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REVIEW

Recent advances in pharmacological research on *Ecklonia* species: a review

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Abstract The genus *Ecklonia* (Lessoniaceae, Phaeophyceae), commonly called kelp (brown algae), is abundant on the coasts of Japan and Korea. During the past few decades, *Ecklonia* species have received tremendous attention for their wide range of therapeutic properties and multiple health benefits, such as great nutritional value and being rich in vitamins, minerals, dietary fiber, proteins, and polysaccharides. Several novel functional ingredients with diversified biological activities have been isolated and possess antimicrobial, antiviral, hepatoprotective, cardioprotective, anti-inflammatory, neuroprotective, anticarcinogenic, immunomodulatory, hypolipidemic, antidiabetic, and antioxidant therapeutic properties. The present review discusses the phytochemical, pharmacological, therapeutic, nutritional, and health benefits of different species of genus *Ecklonia*, as well as their use in the prevention of disease and maintenance of good health.

Keywords Brown seaweed · *Ecklonia* · Therapeutic potential

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Introduction

Seaweed is used as a vegetable and traditional medicine in East-Asian countries such as Japan, Korea, and China. It is an important resource of the marine ecosystem, containing active metabolites with probable nutraceuticals that are rich sources of novel bioactive secondary metabolites and harbor diverse classes of health-promoting molecules, including essential dietary fiber, fatty acids, essential amino acids, and vitamins A, B, C, and E (Kolb et al. 2004). Taxonomic classification divides seaweed into three major classes based more on their pigments and coloration than their genetics: Rhodophyceae (red algae), Phaeophyceae (brown algae), and Chlorophyceae (green algae, also known as macroalgae) (Rajasulochana et al. 2009). Brown algae have been used for thousands of years, but only in modern times have they been recognized to contain bioactive substances such as polysaccharides, lipids, and polyphenols, with various pharmacological properties (Kumar et al. 2008).

Ecklonia is a genus of kelp (brown algae) belonging to the family Lessoniaceae that has an abundance of eckol-type phlorotannins. There are nine species: *Ecklonia biruncinata, Ecklonia brevipes, Ecklonia cava* (EC), *Ecklonia fastigiata, Ecklonia kurome* (EK), *Ecklonia maxima* (EM), *Ecklonia muratii, Ecklonia radiate* (ER), and *Ecklonia stolonifera* (ES) (Hornemann 1828; Moon et al. 2008). EC, an edible marine brown alga, is used as a food ingredient, animal feed, and fertilizer, as well as a raw material in the production of fucoidan and phlorotannin. EC is also used as an herbal remedy in the form of an extract called Seanol, a polyphenolic extract, and Ventol, a phlorotannin-rich natural agent with two major constituents, phlorotannins and sterols (Kang et al. 2003a). ES (turuarame), EK, and ER are edible species traditionally

eaten in Japan and Korea and are rich in phlorotannins and fatty acids.

Ecklonia species are known to exhibit antioxidant (Heo et al. 2005), anti-inflammatory (Kim et al. 2016a), antibacterial (Choi et al. 2011), anti-diabetic (Jung et al. 2008), anticancer (Kong et al. 2009), anti-photoaging (Joe et al. 2006), anti-HIV (Artan et al. 2008), anti-hypertensive (Jung et al. 2006), hepatoprotective (Jung et al. 2014a), and anti-allergic activities (Le et al. 2009). Due to these numerous health benefits, they have been a focal point for researchers eager to elucidate their pharmacological potential. Plenty of information regarding the pharmacological activities of terrestrial plants is available; however, such information is limited for marine species (Shibata et al. 2008). A handful of excellent studies are available regarding the pharmacological activities of *Ecklonia* (Wijesinghe and Jeon 2012; Thomas and Kim 2011; Li et al. 2011; Wijesekara et al. 2010). Also, Jiao et al. (2011) have reported the chemical structures and bioactivities of marine algae. Fourteen years of research and nearly $35 million of clinical studies demonstrate the importance of *Ecklonia* species. *Ecklonia*-derived polyphenols are unlike those found in land-based plants and are quite possibly the most powerful antioxidants found in nature, being 10–100 times more powerful than other polyphenols. The oxygen radical absorbance capacity (ORAC) score of such a polyphenol is more than 8300. The water-soluble polyphenols found in land-based plants have a half-life of about 30 min, and their antioxidant powers decrease very quickly (Seanol 2007).

Various phlorotannins, polysaccharides, enzymatic extracts, and organic extracts from *Ecklonia* exhibit multifaceted beneficial effects when used in pharmaceuticals, nutraceuticals, cosmeceuticals, and functional foods. Thus, this genus has been a target of special attention, and consumer-driven demand has led to the development of marine-derived medicines. Our review summarizes the literature on the biological characterization and pharmacological bioactivity of various *Ecklonia* species, focusing on recent developments in the therapeutic application of extracts and isolates.

Biological activities of extracts from *Ecklonia* species

Antioxidant activity

A shift in the balance between oxidants and antioxidants in favor of oxidants is called oxidative stress (Table 1). It arises when the balance between the production of reactive oxygen species (ROS) and antioxidant defenses changes. Human cells have an inherited antioxidative defense system in the form of various enzymatic and non-enzymatic pathways for removing ROS. Elevated production of ROS increases oxidative stress, leading to cellular dysfunction, and it can eventually contribute to many pathological conditions, including neurological disorders (Agostinho et al. 2010), diabetes (Ceriello 2008), cancer (Perse 2013), asthma (Ma et al. 2016), and dermal disease (Trouba et al. 2002).

An ethanolic extract of EC attenuated H_2O_2-induced comet tail formation and phospho-histone γH2AX expression. Furthermore, it enhanced the level of the phosphorylated form of nuclear factor erythroid 2- related factor 2 (Nrf2) and its nuclear translocation, which was associated with the induction of heme oxygenase-1 (HO-1) and NAD'PH-quinone oxidoreductase-1 (NQO-1). Thus, EC provided cytoprotective effects against oxidative stress in muscle cells via up-regulation of Nrf2-HO-1 and NQO-1 expression through the activation of the mitogen-activated protein kinases (MAPK) pathway, which could be due to its phenolic content (Choi 2016). In another study, ES and EK showed high total phenolic content (TPC) and high antioxidant activity, including 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical and hydroxyl (•OH) radical scavenging, ferrous reducing power, and superoxide ($\bullet O_2^-$) radical scavenging activity. Those results suggest that macroalgal beach-casts could be used as a new natural source for functional foods, cosmetics, medicines, and fertilizer instead of being processed into landfills or incinerated (Kuda and Ikemori 2009). Enzymatic extracts from ER demonstrated more potent antioxidant ability in the ferric reducing ability of plasma (FRAP) and ORAC assays (TPC of 4.4 g) than conventional acidic extracts (TPC of 3.4 g), showing their potential for value-added nutritional products (Charoensiddhi et al. 2015).

Anti-inflammatory activity

Inflammation is a pathological condition that produces highly reactive species. Nitric oxide (NO), a small diffusible molecule responsible for vasodilatation, neurotransmission, and inflammation, is produced by organisms at a basal concentration. However, under stimulation by pathogens, NO is generated in higher amounts by the inducible nitric oxide synthase (iNOS) in activated macrophages (Moncada et al. 1991). Nonsteroidal anti-inflammatory drugs are commercially available medications for inflammatory pain, but their side effects have limited their use. Anti-inflammatory drugs from natural resources have been sought due to the persistent deleterious side effects of commercial medications.

EC dose-dependently suppressed iNOS and cyclooxygenase-2 (COX-2) protein expression and subsequently reduced NO content in phorbol-12 myristate 13- acetate

Table 1 Summary of the biological activities of extracts of *Ecklonia* species

Therapeutic activity	Species	Extracts	Pathway mode	References
Antioxidant activity	*Ecklonia cava*	EtOH extract	Nrf2-HO-1 mediated MAPK	Choi (2016)
	Ecklonia stolonifera	H_2O extract	DPPH, •OH, •$O2^-$ radical-scavenging (Antioxidant)	Kuda and Ikemori (2009)
	Ecklonia kurome			
	Ecklonia radiata	Enzymatic extract	FRAP reducing (Antioxidant)	Charoensiddhi et al. (2015)
Anti-inflammatory activity	*Ecklonia cava*	Dried powder	iNOS/COX-2 expression mast cell	Kim (2014d)
	Ecklonia radiata	Non polar extract	NO mediated inflammation	McCauley et al. (2015)
Anti-diabetic activity	*Ecklonia cava*	Fermented EC/kimchi	α-Glucosidase and α-amylase	Lee et al. (2013b)
			High glucose mediated oxidative stress	Lee et al. (2014)
	Ecklonia kurome	EtOH extract	α-Amylase and α-glucosidase	Xu et al. (2012)
	Ecklonia kurome	Gametophytes	Regulate blood glucose and IFN-γ	Dwiranti et al. (2012)
Hepatoprotective activity	*Ecklonia cava*	EtOAc extract	HFD mediated hepatic steatosis prevention	Park et al. (2015b)
		Commercially available *Ecklonia cava*	Enhanced alcohol metabolizing enzymes	Yamashita et al. (2015)
	Ecklonia stolonifera	EtOH extract	Increased the expression of fatty acid oxidation-related genes	Bang et al. (2016)
Neuroprotective activity	*Ecklonia cava*	*n*-BuOH extract	Regulation of γ -secretase and α–secretase (Dementia)	Kang et al. (2013d)
	Ecklonia cava	70% EtOH extract	Nerve injury	Kim et al. (2014e)
	Ecklonia kurome	MeOH extract	AChE and BACE1 inhibition (Dementia)	Son et al. (2016)
Matrix metalloproteinase inhibitory activity	*Ecklonia cava*	80% EtOH extract	MMP-2 and -9	Bae et al. (2015)
Antibacterial/antiviral activities	*Ecklonia cava*	EtOAc extract	Antibacterial against *E. faecalis*	Kim et al. (2015c)
		EtOH extract	Antibacterial against lactic acid bacteria/*E. tarda*	Lee et al. (2016b)
		EtOH extract	Immunity against *E. tarda*	Lee et al. (2016c)
		Seanol	Mineralization and anti bacterial for bone regeneration	Douglas et al. (2016)
		Gold nanoparticles	Antimicrobial and biocompatibility	Venkatesan et al. (2014)
	Ecklonia kurome	H_2O extract	Antibacterial against *Propionibacterium acnes*	Choi et al. (2011)
Anti-obesity activity	*Ecklonia cava*	*n*-BuOH extract	Reduction of the adipogenic transcription factors	Kim et al. (2013)
		Polyphenolic extract	Regulation of AMPK and SIRT1 in HFD-induced obesity.	Eo et al. (2015)
Antihistamine activity	*Ecklonia cava*	EtOH extract	Histidine decarboxyalase reduction	Kim et al. (2014g); Jung et al. (2013b)
	Ecklonia kurome	Commercial extract	Degranulation of a rat basophilic leukemia cell line	Yoshioka et al. (2013)
	Ecklonia stolonifera	MeOH: chloroform (1: 2, v/v) extract		Sugiura et al. (2012)
Radioprotective activity	*Ecklonia cava*	Enzymatic extracts	NF-κB	Lee et al. (2013c)

(30 nmol/L) and A23187 (1 μmol/L) (PMACI)-stimulated human mast cell line-1 cells. NO production decreased by 25.4 and 46.6% with 50 and 100 μg/mL EC treatments, respectively. Furthermore, EC dose-dependently inhibited both the mRNA and protein expression of tumor necrosis factor (TNF)- α, interleukin (IL)-1β, and IL-6 in PMACI-stimulated human mast cell line-1 cells without any cytotoxic effects. The inhibitory effects of EC on IL-1β (75.0%) and TNF-α (60.6%) production were greater than those on IL-6 (23.0%) at 100 μg/mL. In addition, EC exerted anti-inflammatory action via the inhibition of the extracellular signal-regulated kinase (ERK)/MAPK signaling pathway, suggesting a potent and efficacious anti-inflammatory agent against mast cell-mediated inflammatory diseases (Kim 2014d). In another study, nonpolar extracts of ER strongly inhibited the production of NO. The order of activity was greatest in the non-polar, lipid-rich dichloromethane (CH_2Cl_2) extracts (>76% activity), followed by the intermediate polar ethyl acetate (EtOAc) extracts (>50% activity for all species), with the lowest activity observed in the polar butanol (*n*-BuOH) extracts (McCauley et al. 2015).

