CHAPTER 8

Medicinal Effects of Phlorotannins from Marine Brown Algae

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Contents

Abstract

Brown seaweeds are popular and abundant food in East Asia and also well known for their medicinal effects due to presence of active phenolic constituents. Phlorotannins, the major phenolic group of brown algae, have extensively investigated for their vast array of bioactivities such as antioxidant, anti-inflammatory, anti-cancer, and antidiabetic. They possess promising activity in both *in vitro* and *in vivo* systems showing promising potential to further develop as therapeutic agents. In this chapter, attempts have taken to examine and categorize the reports available on active phlorotannins which have shown strong bioactivities.

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I. INTRODUCTION

The philosophy of Hypocrites ''let food be thy medicine and medicine be thy food'' is a promising approach for prevention or minimization of the increasing incidents of chronic diseases in the world today. There are vast numbers of research going on for inventing and identifying ingredients which are to be used as medicinal foods specifically reducing the risk of specific diseases. Therefore, development and characterization of medicinal food ingredients are among hot topics in the food industry. However, FDA (Food and drug administration) has strong legislation regarding this aspect. FDA has defined medicinal foods in section 5(b) of the orphan drug act and it states as ''A food which is formulated to be consumed or administered entirely under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.'' In the search of medicinal foods, increasing attention has given to marine-based sources. Among them, marine algae are under the limelight, as they are intensively used as a food ingredient, mainly in East Asia. However, their value as a food found to be far more beyond than a wrap of sushi due to low content of lipids, high concentration of polysaccharides, rich in minerals, polyunsaturated fatty acids and vitamins, and presence of vast array of bioactive metabolites (Gupta and Abu-Ghannam, 2011). Intensive efforts are being made by marine scientists to identify and characterize these compounds to exploit them as medicinal ingredients. Despite having found large number of compounds from marine algae with medicinal properties, few of those compounds have shown real potency to be used as a nutraceutical or pharmaceutical. Among them, phlorotannins are the most significant group of biologically active substances that determine the pharmacological value of algae. The phlorotannin content of the brown algae (Phaeophyceae) is found to be highest over red (Rhodophyta) and green algae (Chlorophyta) (Holdt and Kraan, 2011). These brown algal phlorotannins have been extensively characterized for their potential biological activities. Hence, this chapter has focused on discussing the medicinal potential of phlorotannins isolated from marine brown algae.

II. PHLOROTANNINS

Polyphenolic secondary metabolites are a large and diverse group of chemical compounds which exist both in terrestrial and aquatic plants. Polyphenols from terrestrial plants are derived from gallic and ellagic acids, whereas the algal polyphenols are derived from polymerized

phloroglucinol units (Fig. 8.1). These algal polyphenols are termed as phlorotannins and they are biosynthesized via acetate malonate pathway (Arnold and Targett, 2002). The monomeric units are linked through aryl–aryl bonds, and diaryl ether bonds are forming different subgroups of phlorotannins (Glombitza and Pauli, 2003). Their molecular size ranges between 162 Da (phloroglucinol) and 650 kDa (Breton *et al*., 2011).

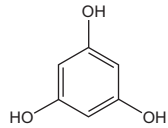
In brown algae (Phaeophyceae), the only group of tannins present is phlorotannins and may constitute up to 15% of the dry weight (Arnold and Targett, 2002). The phlorotannins are localized in physodes of the algae which are membrane-bound cytoplasmic vesicles, and the fusion of physodes with cell membranes results in a secretion of phlorotannins (Li *et al*., 2009). The highest levels of phenolic compounds in brown algae are found either in meristematic or in reproductive regions of the thallus (Breton *et al*., 2011). The phlorotannin's concentration exhibits seasonal variations and has reported that highest polyphenolic content can be obtained in summer (Connan *et al*., 2004). Many brown algal species are popular food mainly in East Asia, and the presence of phlorotannins may affect the palatability due to their astringent taste. And also medicinal values of the brown algae are also related to the presence of phlorotannins. Medicinal values of phlorotannins are related to their structure and especially to the degree of polymerization, where oligo-phenols generally considered more active than highly polymerized compounds (Toth and Pavia, 2001).

