Chapter 11
Brown Algal Polyphenol and Its Pharmaceutical Properties

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Abstract The world's oceans represent an enormous resource for the discovery of potential therapeutic agents. During the last decades, numerous novel compounds have been isolated from marine organisms and many of them have been applied for phamacological industry. Notably, marine algae are known to be one of the most important producers of variety of chemically active metabolites. Among them, 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 considered as promising agents for the development of pharmaceuticals. This contribution focuses on phlorotannins from brown algae and presents an overview of their biological activities and health benefit effects.

Keywords Brown algae · Phlorotannins · Antioxidant · Pharmaceuticals · Biological activities

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11.1 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 potentials [3–5]. Various marine organisms such as algae, tunicates, sponges, soft 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, acid amine, neurotoxins, polysaccharides, chlorophyll, carotenoids, vitamins, minerals, and unique pigments have been discovered. Many of these substances have been demonstrated to possess interesting biological activities [6–14].

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 cells [15]. Therefore, they vary greatly in size from unicellular of 3 to 10 μm to giant kelps up to 70 m long [16]. 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 anti-coagulation, anti-virus, anti-oxidant, anti-allergy, anti-cancer, anti-inflammation, and anti-obesity, anti-diabetes, anti-hypertension, neroprotection, immunomodulation [17–20]. 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 nutrition [21].

The Phaeophyceae (brown algae) is a large group of marine multicellular algae, including of many 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 Wynne [15], 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*, *Himanthalia*, *Sargassum*, and *Dictyota*. Brown seaweeds are rich in polysaccharide, polyphloroglucinol phenolic compounds, and other secondary metabolites such as terpenes, carotenoids, and oxylipins [21] Notably, marine brown algae accumulate a variety of phloroglucinol-based polyphenols, as phlorotannins. These pholorotannins consist of phloroglucinol units linked to each other in various ways, and are of wide occurrence among marine brown algae [22, 23]. 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 activities [23]. This review focuses on phlorotannins from marine brown algae and presents an overview of their chemical properties as well as potential pharmaceutical applications.

11.2 Phlorotannins

11.2.1 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 algae [24, 25]. 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 Pacific [26]. It was found that phlorotannnins have mostly focused on Fucaceae (*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 matter [27–31]. They tend to be concentrated within the outer cortical layers, physode, and the mitotic meristematic and meiotic sporogenous tissues [24, 32]. In addition, Laminariaceous brown algae, such as *Eisenia bicyclis, Ecklonia cava, Ecklonia kurome* were also found to contain a significant amount of phlorotannins [33, 34].

11.2.2 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 phlorotannins [35]. Phlorotannins can be grouped according to the criteria of interphloroglucinol linkages into three primary types including fucols, phlorethols, and fucophlorethols. Fucols is formed by only phenyl linkages, while phlorethols is formed by only arylether bonds and fucophlorethols is formed by both arylether and phenyl linkages.

The structural diversity of phlorotannins increases by adding the number of phloroglucinol units. Each of the primary groups can be grouped into linear phlorotannins, if all extension units have only two interphloroglucinol connections, or branched, if they bind to three or more. 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* [38] and *Analipus japonicas* [39]. The linear phlorethols may have ortho-, meta- or para- oriented biphenyl ether bridges or combinations such as triphlorethol C and tetraphlorethols A and B from *Laminaria ochroleuca* [40]. The branched phlorethols include tetraphlorethol C from *Ecklonia maxima* [41], pentaphlorethol B and hexaphlorethol A from *Cystophora retroflexa* [29].

Furthermore, an additional hydroxyl group on the terminal monomer unit forms other structural motifs of phlorethols such as bifuhalol, trifuhalol A, and trifuhalol B [42, 43]. If an extension unit is bound between meta-oriented phloroglucinol units and it bears the additional hydroxyl group, these are called isofuhalols such as isotrifuhalol [44]. Some fuhalols with more than one additional hydroxyl group have been called hydroxyfuhalols, such as hydroxytrifuhalol B [45]. In addition, another subgroup of phlorethols, the eckols, includes a 1,4-dibenzodioxin system, such as the trimers eckol and dioxinodehydroeckol [41, 46], the tetramers 2-phloroeckol and 7-phloroeckol [47–49], and the hexamer dieckol [50].

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-B [27], meanwhile the branched fucophlorethols is bisfucotriphlorethol A [51], and heterocyclic fucophlorethols is phlorofucofuroeckol A [52].

11.2.3 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 complex [53]. 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 biosynthesis [54]. 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 groups [55]. The polymerization of phloroglucinol in different ways results in formation of various phlorotannins.

11.2.4 Physiological Properties

Phlorotannins are found in physodes, which contribute to the development of the cell wall of brown algae [56]. It has suggested that phlorotannins are likely to be integral structural components of brown-algal cell walls [57]. They are bound to the cell wall during maturation of the plant [58]. Phenolic compounds are bound with four major types of bonds including hydrophobic, hydrogen, ionic, and covalent bond to increase the strength [59]. 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 movement [56].