Anti-diabetic activity

The World Health Organization (WHO) defines diabetes as a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces, which leads to an increased concentration of glucose in the blood, i.e., hyperglycemia. Type 1 diabetes (previously known as insulin-dependent) is characterized by a lack of insulin production. Type 2 diabetes (formerly called non-insulin-dependent) is caused by the body's ineffective use of insulin, often from excess body weight and physical inactivity. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Rathmann and Giani 2004). Intensive insulin therapy carries a high risk of side effects, especially the occurrence of severe hypoglycemia; therefore, research into antihyperglycemic agents has focused on plants used in traditional medicine because they could provide better treatment than the currently used synthetic drugs (McCall 2012).

Kimchi has been a popular side dish in Korea since ancient times. Baechu kimchi is a salt fermented cabbage widely consumed in traditional Korean foods. A recent study revealed that kimchi with added EC extract showed high inhibition against α-glucosidase and α-amylase, with IC_{50} values of 0.58 and 0.35 mg/mL, respectively. Both of those inhibitory activities of kimchi with added *Ecklonia* extracts (KE) were higher than those of kimchi extract alone. The hypoglycemic effect of KE was higher than that of kimchi extract on starch loading. KE suppressed the postprandial blood glucose level in both streptozotocin (STZ)-induced diabetic and normal mice, which indicated a delay in the absorption of dietary carbohydrates consumed (Lee et al. 2013b). In another report, baechu kimchi with added EC extract protected human umbilical vein endothelial cells (HUVECs) from damage induced by high glucose by restoring cell viability and reducing lipid peroxidation and intracellular ROS in a dose-dependent manner. Furthermore, it reduced the overexpression of iNOS, COX-2, and nuclear factor-κB (NF-κB) proteins in HUVECs, indicating its potential as a treatment against high glucose-induced oxidative stress (Lee et al. 2014). EK inhibited carbohydrate-hydrolyzing enzymes, decreased postprandial blood glucose levels, and improved glucose tolerance, decreasing both fasting blood glucose and insulin levels (Xu et al. 2012). EK effectively down-regulated blood glucose in both db/db mice and prediabetic C57BL/6J mice, indicating the presence of the active compounds in the gametophytes. EK regulated metabolism by manipulating the balance among cytokines, including interferon-gamma (IFN-γ) or leptin, resulting in the down-regulation of blood glucose (Dwiranti et al. 2012).

Hepatoprotective activity

The liver is involved in the metabolism of internal and external toxic agents. It has an astounding role in the performance, maintenance, and regulation of homeostasis in the body and is engaged in almost all biochemical pathways of growth, fight against diseases, nutrient supply, energy provision, and reproduction. It plays a vital role in the detoxification of xenobiotics and drugs (Agrawal et al. 2013). Hepatic disease is a term that indicates damage to liver cells, tissues, structures, or function. Because no drug currently available completely or effectively stimulates hepatic function, offers complete protection to the organ, or aids in regenerating hepatic cells, naturally derived hepatoprotective agents are needed to negate the factors that contribute to liver damage.

A polyphenol-rich fraction of EC prepared in Gijang prevented diabetes by regulating various metabolic processes, such as lipogenesis, lipolysis, inflammation, and the antioxidant defense system in livers and adipose tissues affected by nonalcoholic fatty liver disease in high fat diet (HFD)-fed mice. Magnetic resonance imaging/magnetic resonance spectroscopy (MRI/MRS) analysis showed that liver fat and liver volume in HFD-triggered obese mice decreased following Gijang extract treatment. Furthermore, the treatment reduced the mRNA expression levels of inflammatory cytokines and hepatic lipogenesis-related genes and increased the mRNA expression level of cholesterol 7α-hydroxylase 1, the key enzyme in bile acid

synthesis. Thus, Gijang extract ameliorated hepatic steatosis by suppressing inflammation and improving lipid metabolism (Park et al. 2015b). Apart from this, EC increased the activity of alcohol dehydrogenase, aldehyde dehydrogenase, and cyclic adenosine monophosphate (cAMP) concentration, suggesting that it plays a role in the activities of alcohol-metabolizing enzymes and their regulating mechanisms in ethanol-treated hepatocytes. EC inhibited cytochrome P450 2E1 expression related to the production of ROS (Yamashita et al. 2015). A study investigated the protective effect of ES in alcoholic fatty liver and found that ES treatment suppressed adipogenesis and increased the expression of fatty acid oxidation-related genes, e.g., peroxisome proliferator-activated receptor (PPAR)-α and CPT-1, but decreased the expression of sterol regulatory element-binding protein (SREBP)-1, a triglyceride (TG) synthesis-related gene, suggesting that ES extract could be useful in preventing fatty acid oxidation and reducing lipogenesis in ethanol-induced fatty liver (Bang et al. 2016).

Neuroprotective activity

Neurodegenerative diseases are expected to surpass cancer as the second most common cause of death among the elderly by the 2040s (Lilienfeld and Perl 1993). Alzheimer's disease (AD) is characterized by loss of memory and other cognitive functions and accounts for most of the deaths in the elderly. An increase in acetylcholinesterase (AChE) level around β-amyloid plaques and neurofibrillary tangles is a common feature of AD neuropathology (Lam et al. 2016). Parkinson's disease (PD) is a multidimensional progressive disease with many motor and non-motor features, including cognitive dysfunction. Adverse intra- and extracellular effects of toxic α-synuclein are believed to be central to the pathogenesis of PD and other nervous system disorders with Lewy body pathology (Goldman and Postuma 2014; Ingelsson 2016). Many categories of natural and synthetic neuroprotective agents have been reported. Considering the devastating side effects of synthetic neuroprotective agents, there is growing interest in nutraceuticals or other herbal alternatives (Pangestuti and Kim 2011).

A study by Kang et al. (2013d) demonstrated that EC *n*-BuOH extract regulated the expression and activity of γ-secretase and α-secretase, leading to a reduction in Aβ production by the stable cells and a reduction in the basal nuclear location of the PSEN1 responsible for chromosome mis-segregation in neurodegenerative disease. EC and EK together inhibited AChE and BACE1 by 84.41 ± 1.70 and 81.17 ± 2.43%, respectively, reducing neuronal cell death and improving dementia, highlighting their synergistic potential. EK likewise showed the highest result of the 2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay (IC_{50} = 0.07 ± 0.01 mg/mL), which the researchers attributed to its TPC (Son et al. 2016). Kim et al. (2014e) further highlighted the importance of EC for its potential analgesic effects in postoperative pain and neuropathic pain. EC extracts (300 mg/kg) significantly increased the mechanical withdrawal therapy value. The number of ultrasonic distress vocalizations in the treated group of rats was reduced at 6 and 24 h after plantar incision operation (62.8%). EC also increased the paw withdrawal latency in hot-and cold-plate tests in the plantar incision rats. After 15 days of continuous treatment, EC (300 mg/kg) alleviated the spared nerve injury-induced hypersensitivity response, which could revolutionize the use of natural resources for therapeutic treatment.

Matrix metalloproteinase inhibitory activity

Matrix metalloproteinases (MMPs), known as matrixins, are a large family of similar proteolytic enzymes involved in tissue remodeling associated with various physiological and pathological processes, such as morphogenesis, angiogenesis, tissue repair, arthritis, chronic heart failure, chronic obstructive pulmonary disease, chronic inflammation, and cancer metastasis. As a result, MMPs are considered viable drug targets in the therapy of those diseases (Dormán et al. 2010).

According to gelatin zymography results, extracts harvested from EC and *Ecklonia bicyclis* showed higher inhibitory effects on MMP-2 and -9 activity than those from the other marine plants at concentrations of 10, 50, and 100 μg/mL (Bae et al. 2015).

Antibacterial and antiviral activity

The global epidemic of bacterial resistance to existing antibiotics such as β-lactams and quinolones necessitates the discovery of potent candidates from natural resources, both terrestrial and marine. The evolution of antibacterial biomolecules alongside bacteria over millions of years allow them to overcome strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and fluoroquinolone-resistant *Pseudomonas* (Ramanan et al. 2016). Therefore, exploring and developing cheaper and more effective natural antimicrobial agents with better potential and fewer side effects than existing antibiotics, good bioavailability, and minimal toxicity is a public health priority (Pérez et al. 2016).

A recent study showed that EC with ciprofloxacin evinced potent antibacterial activity against *Enterococcus faecalis*, showing synergistic effects. EtOAc exhibited the strongest antibacterial activity, with a minimum inhibitory

concentration (MIC) value of 128 μg/mL against *E. faecalis* strains. Furthermore, the combination of ciprofloxacin and the EtOAc fraction resulted in a $\sum FIC_{min}$ of 0.188 and $\sum FIC_{max}$ range of 0.508–563, suggesting that the ciprofloxacin-EtOAc combination resulted in an antibacterial synergy effect against *E. faecalis* (Kim et al. 2015c). EC led to the strongest growth effects on three lactic acid bacteria and fish pathogenic bacteria in a dose-dependent manner. Secondary metabolites produced by EC significantly inhibited the growth of pathogen bacteria. In a further in vivo study, the co-treatment of EC and *L. plantarum* improved the growth and mortality of *Edwardsiella tarda*-infected zebrafish by regulating the expression of inflammatory molecules such as iNOS and COX-2. Altogether, EC played an important role as a potential prebiotic and protected against the infection caused by *E. tarda* injection in zebrafish (Lee et al. 2016b). EC (1.0%) improved the growth and body weight of olive flounder and decreased its mortality from *E. tarda* without changing its biochemical profile. The supplementation of 1.0% ethanolic extract of EC also enhanced the innate immune response of the fish, as evidenced by a high respiratory burst and increased serum lysozyme and myeloperoxidase activity. Thus, EC acted as a prebiotic by improving the innate immune response in fish infected with pathogenic bacteria (Lee et al. 2016c). Seanol, a seaweed extract rich in phlorotannins, stimulated mineralization with calcium phosphate, increased antibacterial activity, and increased compressive modulus. Seanol and alkaline phosphatase (ALP) interacted in a non-covalent manner. Seanol exhibited antibacterial activity against MRSA with comparable cytotoxicity toward MG-63 osteoblast-like cells, suggesting its mineralizability and antibacterial activity (Douglas et al. 2016). Venkatesan et al. (2014) reported the rapid biological synthesis of gold nanoparticles (Au NPs) using EC by reducing chloroauric acid. Fourier transform infrared (FTIR) spectroscopic analysis showed that Au NPs functionalized with biomolecules (a primary amine group, a hydroxyl group, and other stabilizing functional groups) showed good antimicrobial activity and biocompatibility with a human keratinocyte cell line. The results indicate that AUNPs might have promising applications in drug delivery, tissue engineering, and biosensor development. ER extract prepared by using celluclast-assisted extraction induced significantly higher production of butyrate (9.2 μmol/mL) and promoted the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus,* improving gut health (Charoensiddhi et al. 2016). EC and EK had the strongest inhibitory effects when tested using the agar disk diffusion method, with an MIC of 0.31 mg/mL and no cytotoxicity even at 200 μg/mL, indicating their potential as therapeutic agents for acne vulgaris (Choi et al. 2011).