III. MEDICINAL EFFECTS OF PHLOROTANNINS

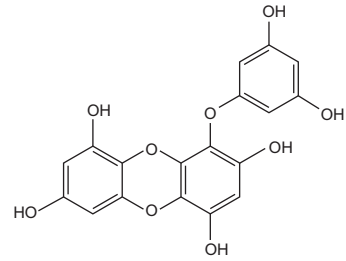
Brown algal phlorotannins have been extensively studied for their potential health benefits and reportedly they have shown promising effects against radical-mediated oxidative stress, photodamage, cancer, allergy, diabetes, inflammation, and viral and microbial infections. Having vast range of biological activities, phlorotannins are believed to be the most promising candidates to be developed as nutraceuticals and pharmaceuticals. This section is covering up the major biological activities of phlorotannins isolated from brown algae.

A. Antioxidant effects

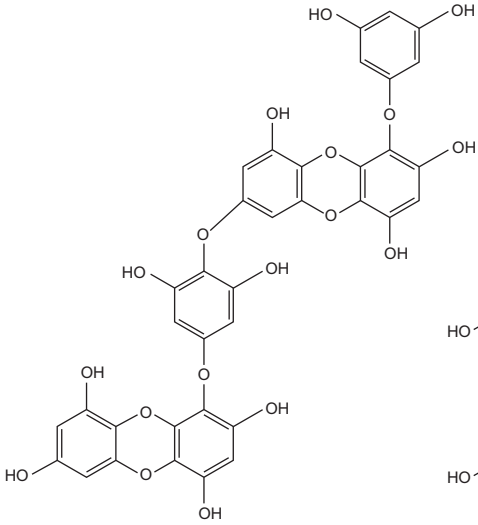
Oxidative stress is a primary cause for development of various human chronic diseases such as cardiovascular disease, cancers, and neurodegenerative diseases. Therefore, wide range of potential metabolites has been evaluated against oxygen-induced damage and hence lowers the risk of human chronic diseases. Among them, brown algae serve as an important bioresource of antioxidative phlorotannins with significant



