Journal of Marine Research, 78, 131–148, 2020

Antioxidant compounds from marine seaweeds and their mechanism of action

by Trishna Debnath[1,2,3], Eun-Kyung Kim[3,4,5], Kwang-Geun Lee[2], Narayan Chandra Debnath[6] and Ramkumar Mathur[1,3]

ABSTRACT

Investigation of natural products has moved toward marine environments as they are a source of many biologically active agents. The natural antioxidant compounds isolated from seaweeds provide a valuable contribution to the innovation of new drugs for chronic diseases associated with oxidative stress. While the antioxidant activity and nutritional benefits of various seaweed products are well recognized, their proper utilization as antioxidants remains at initial stages that require further investigative studies. This review provides a detailed study of isolated antioxidant compounds from seaweeds and their major mechanism of action by focusing on the reports from 2015 to 2019. The report discusses various active antioxidant compounds, including phenolics (e.g., phlorotannins), polysaccharides, and pigments with proven benefits against oxidative stress-related diseases, especially carotenoids, from the aspect of benefits to human health.

Keywords: seaweed, antioxidant compounds, oxidative stress, chronic diseases, mechanism of action

1. Introduction

The marine environment is interesting for its biodiversity, which can range from tiny single-celled organisms to complex and multicelled organisms. There is a continued focus on drug discovery from marine natural products with many important therapeutic agents and drug candidates already revealed (Schwartz 1996; Newman and Cragg 2004; Roberts,

1. School of Medicine & Health Sciences, Department of Geriatrics, University of North Dakota, Grand Forks, ND 58202-9037 USA; https://orcid.org/0000-0002-7364-6991

2. Department of Food Science and Biotechnology, Dongguk University-Seoul, Gyeonggi-do, South Korea

3. Corresponding authors: ***e-mail: trishna.debnath@und.edu; ekkimkr@dau.ac.kr; ramkumar.mathur@und.edu***

4. Department of Food Science and Nutrition, College of Health Science, Dong-A University, Busan 49315, South Korea; https://orcid.org/0000-0002-4832-6427

5. Center for Silver-Targeted Biomaterials, Brain Busan 21 Plus Program, Dong-A University, Busan 49315, South Korea

6. Department of Chemistry, University of North Dakota, ND 58203 USA; https://orcid.org/0000-0001-8785-8170

Wheeler, and Freiwald 2006; Cornish and Garbary 2010). Macroalgae, or seaweeds, are several species of visible, multicellular marine algae that are rich sources of secondary compounds with noticeable antioxidant activities. Seaweeds are used as a foodstuff in several Asian countries, including Korea, Japan, and China, where many different seaweed species are cultivated. Therefore, seaweeds would be sustainable sources of active compounds for the pharmaceutical, cosmeceutical, and nutraceutical industries.

An imbalance between the formation and removal of free radicals can result in a pathological condition, known as oxidative stress. Cellular oxidative stress is associated with several pathologies, such as cancer, diabetes, and neurodegenerative diseases, as well as aging. In the human body, the antioxidant defense system minimizes the overproduction of reactive oxygen species. This understanding has increased the great interest in constituents that act as endogenous and exogenous antioxidants. Reducing oxidative stress is one of the key mechanisms of action of antioxidant compounds. Therefore, the antioxidant activities of natural products have been explored widely through experimental studies.

Accordingly, antioxidant compounds are vastly investigated for their importance in food, drugs, and cosmetics research (Bocanegra et al. 2009; Barahona et al. 2011; Holdt and Kraan 2011). Although many synthetic antioxidants, such as butylhydroxytoluene, butylhydroxyanisole, *tert*-butyl hydroquinone, and propyl gallate, are used in the food and pharmaceutical industries to reduce toxicity of carcinogenic risks to consumers (Safer and Al-Nughamish 1999), there has been growing interest in increasing the application of alternative, safe and low-cost antioxidants from nature.