Anti-obesity activity

Obesity is a leading preventable cause of death worldwide, with increasing rates in both developed and developing countries. As defined by WHO, it is a medical condition in which excess body fat has accumulated to the extent that it can have negative effects on health, and it is often comorbid with diseases such as type 2 diabetes, hypertension, coronary disease, and cancer. In 1997, WHO announced that obesity had reached epidemic proportions worldwide (Kumar and Rao 2013; Caballero 2007). Commercial drugs, such as orlistat; lorcaserin; and a combination of phentermine, topiramate, and bariatric surgery, such as Roux-en-Y bypass or gastric banding, are available. However, concerns about perioperative mortality, surgical complications, and the frequent need for reoperation mean that those procedures tend to be reserved for morbid obesity (Rodgers et al. 2012). Thus, remedies from natural sources are vital, especially those from marine sources.

The anti-adipogenic activity of EC was determined by measuring lipid accumulation in adipocytes. The *n*-BuOH fraction particularly reduced lipid accumulation and glucose consumption; the adipogenic transcription factors PPARγ and SREBP-1c; and the adipogenic specific genes fatty acid binding protein (FABP)-4, FABP-1, fatty acid synthase (FAS), lipoprotein lipase (LPL), hormone-sensitive lipase (HSL), and acyl-CoA synthetase 1 (ACS1) (Kim et al. 2013). EC polyphenol extract regulated fat metabolism, inflammation, and the antioxidant defense system in HFD-induced obese mice. EC polyphenol extract supplementation reduced body weight gain, adipose tissue mass, plasma lipid profiles, hepatic fat deposition, insulin resistance, and the plasma leptin/adiponectin ratio derived from HFD-induced obesity. Furthermore, EC polyphenol extract supplementation selectively ameliorated the hepatic protein levels associated with lipogenesis, inflammation, and the antioxidant defense system, as well as activation of AMPK and sirtuin (SIRT1) to inhibit obesity (Eo et al. 2015).

Antihistamine activity

There has been a worldwide increase in allergic diseases, including atopic dermatitis, asthma, allergic rhinitis, and food allergies, possibly because environmental factors are interacting with genetic factors to sensitize individuals (Tanaka 2014). Numerous studies have been done in the search for anti-allergens, especially from marine resources.

EC extract exhibited excellent inhibitory activity against crude histidine decarboxylase (HDC), reducing overall histamine production by 46.29% and thereby enhancing the safety of mackerel muscle (Kim et al. 2014g). Another report presented a 32% inhibition of HDC at a concentration of 1 mg/mL, reducing histamine poisoning by

decreasing histamine production in mackerel (Jung et al. 2013b). EC and EK together inhibited the degranulation of a rat basophilic leukemia cell line (RBL-2H3), mitigating allergic symptoms and highlighting their synergistic potential (Yoshioka et al. 2013). Phlorotannin-rich ES inhibited enzymatic activity and degranulation in stimulated RBL-2H3 cells in a dose-dependent manner. The MeOH: chloroform (1:2, v/v) (M/C) extract of ES also inhibited enzyme activity and degranulation in stimulated RBL cells in a dose-dependent manner. The active compounds in the M/C extract might be phenolic compounds, such as phlorotannins, because the M/C extract became inactive when the phenolic compounds were removed (Sugiura et al. 2012).

Radioprotective activity

Ionizing radiation produces deleterious effects, deterministic or stochastic, on living organisms, though it can have health benefits in the form of radiation therapy for the treatment of cancer or thyrotoxicosis. The benefits of ionizing radiation are compromised by the side effects that result from radiation-induced damage to normal tissue, and the synthetic agents used to combat those side effects, WR2721 (amifostine), OK-432, and ethiofos, have their own serious side effects, including decreased cellular function, nausea, hypotension, and death (Baliga and Rao 2010; Park et al. 2008). Therefore, investigators have directed their attention toward plants and other natural products.

Enzymatic extracts of EC exhibited radioprotective properties, including the modulation of apoptosis via inhibition of the NF-κB signaling pathway (Lee et al. 2013c).

Biological activity of isolates from *Ecklonia* species

Antioxidant activity

Ecklonia species and their constituents exhibit pronounced inhibitory effects against oxidative stress (Table 2). EC phlorotannins, including phloroglucinol (PG), eckol, dieckol, eckstolonol, and triphlorethol-A (TPA), scavenged intracellular ROS, inhibited lipid peroxidation, and suppressed 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH)-induced cell death in zebrafish embryos. These phlorotannins maintained the positive changes in morphological phenomena; pericardial edema, yolk sac edema, and growth retardation in zebrafish embryos exposed to AAPH were not observed in the groups also exposed to phlorotannins, indicating that the phlorotannins possess prominent antioxidant activity against AAPH-mediated toxicity (Kang et al. 2013a). TPA further exhibited a protective effect against oxidative stress-induced DNA-base damage, especially 8-oxoguanine (8-oxoG), in V79-4 cells. Decreased level of 8-oxoG induced by H_2O_2 were confirmed by an increase in OGG1 mRNA and OGG1 protein levels. TPA restored the expression of nuclear Nrf2, small Maf protein, and the Nrf2-Maf complex and also increased Nrf2 binding to ARE sequences and the resulting OGG1 promoter activity. Sequentially, it maintained the levels of the phosphorylated forms of Akt kinase downstream of phosphatidylinositol 3-kinase (PI3K) and Erk, which are regulators of OGG1, suggesting that OGG1 induction by TPA involves the PI3K/Akt and Erk pathways (Kim et al. 2014a). Eckol from EC also attenuated the high intracellular Ca^{2+} levels stimulated by H_2O_2, decreased the augmented levels of mitochondrial ROS, recovered H_2O_2-diminished ATP level and succinate dehydrogenase activity, and induced manganese superoxide dismutase through phosphorylated AMPK and forkhead box O3a (FoxO3a), which showed a cytoprotective effect on Chang liver cells (Kim et al. 2014b). Fucoidan extracted from EC exhibited prominent effects on peroxyl radical scavenging activity and 2, 2′-azobisdihydrochloride-induced oxidative stress in Vero cells and reduced ROS generation, lipid peroxidation, and cell death in a zebrafish model, proving its antioxidant capacities in vitro and in vivo despite being neither a polyphenol nor a flavonoid. Although, it did not contain a benzene ring or conjugated structure, it exhibited antioxidant potential (Kim et al. 2014c). In another study, 6,6-bieckol, 7-phloroeckol, dieckol, and phlorofucofuroeckol (PFF-A) isolated from EC significantly inhibited high glucose–induced ROS and cell death in zebrafish. Dieckol significantly reduced heart rate, ROS, NO, lipid peroxidation generation, and cell death and also reduced the overexpression of iNOS and COX-2, thereby preventing oxidative stress (Kim et al. 2015a). ES could be used as a natural antioxidant and cytoprotective agent. ES inhibited ROS even at a concentration of 25 μg/mL, yielding five compounds (PFF-A, dieckol, eckstolonol, PG, and eckol) that inhibited total ROS, proving its use as a potent scavenger (Kang et al. 2004). Three active compounds were isolated from ES, PFF-A, dieckol, and dioxinodehydroeckol (DHE), among which PFF-A and dieckol significantly suppressed intracellular ROS in lipopolysaccharide (LPS)-induced RAW264.7 cells, and DHE scavenged DPPH radicals. PFF-A also significantly inhibited the LPS-induced production of NO and prostaglandin E2 (PGE2) through the down-regulation of iNOS and COX-2 protein expression (Kim et al. 2009). Dieckol and PFF-A obtained from boiling water- and organic solvent extracts of EC and ES showed almost 9- and 7- fold stronger antioxidant activity than the standard butylhydroxytoluene, and 6- and 4- fold greater activity than l-ascorbic acid in molar concentration,

Table 2 Summary of the biological activities of the isolates from *Ecklonia* species

Therapeutic activity	Species	Compounds	Pathway/mode	References
Antioxidant activity	*Ecklonia cava*	Phloroglucinol	Intracellular ROS/lipid peroxidation inhibition	Kang et al. (2013a)
		Eckol		
		Dieckol		
		Eckstolonol Triphlorethol-A		
		Triphlorethol-A	PI3 K/Akt and Erk regulation	Kim et al. (2014a)
		Fucoidan	Oxidative stress in vero cells and zebrafish model	Kim et al. (2014c)
		6,6-bieckol,	iNOS/COX-2	Kim et al. (2015a)
		7-phloroeckol		
		Dieckol Phlorofucofuroeckol		
	Ecklonia stolonifera	Phlorofucofuroeckol-A	Oxidative stress	Kang et al. (2004)
		Dieckol		
		Eckstolonol		
		Phloroglucinol		
		Eckol		
		Phlorofucofuroeckol-A	iNOS/COX-2	Kim et al. (2009)
		Dieckol		
		Dioxinodehydroeckol		
		Eckol	DPPH radical	Kang et al. (2003b)
		Phlorofucofuroeckol-A		
		Dieckol		
		Eckstolonol		
		Eckol	HO-1 via JNK, PI3K/Akt	Jun et al. (2014)
	Ecklonia kurome	974-A	DPPH radical	Yotsu-Yamashita et al. (2013)
		974-B		
		Phlorofucofuroeckol-A		
		Phlorofucofuroeckol-B		
		Phloroglucinol		
		Dieckol		
	Ecklonia maxima	Phloroglucinol		Rengasamy et al. (2013)
		Dibenzo [1,4] dioxine-2,4,7,9-tetraol		
		Eckol		
Anti-inflammatory activity	*Ecklonia cava*	Dieckol	iNOS/COX-2 mediated NF- κB	Yang et al. (2016)
			STAT-1 activation	Kang et al. (2015)
		8,8′-bieckol	NO/PGE2/IL-6 via NF-κB	Yang et al. (2014)
		Fucoidan	ROS/NO	Lee et al. (2013a)
	Ecklonia stolonifera	Phlorofucofuroeckol-A	iNOS/COX-2 mediated NF- κB	Kim et al. (2011)
		2-phloroeckol		Wei et al. (2016)
		6,6′-bieckol		
		Phlorofucofuroeckol-A		
		Phlorofucofuroeckol-B		
		974-B		

