

Pharmaceutical Properties of Marine Polyphenols: An Overview

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ABSTRACT

Natural products are non-drug materials that have applied for prevention or treatment of health problem. The use of natural products as pharmaceutical ingredients has got much attention by consumers nowadays. Among them, marine organisms are currently considered as a huge source for the discovery of pharmaceutical agents. During the last decades, numerous novel agents have been achieved from marine organisms and many of them have potential application in pharmaceutical industry. Notably, marine algae are known to be one of the most important producers of variety of chemically active metabolites. Especially, phlorotannins, a polyphenol from brown algae, have been revealed to possess numerous biological activities such as UV-protective, anti-oxidant, anti-viral, anti-allergic, anti-cancer, anti-inflammatory, anti-diabetes, and anti-obesity activities. Therefore, phlorotannins are promising agents for development of pharmaceutical products. This contribution focuses on phlorotannins from brown algae and presents potential application in pharmaceutical field due to its biological activities and health benefit effects.

Keywords: Natural product, Pharmaceutical, Phlorotannins, Algae, Bioactivity.

INTRODUCTION

The marine environment represents approximately half of the global biodiversity. It is a rich source of structurally diverse and biologically active metabolites, which are important for the discovery of potential therapeutic agents^{1, 2}. During the last decades, marine organisms have received much attention in screening marine natural products for their biomedical and pharmaceutical potentials³⁻⁵. Various marine organisms such as algae, tunicates, sponges, soft

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corals, bryozoans, sea slugs, mollusks, echinoderms, fishes, microorganisms, etc. have been subjected for isolation of numerous novel compounds. Consequently, numerous active agents such as lipid, protein, peptide, amino acid, neurotoxins, polysaccharides, chlorophyll, carotenoids, vitamins, minerals, and unique pigments have been discovered. Many of these substances have been demonstrated to possess interesting biological activities⁶⁻¹⁴. Notably, marine algae are known to be one of the most important producers of biomass in the marine environment. Algae are very simple chlorophyll-containing organisms composed of one cell or grouped together in colonies or as organisms with many cells¹⁵. Therefore, they vary greatly in size from unicellular of 3–10 µm to giant kelps up to 70-meter-long. Algae are identified as the microalgae which are found in both benthic and littoral habitats and also throughout the ocean waters as phytoplankton and the macroalgae (seaweeds) which occupy the littoral zone. Phytoplankton comprises diatoms, dinoflagellates, green and yellow–brown flagellates, and blue–green algae while seaweeds are classified into green algae, brown algae, and red algae. Marine algae are known to be a good source of healthy food due to their low content in lipids, high concentration in polysaccharides, natural richness in minerals, polyunsaturated fatty acids and vitamins. Especially, seaweeds are able to produce a great variety of secondary metabolites characterized by a broad spectrum of biological activities such as anti-coagulation, anti-virus, anti-oxidant, anti-allergy, anti-cancer, anti-inflammation, anti-obesity, anti-diabetes, anti-hypertension, neuroprotection, and immunomodulation¹⁶⁻¹⁹. Therefore, marine algae are believed to be a promising source to provide not only novel biologically active substances for the development of pharmaceuticals but also essential compounds for human nutrition²⁰.

The Phaeophyceae (brown algae) is a large group of marine multicellular algae, including various seaweeds. They play an important role in marine environments, both as food and for the habitats they form. Although the division Phaeophyta consists of 13 orders according to the classification of Bold and Wynne¹⁵, only three orders namely *Laminariales*, *Fucales*, and *Dictyotales* have been extensively researched for their phytochemicals. The most studied species of these orders are *Laminaria*, *Ecklonia*, *Undaria*, *Himantalia*, *Sargassum*, and *Dictyota*. Brown seaweeds are rich in polysaccharide, polyphloroglucinol phenolic compounds, and other secondary metabolites such as terpenes, carotenoids, and oxylipins²⁰. Notably, marine brown algae accumulate a variety of phloroglucinol-based polyphenols, as phlorotannins. These phlorotannins consist of phloroglucinol units linked to each other in various ways, and are of wide occurrence among marine brown algae^{21, 22}. Among marine brown algae,

Ecklonia cava, *Ecklonia stolonifera*, *Ecklonia kurome*, *Eisenia bicyclis*, *Ishige okamurae*, *Sargassum thunbergii*, *Hizikia fusiformis*, *Undaria pinnatifida*, and *Laminaria japonica* have been reported for phlorotannins with health beneficial biological activities²².

PHLOROTANNINS

Sources and distribution

Phlorotannins have only been found to exist within brown algae and may constitute up to 15% of the dry weight of brown algae²³. The concentration of phlorotannins is highly variable among different brown seaweeds as well as among different geographical areas. The fucoid species from the Atlantic and the temperate Pacific contain higher concentration of phlorotannins as compared to those obtained from the tropical Pacific²⁴. It was found that phlorotannins have mostly focused on Fucoaceae (*Ascophyllum nodosum* and *Fucus vesiculosus*), Sargassaceae (*Sargassum spinuligerum* and *Carpophyllum angustifolium*), and Cystoseiraceae (*Cystophora retroflexa* and *C. torulosa*) with concentrations ranging from 20 to 250 mg/g dry matter²⁵⁻²⁹. They tend to be concentrated within the outer cortical layers, physode, and the mitotic meristematic and meiotic sporogenous tissues³⁰. In addition, Laminariaceae brown algae, such as *Eisenia bicyclis*, *Ecklonia cava*, *Ecklonia kurome* were also found to contain a significant amount of phlorotannins^{31, 32}.