Marine seaweeds are reported to have an important role in the prevention of human diseases, maintaining good health (Holdt and Kraan 2011). Several studies have indicated that primary and secondary compounds isolated from marine algae show an array of promising and remarkable biological activities and have an active role in the innovation of new drugs for chronic diseases associated with oxidative stress diseases (Thomas and Kim 2011; Wijesekara et al. 2011; Wijesinghe and Jeon 2012; Renju, Kurup, and Bandugula 2014; Huang et al. 2016). This review aims to highlight the types and properties of marine antioxidants isolated from marine seaweeds and their effects on oxidative stress-related diseases, such as cancer, diabetes, arthritis, asthma, cardiovascular diseases, and inflammatory disorders.

2. Homeostasis of marine seaweeds

The seaweeds produce antioxidants for scavenging free radicals, and the stress-management mechanisms of intertidal algae are diverse (Lohrmann, Logan, and Johnson 2004). Some algae (e.g., *Chondrus crispus* and *Mastocarpus stellatus*) produce more antioxidant enzymes, including superoxide dismutase (SOD), ascorbate peroxidase, and glutathione reductase, in winter than in summer as the levels of reactive oxygen species (ROS) are higher in winter as a result of cold stress (Lohrmann, Logan, and Johnson 2004). The production of ROS increases in most macroalgae owing to such environmental stresses as dessiccation, freezing, low temperature, high irradiance, ultraviolet radiation, heavy

metals, and salinity fluctuations (Harker et al. 1999). These environmental stresses induce the formation of singlet oxygen, compromising photosynthesis activity of algae. The high cellular content of antioxidant compounds or the increase of antioxidant enzymes in algae deactivates ROS and minimizes the hazardous effects of ultraviolet light (Karentz et al. 1991). Seaweeds often have evolved photo-inhibition mechanisms to quench the excess production of harmful ROS, produced during the high-level exposure of ultraviolet (i.e., UVA and UVB) radiation. Therefore, the upregulation of antioxidants (carotenoids) and antioxidant enzymes are strategies for maintaining homeostasis in seaweeds.

3. Antioxidant compounds isolated from seaweeds and their mechanisms of action

Seaweeds produce a wide range of antioxidant compounds, including polyphenols, polysaccharides, pigments of β-carotene, astaxanthin, phycocyanin, and phycoerythrin, and sulfated polysaccharides of fucoidans and heterofucans (Jégou et al. 2015; Huang et al. 2016; Rajauria, Foley, and Abu-Ghannam 2016; Agregán et al. 2017; Chakraborty, Maneesh, and Makkar 2017; Chen et al. 2017; Heriyanto et al. 2017; Li et al. 2017; Sathya et al. 2017; Koizumi et al. 2018; Rajauria 2018; Sellimi et al. 2018). Antioxidant compounds extracted from seaweeds have a broad spectrum of beneficial biological properties that include anticancer, antimicrobial, anti-inflammatory, and antidiabetic activities (Wijesekara, Pangestuti, and Kim 2011; Wijesinghe and Jeon 2012; Renju, Kurup, and Bandugula 2014; Boominathan and Mahesh 2015; Huang et al. 2016). These compounds have attracted major interest due to their biological effects. We describe some of the antioxidant compounds isolated from seaweeds (Table 1) and their mechanism of action (Table 2) in the following sections.

