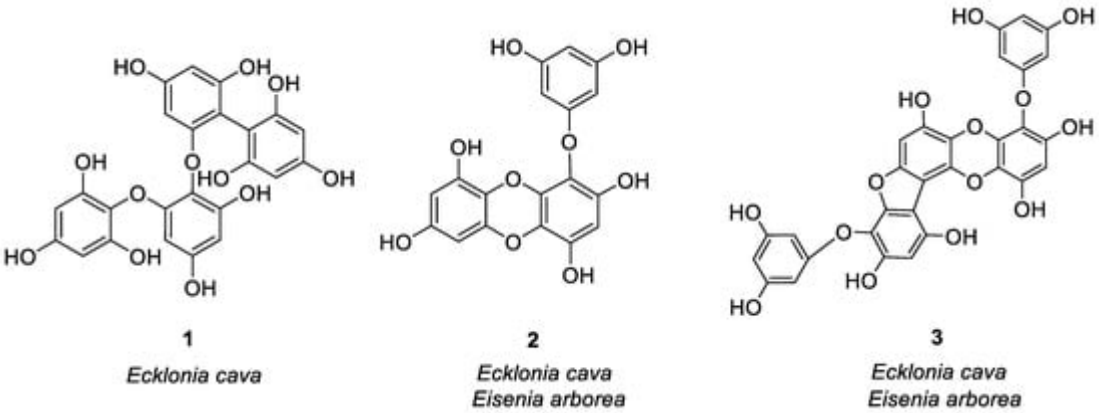
anti-allergic secondary metabolites marine organisms molecular docking

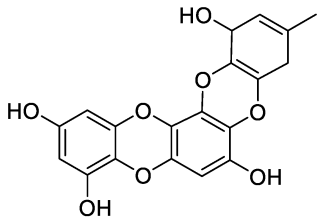
1. Marine Plants

1.1. Natural Products Derived from Marine Plants with Anti-Allergic Activity

In the study of anti-allergy, the most studied marine plants are algae, along with some mangrove plants. Major kinds of algae are red algae, green algae, and brown algae, which are mostly found in intertidal and subtidal zones [1]. Asian countries are rich in algal resources, especially China, Japan, and Korea. Since ancient times, humans have known of marine algae and are using it for different purposes. The secondary metabolites found in it are abundant, because they are rich in proteins, fatty acids, minerals and vitamins, and are often used as food. Some algal species also have great potential as cosmetics, drugs, and drug adjuvants [2], which play an important role to treat fever, cough, dermatitis, allergies, and other diseases [3]. Humans and other biological organisms consume a large amount of polyphenols, which is the largest compound group present in plants [4]. Polyphenols have a wide range of functions like antioxidant capacity, scavenging free radicals, and metal-chelating activity, and it is beneficial to human health, and can be used to treat and prevent cancer, cardiovascular disease, and other pathology [5]. In marine algae, the structure of most anti-allergic natural products is polyphenols. Three compounds were isolated from *Ecklonia cava* by Li et al. [6] which stimulated human basophilic KU812F cells with IgE and anti-IgE antibodies. At 100 μM, the relative levels of histamine released by three compounds **1, 2,** and **3** (**Figure 1**) were 23.97, 44.26 and 34.54%, respectively. Then calcium ionophore A23187 was used to mediate the degranulation of KU812F cells and RBL-2H3 cells. Three compounds at 100 μM inhibited histamine release from both cells. After flow cytometry analysis, it was proved that three compounds play an anti-allergic role by inhibiting FcεRI and IgE binding activity, and the inhibition rates were 30.58, 47.60 and 34.23%, respectively. Compounds **1** and **3** had the strongest inhibitory effect on histamine release, with IC_{50} values of 31.65 μM (RBL-2H3), 44.20 μM (KU812F), 38.87 μM (RBL-2H3), and 65.81 μM (KU812F). These compounds inhibited allergic reactions in a dose-

dependent manner. Han et al. [7] also studied the anti-allergic effect of eckol (compound **2**) separated from *Ecklonia cava* (brown algae) through BMCMC (mouse bone marrow-derived mast cells) stimulated by bovine serum albumin (BSA)/immunoglobulin E (IgE) and allergic reaction models. The results showed for the first time that the compound **2** inhibited mast cell activation by inducing degranulation and cytokine production after IgE/BSA exposure. 100 μg/mL of compound **2** remarkably decreased the release of β-hexosaminidase by inhibiting the production of Th2 cytokines, i.e., IL-5, IL-4, IL-13. It reduced FcεRI expression on the cell surface, and compound **2** binds to the active site of IgE for blocking the IgE binding to FcεRI. Two bioactive phloroglucinol derivatives DHE (compound **4**) and PFF-α (compound **5**) were isolated from *Ecklonia stolonifera* (brown algae) by Shim et al. [8], as shown in **Figure 1**. They studied the effects of these two compounds on human basophilic KU812F cells and found that compounds **4** and **5** inhibited FcεRI expression on the surface of the cell by 16.9 and 15.4% at 50 μM, respectively. At the same time, these two compounds lessened the expression of total FcεRI α chain protein and mRNA in a dose-dependent manner, and inhibited the increase of intracellular Ca^{2+} stimulated by CRA-1, thereby exerting anti-allergic effects. Vo et al. [9] studied the Fucofuroeckol-A (F-A/compound **6**, see **Figure 1**) protective effect obtained from *Ecklonia stolonifera* on UVB-induced RBL-2H3 mast cell allergic reaction. They found that 50 μM F-A inhibited the fusion of granules and plasma membrane by inhibiting the increase of calcium ion concentration in mast cells, thereby inhibiting degranulation of mast cells and reducing histamine release from mast cells (release level 31%). Sugiura et al. [10] isolated and purified six compounds **2**, **3**, **7**–**10** (**Figure 1**) from *Eisenia arborea*, and studied the effect of oral administration of these compounds compared with EGCG, which is a known natural product with anti-allergic activity [11]. Their studies have shown that these compounds exhibited anti-allergic activity by inhibiting the release of chemical mediators like leukotriene B4, prostaglandin E2, and histamine, as well as inhibiting the cyclooxygenase-2 (COX-2) mRNA expression. The inhibitory activity of **3**, **8**, and **9** was the strongest, and the anti-allergic effect was equal to or higher than EGCG. Matsui et al. [12] isolated three compounds from *Sargassum carpophyllum*, and found that compounds **11**, **12,** and **13** (**Figure 1**) inhibited the release of prostaglandin D2, tumor necrosis factor-α and β-hexosaminidase in RBL-2H3 cells stimulated by DNP-HSA, with a value of 50.7, 35.9 and 43.5 μM IC_{50} values. β-hexosaminidase release was employed as an indicator of mast cell degranulation. At 40 μM, all three compounds significantly inhibited ROS production, and compound **13** slightly reduced the level of Ca^{2+}.