Structural diversity and classification

Phlorotannins are formed by the polymerization of phloroglucinol (1,3,5-trihydroxybenzene) monomer units. They are highly hydrophilic components with a wide range of molecular sizes ranging between 126 Da and 650 kDa. The monomeric units are linked through aryl-aryl bonds and diaryl ether bonds forming different subgroups of phlorotannins³³. Phlorotannins can be grouped according to the criteria of interphloroglucinol linkages into three primary types including fucols, phlorethols, and fucophlorethols³⁴. Fucols is formed by only phenyl linkages, while phlorethols is formed by only aryloether bonds and fucophlorethols is formed by both aryloether and phenyl linkages³⁵. The structural diversity of phlorotannins increases by adding the number of phloroglucinol units. Each of the primary groups can be grouped into linear or branched phlorotannins. In fucols, the interphloroglucinol links at meta-relative position construct of the linear phlorotannin such as tetrafucol-A and the branched phlorotannin such as tetrafucol-B, which were isolated from *Fucus vesiculosus*^{36, 37}. Moreover, longer oligomers of phlorotannin such as pentafucols and heptafucols were purified from *Scytothamnus australis*³³ and *Analipus japoni-*

cas³⁸. The linear phlorethols such as triphlorethol C and tetraphlorethols A and B were isolated from *Laminaria ochroleuca*³⁹. The branched phlorethols include tetraphlorethol C from *Ecklonia maxima*⁴⁰, pentaphlorethol B and hexaphlorethol A from *Cystophora retroflexa*²⁷. Furthermore, an additional hydroxyl group on the terminal monomer unit forms other structural motifs of phlorethols such as bifuhalol, trifuhalol A, and trifuhalol B^{41, 42}. The isofuhalols such as isotrifuhalol has an extension unit that bind between meta-oriented phloroglucinol units and it bears the additional hydroxyl group⁴³. Some fuhalols with more than one additional hydroxyl group have been called hydroxyfuhalols, such as hydroxytrifuhalol B⁴⁴. In addition, another subgroup of phlorethols, the eckols, includes a 1,4-dibenzodioxin system, such as the trimers eckol and dioxinodehydroeckol⁴⁰, the tetramers 2-phloroeckol and 7-phloroeckol⁴⁵⁻⁴⁷. In fucophlorethols, the combinations of C-C and C-O-C linkages allow the formation of various compounds in linear, branched and heterocyclic fashions. The linear fucophlorethols is fucodiphlorethol-B⁴⁸, meanwhile the branched fucophlorethols is bisfucotriphlorethol A²⁵, and heterocyclic fucophlorethols is phlorofucofuroeckol A⁴⁹.

Biosynthesis of phlorotannins

Phlorotannins are biosynthesized via the acetate-malonate pathway, also known as the polyketide pathway, in a process which may involve a polyketide synthase-type enzyme complex⁵⁰. However, the exact biosynthetic pathway for phlorotannins is unknown up to now. Therefore, methodologies that monitor phlorotannin synthesis at the genetic or enzymatic levels could be useful to reveal some of the uncertainties regarding phlorotannin biosynthesis⁵¹. Firstly, two molecules of acetyl co-enzyme A are converted into malonyl co-enzyme A through the addition of carbon dioxide. This addition changes the acetyl methyl group into a highly reactive methylene. Secondly, the process of polymerization is assisted to occur with the low required energy. During further synthesis steps, the carbon dioxide, which was added as an activator, is lost. Thirdly, a polyketide chain consisting of an acid moiety is formed, and the co-enzyme is lost. The polyketide chain is transformed by intermolecular ring closure and elimination of water to produce hexacyclic ring systems. Triketide, the cyclization product, is not stable and thus undergoes transformation into the thermodynamically more stable aromatic form, phloroglucinol, consisting of three phenolic hydroxyl groups⁵². The polymerization of phloroglucinol in different ways results in formation of various phlorotannins.

Physiological properties

Phlorotannins are found in physodes, which contribute to the development of the cell wall of brown algae⁵³. It has suggested that phlorotannins are likely to be integral structural components of brown-algal cell walls⁵⁴. They are bound to the cell wall during maturation of the plant⁵⁵. Phenolic compounds are bound with four major types of bonds including hydrophobic, hydrogen, ionic, and covalent bond to increase the strength⁵⁶. The cell wall (alginic acid) and phlorotannins are linked via covalent bonds including the ester bond and the hemiacetal bond, thus requiring strong conditions to degrade. Moreover, phlorotannins have a putative role in brown algal reproduction due to exposing on the surface of the recently fertilized zygotes where they may prevent multiple fertilizations by inhibiting spermatozoid movement⁵³.

A characteristic of phlorotannins is their plasticity to a variety of environmental factors including nutrient environment⁵⁷, light⁵⁸, depth⁵⁹, salinity⁶⁰, grazing⁶¹ or other mechanical wounding⁶². Such plasticity may represent inducible defense against herbivory²³. Suggestions for other adaptive roles for phlorotannins include protection against ultraviolet radiation⁶³ or function as anti-fouling substances⁶⁴. The suggested defensive role of phlorotannins is due to deterring feeding by herbivores⁶⁵ and decreasing their assimilation efficiency by binding with proteins in the gut^{66, 67}.