Table 2 continued

Therapeutic activity	Species	Compounds	Pathway/mode	References
Anti-diabetic activity	*Ecklonia cava*	2,7″-PG-6,6′-bieckol	α-Glucosidase and α-amylase	Lee et al. (2017a)
		6,6′-bieckol	Glucotoxicity reduction	Park et al. (2015a), (2014)
		Dieckol	Decreased blood glucose level	Kang et al. (2013b)
			Insulin resistance	Lee and Jeon (2015)
			Akt up-regulation	Kim et al. (2016b)
		Phlorofucofuroeckol-A	α-Glucosidase and α-amylase	You et al. (2015)
	Ecklonia maxima	Phloroglucinol	α-Glucosidase	Rengasamy et al. (2013)
		Dibenzo [1,4] dioxine-2,4,7,9-tetraol		
		Eckol		
	Ecklonia stolonifera	Eckol	AGE/RLAR	Jung et al. (2008)
		Dieckol		
		7-phloroeckol		
		Fucosterol	PTP1B/α-glucosidase	Jung et al. (2013a)
		Phlorofucofuroeckol-A	PTP1B	Moon et al. (2011)
		Dieckol		
		7-phloroeckol		
Hepatoprotective activity	*Ecklonia cava*	Dieckol	JNK activation via NF-κB inhibition	Lee et al. (2016a)
			Ethanol-induced cell apoptosis	Kang et al. (2013c)
	Ecklonia stolonifera	Dioxinodehydroeckol	Doxorubicin-induced hepatotoxicity	Jung et al. (2014a)
		Eckol		
		Phlorofucofuroeckol-A		
		Dieckol		
		Triphlorethol-A		
		Eckstolonol	Tacrine induced cytotoxicity	Kim et al. (2005)
		Phlorofucofuroeckol-A		
		Eckol	Inhibition of Fas-mediated cell-death proteins	Lee et al. (2012a)
		2-phloroeckol		
		Phloroglucinol	Decreased lipid peroxide	Park (2000)
Neuroprotective activity	*Ecklonia cava*	Dieckol	Erk/Akt phosporylation	Cui et al. (2015)
			Rotenone-induced α-synuclein aggregation	Cha et al. (2016)
		PG (1,3,5-trihydroxybenzene)	Cognitive dysfunction repair	Yang et al. (2015b)
		Phlorofucofuroeckol-A	BChE	Choi et al. (2015b)
	Ecklonia kurome	Oligosaccharide sugar chain	Apoptosis and fibril formation	Hu et al. (2004)
	Ecklonia maxima	Phloroglucinol Dibenzo [1,4] dioxine-2,4,7,9-tetraol	AChE	Kannan et al. (2013)
		Eckol		
	Ecklonia stolonifera	Eckstolonol	Modulation of benzodiazepine	Cho et al. (2014)
		Fucosterol fucoxanthin	BACE1	Jung et al. (2016)
Matrix metalloproteinase inhibitory activity	*Ecklonia stolonifera*	Eckol	TNF-α induced expression of MMP-1	Joe et al. (2006)
		Dieckol		

Table 2 continued

Therapeutic activity	Species	Compounds	Pathway/mode	References
Anticoagulative activity	*Ecklonia kurome*	Fucoidan	Thrombin and factor Xa inhibition	Nishino et al. (1999)
		Phlorofucofuroeckol-A eckol	α2-Macroglobulin/alpha 2-plasmin inhibitor	Fukuyama et al. (1990)
Antibacterial and antiviral activities	*Ecklonia cava*	Dieckol	Blocked the cleavage of SARS-CoV 3CL(pro)	Kanagasabhapathy et al. (2006)
		EC29T	Antibacterial	Kim et al. (2015d)
		Eckol	Viral replication	Kwon et al. (2013)
		Dieckol Phlorofucofuroeckol-7-phloroeckol		
	Ecklonia kurome	Dieckol 8,8′-bieckol	Bactericidal against MRSA	Nagayama et al. (2002)
Anti-obesity activity	*Ecklonia cava*	Triphlorethol-A Eckol dieckol	Regulation of adipogenic transcription factors	Kong et al. (2015)
		Dieckol	Regulation of adipogenic transcription factors via AMPK	Ko et al. (2013)
		Eckol	Regulation of adipogenic transcription factors via C/EBPα	Kim and Nam (2017)
		Dieckol		
		Phlorofucofuroeckol-A		
		Dieckol	Lipid accumulation via AMPKα	Choi et al. (2015a)
		Seapolynol	Triglyceride synthetic enzymes inhibition	Jeon et al. (2015)
	Ecklonia stolonifera	Fucosterol	PPARγ/C/EBPα pathway	Jung et al. (2014b)
			PI3K/Akt, and ERK pathways	Lee et al. (2017b)
	Ecklonia kurome	974- B	Differentiation of fibroblasts	Mori et al. (2014)
Antihistamine activity	*Ecklonia cava*	Dieckol	Mast cell-mediated type I allergic inhibition	Ahn et al. (2015c)
	Ecklonia kurome	Phloroglucinol	Hyaluronidase inhibition	Shibata et al. (2002)
		Eckol		
		Phlorofucofuroeckol-A		
		Dieckol		
		8,8′ bieckol		
Radioprotective activity	*Ecklonia cava*	Phloroglucinol	Radiation-induced apoptosis	Park et al. (2011)
			Apoptosis-related molecules regulation	Ha et al. (2013)
Anticancer and cytotoxic activity	*Ecklonia cava*	Dieckol	NDEA mediated Liver cancer	Sadeeshkumar et al. (2016)
			Regulation of metastasis-related genes (breast cancer)	Kim et al. (2015b)
			Apoptosis (Nephrotoxicity)	Yang et al. (2015a)
			Apoptosis via AKT and p38 (Ovarian cancer)	Ahn et al. (2015a)
		Crude polysaccharides	Regulation of Bcl-2/Bax (Colon cancer)	Ahn et al. (2015b)
	Ecklonia stolonifera	Dieckol	Mitochondrial-dependent pathways (Hep 3B cells)	Yoon et al. (2013)
Ultraviolet protection	*Ecklonia cava*	Dioxinodehydroeckol	Bax/Bcl-2 and caspase pathway	Ryu et al. (2015)
		Fucodiphlorethol G	UVB induced oxidative stress	Kim et al. (2014f)

Table 2 continued

Therapeutic activity	Species	Compounds	Pathway/mode	References
Anti-hypertensive activity	*Ecklonia cava*	Eckol Phlorofucofuroeckol-A Dieckol Phloroglucinol Eckstolonol	ACE inhibitory	Jung et al. (2006)
Anti-HIV activity	*Ecklonia cava*	8,4‴-dieckol	HIV-1 reverse trancriptase	Karadeniz et al. (2014)

respectively (Chowdhury et al. 2014). Three known phlorotannins, eckol, PFF-A, and dieckol, along with one new compound, eckstolonol, were obtained from ES, and the new compound was found to be a potent radical scavenger through its elimination of DPPH radicals (Kang et al. 2003b). Eckol suppressed the production of intracellular ROS and increased glutathione peroxidase (GSH) level in HepG2 cells. It inhibited the production of ROS in H_2O_2-treated HepG2 cells in a dose-dependent manner, and the total relative level of 40 μM eckol was estimated to be 11.2 ± 0.85% compared to the non-treated group, making it a much stronger ROS scavenger than N-acetylcysteine (NAC). The intracellular GSH content in HepG2 cells was dose-dependently enhanced by eckol treatment, indicating higher antioxidant activity than NAC. Thus, eckol mediated the expression of HO-1 in HepG2 cells, which was regulated by Nrf2 activation via the Jun N-terminal kinases (JNK) and PI3K/protein kinase B (Akt) signaling pathways, suggesting that it is a natural antioxidant and cytoprotective agent (Jun et al. 2014). Two novel phlorotannins with a molecular weight of 974, temporarily named 974-A and 974-B, and four known phlorotannins were isolated from the polyphenol powder of EK. The results from the DPPH and DCFH-DA assays showed that the IC_{50} values of 974-A, 974-B, PFF-A, and dieckol were significantly smaller than those of PFF-B and PG (Yotsu-Yamashita et al. 2013). EM and its PG, dibenzo [1,4] dioxine-2,4,7,9-tetraol, and eckol demonstrated strong antioxidant activity and eliminated free radicals. All phlorotannins tested had strong antioxidant activity on DPPH free radicals, with EC_{50} values ranging from 0.008 to 0.128 μM, suggesting that EM is a natural source of potent antioxidants (Rengasamy et al. 2013). The abundance of results suggests that *Ecklonia* species are a potent source of natural antioxidants to counteract oxidative stress, thereby making them candidates for the prevention of various diseases (Fig 1).

Anti-inflammatory activity

EC extract and its major compound (dieckol) significantly increased the survival rate and attenuated liver and kidney damage in mice with a whole-body inflammatory condition by down-regulating pro-inflammatory factors (iNOS, COX-2, TNF-α, IL-6, and HMGB-1) via a NIK/TAK1/IKK/IκB/NF-κB pathway. Additionally, EC increased Nrf2 and HO-1 expression, reducing inflammation (Yang et al. 2016). Dieckol (5 and 10 μM) inhibited the production of a macrophage-derived chemokine, C–C motif chemokine 22, induced by interferon-γ (10 ng/mL) in a dose-dependent manner and inhibited the nuclear translocation of signal transducers and activators of transcription 1 (STAT1). These results showed that dieckol produced anti-inflammatory effects via the down-regulation of STAT1 activation (Kang et al. 2015). In addition, 8,8′-bieckol isolated from EC suppressed key inflammatory mediators such as NO and PGE2 in RAW264.7 macrophages. The inhibition of NO occurred by suppressing LPS-induced expression of iNOS at the mRNA and protein levels in primary macrophages and RAW264.7 cells. Likewise, 8,8′-bieckol reduced the production and mRNA expression of the inflammatory cytokine IL-6, but not that of TNF-α, in RAW264.7 cells. Furthermore, 8,8′-bieckol significantly reduced mortality in LPS-induced septic mice, which indicates that the anti-inflammatory properties of 8,8′-bieckol are associated with the suppression of NO, PGE2, and IL-6 via negative regulation of the NF-κB pathway and ROS production in LPS-stimulated RAW264.7 cells (Yang et al. 2014). Dieckol extracted from EC suppressed LPS-induced iNOS expression in mouse leukemic macrophage Raw 264.7 cells, decreasing both LPS-induced NO production and iNOS promoter-driven transcriptional activity in a dose-dependent manner. Furthermore, it prevented LPS-mediated NF-κB activity. It also diminished LPS-mediated p65 nuclear translocation or IκBα phosphorylation dose-dependently and reduced LPS-induced phosphorylation of MAPKs, especially p38MAPK. Collectively, these findings suggest that dieckol acts as a negative regulator of LPS-mediated iNOS induction by suppressing NF-κB activity, implying a mechanistic role for dieckol in the regulation of the inflammatory response (Choi et al. 2014). The in vivo anti-inflammatory effect of fucoidan from EC was studied using tail-cutting-induced