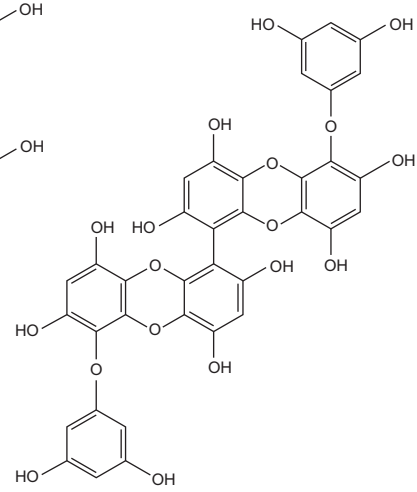
Phloroglucinol



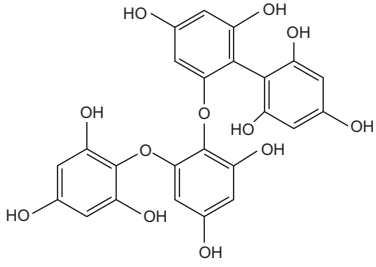
Eckol



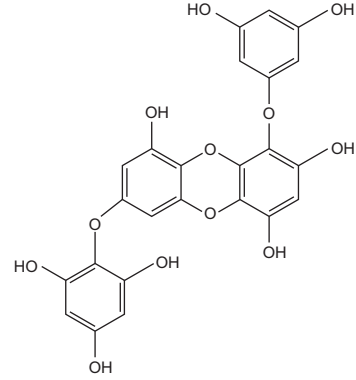
Dieckol



6,6-Dieckol



Fucodiphloroethol G



7-Phloroeckol

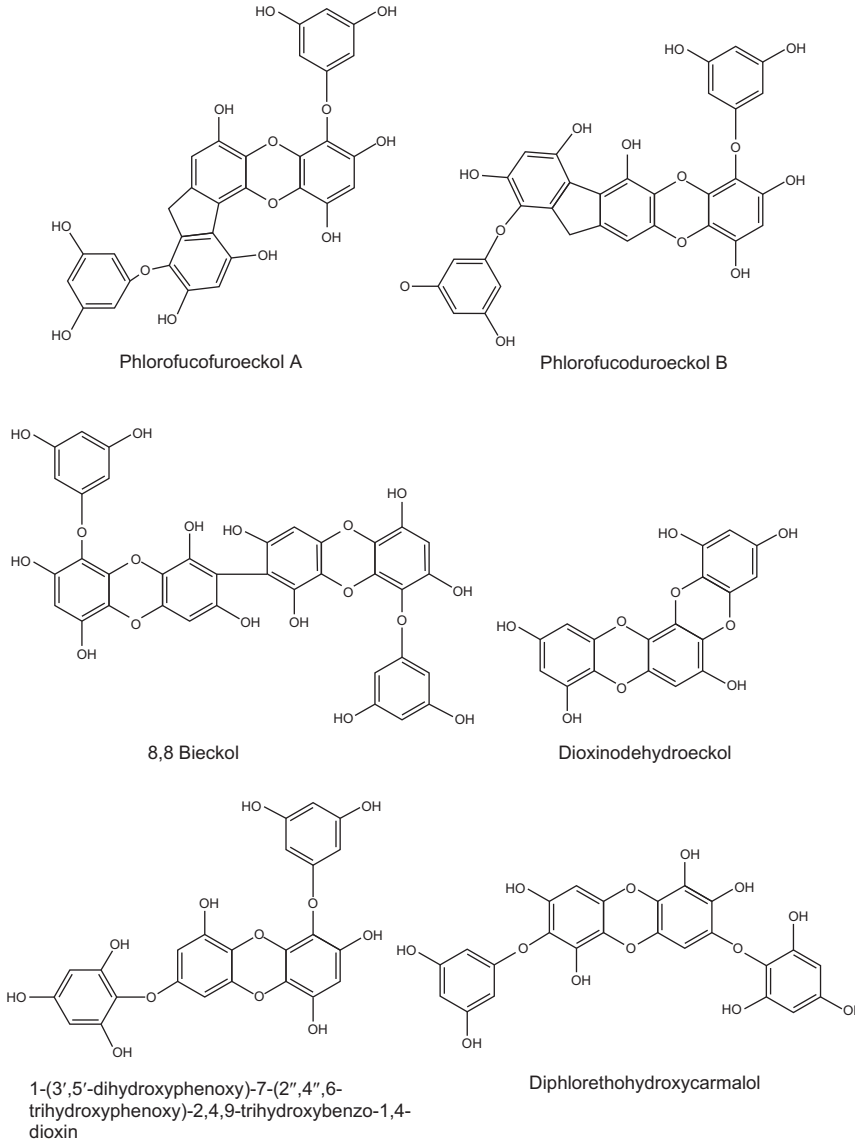


FIGURE 8.1 Structures of phlorotannins isolated from marine brown algae.

pharmaceutical potential. Algae as intertidal organisms require an endogenous antioxidant capacity to withstand UV irradiation and the effects of desiccation from daily tidal fluctuations (Yuan and Walsh, 2006). In brown algae, this antioxidant protection encompasses mainly by

phlorotannins (Yan *et al.*, 1996). Therefore, they have received the greatest attention and have been investigated extensively since they are high free radical scavengers in nature and less toxic than synthetic antioxidants such as BHA and BHT (Jung *et al.*, 2008).

1. Free radical scavenging ability

Unregulated production of free radicals in the cellular systems is responsible in causing cellular damage by oxidizing macromolecules, DNA, proteins, and lipids in the cell. Therefore, antioxidative therapeutics have great demand to act against free radicals. In this aspect, phlorotannins serve as one of the most promising natural antioxidants. Numbers of studies have shown the radical scavenging potential of phlorotannins isolated from marine brown algae. These phlorotannins have shown significant scavenging ability toward hydroxyl, superoxide, alkyl, and DPPH radicals. As shown in Table 8.1, most of the phlorotannin compounds have shown more potent antioxidant activities than commercially available antioxidants α-tocopherol, butylated hydroxyl-anisole (BHA), butylated hydroxytoluene (BHT). And also phlorotannins are investigated for their ability in scavenging reactive oxygen species (ROS) in cellular systems. Diphlorethohydroxycarmalol and 6,6-bieckol isolated from *Ishige okamurae* (Zou *et al.*, 2008); fucodiphloroethol G and dieckol isolated from *Ecklonia cava* (Li *et al.*, 2009) have shown of 77.2%, 78.9%, 75.6%, and 84.3% ROS inhibition at 50 μM, respectively, in H_2O_2-induced RAW264.7 cells. Moreover, Kang *et al.* (2004) have shown strong ROS inhibitory activity of phlorotannins; eckol (IC_{50} 4.04 μM) and phlorofucofuroeckol A (IC_{50} 3.8 μM) isolated from *Ecklonia stolonifera* on rat kidney homogenates of freshly killed male Wistar rats.

