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Phlorotannins

Jayachandran Venkatesan[a], Kishor Kumar Keekan[a], Sukumaran Anil[b], Ira Bhatnagar[c], and Se-Kwon Kim[d], [a] Yenepoya Research Center, Yenepoya (Deemed to be University), Deralakatte, Mangalore, Karnataka, India; [b] Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha University, Chennai, India; [c] Clinical Research Facility, Medical Biotechnology Complex, CSIR-Center for Cellular and Molecular Biology Annexe-II, Uppal Road, Hyderabad, Telangana, India; and [d] Department of Marine Life Sciences, Korean Maritime and Ocean University, Busan, Republic of Korea

Introduction

"Let food be thy medicine and medicine be thy food" is quoted from Hippocrates (Smith, 2004). Plants and animals of marine and terrestrial origins are considered to be main food resources for humans, of which the marine environment is considered to be one of the best and huge reservoirs. It has been repeatedly reported that marine sources consist of animals and plants, which can be potentially used as foods in our daily life (Kim, 2012; Kim and Taylor, 2011). Macroalgae is one of the class of marine plants that has gained much attention in the recent years for health food supplements used as food ingredients and animal feeds in East Asia. These macroalgae are rich sources of soluble dietary fibers, proteins, peptides, carotenoids, polysaccharides, minerals, and potential metabolites (Yang et al., 2016; Sánchez-Camargo et al., 2016). It has also been suggested elsewhere that metabolites derived from macroalgae have potential biological activities such as antibacterial, antioxidant, anti-inflammatory, antiadipogenic, antidiabetic, anti-HIV, and anti-cancer activities (Yang et al., 2016). Owing to ample of these medicinal properties, the marine macroalgae can be considered as a potential health benefitting medicinal food.

Phlorotannins

"Phlorotannin" (1,3,5-trihydroxy benzene), is a group of polyphenolic compounds which are commonly present in the brown algae accounting for about 5–12% of the dry mass (Sathya et al., 2017). The development of phlorotannin can occur through polymerization of phloroglucinol oligomers via acetate-malonate (polyketide) pathway (Li et al., 2011a; Sathya et al., 2017). . *Eisenia bicyclis*, *Ecklonia cava* and *Ecklonia kurome* are commonly found in Japanese and Korean coastal areas. Phlorotannin content in *Eisenia bicycles* accounts for 3% of total dry mass of algae. HPLC results suggest that *E. bicycles* consists of phloroglucinol (0.9%), phloroglucinol tetramer (4.4%), eckol (7.5%), phlorofucofuroeckol A (21.9%), dieckol (23.4%), and 8,8′-bieckol (24.6%), plus some 17.3% of other unknown phenolic compounds (Shibata et al., 2004). However, phlorotannin content in seaweeds can also vary through the individual species, geographic region and extraction techniques (Jégou et al., 2015). Fucodiphlorethol G was isolated from *E. cava* for the first time and acetylated to make different derivatives of the compound (Young et al., 2007).

Extraction Procedure

Phlorotannins (**Fig. 1**) are commonly isolated from the seaweeds, particularly brown algae, through conventional organic solvent isolation followed by chromatographic techniques to purify the compounds (Kim et al., 2016; Koivikko et al., 2007; Venkatesan, Kim, & Shim, 2016). Furthermore, nuclear magnetic resonance spectroscopy is widely used to characterize the structure of compounds. Supercritical carbon dioxide has also been used at times to extract the phlorotannins (Saravana et al., 2017; Sánchez-Camargo et al., 2016).

HPLC-HRMS (high resolution mass spectrometer) is the most commonly used method to characterize phlorotannins (Melanson and Mackinnon, 2015). Folin–Ciocalteu assay is a commonly used technique to quantify the phlorotannin content in a given species. Recently, ^{1}H qNMR was also used to quantify the phlorotannin content in brown algae (Jégou et al., 2015; Parys et al., 2007). Furthermore, Ultra High Performance Liquid Chromatography (UHPLC) has also been employed to study the isomeric complexity between the phlorotannins (Heffernan et al., 2015). Water-Organic solvent mixtures were also used to extract the phlortannins. The details of step by step extraction procedure and purification were given by Gall et al. (2015). Balboa et al. (2015) developed a biorefinery process for the isolation of phlortanin in a single method. In this method, conventional solvent extraction with 96% ethanol, supercritical CO_2 extraction method, and membrance microfiltration were used. Tierney et al. (2013, 2014) developed pressurized a liquid extraction method, which was used to extract the polyphenol compounds from Irish macrolage *Ascophyllum nodosum*, *Pelvetia canaliculata*, *Fucus spiralis* and *Ulva intestinalis* and compared with the traditional solid–liquid extraction techniques in terms of their antioxidant properties. The results suggest that pressurized liquid extraction produces higher phenolic compounds when compared to traditional extraction methods (Tierney et al., 2013, 2014). Two-dimensional liquid chromatography was used to isolate phlorotannin from seaweed (Montero et al., 2014). Centrifugal partition chromatography (CPC) was used to separate the phlorotannins, which were isolated from the ethyl acetate fraction using the solvent system n-hexane:EtOAc:methanol:water (2:7:3:7, v/v). Dieckol (fraction I, 40.2 mg), phlorofucofuroeckol-A (fraction III, 31.1 mg), and

fraction II (34.1 mg) with 2,7-phloroglucinol-6,6-bieckol and pyrogallol-phloroglucinol-6,6-bieckol were isolated from the crude extract (500 mg) by a one-step CPC system (Lee et al., 2014). In another study, a macroporous adsorption resin was used for chromatographic purification of seaweed phlorotannins (**Figs. 2** and **3**). Four different resins (HP-20, SP-850, XAD-7HP, and XAD-2) were tested, and HP-20 resin showed the highest adsorption and desorption capacities (Kim et al., 2014). Compared to organic solvent extract, the recovery yield of dieckol from the boiling water of *E. cava*, *Ecklonia stolonifera*, *Ecklonia bicyclis* was found to be 86%, 93%, and 98%, respectively (Chowdhury et al., 2014).