A characteristic of phlorotannins is their plasticity to a variety of environmental factors including nutrient environment [60], light [61], depth [62], salinity [63], grazing [64] or other mechanical wounding [65]. Such plasticity may represent inducible defense against herbivory [25]. Suggestions for other adaptive roles for phlorotannins include protection against ultraviolet radiation [66] or function as anti-fouling substances [67]. The suggested defensive role of phlorotannins is due to deterring feeding by herbivores [68] and decreasing their assimilation efficiency by binding with proteins in the gut [69, 70].

11.3 Potential Health Benefits

11.3.1 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 factors [71]. It is well known that oxidants are involved in signal transduction and gene activation, and can contribute to host cell and organ damage [72]. Therefore, scavenging of oxidant is considered important in controlling 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 investigated [73]. 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 H_2O_2-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) cells [74]. Eckol was effective to reduce H_2O_2-

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 by Kang et al. 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 death [75]. 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 stress [76].

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 line [77]. 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 embryos [78]. 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 et al. [79]. 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.

UV radiation has a strong oxidative component, and photo-oxidative stress has been directly linked to skin photodamage, 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 radiation [80]. The inhibitory activity on melanogenesis was evidenced via suppression of tyrosinase and melanin synthesis. Meanwhile, 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 cells [81]. 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. These results indicated that phlorotannins from brown algae have potential protective effects against UV-B radiation, which might be applied in cosmeceutical industries.

11.3.2 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 world [82]. 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 μmol/ml, respectively. At twice the MBCs, all *Vibrio parahaemolyticus* were killed within 0.5–2 h, while catechins showed little bactericidal activity within 4 h [83]. Furthermore, Lee and co-workers 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 μg/ml [84]. The MICs of ampicillin against two standard strains of MRSA were dramatically reduced from 512 to 0.5 μg/ml in combination with 1/4 MIC of dieckol (16 μg/ml). Likewise, Phlorofucofuroeckol-A from *E. bicyclis* were also showed anti-MRSA activity with MIC of 32 μg/ml and synergistic action against MRSA in combination with β-lactam antibiotics ampicillin, penicillin, and oxacillin [85]. 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 fungi [88]. 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 human [89].

11.3.3 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 treatment 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. [96] reported that 8,8′-bieckol and 8,4′′-dieckol from *E. cava* exhibited an inhibitory effect on HIV-1 reverse transcriptase and protease. The inhibition against reverse transcriptase of 8,8′-bieckol with a biaryl linkage (IC_{50}, 0.5 μM) is ten-fold higher than that of 8,4′′-dieckol with a diphenyl ether linkage (IC_{50}, 5.3 μM), although these two phlorotannis are dimmers of eckol. They have suggested that the steric hindrance 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 μM). 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 Ki value of 0.78 μM. Meanwhile, this compound also exhibited an uncompetitive inhibition (Ki, 0.23 μM) 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, their study has also revealed shown that diphlorethohydroxycarmalol from *I. okamurae* also has inhibitory effect on HIV-1 [97]. This compound exhibited inhibitory effects on HIV-1 reverse transcriptase and integrase with IC_{50} values of 9.1 μM and 25.2 μM, respectively. However, diphlorethohydroxycarmalol 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 production [98]. This phlorotanins has selectively inhibited the activity of HIV-1 reverse transcriptase enzyme with an IC_{50} of 1.07 μM without any cytotoxicity. Recently, Kwon and colleagues have found that phlorotanins including eckol, 7-phloroeckol, phlorofucofuroeckol, and dieckol possessed antiviral activities with IC_{50} range of 10.8–22.5 μM against porcine epidemic diarrhea virus [99]. These phlorotanins were completely blocked binding of viral spike protein to sialic acids at less than 36.6 μM by hemagglutination inhibition. Notably, phlorofucofuroeckol

and dieckol inhibited viral replication with IC_{50} values of 12.2 and 14.6 μM 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.

11.3.4 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 cytokines [102]. 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 [34, 103]. Especially, dieckol, 6,6′-bieckol, and fucodiphloroethol G exhibited a significantly inhibitory activity with IC_{50} 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. [104] 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 cells. 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 IC_{50} 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 (IC_{50} = 22.0 μM) or Tranilast (IC_{50} = 46.6 μM), a clinically used anti-allergic drug [107]. Thus, these bioactive phloroglucinol derivatives were suggested as a promising candidate for the design of novel inhibitor of FcεRI-mediated allergic reaction.

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 system [108] and allergic reaction [109, 110]. Interestingly, various phlorotanins 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 μM, respectively [111]. The effect of these phlorotannins against hyaluronidase enzyme is stronger than well-known inhibitors such as catechins ($IC_{50} = 620$ μM) and sodium cromoglycate ($IC_{50} = 270$ μM). Notably, 8,8′-bieckol, the strongest hyaluronidase inhibitor among the tested phlorotannins, acted as a competitive inhibitor with an inhibition constant of 35 μM. 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 [112, 113].