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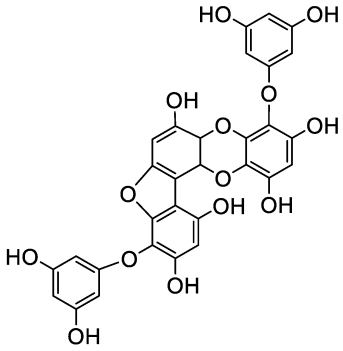
Ecklonia stolonifera



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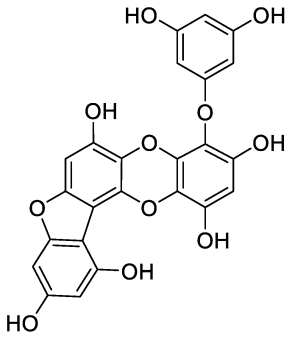
Ecklonia stolonifera



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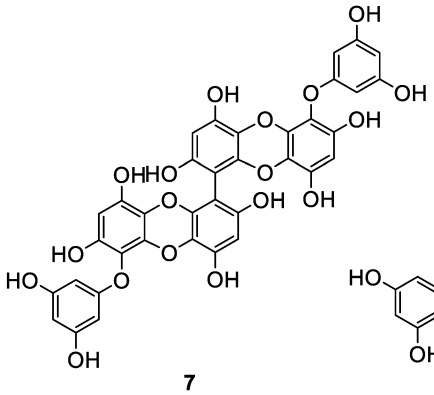
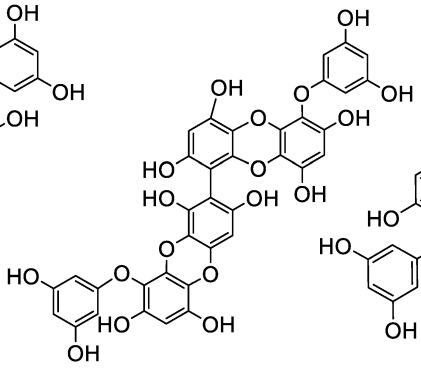
Ecklonia stolonifera



7
Eisenia arborea



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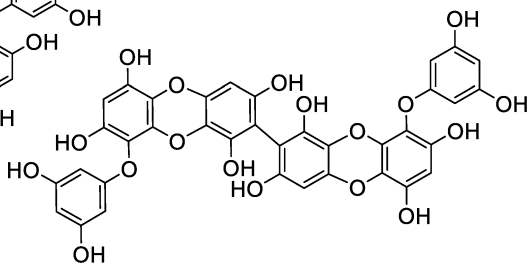
Eisenia arborea



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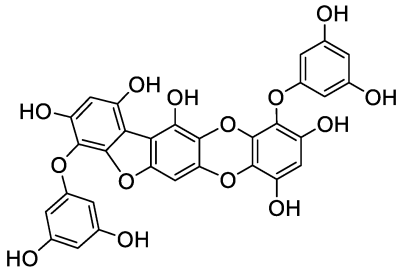
Eisenia arborea



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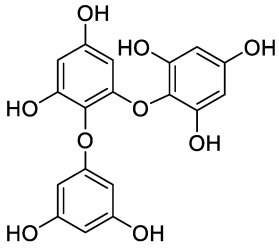
Eisenia arborea



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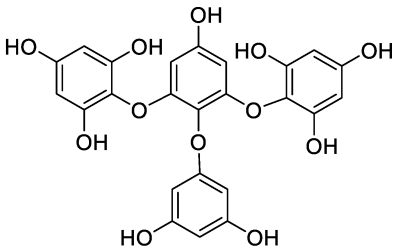
Sargassum carpophyllum



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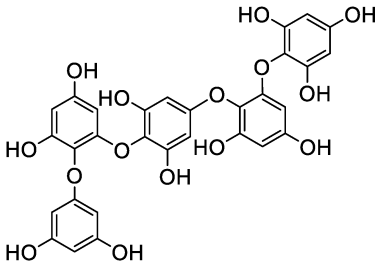
Sargassum carpophyllum



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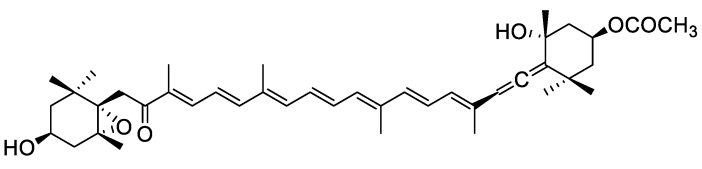
Sargassum carpophyllum