Hydrophilic interaction chromatography techniques were used to extract and determine the phlorotannin content in *Eisenia bicyclics*. The yields of the phlorotannins increased 2–4 times in summer (June–October) and then were decreased to normal levels in winter (November–March). In the extraction of *E. bicyclis*, ethanol percentage in water, extraction time and washing time significantly affected the yield of the extract and the phlorotannins, whereas the temperature and the sample/solvent ratio impacted the extraction to a lesser degree (Kim et al., 2013b).

The use of a microwave-assisted extraction (MAE) method for the extraction of phlorotannins from *Saccharina japonica* Aresch has been evaluated with particular emphasis on the influential parameters, including the ethanol concentration, solid/liquid ratio, extraction time, extraction temperature, and microwave power (He et al., 2013). Biosynthesis of phlorotannins has also been explored (Bertoni, 2013). The UHPLC-HRMS method described was successful in rapid profiling of phlorotannins in brown seaweeds based on their degree of polymerisation. HILIC (Hydrophilic interaction chromatography) was demonstrated to be an effective separation mode, particularly for low molecular weight phlorotannins (Steevensz et al., 2012). Mature thalli contained

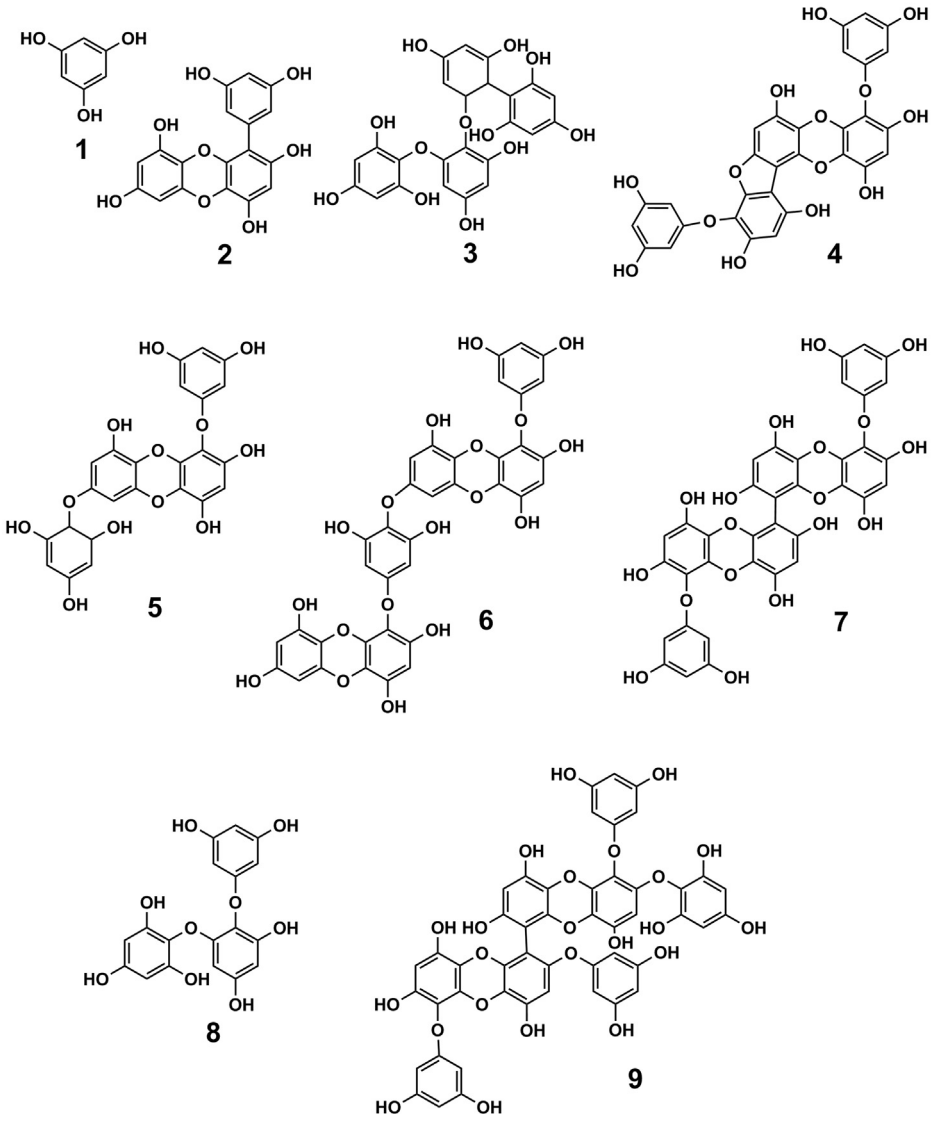

Figure 1 Chemical structures of: (1) phloroglucinol; (2) eckol; (3) fucodiphlorethol G; (4) phlorofucofuroeckol A; (5) 7-phloroeckol; (6) dieckol; (7) 6,6′-bieckol; (8) triphlorethol-A; and (9) 2,7′-phloroglucinol-6,6′-bieckol (Venkatesan, Kim, & Shim, 2016).