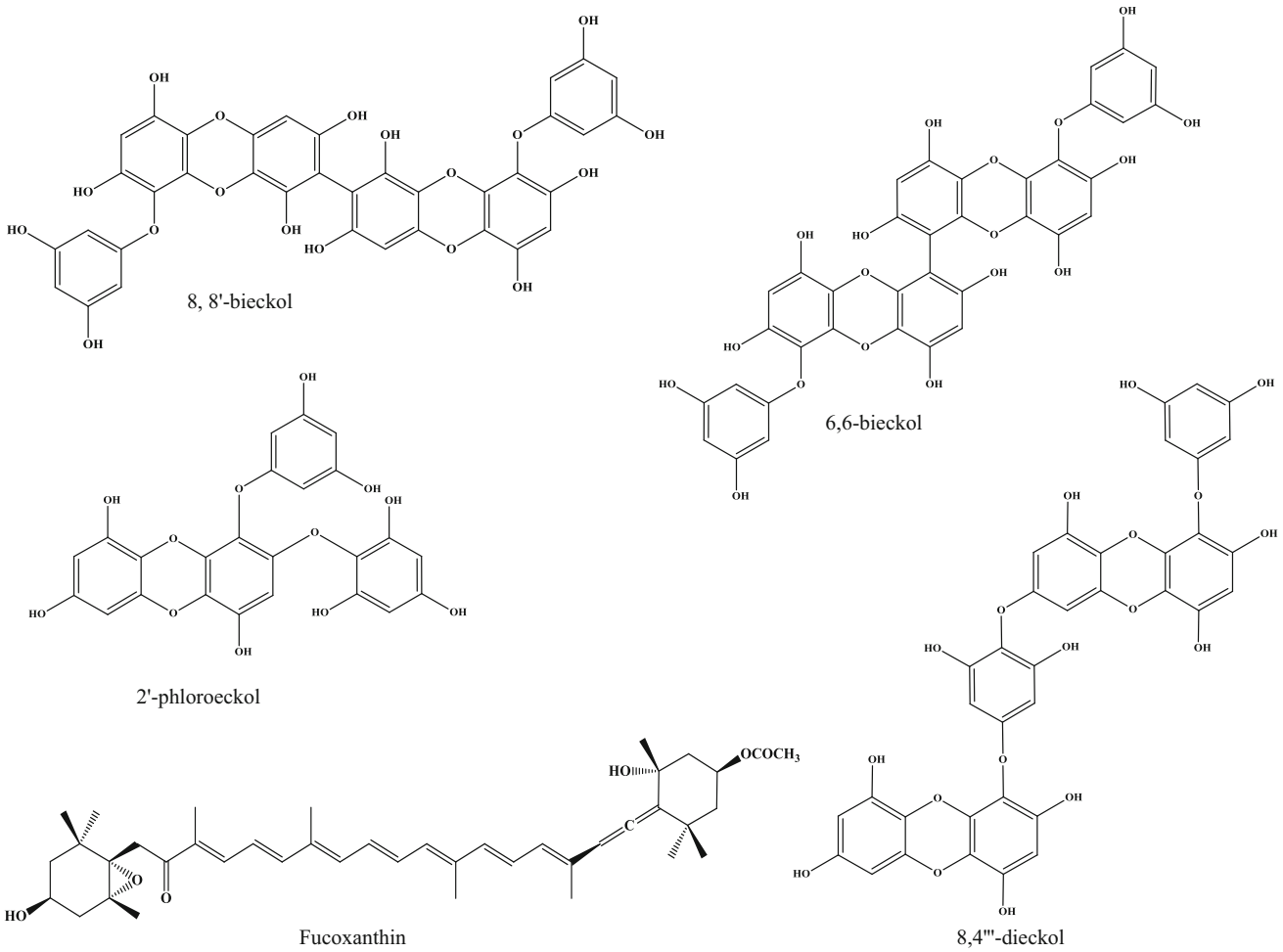


Fig. 1 Structures of active compounds isolated from *Ecklonia* species

and LPS-stimulated zebrafish models; it inhibited tail-cutting-induced and LPS-stimulated ROS and NO generation and also showed a protective effect against the toxicity induced by LPS exposure in zebrafish embryos (Lee et al. 2013a). PFF-A isolated from ES showed potential anti-inflammatory properties in macrophages stimulated by LPS. For this, 20 μM of PFF-A significantly inhibited iNOS and COX-2 mRNA levels induced by LPS stimulation. Similarly, levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α were significantly reduced. PFF-A further inhibited the promoter activities of inflammatory mediators and transcriptional factors. Thus, PFF-A regulated iNOS and COX-2 expression through the NF-κB-dependent transcriptional control associated with the inhibition of multiple signaling proteins, suggesting that PG derivatives could be potential treatments for inflammatory diseases (Kim et al. 2011). The EtOAc fraction of ES, along with its isolated compounds 2-phloroeckol, 6,6′-bieckol, PFF-A, PFF-B, and 974-B, inhibited the production of LPS-induced NO and PGE2 and reduced the expression of iNOS and COX-2 in a dose-dependent manner (Wei et al. 2016).

Anti-diabetic activity

Most of the investigations on phlorotannins, particularly those derived from brown algae, indicate their promising anti-diabetic effects. For example, 2,7″-PG-6,6′-bieckol isolated from EC improved postprandial hyperglycemia through α-glucosidase and α-amylase activity in STZ-induced diabetic mice. It showed higher inhibitory activity than the positive control, acarbose (α-glucosidase IC_{50} of 130.04 μM; α-amylase IC_{50} of 165.12 μM) (Lee et al. 2017a). In addition, 6,6′-bieckol purified from EC at concentrations of 10 or 50 μg/mL significantly inhibited high glucose-induced glucotoxicity and dose-dependently reduced the level of thiobarbituric acid reactive substances (TBARS), generation of intracellular ROS, and the level of NO. Furthermore, 6,6′-bieckol prevented the apoptosis of rat insulinoma cells under high-glucose conditions,

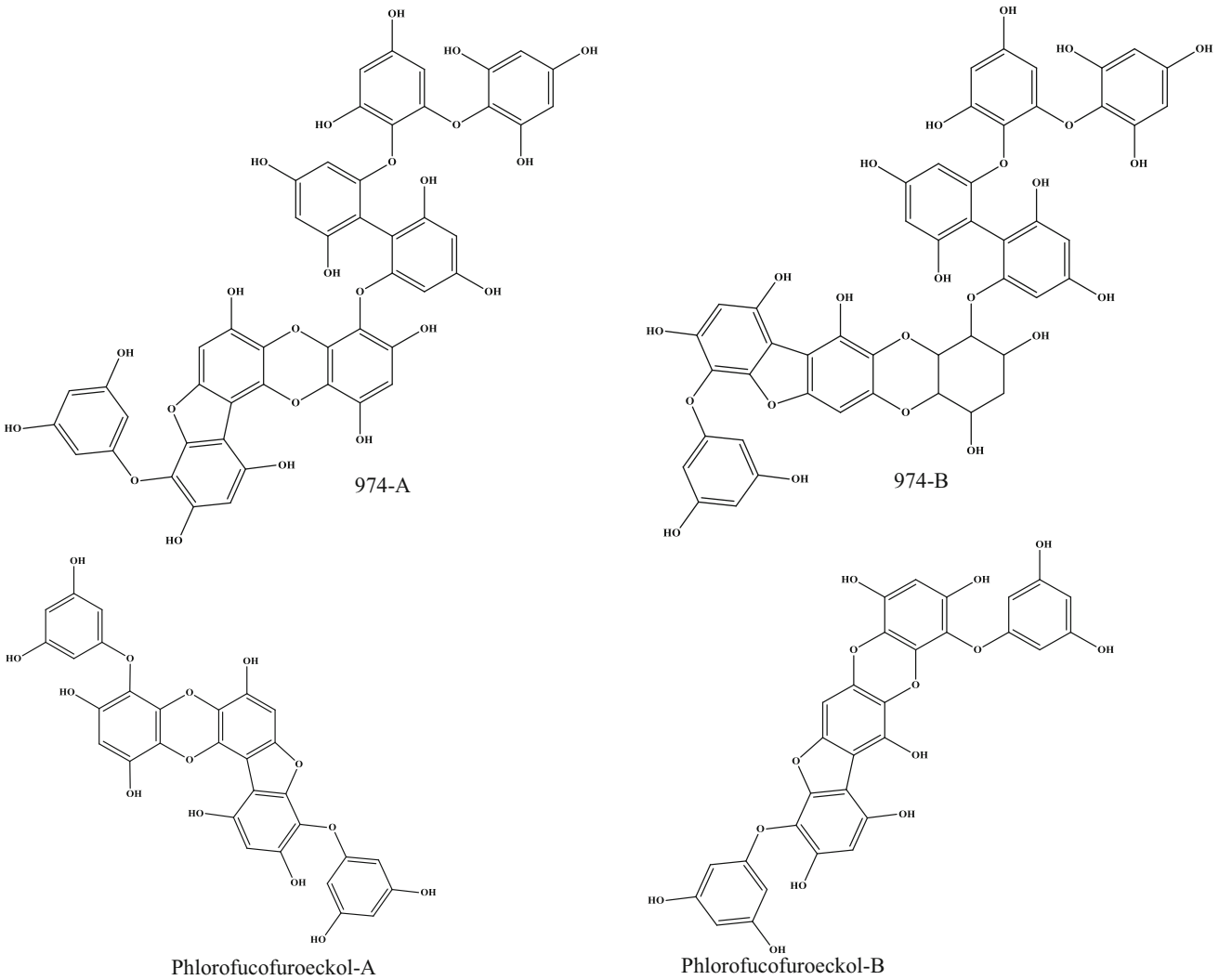
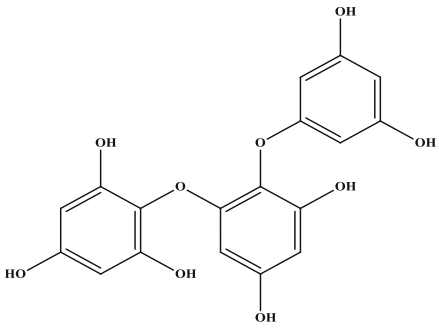


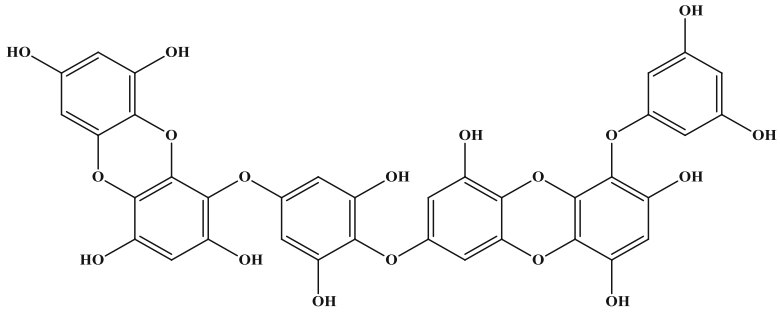
Fig. 1 continued

attributed to increased expression of the anti-apoptotic protein Bcl-2 and reduced expression of the pro-apoptotic protein Bax, establishing EC as a potential nutraceutical candidate for protection against glucotoxicity (Park et al. 2015a). 6,6′-bieckol from EC at concentrations of 10 or 50 μg/mL markedly suppressed high-glucose-induced cytotoxicity and dose-dependently decreased the increased levels of TBARS, ROS, and NO caused by high glucose. In addition, it down-regulated the overexpression of iNOS, COX-2, and NF-κB proteins in HUVECs, indicating its therapeutic ability to treat diabetic endothelial dysfunction and related complications (Park et al. 2014). EC-derived dieckol noticeably decreased blood glucose level, serum insulin level, and body weight. Furthermore, it reduced TBARS and increased the activities of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and GSH-px, in liver tissue. In addition, western blotting analysis revealed that dieckol increased the phosphorylation levels of AMPK and Akt observed in muscle tissues, suggesting that dieckol could be a therapeutic agent for type 2 diabetes (Kang et al. 2013b).

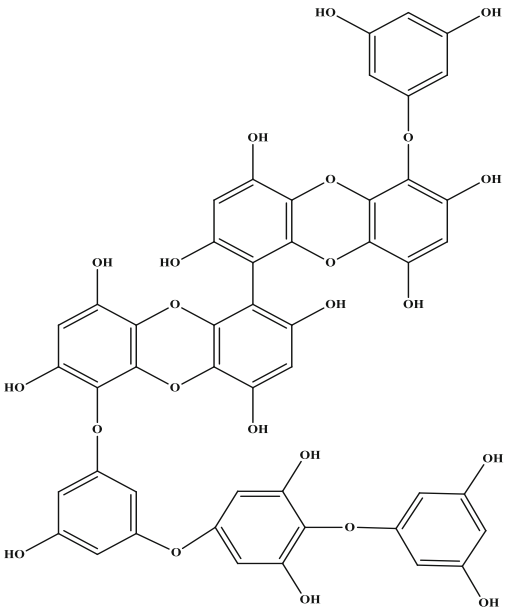
Dieckol-rich extract from EC led to a significant decrease in postprandial glucose level, insulin, and C-peptide level after 12 weeks without any adverse effects. In other words, EC supplementation significantly contributed to lowering postprandial hyperglycemia and reducing insulin resistance (Lee and Jeon 2015). In addition, dieckol improved blood glucose regulation, hepatic glucose metabolic regulation, and Akt up-regulation in alloxan-induced hyperglycemic zebrafish (Kim et al. 2016b). PFF-A isolated from EC showed prominent inhibitory effects against α-glucosidase and α-amylase activities, with IC_{50} values of 19.52 and 6.34 μM, respectively, which were higher than those of acarbose. Moreover, the area under the curve was significantly lower after PFF-A administration (2296 vs.