a. Phenolic compounds

Marine algae are considered a good source of polyphenolic compounds, which are reported to provide a range of biological benefits, including antioxidant, anticancer, antimicrobial, anti-inflammatory, and antidiabetic activities (de Sousa Santos et al. 2015). Consequently, polyphenolic compounds have gained much attention from various research groups and been examined for their possible use in food, cosmetics, and pharmaceutical applications. The antioxidant activities of these compounds have been explored widely through experimental studies. Jégou et al. (2015) reported that phloroglucinol (1,3,5-trihydroxy benzene) is the main phenolic compound in the brown macroalgae of *Cystoseira tamariscifolia*. Brown seaweeds contain highly polymerized forms of phloroglucinol only, known as phlorotannins, with sizes ranging from 400 to 400,000 Da (Lemesheva and Tarakhovskaya 2018). These polymers and their derivatives (e.g., fuhalols, hydroxyfuhalols, and phlorethols) have also been isolated from *Sargassum fusiforme* (Li et al. 2017) and *S muticum* (Montero et al. 2016). Irish seaweed *Himanthalia elongata* is a good source of antioxidants. A plethora of phenolic compounds, namely hydroxybenzaldehyde (*meta/para*), phloroglucinol, kaempferol, cirsimaritin, gallic acid 4-*O*-glucoside, carnosic acid, gallic acid, phlorotannins, hydroxybenzoic acid, hydroxycinnamic acid, and flavonols

Table 1. Antioxidant compounds from seaweeds.

General category	Compounds	Name of algae/seaweeds	Reference
Phenolic compound	Phlorotannins	*Cystoseira tamariscifolia*	Jégou et al. (2015)
	Phlorotannins	*Cystoseira trinodis*	Sathya et al. (2017)
	Phlorotannins	*Sargassum fusiforme* (Harvey)	Li et al. (2017)
	Phlorotannins (fuhalols, hydroxyfuhalols, eckol)	*Bifurcaria bifurcata*	Agregán et al. (2017)
	Phlorotannins (hydroxyfuhalols, eckol)	*Fucus vesiculosus*	Agregán et al. (2017)
Phenolic compound/phenolic acid	Phlorotannins, hydroxybenzoic acid, hydroxycinnamic acid, flavonols subclasses of polyphenols, hydroxybenzaldehyde (meta/para), phloroglucinol, kaempferol, cirsimaritin, gallic acid 4-*O*-glucoside, carnosic acid, gallic acid	*Himanthalia elongate*	Rajauria, Foley, and Abu-Ghannam (2016) Rajauria (2018)
	Phlorotannins (fuhalols, eckol), hydroxybenzoic and rosmarinic acid	*Ascophyllum nodosum*	Agregán et al. (2017)
	Rosmarinic acid	*Bifurcaria bifurcata*	Agregán et al. (2017)
	Caffeic acid, 2,5-dihydroxy benzoic acid, coumaric acid, ferulic acid, syringic acid	*Sargassum plagiophyllum*	Chakraborty, Maneesh, and Makkar (2017)
	Coumaric and ferulic acid	*Fucus vesiculosus*	Agregán et al. (2017)
	Caffeic acid, 2,5-dihydroxy benzoic acid, coumaric acid, ferulic acid, gallic acid, syringic acid	*Anthophycus longifolius*	Chakraborty, Maneesh, and Makkar (2017)
	Coumaric acid, ferulic acid, syringic acid, salicylic, caffeic acid	*Sargassum myriocystum*	Chakraborty, Maneesh, and Makkar (2017)

(*continued*)

Table 1. (Continued)

General category	Compounds	Name of algae/seaweeds	Reference
Polysaccharide	(Glucan) Laminaran	*Cystoseira barbata*	Sellimi et al. (2018)
	Fucoidan	*Sargassum glaucescens*	Huang et al. (2016)
Pigment	Chlorophylide *a*, chlorophyll *c*1, fucoxanthin, violaxanthin, 13- and 13′-*cis* isomers of fucoxanthin, antheraxanthin, zeaxanthin, chlorophyll *a*, Chlorophyll *a*′	*Dictyota dentate, Padina australis, Sargassum crassifolium, Turbinaria conoides*	Heriyanto et al. (2017)
Chlorophyll	Chlorophyll *c*2, chlorophyll *c*1, purpurin-18 *a*, pheophytin *d* phytyl-purpurin-18 *a* chlorophyll *c*1′ 13^2hydroxy-chlorophyllide c2	*Enteromorpha* spp., *Ulva* spp., *Porphyra umbilicalis, Undaria pinnatifida, Laminaria ochroleuca*	Chen et al. (2017)
Carotene	Lutein, zeaxanthin, α-carotene, and β-carotene	*Pyropia yezoensis*	Koizumi et al. (2018)
Flavanol	Epicatechin gallate and catechin	*Anthophycus longifolius*	Chakraborty, Maneesh, and Makkar (2017)
Flavanol	Epicatechin	*Sargassum plagiophyllum*	Chakraborty, Maneesh, and Makkar (2017)
Flavanol	Epigallocatechin gallate, epicatechin	*Sargassum myriocystum*	Chakraborty, Maneesh, and Makkar (2017)