1.5-fold more dieckol (1.82 mg/g-dry tissue) than young thalli. In the tissues of *E. cava*, blade tissue contained more phlorotannins than the stipe or holdfast. Among differently dried thalli, approximately 90% or more dieckol and phlorofucofuroeckol-A were extracted from shadow-dried tissue as compared with lyophilized tissue (Chowdhury et al., 2011). The 2,4-dimethoxybenzaldehyde (DMBA) assay was developed whereby the chemical specifically reacts with phlorotannins to form a coloured product (Stern et al., 1996). Phlorotannins from different regions and species of North American and Australasian marine herbivores vary significantly in terms of structure and function (Van Altena and Steinberg, 1992). Important and chemically characterised phlorotannins with HPLC and NMR techniques are shown in **Figs. 1–3**.

Biological Activities of Phlorotannins

Phlorotannins show promising biological activities such as antioxidant, anti-HIV, antiproliferative, radio protective, antidiabetic, skin protection, and antiallergic activities (Wijesekara et al., 2010) due to their structural properties. Few of them will be discussed here.

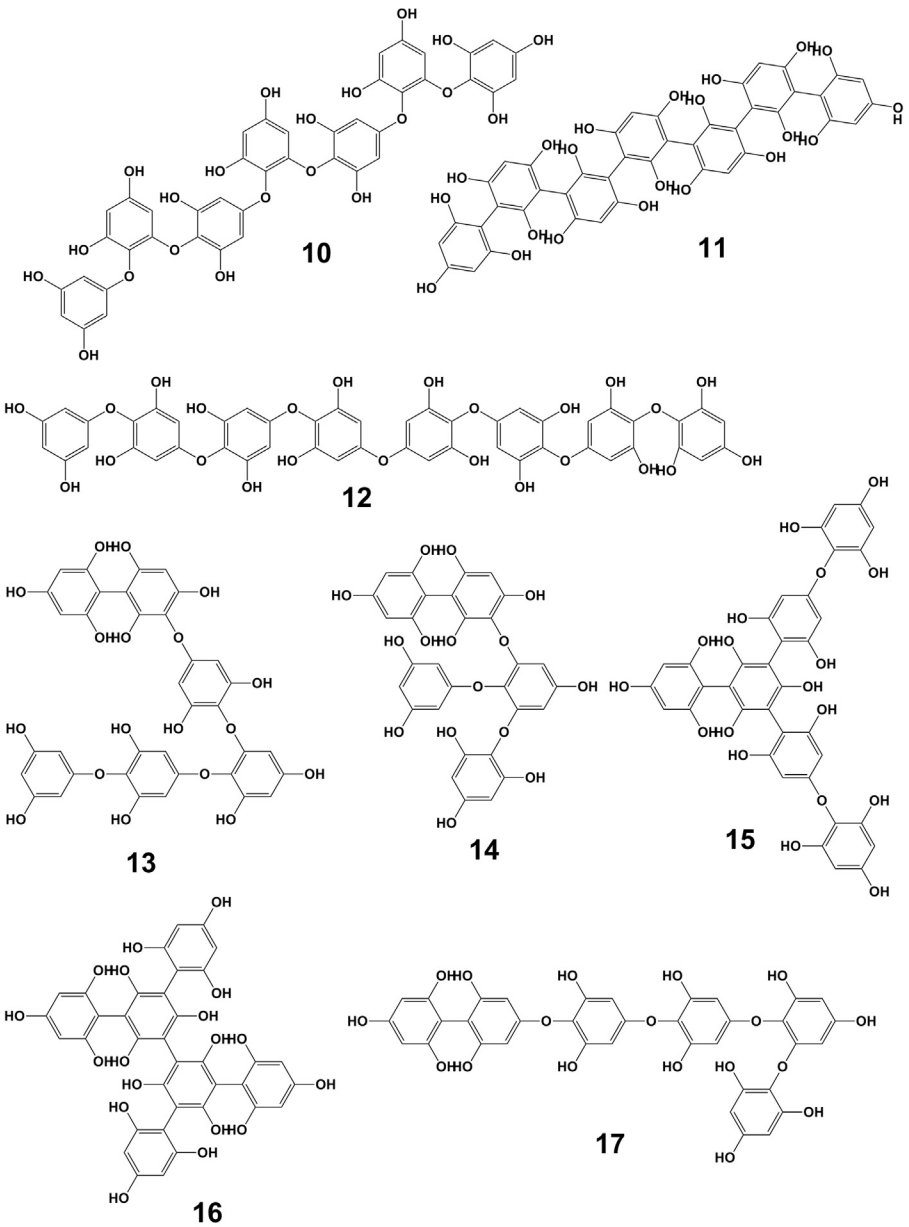

Figure 2 Important structures of phlorotannins isolated from seaweeds, (10) heptaphlorethol, (11) heptafucol, (12) Octaphlorethol A, (13) fucotetraphlorethol A, (14) fucotetraphlorethol J, (15) trifucodiphlorethol A, (16) hexafucol B, and (17) fucotetraphlorethol D (Tierney *et al.* 2014); (Sánchez-Camargo *et al.* 2016); (Lee *et al.* 2016).