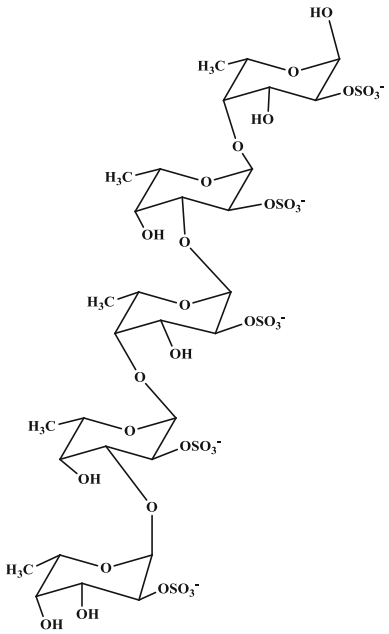
Triphlorethol-A



Dieckol



Pyrogallol-phloroglucinol-6,6'-bieckol



Fucoidan

Fig. 1 continued

2690 mmol min/L) in diabetic mice, indicating its potent anti-diabetic activity (You et al. 2015). The α-glucosidase inhibitory property of EM and its isolated compounds PG, dibenzo [1,4] dioxine-2,4,7,9-tetraol, and eckol exceeded that of the positive control, suggesting their potency as oral anti-diabetic drugs or functional food ingredients, with a promising role in the formulation of medicines and nutritional supplements (Rengasamy et al. 2013). ES exhibited inhibitory activity on glucose-mediated protein damage, advanced glycation end-products (AGE), and rat lens aldose reductase (RLAR), hinting at potential anti-diabetic activity. In spite of negligible activity against AGE, ES phlorotannins, including eckol, dieckol, and 7-phloroeckol, possessed inhibitory activity on glycation, which indicates that PFF-A could be used to prevent diabetic complications (Jung et al. 2008). Likewise, fucosterol from ES inhibited RLAR, human recombinant aldose reductase, protein tyrosine phosphatase 1B (PTP1B), and α-glucosidase activity (Jung et al. 2013a). PFF-A, dieckol, and 7-phloroeckol isolated from ES were potent and non-competitive PTP1B inhibitors, with IC_{50} values ranging from 0.56 to 2.64 μM, and α-glucosidase inhibitors, with IC_{50} values ranging from 1.37 to 6.13 μM. Interestingly, PFF-A and 7-phloroeckol were non-competitive, whereas dieckol exhibited competitive inhibition in a α-glucosidase assay. Thus, isolated phlorotannins from both algae possessed marked PTP1B and α-glucosidase inhibitory activity that could contribute to the development of therapeutic agents to control postprandial blood glucose level and prevent diabetic complications (Moon et al. 2011). Published results clearly indicate the anti-diabetic potential of brown seaweed and its derived components, which could be used as nutraceuticals or functional foods to treat diabetes.

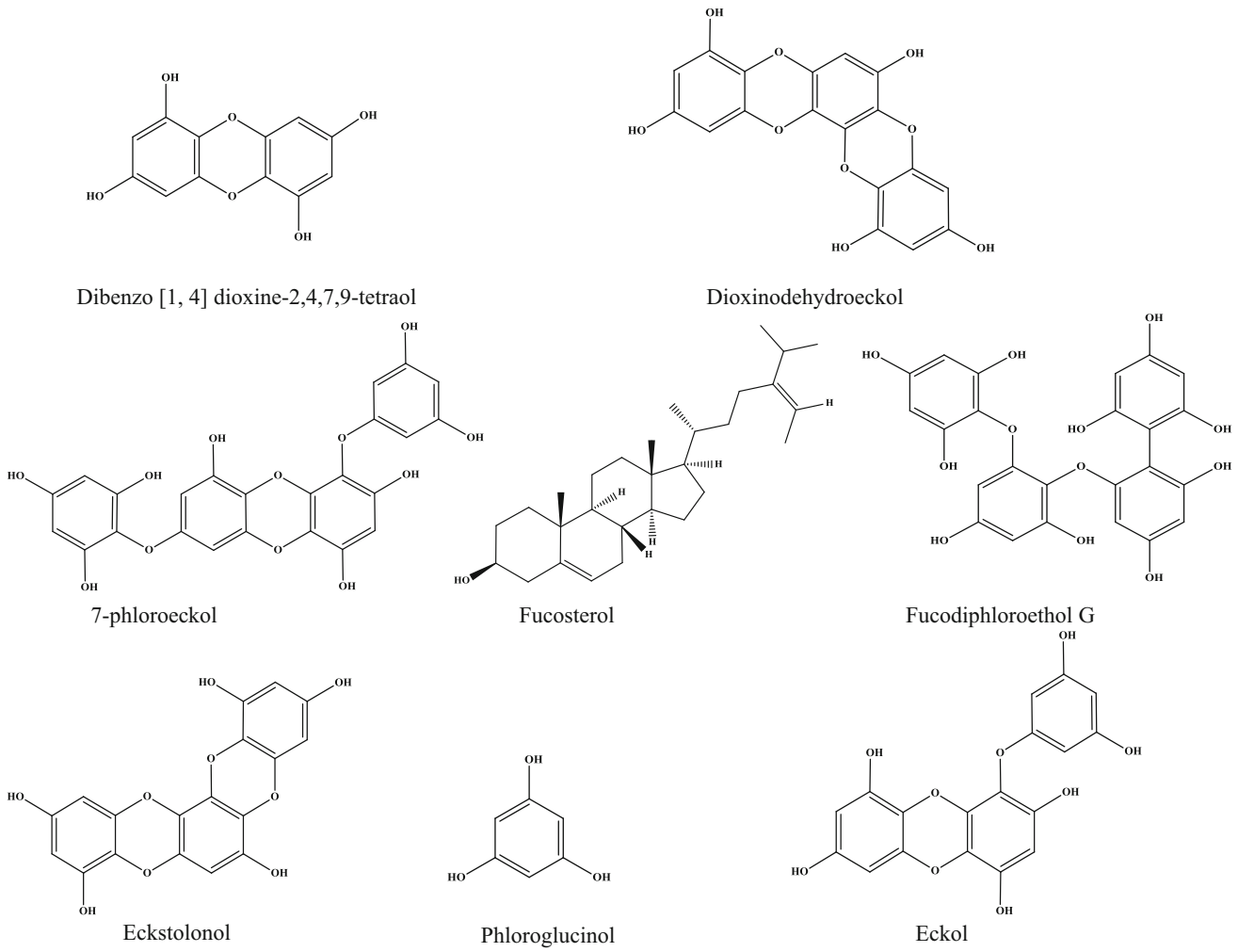


Fig. 1 continued

Hepatoprotective activity

Dieckol from EC exerted cytotoxicity in LX-2, HSC-T6, and HepG2 cells, with reduced fibrosis features (large, spread out, and flattened polygonal shapes) in LX-2 cells compared with the untreated control. In addition, it attenuated the expression of α-SMA and TGF-β1, increased the sub-G1 phase population, induced caspase-3 activation, and cleaved PARP in hepatic stellate cells. Thus, dieckol suppressed liver fibrosis via caspase activation, microRNA-mediated JNK activation, and via NF-κB inhibition (Lee et al. 2016a). An in vitro study of dieckol showed the strongest protective effect and lowest cytotoxicity against ethanol-induced cell apoptosis in Chang liver cells. Western blot analysis revealed reduced cell apoptosis through the activation of B cell lymphoma-extra large (Bcl-xL) and PARP and down-regulation of Bax and caspase-3, providing evidence for this potential protective agent against ethanol-induced liver diseases. In an in vivo study in a zebrafish model, the dieckol-treated group scavenged intracellular ROS and prevented lipid peroxidation and ethanol-induced cell death in embryos (Kang et al. 2013c). ES and its isolated phlorotannins DHE, eckol, PFF-A, dieckol, and TPA, exhibited potential protective effects against doxorubicin-induced hepatotoxicity, with corresponding EC_{50} values of 2.0, 3.4, 8.3, 4.4, 5.5, and 11.5 μg/mL, respectively (Jung et al. 2014a). Ethanolic extracts from ES, along with isolated eckstolonol and PFF-A, protected HepG2 cells against the cytotoxic effects of tacrine, with EC_{50} values of 62.0 and 79.2 μg/mL, respectively, making them comparable to silybin (50.0 μg/mL). Thus, phlorotannins derived from marine brown algae might be useful sources for novel hepatoprotective agents (Kim et al. 2005). Eckol and 2-phloroeckol from ES showed hepatoprotective activity in tacrine-treated HepG2 cells by inhibiting the expression of Fas-mediated cell-death proteins, including tBid, caspase-3, and poly(ADP-ribose) polymerase, and suppressing the release of

cytochrome c from mitochondria to the cytosol in a dose-dependent manner (Lee et al. 2012a). PG isolated from ES decreased the formation of lipid peroxide in acetaminophen (800 mg/kg, i.p.)-induced rats. Though the activities of cytochrome P-450, aminopyrine *N*-demethylase, and aniline hydroxylase were unchanged, PG restored enzyme activity in the livers of pretreated-rats, suggesting that acetaminophen-induced hepatic lipid peroxidation could be reduced by enhancing the activity of glutathione S-transferase (GST) (Park 2000). All of these data suggest that *Ecklonia* species could be potent hepatoprotective agents.

Neuroprotective activity

Dieckol isolated from EC suppressed the phosphorylation of ERK in LPS-stimulated BV-2 microglia (1 μg/mL), attenuated Akt phosphorylation, and increased the expression of $gp91^{phox}$, a catalytic component of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex responsible for microglial ROS generation. Furthermore, dieckol offered neuroprotection, as confirmed in an enhanced green fluorescent protein-transfected B35 neuroblastoma cell line (Cui et al. 2015). Dieckol isolated from EC showed potent activity on rotenone-induced oxidative stress in SH-SY5Y cells, a human dopaminergic neuronal cell line. It reduced rotenone-induced cell death and retarded rotenone-induced α-synuclein aggregation in α-synuclein-overexpressing SH-SY5Y cells, which prevented α-synuclein aggregation, adding to its role in the prevention of PD (Cha et al. 2016). PG (1,3,5-trihydroxybenzene) from EC attenuated the increase in ROS accumulation induced by oligomeric Aβ1–42 treatment in the HT-22 hippocampal cell line and ameliorated the reduction in dendritic spine density induced by Aβ1–42 treatment in rat primary hippocampal neuron cultures. Also, PG attenuated cognitive dysfunction in the hippocampal region, indicating its anti-AD effects (Yang et al. 2015b). Another report showed that PFF-A from EC had particularly potent inhibitory activity (IC_{50} = 0.95 μM) for butyrylcholinesterase (BChE), more than 100-fold greater than for AChE. Other polyphenols (PFF-A, eckol, 6,6′-bieckol, 8,8′-bieckol, and dieckol) inhibited glycogen synthase kinase 3β, which is related to the formation of hyperphosphorylated tau and generation of Aβ. Additionally, PFF-A inhibited amyloid precursor protein biosynthesis and showed very strong BACE1 inhibitory activity, with a submicromolar IC_{50}, making it an interesting potential drug candidate for AD (Choi et al. 2015b).