PHARMACEUTICAL PROPERTIES OF PHLOROTANNINS

Antioxidant and UV-protective activities

The oxidants such as superoxide anion radicals, hydroxyl radical species, and hydrogen peroxide are often generated by biological oxidation reactions of exogenous factors⁶⁸. It is well-known that oxidants are involved in signal transduction and gene activation and can contribute to host cell and organ damage⁶⁹. Therefore, scavenging of oxidant is considered to be important to control various diseases. Interestingly, phlorotannins from marine brown algae have been evidenced to be effective to scavenge oxidants in non-cellular and cellular systems. According to Ahn and colleagues, the antioxidant activities of three phlorotannins including phloroglucinol, eckol and dieckol purified from *Ecklonia cava* collected in Jeju Island have been investigated⁷⁰. It reported that all the phlorotannins have the potential DPPH, alkyl, hydroxyl and superoxide radical scavenging activities. Eckol exhibit the most strong antioxidant activity via scavenging 93% of DPPH. Moreover, these phlorotannins were effective to protect DNA against H₂O₂-induced damage. In the same trend, Kang and colleagues have also investigated the cytoprotective effect of eckol from

E. cava against oxidative stress induced cell damage in Chinese hamster lung fibroblast (V79-4) cells⁷¹. Eckol was effective to reduce H₂O₂-induced cell death in V79-4 cells, inhibit radiation-induced cell damage, and scavenge intracellular ROS production. Moreover, eckol was able to increase the activity of catalase and its protein expression via increasing phosphorylation of extracellular signal-regulated kinase and activity of nuclear factor κB. In another study of Kang and colleagues, triphlorethol-A from *E. cava* was found to reduce intracellular hydrogen peroxide generated by gamma-ray radiation, thus protecting against radiation-induced membrane lipid peroxidation, cellular DNA damage, and cell death⁷². Furthermore, triphlorethol-A augments cellular antioxidant defense capacity through induction of HO-1 expression via ERK-Nrf2-ARE signaling pathway, thereby protecting cells from oxidative stress⁷³. Notably, Li and colleagues have isolated several phlorotannins from *E. cava* such as phloroglucinol, eckol, fucodiphloroethol G, phlorofucofuroeckol A, dieckol, and 6,6'-bieckol. All phlorotannins were found to possess antioxidant properties via scavenging free radicals, protecting membrane protein from oxidant-induced damage, enhancing cellular glutathione level in RAW264.7 cell line⁷⁴. Likewise, several phlorotannins including phloroglucinol, eckol, dieckol, eckstolonol and triphloroethol A from *E. cava* were investigated for their activity against AAPH-induced oxidative stress toxicity in zebrafish embryos⁷⁵. All phlorotannins were able to scavenge intracellular ROS, prevent lipid peroxidation and reduce AAPH-induced cell death in zebrafish embryos. In an *in vivo* study, the role of eckol from *E. cava* as a radioprotective agent against the gamma ray-induced damage has been investigated by Park and colleagues⁷⁶. It has been determined that eckol significantly decreased the mortality of lethally irradiated mice via improving the hematopoietic recovery, repairing the damaged DNA in immune cells and enhancing their proliferation. Therefore, eckol is considered as a potential candidate for adjuvant therapy of radiation-exposed cancer patients. Recently, the antioxidant properties of phlorotannins from brown seaweed *Cystoseira trinodis* and *Carpophyllum flexuosum* was investigated⁷⁷⁻⁷⁸. It indicated that the antioxidant activities of these seaweed were due to phlorotannins content and structure.

UV radiation has a strong oxidative component, and photo-oxidative stress has been directly linked to skin photo-damage and associated with abnormal cutaneous reactions such as epidermal hyperplasia, accelerated breakdown of collagen, and inflammatory responses. Herein, dieckol from *E. cava* has been found to be able to inhibit melanogenesis and protect against photo-oxidative stress induced by UV-B radiation⁷⁹. The inhibitory activity on melanogenesis was evidenced via suppression of tyrosinase and melanin synthesis. Meanwhi-

le, protective activity was observed via scavenging intracellular ROS, preventing DNA damage, and increasing cell viability. Additionally, Fucofuroeckol-A from *E. stolonifera* was also found as protective agent against UVB-induced allergic reaction in RBL-2H3 mast cells⁸⁰. It was revealed that F-A significantly suppress mast cell degranulation via decreasing histamine release as well as intracellular Ca^{2+} elevation induce by UVB. Notably, the protective activity of F-A against mast cell degranulation was found due to scavenging ROS production. According to Klervi and colleagues, the ethyl acetate fraction of brown macroalga (*Halidrys siliquosa*) appeared to be a broad-spectrum UV-A absorber⁸¹. This activity was found due to the present of four phenolic compounds including trifluhalols, tetrafluhalols, diphlorethols, and triphlorethols. These results indicated that phlorotannins from brown algae have potential protective effects against UV radiation, which might be applied in cosmeceutical industries.