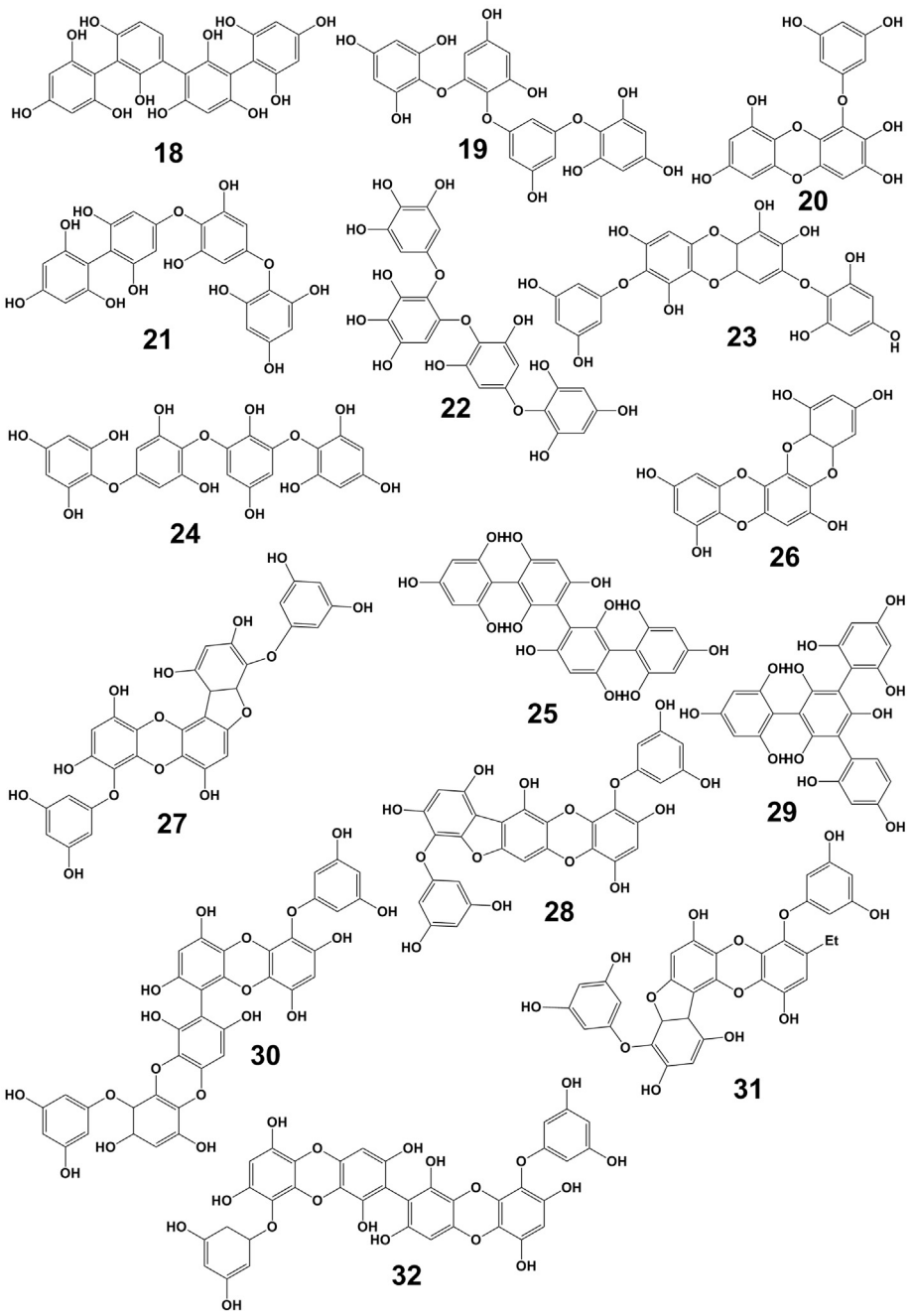

Figure 3 Important structures of phlorotannins from seaweed, (18) Tetrafucol A, (19) Tetraphlorethol B, (20) Eckol, (21) Fucodiphlorethol, (22) Tetrafuhalol A, (23) Diphloethohydroxycarmalol (24) Tetraisofuhalol, (25) Tetrafucol A, (26) dioxinodehydroeckol (27) Phlorofucofuroeckol, (28) Phlorofucofuroeckol B (29) Tetrafucol B (30) 6,8-bieckol, (31) phlorofucofuroeckol A, and (32) 8,8′-bieckol (Lopes *et al.* 2012) (Sugiura *et al.* 2007) (Parys *et al.* 2007) (Lee *et al.* 2012).

Antimicrobial Activity

The antibacterial activities of phlorotannins have been reported in the literature by several research groups (Shannon and Abu-Ghannam, 2016), and phlorotannins have the ability to bind to the bacterial protein and cause cell lysis. The phenolic group of phlorotannins can bind with the amino group of bacterial proteins (Wang et al., 2009). Eom et al. (2012, 2013, 2014) reported the effective ways to overcome methicillin-resistant *Staphylococcus aureus* growth by phlorofucofuroeckol-A, which is derived from *E. bicyclics* marine algae. The phlorotannins suppressed mecI, mecR1,and mecA gene expression in a dose-dependent manner (Eom et al., 2012, 2013, 2014). Lopes et al. (2013) reported the antifungal activity of phlorotannins against dermatophytes and