14
Symbiodinium sp

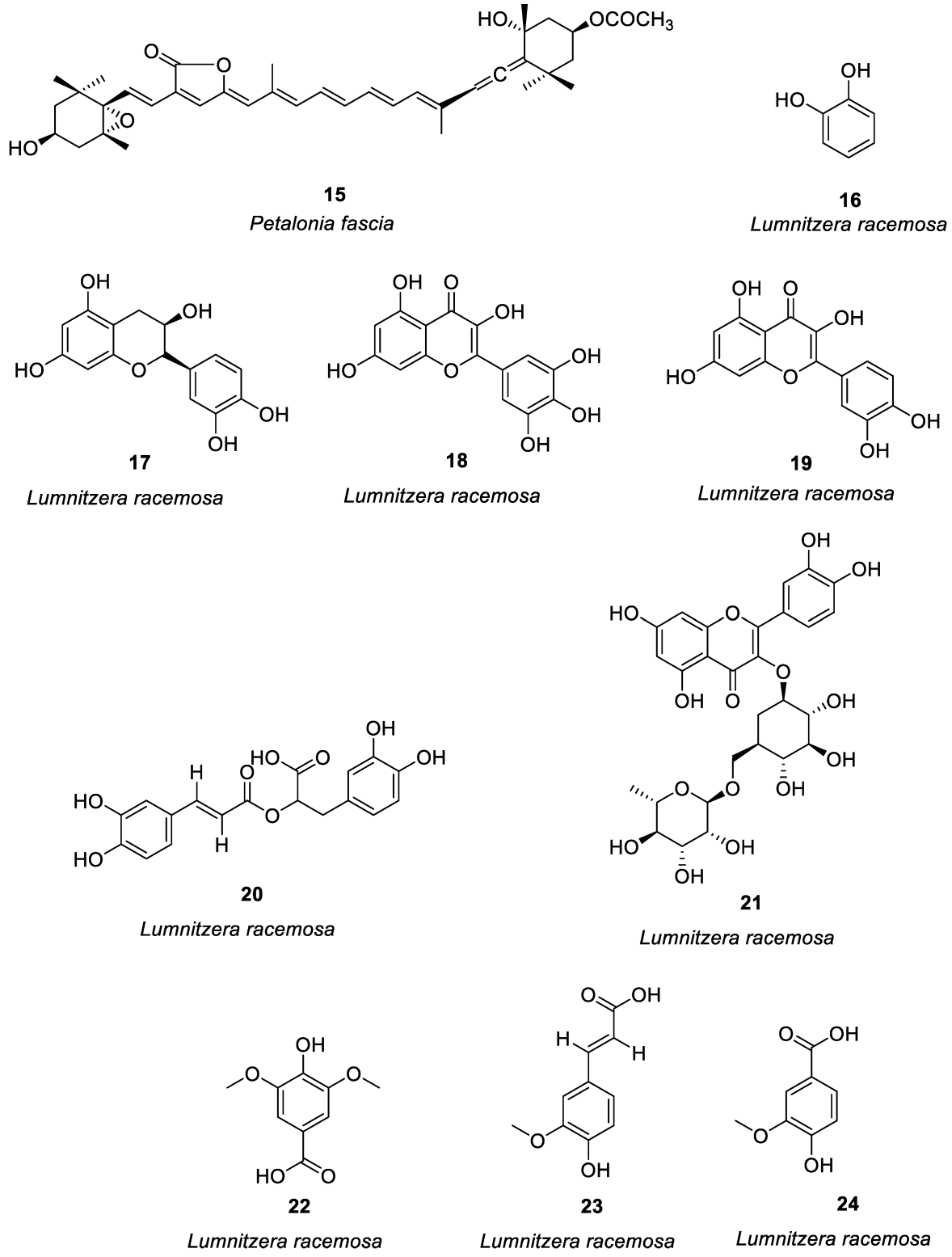


Figure 1. Structures of compounds **1**–**24**.

Other compounds of brown algae also have good anti-allergic effects. Onodera et al. [13] compared Peridinin **14** and fucoxanthin **15** (**Figure 1**) isolated from *Symbiodinium sp* and *Petalonia fascia,* respectively. They found that topical application was better, and that compound **14** better inhibited delayed-type hypersensitivity compared to

compound **15**. Compound **14** may be a potential drug for inhibiting allergic inflammation by inhibiting the migration of ear eosinophils to eotaxin and the production of eotaxin.

1.2. Crude Extracts from Marine Plants as Potential Sources with Anti-Allergic Activity

Kim et al. [14] treated ovalbumin (OVA)-sensitized mice with Ecklonia cava (EC) extracts, and found that EC extracts significantly inhibited allergic responses before the last airway OVA challenge. IL-4, IL-5, and Th2 cytokines play an imperative role in the instigation of allergic response. Han et al. [15] studied the anti-allergic effects of ethanolic extract of copper algae on passive cutaneous anaphylaxis and IgE/BSA-mediated mouse bone marrow activation of mast cells. Studies showed that the extract of copper algae (SHE) inhibited the β-hexosaminidase and histamine release, and substantially inhibited the degranulation of bone marrow mesenchymal stem cells. In addition, flow cytometry analysis showed that SHE markedly decreased the FcεRI binding to IgE and FcεRI expression on the surface of BMCMCs, and regulated the expression levels of mRNA of cytokines and chemokines in IgE/BSA-stimulated BMCMCs, thereby improving activation of mast cells stimulated by immunoglobulin E/bovine serum albumin. Herath et al. [16] studied whether *Sargassum horneri* ethanol extract (SHE) attenuated the effects of atmospheric particulate matter (PM) exposure on asthma. By lowering mRNA levels of the transcription factors STAT5 and GATA3, they discovered that copper algae blocked Th2 polarization and decreased the expression of IL-4, IL-5, IL-13, and Th2 cytokines in lung tissue homogenates of mice with asthma caused by PM. Additionally, oral administration of SHE dramatically decreased mast cell activation, serum IgE levels, and PM-aggravated Th2 and Th17 responses in asthmatic mice. Compounds with potential anti-allergic activity are present in red algae in addition to the structure and chemical characteristics of the anti-allergic natural products in brown algae, which have also been thoroughly investigated. Jung et al. [17] used a 95% ethanol extraction method to extract *Laurencia undulata* (LU) and showed that it contains an enormous quantity of polyphenols, and observed its anti-asthmatic effect on ovalbumin (OVA)-induced allergic respiratory reactions in mice. The results showed that LU administered prior to the last airway OVA challenge significantly inhibited allergic reactions. Shi et al. [18] investigated the anti-allergic effects of sulfated polysaccharide from *Porphyra haitanensis* (PHPS) administered orally on mice that were allergic to tropomyosin (TM). The findings of that experiment revealed that PHPS can stimulate the Treg/Th1 cytokines production like IL-10 and interferon-γ in the presence or absence of allergens. Han et al. [19] applied RASP (red algae sulfated polysaccharide) to effervescent tablets for anti-allergy research, and it was acquired by extraction of *Gracilaria lemaneiformis* and *Porphyra haitanensis*. As a result of RASP treatment, serum IgE levels, mast cell protease-1, and histamine were reduced. RASP treatment can reduce IL-4, significantly increases IFN-γ, and IFN-γ as Th1 cytokines, and promotes Th1 cell differentiation, thereby regulating allergic reactions caused by Th1/Th2 immune response imbalance. The natural products found in microalgae also have anti-allergic properties. Additionally, anti-allergic compounds have also been found in green algae. Raman et al. [20] observed that the crude extract of *Enteromorpha compressa* reduced the level of IgE induced by food allergens such as ovalbumin and that it enhanced immune function by decreasing plasma cell generation of IgE antibodies against food allergens. Cryptomonas, another algal species, has also been shown to have anti-allergic properties. The effect of *Polyopes affinis* ethanol extract on Th2-mediated allergen-induced airway inflammation in an asthmatic mouse model was evaluated by Lee et al. [21]. Researchers found that