An oligosaccharide sugar chain derived from EK inhibited the toxicity induced by the Aβ protein in both primary cortical cells and the SH-SY5Y cell line, inhibiting apoptosis and fibril formation and indicating its potency for AD (Hu et al. 2004). EM exhibited potent activity against AChE, as did its isolated compounds PG, dibenzo [1,4] dioxine-2,4,7,9-tetraol, and eckol, highlighting its potential as a functional food ingredient for the management of neurodegenerative disorders (Kannan et al. 2013). A phlorotannin preparation (PP) containing eckstolonol from ES and EC exhibited a hypnotic effect by modulating the benzodiazepine site of the γ-amino butyric acid receptor. PP (>250 mg/kg) decreased sleep latency and increased non-rapid eye movement sleep (NREMS). Likewise, eckstolonol significantly decreased sleep latency (>12.5 mg/kg) and increased the amount of NREMS (50 mg/kg). In addition, the hypnotic effects were completely abolished by pretreatment with flumazenil, suggesting that the phlorotannins could potentially be used as an herbal medicine for insomnia and offering a promising structure for the development of novel sedative–hypnotics (Cho et al. 2014). Fucosterol and fucoxanthin from ES showed non-competitive and mixed-type inhibition against β-site amyloid precursor protein cleaving enzyme 1 (BACE1). Furthermore, molecular docking simulation results demonstrated the effective binding of isolated compounds by the BACE1 enzyme, suggesting that both compounds could be used beneficially in the treatment of AD and providing potential guidelines for the design of new BACE1 inhibitors (Jung et al. 2016).

Matrix metalloproteinase inhibitory activity

Isolated eckol and dieckol attenuated TNF-α induced expression of MMP-1 and basal expression, though the expression of TIMP-1 was not affected. However, they did reduce both NF-κB and AP-1 reporter gene activity, which strongly indicates their MMP inhibitory potential. One study demonstrated the inhibitory effect of eckol and dieckol isolated from ES on MMP-1 expression in human dermal fibroblasts, suggesting the possibility of developing an agent to prevent and treat skin aging (Joe et al. 2006). Obviously, marine sources outweigh terrestrial sources in abundance in the development of safe MMP nutraceuticals.

Anticoagulative activity

Anticoagulation occurs by inhibiting the key serine proteases thrombin and factor Xa, facilitated by accelerating the activity of the major physiological serine protease inhibitor SERPIN-antithrombin III. Heparin, a highly sulfated polysaccharide present in mammalian tissues, is commercially used as a blood anticoagulant. It has anti-hemostasis, fibrinolytic potentiation, and anti-lipemic activity in addition to coagulation activity. Though it is a primary anticoagulant, difficulty in isolating it and its hemorrhagic side effects limit its use and drive researchers to search for novel anticoagulants from natural resources

free from cytotoxicity (Shanmugam and Mody 2000). Studies of the anticoagulant bioactivity of brown seaweeds suggest that they have more than one mechanism of action, including the direct and indirect inhibition of thrombin through the activation of thrombin inhibitors (e.g., antithrombin and heparin cofactor). Interestingly, the algal fucans were found to have anticoagulant activity through a direct inhibition of thrombin, whereas the invertebrate fucans showed activity through an indirect inhibition of the enzyme, which required antithrombin and heparin cofactor II, and that has driven the rapid discovery of anticoagulants from marine resources (Jiao et al. 2011).

Fucoidan isolated from EK significantly inhibited the generation of thrombin and factor Xa in the intrinsic pathway. Furthermore, it inhibited the formation of prothrombin-activating complex (i.e., prothrombinase); the IC_{50} of thrombin generation was one-tenth to one-seventh that of the activity of the thrombin in plasma, whereas the antithrombin activity of fucoidan was mediated by heparin cofactor II in plasma. This further highlights the relationship between the molecular weight of sulfated polysaccharides and their anticoagulant activity such that the higher molecular weight fucans show greater anticoagulant activity than sulfates with a lower molecular weight (Nishino et al. 1999, 1991a). Sulfated polysaccharides, mainly 3-linked and 3, 4- disubstituted fucopyranosyl residues isolated from EK, exhibited potent anticoagulant activity (Nishino et al. 1991b). Some potent and novel antiplasmin inhibitors such as PFF-A and eckol isolated from EK inhibited the action of alpha 2-macroglobulin ($IC_{50} = 1.0$ μg/mL) and alpha 2-plasmin inhibitor ($IC_{50} = 0.3$ μg/mL), the main plasmin inhibitors in plasma (Fukuyama et al. 1990, 1989). Thus, the development of antithrombotic algal polysaccharides would be advantageous because their use would avoid the potential for contamination with prions or viruses present in commercial heparins, which are obtained from pig and bovine intestines. Moreover, with more specific activities or targets, algal sulfated polysaccharides could find applications complementary to heparin.

Antibacterial and antiviral activities

Dieckol from EC significantly blocked the cleavage of SARS-CoV 3CL(pro) in a cell-based assay without showing any toxic effects and exhibited a high association rate in the SPR sensorgram, forming strong hydrogen bonds to the catalytic dyad (Cys145 and His41) of the SARS-CoV 3CL(pro) (Park et al. 2013). Both phlorotannins from EC and isolated epibiotic bacteria showed potent antibacterial activity in close affiliation with the genus *Bacillus* (Kanagasabhapathy et al. 2006). Another novel bacterial strain, designated EC29T, was isolated from EC, and it showed potent antibacterial activity (Kim et al. 2015d). Another study suggested that the compounds eckol, dieckol, PFF, and 7-phloroeckol exhibited potent antiviral activity, with IC_{50} ranging from 10.8 ± 1.4 to 22.5 ± 2.2 μM against porcine epidemic diarrhea. These compounds completely blocked the binding of viral spike protein to sialic acids at concentrations less than 36.6 μM by hemagglutination inhibition. PFF and dieckol inhibited viral replication with IC_{50} values of 12.2 ± 2.8 and 14.6 ± 1.3 μM, respectively, in the post-treatment assay and exhibited stronger inhibition of viral RNA and viral protein synthesis in later stages (18 and 24 h) than in early stages (6 and 12 h), suggesting their potential as natural therapeutic drugs against coronavirus infection (Kwon et al. 2013). Dieckol and 8,8′-bieckol (hexamers) isolated from EK were tested against the food-borne pathogenic bacteria *Campylobacter jejuni* with an MIC of 50 mg/L and 0.03 μmol/mL, respectively, which were effective against MRSA as determined by a broth microdilution method. The bactericidal effects of the phlorotannins were more pronounced than those of the catechins (Nagayama et al. 2002).

Anti-obesity activity

One study showed that *n*-BuOH fractions with isolated phlorotannins (TPA, eckol, and dieckol) increased glycerol secretion and reduced the regulation of adipogenic transcription factors, PPARγ, CCAAT/enhancer-binding protein (C/EBPα), and TNFα. Those phlorotannins also reduced the differentiation-dependent factor 1/SREBP-1c and downstream genes such as FABP-4, fatty acid transport protein-1, FAS, leptin, and ACS1, whereas they increased the mRNA expression of hormone-sensitive lipase while suppressing perilipin expression to treat obesity (Kong et al. 2015). Dieckol from EC down-regulated the expression of PPARγ, C/EBPα, SREBP-1, and FABP-4, showing anti-adipogenic effects on adipocyte differentiation through the activation and modulation of the AMPK signaling pathway to improve obesity (Ko et al. 2013). Enzyme-treated EC and its isolated compounds (eckol, dieckol and PFF-A) exhibited potent adipogenic activity in 3T3-L1 adipocytes. Dieckol was found to be the major compound in the enzymatic extract, with a concentration of 16 mg/g. In addition, 50 μg/mL of EC extract inhibited glucose utilization and TG accumulation, as confirmed by Oil Red O staining. Additionally, it decreased the expression of CCAAT/(C/EBP)α, SREBP-1c, adipocyte-FABP, FAS, and adiponectin. Thus, EC prevented adipogenesis by affecting the activation of the C/EBPα signaling pathway and the resulting adipogenesis-related gene expression (Kim and Nam 2017). In a similar report, dieckol from EC inhibited lipid accumulation via activation of AMPKα signaling and cell-cycle arrest in 3T3-L1 cells and mouse

and zebrafish models (Choi et al. 2015a). Seapolynol derived from EC inhibited triglyceride synthetic enzymes such as diacylglycerol acyltransferase 1, GPAT3, Kruppel-like factor 4 (KLF4), KLF5, C/EBPβ, C/EBPδ, and protein C-ets-2, whereas it up-regulated KLF2, an anti-early adipogenic factor, preventing metabolic disorders (Jeon et al. 2015). Fucosterol was isolated from the strong anti-adipogenic CH_2Cl_2-soluble fraction from ES, with significant inhibition (40.5%) of intracellular lipid accumulation at a non-toxic concentration. The anti-adipogenic activities of ES, along with the isolated fucosterol, reduced lipid content in a concentration-dependent manner without showing any cytotoxicity. Fucosterol treatment also yielded a decrease in the expression of the adipocyte markers PPARγ and C/EBPα in a concentration-dependent manner. Taken together, these results suggest that fucosterol inhibits the expression of PPARγ and C/EBPα, resulting in a decrease in lipid accumulation in 3T3-L1 pre-adipocytes, thereby indicating the potential of ES and its bioactive component fucosterol as anti-obesity agents (Jung et al. 2014b). Similarly, fucosterol isolated from ES down-regulated the insulin-triggered PI3K/Akt and ERK pathways, which subsequently decreased the expression of adipogenic transcription factors, including PPARc, C/EBPa, and SREBP-1. In addition, fucosterol enhanced SirT1 expression and decreased phospho-FoxO1 expression, which resulted in the activation of FoxO1 and revealed that fucosterol inhibited adipogenesis of 3T3-L1 preadipocytes at concentrations of 25 and 50 μM through the modulation of the FoxO1 signaling pathway (Lee et al. 2017b). Compound 974-B isolated from EK inhibited the differentiation of mouse embryonic fibroblasts and 3T3-L1 cells into adipose cells by acting as the peptidyl prolyl cis/trans isomerase inhibitor responsible for the uptake of TG and the differentiation of fibroblasts into adipose cells in response to insulin stimulation without inducing cytotoxicity. This finding suggests that 974-B could be a lead drug candidate for obesity-related disorders (Mori et al. 2014). Altogether, these results suggest that several *Ecklonia* species possess potent activity that might be exploited in adjunct therapy for obesity.

Antihistamine activity

Dieckol from EC inhibited mast cell activation and mast cell-mediated type I allergic reactions caused by IgE-specific antigen, mainly through the marked downstream signaling of FcεRI. A high dose of dieckol suppressed hypersensitive reactions, offering another target molecule for the prevention or treatment of mast cell-dependent allergic diseases (Ahn et al. 2015c). Six phlorotannins isolated from EK, PG, an unknown tetramer, eckol, PFF-A, dieckol, and 8,8′ bieckol, inhibited hyaluronidase at concentrations of 280, 650, >800, 140, 120, and 40 μM, respectively. Also, 8,8-bieckol, the strongest hyaluronidase inhibitor, acted as a competitive inhibitor with an inhibition constant (*Ki*) of 3.5 μM (Shibata et al. 2002).

Radioprotective activity

Park et al. (2011) described the multi-faceted protection mechanisms of PG against oxidative stress caused by ionizing radiation in mice. PG inhibited apoptosis and strengthened hematopoiesis. It increased the viability of splenocytes without cytotoxicity and significantly enhanced the proliferation of splenocytes by limiting the increment of sub-G(1) DNA contents via the inhibition of ROS production in 2 Gy-irradiated splenocytes. In addition, PG significantly decreased DNA damage and the number of apoptotic fragments in lymphocytes during oxidative stress and increased the counts of endogenous spleen colony forming units (CFUs) compared with control mice exposed to ionizing radiation. A similar study confirmed that PG protected against small intestine damage caused by ionizing radiation, raising the apoptosis threshold of jejunal crypt cells. PG regenerated the intestinal crypts and down-regulated the expression level of proapoptotic molecules such as p53, Bax, and Bak in the small intestine. PG further augmented antiapoptotic molecules such as Bcl-2 and Bcl-X(S/L) (Ha et al. 2013).