2. Photoprotective ability

Ultraviolet B (UVB; 280–320 nm) radiation of the sun is highly oxidative and directly triggers photodamage of the skin cells. This UVB radiation induces the overproduction of ROS which interacts with cellular DNA, proteins, and lipids to alter their cellular functions (Heo *et al.*, 2010). Regular intake of antioxidants would be an useful strategy to combat UVB induced photodamage. Yan *et al.* (1997) and Hupel *et al.* (2011) have shown that brown algae are more tolerant to UVB irradiation due to the presence of phlorotannins. Therefore, these phlorotannins have been isolated from algae and investigated for their possible application in reducing the photodamage of the skin. Dieckol was found to be the most potent phlorotannin to protect the cells from UVB irradiation (50 mJ cm^{-2}). Heo *et al.* (2009) have found that dieckol (100 μM) isolated from *E. cava* increase the cell survival up to 77.1% in UVB irradiated human dermal fibroblasts (HDF). And also they have shown that the DNA damage due to UVB irradiation was also inhibited by 57.8% with

TABLE 8.1 Radical scavenging activities of phlorotannins from brown algae

Compound	Radical scavenging activity IC_{50} (μM)				Source	Reference
	Hydroxyl	Superoxide	Alkyl	DPPH		
Phloroglucinol	392.5	115.2	128.9	NA	*Eclonia cava*	Li *et al.* (2009)
Eckol	51.8	26.5	28.4	22.89		
Fucodiphloroethol G	33.5	18.6	18.1	14.72		
Phlorofucofuroeckol A	39.2	21.6	21.4	17.66		
7-phloroeckol	39.6	21.9	22.7	18.64		
dieckol	28.6	16.2	14.5	8.28		
6,6′-bieckol	29.7	15.9	17.1	8.69		
Diphlorethohydroxycarmalol	28.7	15.4	17.3	9.1	*Ishige okamurae*	Zou *et al.* (2008)
8,8′-bieckol	NA	NA	NA	59	*Ecklonia arborea*	Sugiura *et al.* (2008a)
Phlorofucofuroeckol B	NA	NA	NA	81		
Catechin	NA	NA	NA	10		Kang *et al.* (2003)
BHA	NA	NA	NA	34		
BHT	NA	NA	NA	144		
A-tocopherol	NA	NA	NA	17		

NA, not analysed.

the treatment of 50 μM dieckol. Moreover, Ko *et al*. (2011) have also studied on the photoprotective effect of dieckol from *E. cava* using human epithelial keratinocytes (HaCat) and have found that dieckol treatment (100 μM) on UVB irradiated cells induces the cell survival up to 88.42%. Further, they have studied this promising photoprotective effect of dieckol using zebrafish as an alternate animal model system. Their results indicate that the ROS formation in UVB irradiated zebra fish embryos was significantly inhibited by the dieckol treatment (50 μM). ROS levels were measured using image analysis and fluorescence micrographs, and dieckol has also shown a typical fluorescence micrograph of the nonirradiated zebrafish. Diphlorethohydroxycarmalol isolated from *I. okamurae* has also been studied for its photoprotective ability in UVB (50 mJ cm^{-2}) irradiated HDF cells. It has shown 45.57% ROS scavenging ability and 49.33% inhibition of DNA damage at 250 μM concentrations (Heo *et al*., 2010).