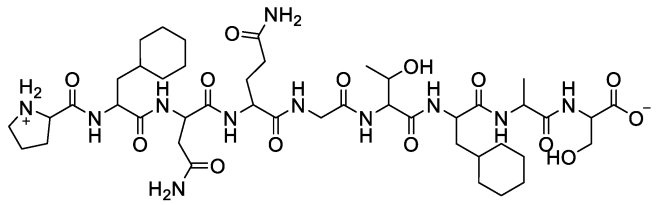
continual intraperitoneal injection of *P. affinis* ethanol extract before the last respiratory OVA challenge significantly inhibited the response and reduced ovalbumin-specific IgE by 72%.

Mangrove is a wetland woody plant community composed of evergreen trees or shrubs mainly composed of mangrove plants growing in the intertidal zone of tropical and subtropical coasts. Acharyya et al. [22] studied the anti-allergic activity of the Ethanol extract of *Lumnitzera racemosa* and the polyphenols related to this activity (**16**–**24**, see **Figure 1**). Oral administration of the ethanol extract of *L. racemosa* significantly reduced the number of sneezes, scratches, and nasal pain, as well as the number of lymphocytes, neutrophils, and eosinophils, and significantly inhibited TDI-induced allergic symptoms. (See **Table 1** for details on compounds).

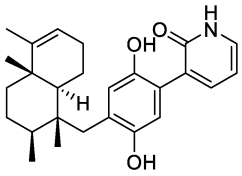
2. Marine Animals

2.1. Natural Products Derived from Marine Animals with Anti-Allergic Activity

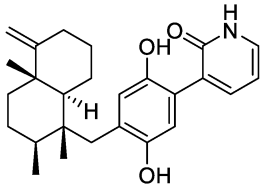
In the study of anti-allergy, marine animals mainly include sponges, mollusks, sea cucumbers, corals, etc. A variety of marine animals, including sponges, mollusks, and fish also have anti-allergic properties. The sponge was the first multicellular animal, living in the ocean 600 million years ago, with a high capacity for filtration [23]. In mollusks, sea cucumbers and abalone are the main sources of anti-allergy compounds. Ko et al. [24] investigated the passive cutaneous anaphylaxis of gastrointestinal digestive components of the intestinal digestive digest of abalone *Haliotis discus hannai* and a bioactive peptide (compound **25,** see **Figure 2**) was isolated from the gastrointestinal digestion. Histamine release could be reduced by 300μg/mL of compound **25**. Mice treated with compound **25** showed significant inhibition of the immunoglobulin E-mediated PCA response. By regulating PMA + A23187, compound **25** stimulates HMC-1 cells to produce tumor necrosis factor-α, IL-1, and IL-6 reduces the release of histamine and has anti-allergic activity.



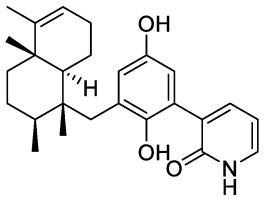
25
Haliotis discus hannai



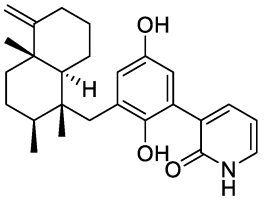
26
Sponge



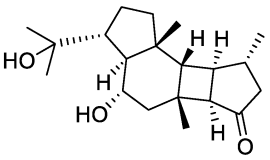
27
Sponge



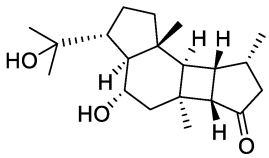
28
Sponge



29
Sponge



30
Hippospongia lachne



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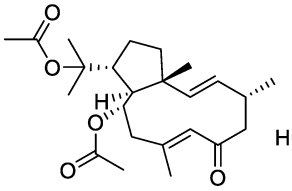
Hippospongia lachne