Antimicrobial activity

Infectious diseases caused by bacteria and fungi are still a major threat to public health, despite the tremendous progress in human medicine. Increasing resistance of clinically important bacteria to existing antibiotics is a major problem throughout the world⁸². The discovery of novel antimicrobial compounds for clinical application is necessary to check the global crisis of antibiotic resistance. In this regard, phlorotannins from brown algae have been found to possess antimicrobial effect against food-borne pathogenic bacteria, antibiotic resistance bacteria, and pathogenic fungi. According to Nagayama and colleagues, the oral administration of phlorotannins from *E. kurome* on mice results in effective inhibition against methicillin-resistant *Staphylococcus aureus* (MRSA). The minimum bactericidal concentrations (MBCs) of eckol, phlorofucofuroeckol A, dieckol, and 8,8'-bieckol against *Campylobacter jejuni* were 0.08, 0.08, 0.03, and 0.03 $\mu\text{mol/ml}$, respectively. At twice the MBCs, all *Vibrio parahaemolyticus* were killed within 0.5-2 h, while catechins showed little bactericidal activity within 4 h⁸³. Furthermore, Lee and collaborators have determined that dieckol from *E. stolonifera* exhibited antibacterial activity against methicillin-susceptible *S. aureus* (MSSA) and MRSA in a range of minimum inhibitory concentrations (MICs) of 32 to 64 $\mu\text{g/ml}$ ⁸⁴. The MICs of ampicillin against two standard strains of MRSA were dramatically reduced from 512 to 0.5 $\mu\text{g/ml}$ in combination with 1/4 MIC of dieckol (16 $\mu\text{g/ml}$). Likewise, Phlorofucofuroeckol-A from *E. bicyclis* were also showed anti-MRSA activity with MIC of 32 $\mu\text{g/ml}$ and synergistic action against MRSA in combination with β -lactam antibiotics ampicillin, penicillin, and oxacillin⁸⁵.

Thereby, phlorotannins- β -lactam antibiotics combinations exert a synergistic effect against MRSA, indicating the promising treatment of MRSA infections. In addition, it has shown that phlorofucofuroeckol-A from *E. cava* and *E. bicyclis* exhibited effective inhibition against *Propionibacterium acnes*, which may be useful as natural additives in anti-acne cosmetic products^{86, 87}. Although the relationship between the structure and anti-bacterial activity of the phlorotannins is limited, their inhibitory activity may be suggested to depend on the degree of polymerization of phlorotannin derivatives.

Besides, the purified phlorotannins extracts from three brown seaweeds including *Cystoseira nodicaulis*, *C. usneoides*, and *Fucus spiralis* displayed their antifungal activity against human pathogenic yeast and filamentous fungi⁸⁸. It was revealed that *C. albicans* ATCC 10231 was the most susceptible among yeast, while *Epidermophyton floccosum* and *Trichophyton rubrum* were the most susceptible among dermatophytes. It was found that *C. nodicaulis* and *C. usneoides* seem to act by affecting the ergosterol composition of the cell membrane of yeast and dermatophyte, respectively. Meanwhile, *F. spiralis* influenced the dermatophyte cell wall composition by reducing the levels of chitin. Moreover, phlorotannins from *F. spiralis* inhibited the dimorphic transition of *Candida albicans*, leading to the formation of pseudohyphae with diminished capacity to adhere to epithelial cells. On the other hand, the potential fungicidal activity of dieckol from *E. cava* was also found due to inhibition of *Trichophyton rubrum* associated with dermatophytic nail infections in human⁸⁹.

Anti-HIV activity

Human immunodeficiency virus type-1 (HIV-1) is the cause of acquired immune deficiency syndrome (AIDS) which has been a major human viral disease with about 33.2 million people infected worldwide up to now^{90, 91}. Antiviral agents that interfere with HIV at different stages of viral replication have been developed^{92, 93}. However, failure in anti-AIDS treatment⁹² is observed by the emergence of resistant virus, cross-resistance to drugs and cell toxicity^{94, 95}. Therefore, the search for potential candidates containing higher inhibitory activity against various HIV strains is increasing in pharmaceutical industry. Accordingly, phlorotannins from brown algae have been revealed to possess anti-HIV activity. For the first time, Ahn et al. (2004) reported that 8,8'-bieckol and 8,4'''-dieckol from *E. cava* exhibited an inhibitory effect on HIV-1 reverse transcriptase and protease⁹⁶. The inhibition against reverse transcriptase of 8,8'-bieckol with a biaryl linkage (IC_{50} , 0.5 μ M) is ten-fold higher than that of 8,4'''-dieckol with a diphenyl ether linkage (IC_{50} , 5.3 μ M), although these two phlorotannins are dimers of eckol. They have suggested that the steric hind-