11.3.5 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 [114, 115]. It is associated with a large range of mediators that initiate the inflammatory response, recruit and activate other cells to the site of inflammation [116]. 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 cancer [115]. 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-1α-induced proteoglycan degradation [117]. 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-1β and interleukin-6 production in lipopolysaccharide stimulated RAW 264.7 cells [118]. Additionally, pretreatment of phlorotannin-rich extracts of *Ascophyllum nodosum* caused reduction of LPS-induced TNF-α and IL-6 release in macrophages [119]. 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 cells [120]. 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-κB) and nuclear translocation of p50 and p65 subunits of NF-κB, thus inhibiting LPS-induced NF-κB 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, PGE_2, and pro-inflammatory cytokines such as IL-1β, 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-κB [121]. Similar observations were also made in their earlier study related to the inhibitory activity of this phlorofucofuroeckol A on NO and PGE_2 production and iNOS and COX-2 expression in RAW 264.7 murine macrophage cells [122]. Besides, phlorotanins from *E. arborea* also exhibited inhibitory effect on NO production in LPS-stimulated RAW 264.7 cells [123] and mouse ear edema induced by arachidonic acid, 12-O-tetradecanoyl phorbol-13-acetate, and oxazolone [124]. Notably, 8,8′-bieckol from *E. bicyclis* showed the pronouncedly inhibitory effects on soybean lipoxygenases and 5-lipoxygenases with IC_{50} values of 38 and 24 μM, 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 A_2, cyclooxygenase, and lipoxygenases, which correlated to suppression in synthesis and release of leukotoriene and prostaglandin from RBL cells [113].

11.3.6 Anti-cancer Activity

Cancer can be defined as a disease in which a group of abnormal cells grows uncontrollably by disregarding the normal rules of the cell division [126]. 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 carcinogens [127]. It is necessary to avoid exposure to cancer-causing biological, chemical, and physical agents, and consume chemopreventive 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 [128, 129]. Recently, phlorotannins have been reported as novel promising anti-cancer agent for breast cancer. Kong et al. [130] has indicated that dioxinodehydroeckol from *E. Cava* exerted anti-proliferative activity against human breast cancer cells via induction of apoptosis. 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 cells [131].

On the other hand, the anti-cancer activity of *S. muticum* polyphenol-rich seaweed was shown via inhibiting the proliferation of breast cancer cells with IC_{50} of 22 μg/ml and inducing apoptosis from 13 to 67% by accumulation of cells at sub-G1 phase [132]. Parys et al. [133] reported that trifucodiphlorethol A, trifucotriphlorethol A and fucotriphlorethol A from *Fucus vesiculosus* were the potential chemopreventive agents due to their capacity to inhibit the activity of aromatase related to carcinogenesis from breast cancers. For the first time, Kim and colleages have determined the inhibitory effects of phlorotannins isolated from E. cava on MMP activities in cultured human cell lines without any cytotoxic effect [134].

11.3.7 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 has 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 levels [135]. Rengasamy et al. [136] 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 activities. 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 μg/ml GAE and 20 μg/ml GAE [131]. 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 μg/ml [137]. Moreover, dieckol and eckol from *Eisenia bicyclis* exhibited the inhibitory activity on α-amylase up to 97.5 and 87.5% at 1 mM [138]. Meanwhile, α-glucosidase was inhibited by phlorofucofuroeckol-A, dieckol, and 7-phloroeckol 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, respectively [139]. The ingestion of methanolic extract of *E. stolonifera* suppressed the increase in plasma glucose and lipid peroxidation levels in unfasted KK-A(y) mice [140]. 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 [141]. 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 was significantly suppressed in the dieckol administered group in the streptozotocin-induced diabetic mice [142]. 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 model [143].

11.3.8 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 storage [144]. 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 phlorofucofuroeckol 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 [145]. Meanwhile, phlorotannin dieckol from *E. cava* exhibited great potential adipogenesis inhibition and downregulated the expression of peroxisome proliferator-activated receptor-γ, CCAAT/enhancer-binding proteins, sterol regulatory element-binding protein 1 (SREBP1) and fatty acid binding protein 4 [146]. Moreover, diphlorethohydroxycarmalol (DPHC) from *Ishige okamurae* was showed to inhibit population growth and induce apoptosis in 3T3-L1 preadipocytes [147]. 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 disorders [148].

11.3.9 Other Biological Activities

According to Ahn et al. [149], 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-κB) signaling pathway.

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 plots [150]. Meanwhile, eckol, phlorofucofuroeckol 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 μM, respectively [151].

11.4 Conclusion

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 a 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 bioefficacy of phlorotannins. Collectively, phlorotannins from brown algae are believed to play an important role in the development of novel products that can prevent and/or treatment of chronic diseases.

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