Table 2. Mechanism of action of antioxidant compounds from seaweeds. (↑ indicates up regulated and ↓ indicates down regulated.)

Compounds/extracts	Seaweeds/source	Action	Host/media	Reference
Phloroglucinol	*Ecklonia cava*	H2O2 induced cell viability↓, Heme oxygenase-1 (HO-1)↑, ROS production↓, DNA damage↓, apoptosis↓, mitochondrial dysfunction↓, Bcl-2↓, caspase-9 and -3↓, PARP↓, Bax↑	H2O2 induced HaCaT human keratinocytes	Park et al. (2019)
Fucoidan	*Sargassum glaucescens*	1,1-diphenyl-2-picrylhydrazyl (DPPH)↓, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)↓, reducing power↑	In vitro	Huang et al. (2016)
Diphlorethohydroxycarmalol	*Ishige okamurae*	Cytotoxicity↑, reactive oxygen species (ROS)↓, activated Nrf2 transcription factor, antioxidant mRNA↑, detoxification enzymes↑, glyoxalase-1 mRNA↑, glycation↓	Methylglyoxal-induced human embryonic kidney cell line cells	Cha et al. (2018)
Ethanol extracts	*Sargassum serratifolium*	Cytotoxicity↑, ROS↓, heme oxygenase-1↑, nuclear factor-erythroid 2 related factor 2↑, Bcl-2↓, pro-caspase-3↓	H2O2 induced SW1353 human chondrocytes	Park et al. (2018)
Fucoidan	*Sargassum hemiphyllum*	H2O2 formation↓, HIF-1↓, vascular endothelial growth factor↓, PI3K/Akt/mTOR/p70S6K/4EBP-1 phosphorylation↓, tumor angiogenesis and growth↓	Hypoxia-stimulated human bladder cancer cells (T24), athymic nude mice (BALB/c)	Chen et al. (2015)
Fucoidan	Brown sea weeds (purity >98%; Cool Chemistry Co., Ltd. Beijing, China)	Alanine aminotransferase↓, aspartate aminotransferase↓, ROS↓, malondialdehyde↓, superoxide dismutase↑, glutathione↑, catalase (CAT)↑, CYP2E1↓, pJNK↓, Bax↓	ICR mice, human hepatocyte HL-7702 cell	Wang et al. (2018)
Fractions	*Sargassum muticum*	Hydrogen peroxide↓, caspase-9↓	Human cell line MCF-7	Pinteus et al. (2017)

(*continued*)

Table 2. (Continued)