rance of the hydroxyl and aryl groups near the biaryl linkage of 8,8'-bieckol caused to the potent inhibitory activity. Moreover, 8,8'-bieckol selectively inhibits reverse transcriptase over protease and inhibitory effect is comparable to the positive control nevirapine (IC_{50} , 0.28 μ M). Moreover, kinetic study showed that 8,8'-bieckol inhibited the RNA-dependent DNA synthesis activity of HIV-1 reverse transcriptase noncompetitively against dUTP/dTTP with a K_i value of 0.78 μ M. Meanwhile, this compound also exhibited an uncompetitive inhibition (K_i , 0.23 μ M) with respect to a homopolymeric template/primer, $(rA)_n(dT)_{15}$. A possible suggestion for this phenomenon is that 8,8'-bieckol binds to HIV-1 reverse transcriptase only after the template/primer initially binds to the enzyme. Furthermore, Ahn et al. (2006) has shown that diphloretohydroxycarmalol from *I. okamurae* also has inhibitory effect on HIV-1⁹⁷. This compound exhibited inhibitory effects on HIV-1 reverse transcriptase and integrase with IC_{50} values of 9.1 μ M and 25.2 μ M, respectively. However, diphloretohydroxycarmalol did not show an inhibitory activity against HIV-1 protease. In the same trend, 6,6'-bieckol from *E. cava* has been found as a potent wild inhibition against HIV-1 induced syncytia formation, lytic effects, and viral p24 antigen production⁹⁸. This phlorotannin has selectively inhibited the activity of HIV-1 reverse transcriptase enzyme with an IC_{50} of 1.07 μ M without any cytotoxicity. Recently, Kwon and colleagues have found that phlorotannins including eckol, 7-phloroeckol, phlorofucofuroeckol, and dieckol possessed antiviral activities with IC_{50} range of 10.8 – 22.5 μ M against porcine epidemic diarrhea virus⁹⁹. These phlorotannins were completely blocked binding of viral spike protein to sialic acids at less than 36.6 μ M by hemagglutination inhibition. Notably, phlorofucofuroeckol and dieckol inhibited viral replication with IC_{50} values of 12.2 and 14.6 μ M in the post-treatment assay, respectively. Interestingly, phlorofucofuroeckol and dieckol inhibited both viral entry by hemagglutination inhibition and viral replication by inhibition of viral RNA and viral protein synthesis, but not viral protease.

Anti-allergic activity

Allergic disease including allergic rhinitis, asthma, and atopic eczema are among the commonest causes of chronic ill-health. It is caused by an exaggerated reaction of the immune system to harmless environmental substances, such as animal dander, house dust mites, foods, pollen, insects, and chemical agents^{100, 101}. Allergic reaction is characterized by the excessive activation of mast cells and basophils by immunoglobulin E (IgE) from B cells, resulting in the release of preformed inflammatory mediators from secretory granules such as histamine and β -hexosaminidase, the generation and secretion of the newly

synthesized substances such as leukotrienes, prostaglandins, and cytokines¹⁰². These mediators cause allergic inflammatory responses due to airway constriction, mucous production, and recruitment of inflammatory cells. So far, a large number of anti-allergic agents from natural products have been identified based on the specific assay system or screening approaches. Recently, phlorotannins from brown algae have been determined as potential natural inhibitors of allergic reactions due to suppression of allergic degranulation, inhibition of hyaluronidase enzyme, and blockade of FcεRI activities. Several bioactive phloroglucinol derivatives including fucodiphloroethol G, eckol, dieckol, 6,6'-bieckol, phlorofucofuroeckol A, and 1-(3',5'-dihydroxyphenoxy)-7-(2'',4'',6-trihydroxyphenoxy)-2,4,9-trihydroxydibenzo-1,4-dioxin were isolated from *E. cava* and evidenced against A23187 or FcεRI-mediated histamine release from KU812 and RBL-2H3 cells^{103, 32}. Especially, dieckol, 6,6'-bieckol, and fucodiphloroethol G exhibited a significantly inhibitory activity with IC₅₀ range of 27.80 – 55.12 μM. The inhibitory mechanism of these compounds was determined to be due to blocking the binding activity between IgE and FcεRI. Similarly, Shim et al. (2009) have proved that phlorotannins of dioxinodehydroeckol and phlorofucofuroeckol A from *E. stolonifera* induced a suppression of the cell surface FcεRI expression, and total cellular protein and mRNA levels of the FcεRI α chain in KU812 cells¹⁰⁴. Further, both of these compounds exerted inhibitory effects against intracellular calcium elevation and histamine release from anti-FcεRI α chain antibody (CRA-1)-stimulated cells. In another study, phlorotannin PFF-B obtained from *E. arborea* exposed strong inhibitory activity against histamine and β-hexosaminidase release with IC₅₀ value of 7.8 μM^{105, 106}. Obviously, PFF-B had a 2.8–6.0 times greater inhibitory activity than those of epigallocatechin gallate (IC₅₀=22.0 μM) or Tranilast (IC₅₀=46.6 μM), a clinically used anti-allergic drug¹⁰⁷. Thus, these bioactive phloroglucinol derivatives were suggested as a promising candidate for the design of novel inhibitor of FcεRI-mediated allergic reaction. For the first time, the anti-allergenicity of phlorotannin from four edible seaweed species of *Fucus* genus was evaluated by Barbosa and colleagues¹⁰⁸. It was found that *Fucus* was able to inhibit mast cell degranulation via decreasing histamine and beta-hexosaminidase release from the activated RBL-2H3 cells, contributing to the valorisation of *Fucus* spp. both as food and for nutraceutical applications.

Hyaluronidase depolymerizes the polysaccharide hyaluronic acid in the extracellular matrix of connective tissue, which is found both in organs and in body fluids. It is mainly known to be involved in the permeability of the vascular system¹⁰⁹ and allergic reaction^{110, 111}. Interestingly, various phlorotannins such

as phlorofucofuroeckol A, dieckol, and 8,8'-bieckol from *E. bicyclis* are able to inhibit hyaluronidase enzyme with IC_{50} values of 140, 120, and 40 μ M, respectively¹¹². The effect of these phlorotannins against hyaluronidase enzyme is stronger than well-known inhibitors such as catechins ($IC_{50}=620$ μ M) and sodium cromoglycate ($IC_{50}=270$ μ M). Notably, 8,8'-bieckol, the strongest hyaluronidase inhibitor among the tested phlorotannins, acted as a competitive inhibitor with an inhibition constant of 35 μ M. Likewise, several phlorotannins of 6,6'-bieckol, 6,8'-bieckol, 8,8'-bieckol, PFF-A, and PFF-B from *E. arborea* were also confirmed as strong inhibitors of hyaluronidase^{113, 114}.