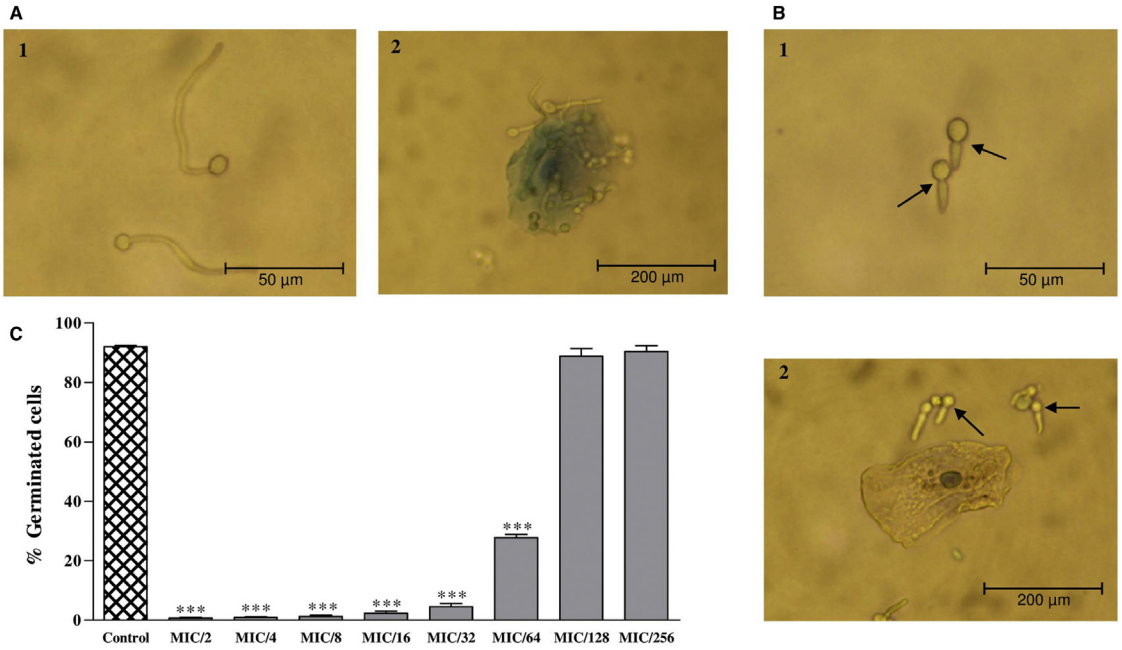

Figure 4 Effect of purified phlorotannins extracts from *F. spiralis* in the dimorphic transition of *C. albicans* ATCC 10231 (Untreated control cells - A1; cells treated with extract at MIC/32 – B1), in the adherence of the yeast to the epithelial cells (Untreated control cells – A2; cells treated with extract at MIC/32 - B2) and in the germ tube formation (C). The figure was adapted with permission from Lopes et al. (2013).

yeasts. Antimicrobial activity of phlorotannins against Gram positive and Gram negative bacteria was checked and the phlorotannin extracts were found to have excellent antimicrobial inhibition activity (Lopes et al., 2012) as shown in **Fig. 4**. Recently, marine-derived compounds have shown potential biological activity in terms of antibacterial effects as well (Lee et al., 2016).

Antioxidant Activity

Food industry often searches for antioxidant molecules to prevent the food from spoilage. Natural derived antioxidants are considered to be safe for human health. Phlorotannins have ability to scavenge the reactive oxygen species (ROS) such as hydroxyl, peroxyl, superoxide radicals (Kirke et al., 2017). In addition to this, phlorotannins can act as total antioxidant with high reducing power activity. DPPH free radical scavenging of *Sargassum aquifolium* species were the highest, corresponding to 6.770 ± 0.001 mg phlorotannin g^{-1} dry weight (DW), 6.1290 ± 0.0200 mg ascorbic acid g^{-1} DW, 19.7210 ± 0.0300 mg $FeSO_4$ g^{-1} DW and 76.28 ± 0.20% of 25 µg DPPH mL^{-1} extract (Cuong et al., 2016). It is obvious to say that higher amounts of phlorotannin content show higher antioxidant activity (Charoensiddhi et al., 2014; Wang et al., 2012). The general method to check the antioxidant activity of compound were as follows with the small modifications (Yotsu-Yamashita et al., 2013). First, 5 µL of sample solution were mixed with 95 µL of 1:1 volume of 0.4 M ethanolic solution of DPPH and 100 mM aqueous MES (sodium 2-(N-morpholino)ethanesulfonate) buffer (pH 6.0) for 1 min. Further, the plates were incubated for 30 min at 37 °C and read at 517 nm. The radical scavenging activity of the sample was calculated using the following formula:

$$A_{sample}/A_{control} \times 100$$

A_{sample} is the absorbance of DPPH incubated with test compound; $A_{control}$ is the absorbance of DPPH incubated without compound.

The following experiments are the most commonly used assays to measure the radical scavenging activities of the bioactive compounds.

- Ferric reducing/antioxidant power (FRAP) assay (Quéguineur et al., 2013) (Quéguineur et al., 2012)
- DCFH-DA (Dichloro-dihydro-fluorescein diacetate) assay (Yotsu-Yamashita et al., 2013)
- Trolox equivalent antioxidant capacity (TEAC) assay (Audibert et al., 2010)
- Electron spin resonance spectroscopy (Ahn et al., 2007)

The most important antioxidant activities of phenolic compounds and phlorotannins from the brown seaweed have been discussed in a previous review (Balboa et al., 2013). These reviews are also useful to get more information on antioxidant activities of other polysaccharides, proteins, peptides, lipids, terpenoids and steroids (Balboa et al., 2013; Li and Kim, 2011). Trifucodiphlorethol A, trifucotriphlorethol A as well as fucotriphlorethol A can significantly scavenge the ROS with IC_{50} range around 10.0–14.4 µg/mL

(Parys et al., 2010). Fig. 1 shows the important phlorotannins, which were isolated from *E. cava*. All the isolated compounds showed promising biological activity in terms of their antioxidant properties (Li et al., 2009).

The phlorotannins from *E. cava, E. kurome, and E. bicyclics* had significant radical scavenging activities against the superoxide anion (IC_{50}: 6.5–8.4 μM) and DPPH (IC_{50}: 12–26 μM), which were more effective as compared with ascorbic acid and α-tocopherol (Shibata et al., 2008). In another study, diphlorethohydroxycarmalol was isolated from brown algae, *Ishige okamurae* and antioxidant activity was evaluated as IC_{50} value of DPPH to be 3.41 μM and 4.92 μM (Heo et al., 2008). The scavenging activity of the fraction against superoxide anion radicals was estimated to be 1.0 mg/mL (IC_{50}), which was approximately five times stronger than that of catechin (Nakai et al., 2006). The IC_{50} values of 974-A, 974-B, phlorofucofuroeckol-A, and dieckol were significantly smaller than those of phlorofucofuroeckol-B, phloroglucinol, α-tocopherol, and ascorbic acid (Yotsu-Yamashita et al., 2013).