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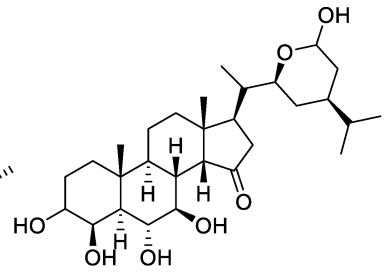
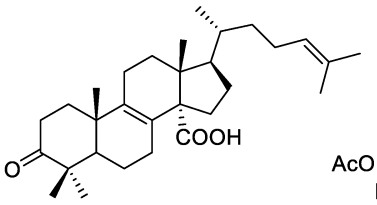
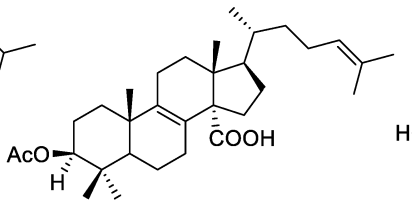
Hippospongia lachne



33
Petrosia sp



34
Penares incrustans



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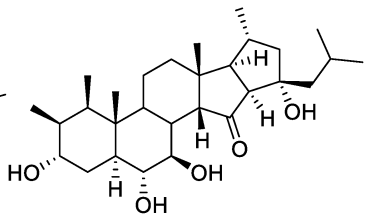
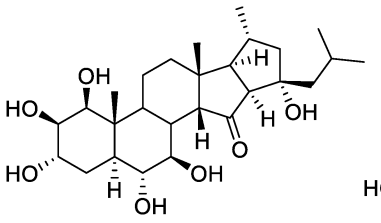
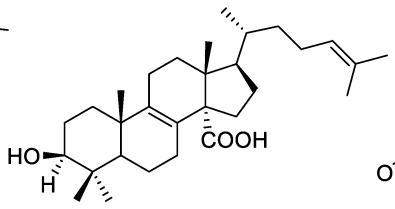
Penares incrustans



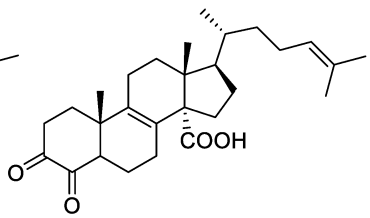
36
Xestospongia bergquistia



37
Xestospongia bergquistia



38
Penares incrustans



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Penares incrustans

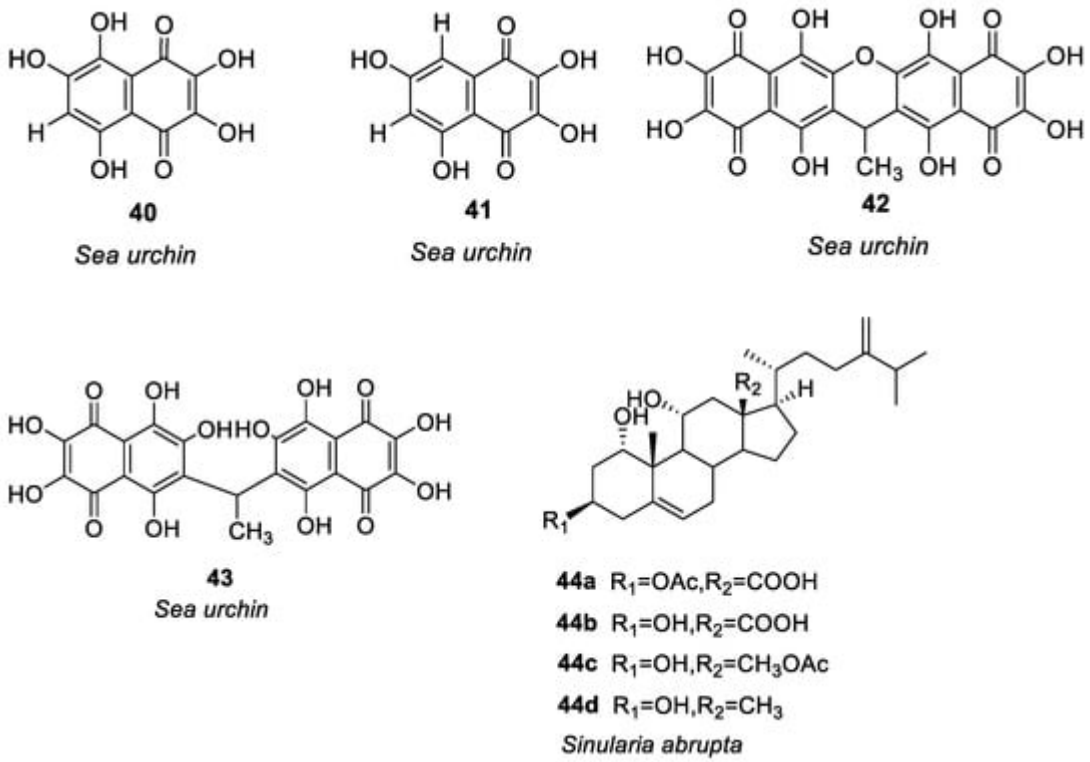

Figure 2. Structures of compounds **25**–**44**.

Jiao et al. [25] identified anti-allergic terpenoids isolated from the marine sponge *Dysidea villosa* and they found that four compounds, **26**–**29** (**Figure 2**), suppressed the release of degranulation marker β-hexosaminidase with IC_{50} values of 8.2, 10.2, 19.9 and 16.2 μM, respectively, in a dose-dependent manner. As a result of antigen stimulation, the production of LTB 4 and IL-4 in RBL-2H3 mast cells was dose-dependently inhibited. Compound **26** demonstrated the greatest anti-allergic activity out of the four compounds. In some studies it has been shown that mast cell activation is inhibited by compound **26** by inhibiting the signaling pathway of Syk/PLCγ-1, thereby inhibiting mast cell degranulation and down-regulating LTB 4 and IL-4 production. Hong et al. [26] isolated three compounds (including **30**–**32**, see **Figure 2**) from the South China Sea sponge *Hippospongia lachne* to find that they inhibited IgE-stimulated RBL-2H3 cells from releasing β-hexosaminidase. It was found that compounds **30** and **31** had higher β-aminocaproic glycosidase inhibitory activity. LTB4 production by activated RBL-2H3 cells was significantly inhibited by compounds **30** and **31** with IC_{50} values of 49.37 and 23.91 μM, respectively. Andrew et al. [27] found that the marine sponge *Petrosia sp.* contained a sterol-like compound called IZP-94005 (Compound **33** as shown in **Figure 2**). Both in vivo and in vitro allergic reactions were studied using ovalbumin-induced bronchoconstriction and smooth muscle contractions. Based on a concentration-dependent inhibition of OVA-stimulated sensitized tracheal ring response, IZP-94005 had an IC_{50} of 10 μM. A substantial lowering in histamine release was observed after the application of IZP-94005. Shoji et al. [28] isolated two new triterpenoids with 14 carboxyl groups from the Okinawan marine sponge *Penares incrustans*. Anti-IgE-induced histamine release from rat peritoneal mast cells was inhibited by compounds **34** and **35** (**Figure 2**) with IC_{50} values of 1.5 μM and 10 μM, respectively. It was found that compound **34** was 17 times more potent in nature than disodium cromoglycerate (DSCG). Takei et al. [29] characterized the Okinawan marine sponge *Xestospongia bergquistia* and isolated different terpenoids from it. Dose-dependent inhibition of the release of histamine from mast cells in male Wistar