B. Anticancer effects

1. Antiproliferative activity

Cancer is possibly one of the most dangerous diseases, and cure for it has not yet found. Therefore, prevention of cancer through good diet practices is a well-promoted chemoprevention strategy. Marine edible seaweeds are promising candidates in this regard. Phlorotannins isolated from edible marine alga *E. cava* (dioxinodehydroeckol and 1-(3′,5′-dihydroxyphenoxy)-7-(2″,4″,6-trihydroxyphenoxy)-2,4,9-trihydroxybenzo-1,4-dioxin) have shown antiproliferative effects on human breast cancer cells (MCF-7). Among them, dioxinodehydroeckol has shown stronger ability in inducing apoptosis accounting for 55% cell death at 100 μM treatment (Kong *et al*., 2009). Moreover, Yang *et al*. (2010) have also found that the phlorotannin extracts from *Laminaria japonica* show antiproliferative effects on human hepatocellular carcinoma cells, IC_{50} 200 μg/ml (BEL-7402) and murine leukemic cells, IC_{50} 120 μg/ml (p388).

2. Inhibition of cancer metastasis

Invasion and migration are the principal mechanisms involved in cancer mortality, leading to spread of the cancer from its originated place to another site. In this invasion process, number of proteolytic enzymes contributes to the degradation of environmental barriers, such as the extracellular matrix (ECM) and basement membrane. Matrix metalloproteinase 2 and 9 (MMP 2,9) are principal enzymes responsible for ECM degradation, which are essential in the invasive growth, metastasis, and angiogenesis of cancer. Therefore, inhibition of these enzyme expressions is a therapeutic target to prevent cancer metastasis, and phlorotannins have found to be potent inhibitors. Zhang *et al*. (2010) have found that 6′6′-bieckol (100 μM)

isolated from brown alga *E. cava* significantly downregulated the expression of MMP 2,9 in an *in vitro* model of activated human fibro-sarcoma cells (HT1080). And this down regulation was found to be a cause of 6′6′-bieckol-mediated blocking of NF-κB signaling which regulate the expression of MMP 2,9. Polyphenolic extracts of *E. cava* has potential inhibitory effect against MMP 2,9 expression in human lung cancer cells (A549) through modulating Akt signaling pathway (Lee *et al.*, 2011). Similarly, *E. cava* extract consisting of 57.98 ± 0.45% of phlorotannins (500 μM) has shown potent inhibitory activity against MMP 2,9 expression in HT1080 cells. Interestingly, this inhibition was found to be more potent than the commercially available MMP inhibitory drug doxycycline (10 μg/ml). Angiogenesis is the process where new blood vessels are made to facilitate the invasion of cancers, and fucodiphloroethol G from *E. cava* has inhibited this process in an angiogenesis-induced cellular model (Li *et al.*, 2011). These findings show that especially the edible brown alga is a promising material to be included in the diet and for development of pharmaceuticals for chemoprevention.

C. Antiallergic effects

Allergic diseases are affecting approximately one-third of the general population in the world, and due to environmental changes and food habits, the prevalence and incidents of allergies are increasing. Wealth of research has been done to find antiallergic compounds, and phlorotannins or phlorotannin extracts from edible brown algae have shown promising potential in antiallergic therapy *in vivo* and *in vitro* models. Hyaluronidase enzyme is known to play an important role in allergic reaction, and Samee *et al.* (2009) have found that *Sargassum tenerrimum* phlorotannin extract is a strong inhibitor of hyluronidase (IC_{50} 21 μg/ml). It is more potent than the commercially antiallergic drug disodium cromoglycate (IC_{50} 39 μg/ml) and almost similar to the natural inhibitor catachin (IC_{50} 20 μg/ml). 6′6′-bieckol (Le *et al.*, 2009), fucodiphloroethol G, and phlorofucofuroeckol A (Li *et al.*, 2008) isolated from *E. cava* have also shown significant antiallergic activity by inhibiting histamine release by modulating the binding between IgE and FcεRI receptors which mediate the allergen release in human basophilic leukemia (KU812) and rat basophilic leukemia (RBL-2H3). Further, Sugiura *et al.* (2007) have found the β-hexosaminidase enzyme (equivalent to histamine) inhibitory activity of phlorofucofuroeckol-B (IC_{50} 7.8 μM) from brown alga *Eisenia arborea* which showed strongest inhibitory activity over antiallergic drug tranilast (IC_{50} 46.6 μM) and epicatechin gallate (IC_{50} 22 μM). And the presence of this very strong antiallergen would be the reason for shown *in vivo* antiallergic effects in brown Norway rats fed with dried *E. arborea* powder (Sugiura *et al.*, 2008b).