Anti-inflammatory Activity

Chronic inflammation is one of the main reasons behind majority of diseases. Several kind of anti-inflammatory drugs are available in the market to treat the inflammatory diseases, but those drugs are often associated with some side effects. Therefore, much attention has been paid to natural marine-based anti-inflammatory compounds (Cheung et al., 2016; Balboa et al., 2012; Shin et al., 2006). Marine-based compounds are unique and have proven to be potentially useful to treat inflammatory diseases. Yang et al. (2016) proposed that the phlorotannin-rich *E. cava* can be used to treat sepsis. Eom et al. (2017) investigated anti-inflammatory effects of eckol on *Propionibacterium acnes* induced human skin keratinocytes (HaCaT) cells. The functions of eckol in production of nitric oxide, matrix metalloproteinase 2 and 9, NO synthase, cyclooxygenase-2 and necrosis factor-α were also studied. Eckol significantly inhibited the expression or formation of proinflammatory mediators and cytokines in HaCaT cells (Eom et al., 2017). In most of the studies, LPS (lipopolysaccharide) was used to induce the inflammation in RAW 264.7 cells. Kang et al. (2015) reported that diphlorethohydroxycarmalol reduced interleukin 6 (IL-6), DPHC (12.5 and 100 μM) and suppressed the phosphorylation and nuclear translocation of NF-kappa (NF κB). In another study, Wijesinghe et al. (2013) reported that phlorotannin-rich fermented *E. cava* by-product extract dose-dependently inhibited nitric oxide production, prostaglandin-E2 production and suppressed inducible nitric oxide synthase and cyclooxygenase-2 expressions in LPS stimulated RAW 264.7 cells. Sugiura et al. (2013) reported the inhibitory effect of histamine release from rat basophile leukaemia (RBL) 2H3 cells. The anti-inflammatory activity potential of the methanolic extract and its fractions from *Eisenia bicyclis* was in the order of dichloromethane > methanol > ethyl acetate > n-butanol (Jung et al., 2013). 6,6′-Bieckol, and phlorofucofuroeckol A also suppressed LPS-induced iNOS, COX2 and PEG2 production and inflammatory cytokine expression in macrophages (Yang et al., 2012; Kim et al., 2009, 2011a).

Antiproliferative Activity

Phlorotannin derived from *Sargassum muticum* showed antiproliferative effect against HT-29 cells (Montero et al., 2016). Compounds from *E. cava* have shown cytotoxic action against HeLa, HT1080, A549, and HT-29 cells (Li et al., 2011b). In another study, the antiproliferative effect of phlorotannins derived from *Laminaria japonica* was evaluated against hepatocellular carcinoma cells (BEL-7402) and murine P388 leukemic cells (Yang et al., 2010).

Antitumor Activity

Antitumor effect of phlorotannin-rich extract with cisplatin were checked and results (Fig. 5) suggest that the combination improved the properties of cisplatin due to the synergetic effect (Yang et al., 2015).

Dieckol was isolated from *E. stolonifera* and its anticancer activity was checked against human Hep3B hepatocellular carcinoma cells. The compound has excellent ability to control cancer cell proliferation in a dose-dependent manner. In addition to this, important genes were expressed such as caspases-3, 7, 8 and 9 (Yoon et al., 2013). In another study, phlorotannin eckol suppressed stemness and malignancies in glioma stem-like cells (Hyun et al., 2011).

Antidiabetics Activity

Diabetes mellitus is a chronic disease and mainly classified as type 1 and type 2. Type 2 diabetes incidence in people has increased considerably throughout the world due to the consumption of high-fat and carbohydrate foods. Even though, several chemically-derived antidiabetic drugs are available to treat diabetes, the problem persists with adverse side effects. Ultimately, there is a need to find effective molecules with less or none side effects. Polyphenol-rich molecules from marine seaweeds show promising effects in treating diabetes mellitus in terms of digestive enzymes, hepatic glucose metabolizing enzymes, lipid peroxidation and lowering the glucose plasma levels (Murugan et al., 2015).

Lee and Jeon (2015) conducted a study on intake of dieckol-rich extract and measured the glycemic parameters, serum biochemistry and hematology. About 80 pre-diabetic male and female adults were randomized and separated into two groups, namely, placebo control and dieckol-rich extract (1500 mg/day). The results showed that dieckol rich extract group decreased in insulin and C-peptide levels in 12 weeks, however there is no significant difference between the groups (Lee and Jeon, 2015). Antidiabetic