rats was observed with compounds **36** and **37** (**Figure 2**). Release of histamine from IgE-activated mast cells was blocked by compounds **36** and **37** at 100 μM each. PI-PLC activity and inhibition of IP3 production were initiated by compound **36** in a dose-dependent manner. Aside from inhibiting calcium mobilization in intracellular calcium stores, compound **36** also inhibited calcium influx. Isolation of two terpenoids from the Okinawan marine sponge *Penares incrustans* was also performed by Takei et al. [30]. It was shown that compounds **38** and **39** (**Figure 2**) inhibited anti-IgE-induced histamine release in Wistar rats. At 100 μM, the anti-IgE-induced histamine release was inhibited at 90.7 ± 2.3%, 0.5 and 1.5 μM $IC_{50,}$ respectively. There was a dose-dependent inhibition of PLA2 (phospholipase A2) activity with both compounds. This system was able to measure the IC_{50} values for PLA2 activity at 2 and 0.1 μM, respectively. (See **Table 1** for details on compounds).

Pozharitskaya et al. [31] isolated and studied the anti-allergic effect of compounds (**40**–**43**, see **Figure 2**) of green sea urchin shell pigment. Green sea urchin shell pigment compounds had a dose-dependent inhibitory effect on histamine-induced ileum contraction in guinea pigs, ID_{50} = 1.2μg/mL. The inhibitory effect on the ocular allergic inflammation model was better than that of the reference drug olopatadine.

Most of the compounds isolated from soft corals belong to terpenoids, which mainly have cytotoxicity and anti-tumor activity, especially lactone diterpenoids, while compounds with anti-allergic activity account for a minority [32]. Shoji et al. [33] isolated four compounds (**44a**–**44d**, see **Figure 2**) from the soft coral *Sinularia abrupta*. Compounds **44a**–**44d** inhibited anti-IgE-induced histamine release from rat peritoneal mast cells in a dose-dependent manner. The IC_{50} values of **44a**–**44d** were 0.04, 0.6, 1.5, and 0.2 μM, respectively. It is 6500 times more potent than the well-known anti-allergic drug sodium cromoglycate (IC_{50} = 262 μM).

2.2. Crude Extracts from Marine Animals as Potential Sources with Anti-Allergic Activity

A research study by Kim et al. [34] examined the ability of oral administration of LMW-AV (low molecular weight peptides) acquired from gastrointestinal digestion of Abalone viscera (AV) to treat (AD) atopic dermatitis in a dermatitis-induced model stimulated with Dermatophagoides farinae. In AD-like lesions, LMW-AV inhibited the expression of chemokines and cytokines related to Th2, and it inhibited serum IgE levels. Eosinophils were decreased as a result of oral LMW-AV treatment, skin thickness was reduced, mast cell infiltration into the epidermis was inhibited, and skin edema was reduced.

Lee et al. [35] investigated the anti-allergic activity of sea cucumber and demonstrated that the liquid salting-out extract of sea cucumber activated and recruited regulatory T and Treg cells that improved allergic airway inflammation. Moreover, sea cucumber extract rich in palmitoleic acid inhibited IgE better than extracts poor in palmitoleic acid, whereas palmitoleic acid lowers serum total immunoglobulin E (IgE) concentrations.

Fish have a rich diversity due to their complex living environment. There is a variety of biological activities associated with different parts of fish. Willemsen [36] found that fish oil has an effect on decreasing allergic symptoms when high n-3LCPUFA intake is coupled with low n-6PUFA intake, whereas TH2 and TH1 reactions are

reduced by N-3LCPUFA (fish oil), Treg frequency increases, and IgE level is reduced, which indicates that this oil has the potential for anti-allergic activity. Aryani et al. [37] examined the anti-allergic properties of charcoal from the inedible part of *Channa pleurophthalmus Blkr*, (Kerandang fish), and anti-hyaluronidase activity was determined by anti-hyaluronidase test. Based on the results, caudal fin charcoal extract exhibited the highest inhibitory effect and pectoral fin charcoal extract exhibited the lowest inhibitory effect. With four mg/mL, ethyl acetate extract concentration of caudal fin charcoal showed the greatest inhibitory effect on hyaluronidase. A potential anti-allergic drug can be developed from its non-edible parts.