Anti-inflammatory activity

Inflammation is a critically important aspect of host responses to various stimuli including physical damage, ultra violet irradiation, microbial invasion, and immune reactions^{115, 116}. It is associated with a large range of mediators that initiate the inflammatory response, recruit and activate other cells to the site of inflammation¹¹⁷. However, excessive or prolonged inflammation can prove harmful, contributing to the pathogenesis of a variety of diseases, including chronic asthma, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, psoriasis, and cancer¹¹⁶. Currently, several classes of drugs such as corticosteroids, nonsteroidal anti-inflammatory drugs, and aspirin are used to treat the inflammatory disorders. All these therapeutics help to alleviate the symptoms but, especially after long-term and high-dose medication, they can have quite substantial side-effects. Therefore, there is still a vital need for the development of new anti-inflammatory drugs with satisfactory tolerability for long-term use. Herein, phlorotannins have been evidenced as potential agents for down-regulation of inflammatory responses. Phlorotannin-rich extracts of *E. cava* showed significant suppression of PGE_2 generation in LPS-treated RAW 246.7 cells, and significant inhibition of human recombinant interleukin-1 α -induced proteoglycan degradation¹¹⁸. Moreover, the phlorotannin-rich the fermented *E. cava* processing by-product extract was reported to inhibit NO and PGE_2 production, suppress the inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expressions, and attenuate interleukin-1 β and interleukin-6 production in lipopolysaccharide stimulated RAW 264.7 cells¹¹⁹. Recently, phlorotannin 6,6'-bieckol from *E. cava* was found to inhibit NO and PGE_2 production by suppressing the expression of iNOS and COX-2 at the mRNA and protein levels in LPS-stimulated primary macrophages and RAW 264.7 macrophage cells¹²⁰. Moreover, 6,6'-bieckol down-regulated the production and mRNA expression of the inflammatory cytokines TNF- α and IL-6. The pretreatment of 6,6'-bieckol decreased LPS-induced transactivation

of nuclear factor-kappa B (NF- κ B) and nuclear translocation of p50 and p65 subunits of NF- κ B, thus inhibiting LPS-induced NF- κ B binding to the TNF- α and IL-6 promoters. On the other hand, Kim and collaborators have evidenced that phlorofucofuroeckol A from *E. stolonifera* attenuated the productions and expression of NO, PGE₂, and pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α in LPS-stimulated microglia. Profoundly, phlorofucofuroeckol A treatment showed inactivation of c-Jun NH₂-terminal kinases (JNKs), p38 mitogen-activated protein kinase (MAPK), Akt, and NF- κ B¹²¹. Likewise, Kim et al. (2009) have shown the inhibitory activity of this phlorofucofuroeckol A on NO and PGE₂ production and iNOS and COX-2 expression in RAW 264.7 murine macrophage cells¹²². Besides, phlorotannins from *E. arborea* also exhibited inhibitory effect on NO production in LPS-stimulated RAW 264.7 cells¹²³ and mouse ear edema induced by arachidonic acid, 12-O-tetradecanoyl phorbol-13-acetate, and oxazolone¹²⁴. Notably, 8,8'-bieckol from *E. bicyclis* showed the pronouncedly inhibitory effects on soybean lipoxygenases and 5-lipoxygenases with IC₅₀ values of 38 and 24 μ M, respectively. Meanwhile, dieckol presented a significant inhibition of COX-1 with inhibition rate of 74.7%¹²⁵. Similarly, 6,6'-bieckol, 6,8'-bieckol, 8,8'-bieckol, PFF-A, and PFF-B from *E. arborea* were also confirmed as strong inhibitors of phospholipase A₂, cyclooxygenase, and lipoxygenases, which correlated to suppression in synthesis and release of leukotriene and prostaglandin from RBL cells¹¹⁴. Recently, phlorotannin-rich extract of the edible brown alga *E. cava* against hyper-inflammatory response in LPS-induced septic shock mouse model was also investigated¹²⁶. Dieckol, a major compound in the extract, reduced mortality, tissue toxicity, and serum levels of the inflammatory factors in septic mice and suppressed the septic shock through negative regulation of pro-inflammatory factors via the NIK/TAK1/IKK/I κ B/NF κ B and Nrf2/HO-1 pathways. In addition, Barbosa and colleagues have demonstrated the marked potential of *Fucus* sp. and their phlorotannin-purified extracts to act upon different mediators important in the pathophysiology of inflammatory-related conditions¹²⁷. The anti-inflammatory potential of the purified phlorotannin extracts in both cell and cell-free systems was observed. Therefore, the phlorotannin extracts from *Fucales* arise as potentially beneficial in inflammation-related conditions, effectively acting upon enzymatic and non-enzymatic inflammatory target.