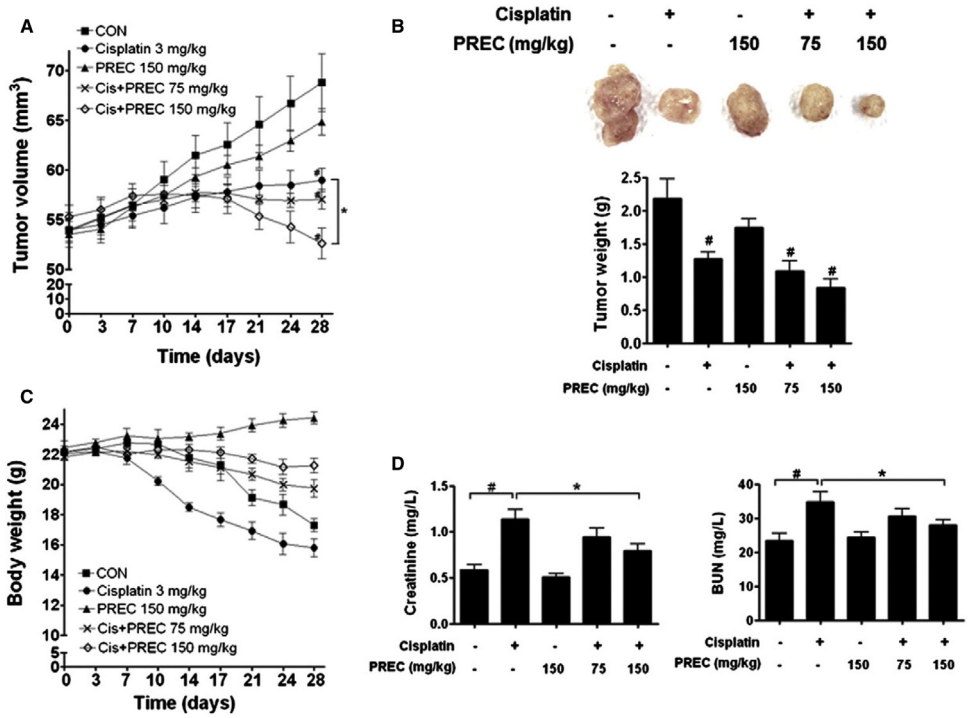

Figure 5 Phlorotannins improve the antitumor activity of cisplatin. SKOV3 xenograft treated three times per week for 4 weeks (A), tumor weight after the experiment has been conducted (B), mouse body weight changes (C), Plasma creatinine and BUN levels were measured using a calorimeter testing kit. The figure was adapted with permission from (Yang et al., 2015).

effect of phlorotannins can follow diverse mechanisms, such as to improve insulin resistance or inhibition of hepatic glucose by stimulating GK (Hepatic glucokinase) activity (Lee and Jeon, 2013). Dieckol isolated from brown seaweed significantly attenuated type II diabetes which was investigated in C57BL/KsJ-db/db mouse model. Dieckol was administered through intraperitoneal route at 10 mg/kg and 20 mg/kg dose for 14 days. The results show that reduced thiobarbituric acid reactive substances (TBARS), as well as increased activities of antioxidant enzymes including SOD, catalase (CAT) and GSH-px in liver tissues were observed in the dieckol administered group (Kang et al., 2013d). Even though the phlorotannins from *E. kurome* showed some amount of toxicity, their consumption might be useful in ameliorating diabetics-related complications (Xu et al., 2012).

Extracts from *Palmaria*, *Ascophyllum* and *Alaria* inhibited α-amylase activity to some extent, but *Ascophyllum* extracts were very effective with an IC_{50} of approximatively 0.1 μg/mL gallic acid equivalent (GAE). The *Ascophyllum* extracts inhibited α-glucosidase, another key enzyme involved in starch digestion and blood glucose regulation, at low levels, e.g. IC_{50} of approximatively 20 μg/mL GAE (Nwosu et al., 2011). It is evidenced that diphlorethohydroxycarmalol (DPHC) has the ability to reduce the effects of α-glucosidase and α-amylase. The IC_{50} values of DPHC against α-glucosidase and α-amylase were 0.16 and 0.53 mM, respectively. In addition to this, increased postprandial blood glucose levels were significantly suppressed in the DPHC-administered group than those in the streptozotocin-induced diabetic or normal mice. Moreover, the area under curve (AUC) was significantly reduced via DPHC administration (2022 versus 2210 mmol min/L) in the diabetic mice as well as it delayed the absorption of dietary carbohydrates (Toume et al., 2004; Lee et al., 2012). High glucose (30 mM) treatment induced the death of rat insulinoma cells, but treatment with 10 or 50 μg/mL 6,6′-bieckol significantly inhibited the high glucose-induced glucotoxicity. In addition to this, usage of 6,6′-bieckol significantly reduced the level of TBARS, generation of intracellular ROS and NO level, all of which were increased at high glucose concentrations (Park et al., 2015).

Radio-Protective Effects

Drug-induced toxicity such as ototoxicity from platinum-based compounds and aminoglycosides, often leads to hearing loss and hair loss. This may be caused because of the extensive formation of reactive species. Several small molecules have been used to suppress the reactive oxygen species to prevent further damages (Shin et al., 2014). Some of the compounds from marine resources have also been used such as dieckol and dioxinodehydroeckol (DHE) from *E. cava*. Chang et al. (2016) investigated drug-induced ototoxicity with dieckol in mice model; mice pre-treated with gentamicin were later exposed to dieckol for 48 h. Partial protection of gentamycin induced hair loss was observed after the treatment of dieckol (Chang et al., 2016). DHE has been explored for protective effect against UVB-induced damages in HaCaT cells. The cells were exposed to 20 mJ cm^{-2} of UVB irradiation which is the minimal

erythema dose (MED) for individuals to be able to tan. Furthermore, the expression levels of Bax/Bcl-2 and caspase-3, -8, -9, which are the genes associated with apoptosis were investigated when cells were either treated with DHE doses after UVB irradiation or exposed to UVB only. Clear UVB-protective effects were observed in DHE-treated cells (Ryu et al., 2015). In another study, DPHC was used to protect from UVB-induced DNA damages in HaCaT cells (Piao et al., 2015).