3. Marine Microorganisms

Natural Products Derived from Marine Microorganisms with Anti-Allergic Activity

Harunari et al. [38] studied the activity of Hyaluromycin **45** (**Figure 3**), a new member of the rubromycin family isolated from marine-derived *Streptomyces* sp., which is composed of γ-rubromycin core structure with 2-amino-3-hydroxycyclopent-2-enone (C5N) unit as amide substituent of the carboxyl group. The enzyme hyaluromycin imparts a major role in allergic responses and in mast cell degranulation. Researchers found that hyaluromycin had a 25-fold higher inhibitory effect against hyaluronidase than the plant terpenoid glycyrrhizic acid with 14 μM IC_{50} value, therefore providing new insights in the development of anti-allergic drugs. Niu et al. [39] isolated a polyketone compound **46** (**Figure 3**) from a deep-sea-derived fungus *Graphostroma sp.* and tested its biological activity in IgE-mediated rat basophilic leukemia-2H3 cells. Compound **46** can also be isolated from the fermentation broth of Streptomyces sp. The findings showed that compound **46** significantly inhibited histamine release and degranulation in RBL-2H3 cells, with a 13.7 μM IC_{50} value. It was found that the methyl group present at C-3, the C-6 hydroxyl group, and the methoxy group at C-7 were essential for anti-food allergy activity. They also isolated eight tetracyclic diterpenoids from the deep-sea fungus *Botryotinia fuckeliana* in the western *Pacific* [40]. Compound **47** (**Figure 3**) was found with a novel 6/6/5/5 tetracyclic carbon skeleton. Compared with loratadine (positive control and IC_{50} = 0.1 mM), compound **47** showed anti-allergic effects in RBL-2H3 cells (IC_{50} = 0.2 mM).

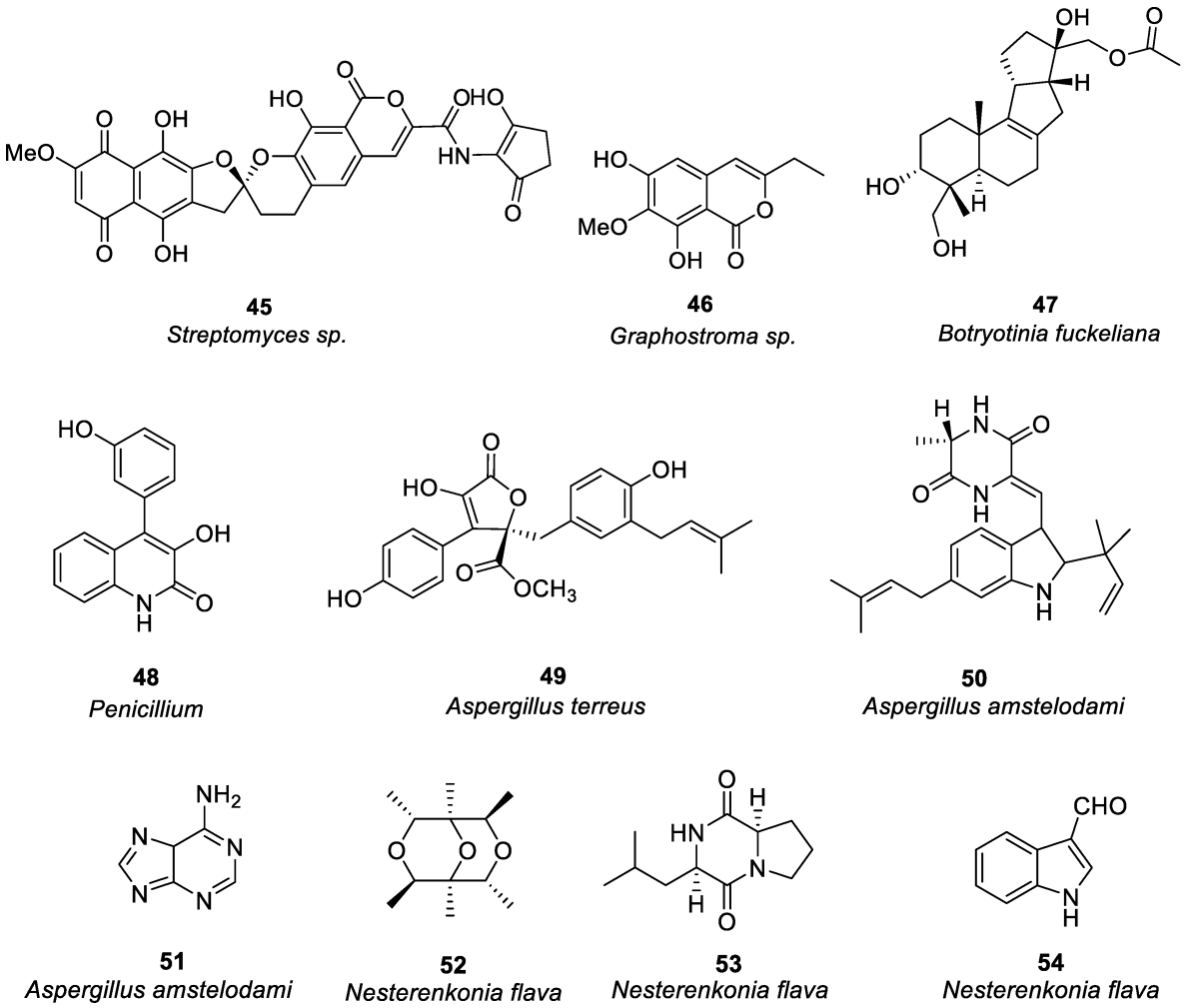

Figure 3. Structures of compounds **45**–**54**.

Shu et al. [41] isolated an alkaloid **48** (**Figure 3**) from *Penicillium*, i.e., deep-sea fungus. Their study revealed that compound **48** significantly reduced β-hexose release and histamine in RBL-2H3 cells induced by ovalbumin (OVA) in a dose-dependent manner (IC_{50} = 6.67 μg/ml), and it had no cytotoxic effect on RBL-2H3. There was a dose-dependent decrease in mast cell protease-1, histamine, immunoglobulin E, and tumor necrosis factor-α levels, and an increase in IL-10 production. The increase of calcium ions is the key process of MC secretory granule translocation. Compound **48** significantly inhibited the accumulation of calcium ions in RBL-2H3 cells in a dose-dependent manner, thereby blocking the activation of macrophages and inhibiting mast cell degranulation.