Anticancer and cytotoxic activity

Cancer is the uncontrolled growth of cells that can invade and spread to distant sites of the body. Cancer can have severe health consequences and is a leading cause of death. Lung, prostate, colorectal, stomach, and liver cancer are the most common types of cancer in men, whereas breast, colorectal, lung, uterine cervix, and stomach cancer are the most common types among women. More than 30% of cancer deaths could be prevented by modifying or avoiding key risk factors. Cancer results from a mutation in the chromosomal DNA of a normal cell, which can be triggered by both external factors (tobacco, alcohol, chemicals, infectious agents, and radiation) and internal factors (hormones, immune conditions, inherited mutations, and mutations occurring in metabolism) (Croce 2008; Ferlay et al. 2015). In Korea, cancer accounts for one in four deaths (27.6%), and more than 200,000 new cancer cases were diagnosed in 2012 (Oh et al. 2016). Although antineoplastic drugs and chemotherapy are available, the deleterious effects of those medications have driven researchers to derive new drug candidates from natural products.

Dieckol isolated from EC prevented *N*-nitrosodiethylamine (NDEA)-induced rat hepatocarcinogenesis. Dieckol

administered orally (40 mg/kg body weight) for 15 weeks with 0.01% NDEA through the drinking water reversed the activities of hepatic marker enzymes such as aspartate transaminase, alanine transaminase, ALP, gamma glutamyl transferase, lactate dehydrogenase, α-fetoprotein, and total bilirubin and increased the elevation of cytochrome p450. Dieckol also decreased lipid peroxidative markers (TBARS, lipid hydroperoxides, protein carbonyl content, and conjugated dienes) and decreased the antioxidant cascade viz enzymatic antioxidants (such as SOD, CAT, glutathione peroxidase, GST, glutathione reductase) and non-enzymatic antioxidants (such as reduced glutathione, vitamin C, and vitamin E). Dieckol was more effective at 40 mg/kg than at 10 and 20 mg/kg body weight and protected the liver from cancer (Sadeeshkumar et al. 2016). Likewise, dieckol showed anti-breast cancer activity by regulating the expression of metastasis-related genes (Kim et al. 2015b). EC and its major phlorotannin (dieckol) increased the tumor growth-inhibitory effect of cisplatin and reduced cisplatin-induced nephrotoxicity and weight loss in SKOV3-bearing mice. Furthermore, they enhanced cisplatin-induced apoptosis by stimulating caspases in SKOV3 and A2780 ovarian cancer cells via down-regulation of Akt and NF-κB signaling. Thus, EC suppressed cisplatin-induced ROS production and cell death in normal HEK293 kidney cells, and its major compound dieckol evidently enhanced the suppression of tumor growth by cisplatin with less weight loss and kidney damage in a mouse model (Yang et al. 2015a). Dieckol from EC exhibited cytotoxic effects on A2780 and SKOV3 ovarian cancer cells, induced the apoptosis of SKOV3 cells, and suppressed tumor growth without any significant adverse effect in the SKOV3-bearing mouse model. Furthermore, it activated caspase-8,-9, and -3; caused mitochondrial dysfunction; and suppressed the levels of anti-apoptotic proteins. Thus, dieckol enhanced intracellular ROS, and the antioxidant *N*-acetyl-L-cysteine (NAC) noticeably reversed the caspase activation, cytochrome c release, Bcl-2 down-regulation, and apoptosis caused by dieckol through AKT and p38 (Ahn et al. 2015a). In another investigation, Ahn et al. (2015b) showed the anticancer effects of crude polysaccharides isolated from EC enzymatic extracts, using amyloglucosidase (AMG), viscozyme, protamex, and alcalase enzymes against a colon cancer cell line. Among the tested extracts, crude polysaccharides of protamex showed the highest inhibitory effect against the growth of CT-26 cells and dose-dependently increased the formation of apoptotic bodies and the percentage of Sub-G1 DNA content. Furthermore, crude polysaccharides of protamex activated caspase 9 and PARP to regulate the expression of Bax and Bcl-2 and showed the highest inhibitory effect against the growth of CT-26 cells, attributed to their high fucose and sulfated group content, demonstrating anticancer effects on colon cancer cells via regulation of the Bcl-2/Bax signal pathway. Additionally, dieckol isolated from ES reduced the number of viable cells and increased the number of apoptotic cells, increased the expression levels of cleaved caspases-(3, 7, 8, and 9) and cleaved poly(ADP-ribose) polymerase, increased the permeability of mitochondrial membranes, and increased the release of cytochrome c from mitochondria into the cytosol with an apoptosis-inducing factor. Thus, dieckol induced apoptosis via the activation of both death receptors and mitochondrial-dependent pathways in human hepatocellular carcinoma (Hep3B) cells (Yoon et al. 2013).

Ultraviolet protection

The skin is the human body's largest organ and is colonized by diverse microorganisms, most of which are harmless or even beneficial to their host. It acts as an anatomical barrier that is tough when intact and prevents the entry and colonization of many microbes (Grice and Segre 2011). However, continuous exposure to ultraviolet (UV) light leads to various complications correlated with various pathological consequences, such as photo-damage of the skin, which is characterized by distinct alterations in the composition of the dermal extracellular matrix and results in wrinkles, laxity, coarseness, mottled pigmentation, and histological changes that include increased epidermal thickness and connective tissue alteration (Rittie and Fisher 2002). Therefore, varieties of anti-photoaging or photoprotective compounds from algae and other marine organisms have been isolated.

DHE from EC exerted a preventive effect against UVB-induced apoptosis in human keratinocyte (HaCaT) cells, indicating its benefit as a repair agent for skin damage caused by UVB (Ryu et al. 2015). Fucodiphlorethol G from EC reduced UVB radiation-induced loss of mitochondrial membrane potential, the generation of apoptotic cells, and active caspase-9 expression. Thus, it prevented oxidative damage-mediated apoptosis induced by UVB irradiation (Kim et al. 2014f). DHE from ES inhibited cellular melanin content and the expression of melanogenesis-related proteins, including microphthalmia-associated transcription factor and tyrosinase and tyrosinase-related proteins TRP-1 and TRP-2, stimulating the phosphorylation of Akt in a dose-dependent manner without affecting the phosphorylation of ERK (Lee et al. 2012b).

Anti-hypertensive activity

Angiotensin-I-converting enzyme (ACE) plays an important physiological role in the regulation of blood pressure by converting angiotensin I to angiotensin II, a potent vasoconstrictor. Some commercial drugs, such as captopril,

ramipril, lisinopril, and enalapril, have unfortunate side effects like cough, taste disturbances, skin rashes or angioneurotic edema, so novel compounds such as phlorotannins have been derived from marine organisms as potential ACE inhibitors (Wijesekara and Kim 2010).

Jung et al. (2006) reported that, among the seven enzymatically hydroxylated brown algal species, EC was a potent ACE inhibitor with an IC_{50} value of 0.3 μg/mL. Eckol, PFF-A, and dieckol from ES showed potent ACE inhibiting activity with IC_{50} values of 70.82 ± 0.25, 12.74 ± 0.15, and 34.25 ± 3.56 μM, respectively, showing the importance of ES.

Anti-HIV activity

The human immunodeficiency virus (HIV) infects cells of the immune system by destroying or impairing their function, ultimately causing immune deficiency and opening the door to opportunistic infections, thereby causing acquired immune deficiency syndrome (AIDS). Approximately 36.7 million people were living with HIV at the end of 2015. As of mid-2016, 18.2 million people were receiving antiretroviral treatment worldwide. Seven out of ten pregnant women living with HIV received anti-retroviral treatment (WHO 2016). More than 30 approved commercial drugs are available for the treatment of AIDS. These drugs keep the disease under control; however, they are often associated with the emergence of cross-resistant HIV strains and various side-effects (Sánchez and Holguín 2014; Haas et al. 2004). So, the need for potential nutraceuticals, especially from marine organisms, to fight this vicious disease is vital.

8,4‴-dieckol from EC at noncytotoxic concentrations repressed HIV-1 activated syncytia formation, lytic effects, and viral p24 antigen production. Furthermore, it selectively inhibited the activity of HIV-1 reverse transcriptase enzyme with 91% inhibition at 50 μM. Therefore, it showed high potential and could be considered as a drug candidate for the development of a new generation of therapeutic agents (Karadeniz et al. 2014).

Miscellaneous

Other pharmacological activities include immunomodulatory, aphrodisiac, anti-hair loss, hearing repair, urinary tract infection remedy, hair growth performance, cosmetic whitening, osteoarthritis, and bone-related conditions. One study suggested that sulfated polysaccharides from EC induced T and B cell responses via both the JNK and NF-kB pathways (Ahn et al. 2013). *Ecklonia bicyclis* together with the novel drug tradamixina improved male sexual function in elderly men, particularly libido, mild-moderate erectile dysfunction, ejaculation function, and sexual quality of life (Sansalone et al. 2014). Purified polyphenols from EC increased fibroblast survival in human dermal papilla cells, preventing hair loss (Shin et al. 2016). Dieckol isolated from EC suppressed EA.hy926 cell proliferation induced by vascular endothelial growth factor, demonstrating its anti-proliferative and anti-migratory effects through a MAPK molecular signaling cascade and suggesting its potential as an anti-angiogenic candidate (Li et al. 2015). DHE from EC enhanced osteoblast differentiation, as evidenced by increased cell proliferation, alkaline phosphatase activity, and intracellular cell mineralization, along with enhanced levels of osteoblastogenesis markers at 20 μM in MC3T3-E1 pre-osteoblasts. Furthermore, DHE up-regulated phosphorylated ERK and c-JNK, which were also stimulated by the BMP signaling pathway (Ahn et al. 2016). A polyphenol-rich extract from EC showed potent radical-scavenging activity and decreased the ABR threshold shifts, suggesting its potential as a preventive agent against temporary threshold shift (Chang et al. 2016). Water-soluble sulfated fucans isolated from EC induced the degradation of Iκ-B and the phosphorylation of MAPK in RAW264.7 cells, implying that they might stimulate RAW264.7 cells through the activation of the NF-κB and MAPK pathways (Cao et al. 2014). The EtOAc fraction of EC resulted in elongation of the hair shaft in cultured human hair follicles and activated transition of the hair cycle from the telogen to the anagen phase in the dorsal skin of C57BL/6 mice. Furthermore, it induced an increase in IGF-1 expression in human dermal papilla cells (Bak et al. 2013). EC and its phlorotannins TPA, eckol, and dieckol attenuated the pathophysiological consequences of osteoarthritis and enhanced osteoblast differentiation, as indicated by increased alkaline phosphatase activity and raised levels of osteoblastogenesis, preventing osteoporosis (Karadeniz et al. 2015).

Conclusion and future perspectives

Undoubtedly, *Ecklonia* species and their active metabolites are potential candidates for drug development, as shown by their plethora of activities against various diseases. Our review provides current information on the biological and pharmacological potential of this genus, which could be further used for the development of nutraceuticals. Screening and study of the interactions between these algae and their constituents and human systems threatened by disease need to continue. Therefore, we recommend rapid screening and isolation to develop novel functional ingredients from *Ecklonia* species. The future of pharmaceuticals based on natural products seems promising.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

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