Doxorubicin-induced hepatotoxicity was protected with several brown seaweed extracts (Jung et al., 2014b). In another study, Kang et al. (2013c) used zebrafish model to check the protective effect against ethanol-induced damages. Phloroglucinol, eckol and dieckol were used, and dieckol showed highest protective effect against ethanol-induced cell apoptosis. Furthermore, the dieckol-treated group scavenged intracellular ROS and prevented lipid peroxidation and ethanol-induced cell death in the zebrafish embryo (Kang et al., 2013c). From the same group, reports suggest that most of the phlorotannins possess noticeable free radical scavenging activity, which can be potentially useful in diseases concerned with oxidative stress (Kang et al., 2013b). Eckstolonol from *E. cava* showed the protective effective against UVB-induced ROS in human keratinocytes (HaCaTs). Cell viability was decreased by UVB radiation and restored by the treatment with different eckstolonol concentrations (0, 5, 50, 100, and 200 μM). Furthermore, eckstolonol reduced UVB-induced ROS, lipid peroxidation, damaged DNA levels, and cell death (Jang et al., 2012). In another study, Heo et al. (2010) showed the UVB-protective effect of DPHC via damaged DNA tail length and morphological changes in fibroblast. Dieckol also showed protective effect from the UVB-induced damages (Heo et al., 2009), and phloroglucinol and eckol showed strong protective effects against gamma irradiated damages (Moon et al., 2008; Kang et al., 2010).

Antiadipogenic Activity

Obesity is one of the most common health problems, which leads to several diseases such as type 2 diabetics, cardiovascular diseases, and hypertension. Increase in the number of mature adipocytes is the main cause of obesity (Kim et al., 2013a). Some of the phlorotannins have shown inhibitory activity towards adipogenesis and obesity. Kang et al. (2015) investigated the phlorotannin from *E. cava* for inhibitory effect of adipogenesis. The researchers also examined the adipogenic activities by measuring glycerol release level and adipogenic-related gene expression in differentiating 3T3-L1 preadipocytes. The phlorotannin increased glycerol secretion and reduced glucose consumption level in cells. In addition, effects on PPARγ, C/EBPα and differentiation-dependent factor 1/sterol regulatory element-binding protein 1c, as well as downstream genes such as fatty acid binding protein-4, fatty acid transport protein-1, fatty acid synthase, leptin and acyl-CoA synthetase 1 were also studied (Kong et al., 2015). In another study by Karadeniz et al. (2015), it was reported that phlorotannin suppressed adipogenesis in preadipocytes. Triphlorethol-A, eckol and dieckol were checked against the antiadipogenesis activity. Phlorotannin (20 μM) reduced lipid accumulation and suppressed the adipogenic differentiation markers (Karadeniz et al., 2015). In another study, dieckol from *E. cava* suppressed lipid accumulation in animal model. Mice were used in the study with normal diet, high-fat diet and dieckol-treated groups. Dieckol-supplemented groups showed significant decreases in body weight gain (36%) when compared with the high-fat diet group. In addition, dieckol downregulated the adipogenic factors and decreased the triacylglycerol content in MT3-L1 cells (Choi et al., 2015).

Phloroglucinol, eckol, dieckol, dioxinodehydroeckol, and phlorofucofuroeckol A from *E. stolonifera* were isolated and checked for their abilities to inhibit adipogenesis over a range of concentrations (12.5–100.0 μM). Phloroglucinol, eckol, and phlorofucofuroeckol A significantly and concentration-dependently inhibited lipid accumulation in 3T3-L1 cells without affecting cell viability. All the five compounds reduced the expression levels of several adipocyte marker genes, including PPARγ and CCAAT/enhancer-binding protein α (C/EBPα) (Jung et al., 2014a). In another study, dieckol showed adipogenesis inhibition and down-regulated the expression of PPARγ, CCAAT/enhancer-binding proteins (C/EBP$_\alpha$), sterol regulatory element-binding protein 1 (SREBP1) and fatty acid binding protein 4 (FABP4) in a dose-dependent manner. The specific mechanism mediating the effects of dieckol was confirmed by AMP-activated protein kinase (AMPK) activation (Ko et al., 2013).

Other Activities

Several other biological activities of phlorotannins have been reported earlier in the literature. These include sleep induction (Cho et al., 2012, 2014b), arousal inhibitory effect (Cho et al., 2014a), SARS-CoV 3CL inhibition (viral replication) (Park et al., 2013), antiviral activity (Kwon et al., 2013), anti-Alzheimer disease (Kang et al., 2013a), inhibitory effect against melanin synthesis (Kang et al., 2012c), neuroprotection (Kang et al., 2012b), hepatoprotection (Kang et al., 2012a; Kim et al., 2011b), osteogenesis (Ali and Hasan, 2012), neuraminidase inhibitory activity (Ryu et al., 2011), and inhibition of high glucose-induced oxidative stress (Lee et al., 2010). Other reported effects include antioxidant (Kim et al., 2010), anti-arthritis (Ryu et al., 2009), hepatocellular carcinoma inhibition (Yoon et al., 2008), inhibition of glycosidase (Shibata et al., 2002, 2003), antiplasma inhibitor (Fukuyama et al., 1989a, 1989b, 1990; Nakayama et al., 1989), carbolytic enzyme inhibition activity (Kellogg et al., 2014), antiallergic activity (Ahn et al., 2015; Sugiura et al., 2006, 2007; Le et al., 2009) and anti-HIV activity (Karadeniz et al., 2014; Ahn et al., 2004; Artan et al., 2008; Vo and Kim, 2010).

Conclusion

To conclude, the information provided in this chapter point to phlorotannins as excellent materials to treat various diseases at a lower concentration due to their exceptional biological activity. Recently, considerable attention has been paid on natural materials for the development of cosmeceuticals, pharmaceuticals and nutraceuticals. Currently, few companies around the world have been utilizing the extract of phlorotannin for the development of cosmeceutical and nutraceutical products. However, the utilization of seaweed in many countries is not yet well-explored.

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