Uras et al. [42] purified butyrolactone I (compound **49,** see **Figure 3**) from *Aspergillus terreus*. Inhibition of calcium ion carrier A23187 and antigen-induced degranulation is manifested by its significant anti-allergic activity, with 39.7 and 41.6 μM, IC_{50} values. Elsbaey et al. [43] isolated two compounds (**50**, **51,** see **Figure 3**) from the white bean culture of the endophytic fungus *Aspergillus amstelodami*. Anti-allergic activity of quercetin was determined in 100 μM RBL-2H3. Both compounds significantly reduced the release of β-hexosaminidase and had no significant cytotoxicity to cells. These compounds may have some anti-allergic effects, although they have a lower efficacy than quercetin. Xie et al. [44] isolated a new cyclic ether compound nesterenkoniane (**52**) and 12 known compounds from *Nesterenkonia flava*, an actinomycete originating from the deep sea (see **Figure 3**). By employing IgE-

mediated rat mast cell RBL-2H3 as a model, cyclo-(D)-proline-(D)-leucine (compound **53,** see **Figure 3**) and indole-3-carbaldehyde (compound **54,** see **Figure 3**) showed significant anti-allergic activity with 69.95 and 57.12 μg/mL IC_{50} values, respectively. (See **Table 1** for details on compounds).

Table 1. Research Overview of Marine Natural Products with Anti-allergy Activities.

Source of Compounds	The Sources of Isolation	Number of Compounds	Range of Dosage	Structure Type	Test System	Targets/Pathway/Process Mechanism	Reference
Marine Plants	*Ecklonia cava*	Compound **1**–**3**	100 μM	Polyphenol	Human basophilic KU812F cells and RBL-2H3 cells	FcεRI and IgE binding activity, histamine release, degranulation of cell	[6]
	Ecklonia stolonifera	Compound **4**–**5**	50 μM	Polyphenol	Human basophilic KU812F cells	The expression of FcεRI, intracellular Ca^{2+}	[8]
	Ecklonia stolonifera Okamura	Compound **6**	50 μM	Polyphenol	RBL-2H3 mast cell	Ca^{2+} concentration, mast cell degranulation, histamine release	[9]
	Eisenia arborea	Compound **2**,**3**,**7**–**10**	10–200 μM	Polyphenol	DNP-BSA-induced RBL-2H3 mast cell	Release of histamine, leukotriene B4 and prostaglandin E2, H_1 receptor	[10]
	Sargassum carpophyllum	Compound **11**–**13**	40 μM	Polyphenol	DNP-HSA-induced RBL-2H3 cells	Release of β-hexosaminidase, mast cell degranulation	[12]
	Symbiodinium sp., *Petalonia fascia*	Compound **14**–**15**	50 μg	Carotenoid	BALB/cAJc1 mice	Migration of eosinophils	[13]
	Lumnitzera racemosa	Compound **16**–**24**	/	(Ethanol extract)	Toluene 2,4-diisocyanate (TDI)-induced allergic model mice	IgE	[22]
Marine Animals	*Haliotis discus hannai*	Compound **25**	50 mg/kg	Polypeptide	Passive cutaneous anaphylaxis in mice	Histamine release, FcεRI and IgE binding activity	[24]

Source of Compounds	The Sources of Isolation	Number of Compounds	Range of Dosage	Structure Type	Test System	Targets/Pathway/Process Mechanism	Reference
	Sponge	Compound **26**–**29**	250 μg/mL	Terpenoids	RBL-2H3 mast cells	β-hexosaminidase, Syk/PLCγ-1, mast cell degranulation	[25]
	Hippospongia lachne	Compound **30**–**32**	200 μg/mL	(Ethanol extract)	IgE-stimulated RBL-2H3 cells	β-hexosaminidase	[26]
	Petrosia sp.	Compound **33**	3–30 μM	Sterol	OVA-induced mice	Histamine release levels	[27]
	Penares incrustans	Compound **34**–**35**	0–10 μM	Triterpenoids	Anti-IgE-induced mast cells	Histamine release	[28]
	Xestospongia bergquistia, Penares incrustans	Compound **36**–**39**	100 μM	Terpenoids	Anti-IgE-induced male Wistar rats' mast cells	IP3 production, Histamine release, intracellular Ca2+, PLA2	[29][30]
	Green sea urchin	Compound **40**–**43**	1.2 μg/mL	Polyhydroxy-1,4-naphthoquinone	Histamine-induced guinea pigs	β-hexosaminidase	[31]
	Sinularia abrupta	Compound **44**	0.04–1.5 μM	Polyhydroxysteroid	Anti-IgE-induced mice	Mast cell, histamine release	[33]
Marine Microorganisms	*Streptomyces* sp.	Compound **45**	/	Macrolide	/	Mast cell degranulation, hyaluronidase	[38]
	Graphostroma sp. Botryotinia fuckeliana	Compound **46**–**47**	0–200 μM	Tetracyclic diterpenoids	RBL-2H3 cells	Histamine release, mast cell degranulation	[39][40]
	Penicillium	Compound **48**	20 mg/kg	Quinoline alkaloid	OVA-induced RBL-2H3 cells	β-hexose and histamine, mast cell degranulation, IgE	[41]
	Aspergillus terreus	Compound **49**	100 μM	Hemiterpenes	RBL-2H3 cells	β-hexosaminidase, IgE	[42]
	Aspergillus	Compound	100	β-lactams,	RBL-2H3	β-hexosaminidase	[43]

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Source of Compounds	The Sources of Isolation	Number of Compounds	Range of Dosage	Structure Type	Test System	Targets/Pathway/Process Mechanism	Reference
	amstelodami	**50**–**51**	μM	adenine	cells		
	Nesterenkonia flava	Compound **52**–**54**	1.0–80.0 μg/mL	Cycloethers, diketopiperazine, alkaloid	RBL-2H3 cells	IgE, β-hexosaminidase	[44]

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