D. Anti-inflammatory effects

Chronic inflammation is a pathophysiological condition of the body associated with various disorders such as arthritis, neurodegenerative diseases, cancer, diabetes, and cardio vascular disease. Scientists are in search of natural anti-inflammatory agents and phlorotannins have also getting much attention due to the shown promising anti-inflammatory potential. Ryu *et al*. (2009) have shown anti-inflammatory effects of dieckol and 1-(3′,5′-dihydroxyphenoxy)-7-(2″,4″,6-trihydroxyphenoxy)-2,4,9-trihydroxybenzo-1,4-dioxin as therapeutics to treat arthritis. Both phlorotannins have suppressed the unregulated expression of cyclooxygenase-2 (COX-2), inducible nitric oxide (iNOS), MMP 1,3,13 in activated human osteosarcoma cells (MG63). Phloroglucinol, the monomer unit, has also exerted significant anti-inflammatory activity by inhibiting inflammatory mediators (tumor necrosis factor α, Interleukin 1β, interleukin 6, nitric oxide, and prostaglandin E_2) in lipopolysaccharide-stimulated RAW264.7 cells (Kim and Kim, 2010). Overactivation of microglial cells is leading to chronic neurodegenerative diseases due to expression of neurotoxic inflammatory mediators. Dieckol isolated from *E. cava* has shown potent inhibitory activity on these inflammatory mediators and their respective downstream enzymes (cytokines, iNOS, COX-2) in lipopolysaccharide activated microglial cells (BV-2) (Jung *et al*., 2009). Interestingly, in all these findings, the signaling mechanism of phlorotannin-mediated anti-inflammatory effect was found to be through deactivation of NF-κB, the transcription factor regulated the inflammatory gene expression.

E. Antidiabetic effects

Diabetes mellitus is a chronic metabolic disorder which can damage many systems in the body, such as blood vessels and nerves. It is one of the world's most serious health concerns, developing increasingly with the dietary patterns and age. The control of blood glucose levels is very important in hyperglycemic patients, and α-glucosidase inhibitors are a cost-effective means to preventing the progression of diabetes. Fucodiphloroethol G (IC_{50} 19.52 μM), dieckol (IC_{50} 10.79 μM), 6,6′-bieckol (IC_{50} 22.22 μM), 7-phloreckol (IC_{50} 49.49 μM), and phlorofucofuroeckol A (IC_{50} 19.71 μM) from *E. cava* have shown significant inhibition of α-glucosidase (Lee *et al*., 2009). Several other studies have conducted to investigate *in vivo* antidiabetic effects by feeding phlorotannin extracts to diabetic mouse models. *Ecklonia stolonifera* extracts have shown strong inhibition of α-glucosidase in noninsulin dependent diabetic mice (Iwai, 2008). Feeding with *E. cava* extract (Kang *et al*., 2010) and *I. okamurae* extract (Min *et al*., 2011) have resulted in reduction of the plasma glucose

level and improve insulin resistance in type 1 mellitus rats and C57BL/-KsJ-db/db mice, respectively. Diabetes is closely related to the diet, and incorporating these brown algae as medicinal dietary supplements would be a promising prevalence strategy of diabetes.

IV. CONCLUSIONS

Marine brown seaweeds are abundant in phlorotannins compared to other marine plants. These phlorotannins are a highly diverse group depending on their structure, and polymerizations and oligomers serve as most promising bioactive materials. Many reports have been published on strong activities of phlorotannin oligomers against oxidative stress, cancer, inflammation, allergy diabetes, and few other disorders *in vitro* and *in vivo*. Among them, *E. cava* has been studied extensively as it produces number of highly active phlorotannins. Phlorotannin derivatives are capable of modulating cellular signaling and thereby they regulate the adverse conditions of the body. Finally, it can be suggested that marine brown algal phenolic extracts or isolated phlorotannins should be developed as medicinal foods or therapeutics for human health applications.

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