Anti-cancer activity

Cancer can be defined as a disease in which a group of abnormal cells grow uncontrollably by disregarding the normal rules of the cell division¹²⁸. Cancers may be caused in one of three ways, namely incorrect diet, genetic predisposition, and via the environment. At least 35% of all cancers worldwide are caused

by an incorrect diet. Meanwhile, genetic predisposition caused about 20% of cancer cases, thus leaving the majority of cancers being associated with a host of environmental carcinogens¹²⁹. It is necessary to avoid exposure to cancer-causing biological, chemical, and physical agents, and consume chemo-preventive agents to reduce cancer risk. A promising approach is associated with natural products that are available as anti-cancer agents against commonly occurring cancers occurring worldwide^{130, 131}. Recently, phlorotannins have been reported as novel promising anti-cancer agent for breast cancer. Kong et al. (2009) has indicated that dioxinodehydroeckol from *E. Cava* exerted anti-proliferative activity against human breast cancer cells via induction of apoptosis¹³². Dioxinodehydroeckol treatment caused the increase in caspase (-3 and -9) activity, DNA repair enzyme poly-(ADP-ribose) polymerase (PARP) cleaved, and pro-apoptotic gene (Bax, p53, and p21) and the decrease in anti-apoptotic gene Bcl-2 and NF-κB activation. Moreover, phlorotannins-rich extracts from *Palmaria*, *Ascophyllum* and *Alaria* also inhibited the proliferation of colon cancer cells¹³³. On the other hand, the anti-cancer activity of *S. muticum* polyphenol-rich seaweed was shown via inhibiting breast cancer cell proliferation with IC₅₀ of 22 µg/ml and inducing apoptosis from 13% to 67% by accumulation of cells at sub-G1 phase¹³⁴. Parys et al. (2010) reported that trifucodiphloretol A, trifucotriphloretol A and fucotriphloretol A from *Fucus vesiculosus* were the potential chemo-preventive agents due to their capacity to inhibit the activity of aromatase related to carcinogenesis from breast cancers¹³⁵. For the first time, Kim and colleagues have determined the inhibitory effects of phlorotannins isolated from *E. cava* on MMP activities in cultured human cell lines without any cytotoxic effect¹³⁶. Recently, the anti-proliferative effect of various brown algae including *Cystoseira crinita*, *Cystoseira stricta*, and *Sargassum vulgare* on the human epithelial cell line Caco-2 was evidenced via arresting in G phases along with an increment in sub-diploid cell population¹³⁷. The anti-proliferative effect of these algae was correlated with their polyphenol and flavonoid contents. Moreover, the phlorotannins recovered from hydrothermal treatment of *Sargassum muticum* were showed the anti-proliferative properties against lung adenocarcinoma A549 cells and colon carcinoma HCT-116 cells¹³⁸. These results imply that seaweeds which are rich in phlorotannins may be used in anti-cancer drug research programs.

Anti-diabetic activity

Diabetes mellitus is a chronic metabolic disorder involved in hyperglycaemia, resulting from the deficiency in the production of insulin by the pancreas. Up to now, numerous therapeutics have been proposed to control hyperglycaemia in diabetic patients. Especially, α-amylase and α-glucosidase are enzymes related

to hyperglycaemia due to the starch hydrolysis and release of the glucose monomers for subsequent absorption by the small intestine. Therefore, the inhibition of these enzymes reduces the availability of free glucose monomers and consequently decreases blood glucose levels¹³⁹. Rengasamy et al. (2013) has isolated three phlorotannins including dibenzo (1,4) dioxine-2,4,7,9-tetraol and eckol from *E. maxima* and evaluated their alpha-glucosidase inhibitory activities¹⁴⁰. The inhibitory activities of dibenzo (1,4) dioxine-2,4,7,9-tetraol and eckol on enzyme alpha-glucosidase were 33.7 and 11.2 μM , respectively. A phenolic-rich extract from *Ascophyllum* was effective to inhibit α -amylase and α -glucosidase with IC_{50} of 0.1 $\mu\text{g}/\text{ml}$ GAE and 20 $\mu\text{g}/\text{ml}$ GAE¹³³. The presence of fucophloroethol structures with degrees of polymerization from 3 to 18 monomer units in *Fucus distichus* is responsible for its inhibition on α -glucosidase and α -amylase, with IC_{50} values of 0.89 and 13.9 $\mu\text{g}/\text{ml}$ ¹⁴¹. Moreover, dieckol and eckol from *Eisenia bicyclis* exhibited the inhibitory activity on α -amylase up to 97.5 and 87.5% at 1 mM ¹⁴². Meanwhile, α -glucosidase was inhibited by phlorofucofuroeckol-A, dieckol, and 7-phloroecol from *E. stolonifera* and eckol and dioxinodehydroeckol from *E. bicyclis* with IC_{50} of 1.37, 1.61, 6.13, 22.78, and 34.6 μM , respectively¹⁴³. The ingestion of methanolic extract of *E. stolonifera* suppressed the increase in plasma glucose and lipid peroxidation levels in unfasted KK-A(y) mice¹⁴⁴. Furthermore, various phlorotannins from *E. stolonifera* exhibited the inhibitory activities on aldose reductase, which are highly implicated in hyperglycemia and oxidative stress. The IC_{50} values of phloroglucinol derivatives are 21.95 - 125.45 μM ¹⁴⁵. Besides, dieckol from *E. cava* has evidenced prominent inhibitory effect against alpha-glucosidase and alpha-amylase with IC_{50} values of 0.24 and 0.66 mM , respectively. The increase of postprandial blood glucose levels were significantly suppressed in the dieckol administered group in the streptozotocin-induced diabetic mice¹⁴⁶. Recently, three phlorotannins, eckol, dieckol and phlorofucofuroeckol-A from *E. bicyclis* were revealed for their anti-diabetic activity of alloxan-induced type1 and insulin-induced type 2 in the zebrafish model¹⁴⁷. Notably, the inhibition of the catalytic reaction of α -glucosidase by minor phlorotannin derivatives from *E. cava* were demonstrated with IC_{50} values ranging from 2.3 ± 0.1 to 59.8 ± 0.8 μM . Compounds 2–5 inhibited the catalytic reaction of α -glucosidase in non-competitive and competitive manners¹⁴⁸.

Anti-obesity

Obesity is a major obstacle in human health and life quality, resulting in many chronic diseases. It is due to a chronic imbalance between energy intake and energy expenditure, leading to the increased fat storage¹⁴⁹. Interestingly, a series of anti-obesity components derived from marine origin have been found,

especially phlorotannins. Herein, three phlorotannins from *E. stolonifera* including phloroglucinol, eckol, and phlorofuocofuroeckol A significantly inhibited lipid accumulation in 3T3-L1 cells via reducing the expression of adipocyte marker genes such as proliferator activated receptor γ and CCAAT/enhancer-binding protein α ¹⁵⁰. Meanwhile, phlorotannin dieckol from *E. cava* exhibited great potential adipogenesis inhibition and down-regulated the expression of peroxisome proliferator-activated receptor- γ , CCAAT/enhancer-binding proteins, sterol regulatory element-binding protein 1 (SREBP1) and fatty acid binding protein 4¹⁵¹. Moreover, diphloretohydroxycarmalol (DPHC) from *Ishige okamurae* was showed to inhibit population growth and induce apoptosis in 3T3-L1 preadipocytes¹⁵². The peptidyl prolyl cis/trans isomerase Pin1 enhances the uptake of triglycerides and the differentiation of fibroblasts into adipose cells in response to insulin stimulation. However, phlorotannin called 974-B from *E. kurome* was showed to inhibit the differentiation of mouse embryonic fibroblasts and 3T3-L1 cells into adipose cells without inducing cytotoxicity, suggesting a lead drug candidate for obesity-related disorders¹⁵³.

Other biological activities

According to Ahn et al. (2010), phloroglucinol from *E. cava* possesses the activation activity on immune response. The phloroglucinol elicited the proliferation of lymphocytes without cytotoxicity and enhanced IL-2 production by activating the nuclear factor-kappaB (NF- κ B) signaling pathway¹⁵⁴.

Inhibition of angiotensin I-converting enzyme (ACE) activity is the most common mechanism underlying the lowering of blood pressure. Dieckol from *E. cava* was found as potent ACE inhibitor with IC_{50} value of 1.47 mM. It is a non-competitive inhibitor against ACE according to Lineweaver-Burk plots¹⁵⁵. Meanwhile, eckol, phlorofuocofuroeckol A, and dieckol from *E. stolonifera* were also determined to manifest the marked inhibitory activity against ACE, with IC_{50} values of 70.82, 12.74, and 34.25 μ M, respectively¹⁵⁶.

Neurodegenerative diseases are characterized by progressive dysfunction and death of neurons. Recently, neuroprotective effects of phlorotannins from brown seaweed have been evidenced by various experimental models. Um and colleagues have reported that phlorotannin-rich fraction from *Ishige foliacea* brown seaweed prevents the scopolamine-induced memory impairment in mice¹⁵⁷. It reduced acetylcholinesterase activity in the brain and significantly decreased lipid peroxidation levels, but increased glutathione levels and superoxide dismutase activity. Moreover, the expression levels of brain-derived neurotrophic factor, tropomyosin receptor kinase B, the phosphorylated extracellular signal-regulated kinase, and cyclic AMP-response element-binding

protein were increased by *I. foliacea* phlorotannin. In addition, the neuroprotective effect of dieckol from *E. cava* on rotenone-induced oxidative stress in a human dopaminergic neuronal cell line SH-SY5Y was also determined by Cha and colleagues¹⁵⁸. Dieckol reduced the intracellular reactive oxygen species and cytochrome C release, cell death, and α -synuclein aggregation in SH-SY5Y cells. Likewise, it was found that eckmaxol, a phlorotannin from *E. maxima*, could produce neuroprotective effects in SH-SY5Y cells via directly acting on glycogen synthase kinase 3β ¹⁵⁹. Accordingly, phlorotannin from the brown algae could be a potential therapeutic agent for the prevention of neurodegenerative diseases.

RESULTS AND DISCUSSION

Finding the safe and efficient agents from natural products for prevention and treatment of chronic diseases are always necessary. Herein, phlorotannins from brown algae have been identified with various biological activities and health benefit effects. The extensive discoveries of phlorotannins underlying structure-activity relationship will provide clear evidence on their actions against diseases. Moreover, the further studies due to the bioavailability involving in liberation, absorption, distribution, metabolism, and elimination phases will ensure the bio-efficacy of phlorotannins. Collectively, phlorotannins from brown algae are believed to play an important role in the development of promising pharmaceutical products that can prevent and/or treat various chronic diseases.

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CONFLICT OF INTEREST

There are no conflicts to declare.

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