Compounds/extracts	Seaweeds/source	Action	Host/media	Reference
Fucoidan	*Turbinaria conoides*	Anti-proliferative activities	Lung cancer A549 cells	Alwarsamy et al. (2016)
Fucoidan	*Fucus vesiculosus*	Cell viability↓, apoptosis↑,Bax↑,Bcl-2↓, PARP↑, cytochrome *c (cytosolic)*↑, cytochrome *c (mytochondria)*↓, hTERT↓, telomerase↓, p-PI3K↓, p-Akt↓	5637 human bladder cancer	Han et al. (2017)
Fucoxanthin and fucoxanthinol	Purity >98%; Third Institute of Oceanography State Oceanic Administration, with a chemical	ROS↓, apoptosis↑, cell viability↓, Bcl-2/Bax↑	Tributyltin-induced HepG2 cells	Zeng et al. (2018)
Fractions, diterpenes eleganolone and eleganonal	*Bifurcaria bifurcata*	DPPH↓, oxygen radical absorbance capacity↓, ferric reducing antioxidant power↓, H2O2 production↓, neuroprotective activities	In vitro, 6-hydroxydopamine (6-OHDA) induced human neuroblastoma cell line (for neuroprotective effects)	Silva et al. (2019)
Phlorotannins and dieckol	*Ecklonia cava*	NF-κB↓, mitogen-activated proteinkinase↓, tartrate-resistant acid phosphatase↓, cathepsin K↓, and matrix metalloproteinase-9↓, nuclear factor of activated T cells-1↓, c-fos↓, ROS↓, heme oxygenase-1↑	RAW 264.7 cells	Kim et al. (2019)
Phlorotannins	*Ascophyllum nodosum*	Gastrointestinal modifications, IL-8↑	Human blood and urine (N = 24 volunteers, 12 female and 12 male)	Corona et al. (2016)
Fucoidan	*Sargassum hemiphyllum*	Improved the disease control rate in metastatic	Human (colorectal cancer patients)	Tsai et al. (2017)
Fucoidans	*Mozuku of Cladosiphon novae-caledoniae kylin*	Quality of life↑, interleukin-1β(IL-1β), IL-6↓, and tumor necrosis factor-α (TNF-α) ↓	Advanced cancer patients	Takahashi et al. (2018)
(Poly)phenol	*Ascophyllum nodosum*	DNA damage↑, no significant changes observed on the oxidant capacity, C-reactive protein, and inflammatory cytokines	Human (obese population)	Baldrick et al. (2018)

(a subclass of polyphenols), have been identified in this seaweed (Rajauria, Foley, and Abu-Ghannam 2016; Rajauria 2018). These phenolic antioxidant compounds could provide a new understanding of the health benefits of *H. elongata* as a potential functional ingredient in food and pharmaceutical research.

Agregán et al. (2017) analyzed the phenolic compounds from the extracts of three seaweeds: *Ascophyllum nodosum, Bifurcaria bifurcate*, and *Fucus vesiculosus*. Chakraborty, Maneesh, and Makkar (2017) evaluated the antioxidant activities of three brown seaweeds: *Anthophycus longifolius, Sargassum plagiophyllum*, and *S. myriocystum*. In the same study, the ethyl acetate (EtOAc) and methanolic (MeOH) extracts of these seaweeds were analyzed for the presence of phenolic acids and chroman flavanols. Among them, the phenolic acids identified in *A. longifolius* were caffeic acid, 2,5-dihydroxy benzoic acid, coumaric acid, ferulic acid, gallic acid, and syringic acid (EtOAc extracts), and the flavanols were epicatechin gallate and catechin (MeOH extract). Caffeic acid, 2,5-dihydroxy benzoic acid, coumaric acid, ferulic acid, syringic acid, and epicatechin were found to be abundant in the extract of *S. plagiophyllum* (EtOAc and MeOH). Both fractions of *S. myriocystum* (EtOAc and MeOH) contained coumaric acid, ferulic acid, syringic acid, and flavanols (epigallocatechin gallate, epicatechin). In addition, salicylic acid was found only in the EtOAc fraction, whereas MeOH extract contained hydroxyl cinnamic acid derivatives of caffeic acid (Chakraborty, Maneesh, and Makkar 2017).

Some important brown algae species, including *Ascophyllum nodosum, Bifurcaria bifurcate, Cladophora rupestris, Codium fragile, Dictyopteris polypodioides, Fucus vesiculosus, Laminaria japonica, Laminaria ochroleuca, Laurencia obtuse, Lessonia trabeculata*, and *Lessonia nigrescens* have been investigated for their phenolic compound extraction and in vitro biological activities (Topuz et al. 2016; Kolsi et al. 2017; Agregán et al. 2018; Yuan et al. 2018; Otero, López-Martínez, and García-Risco 2019). Alghazeer et al. (2018) studied the potential antioxidant and anticancer activities of crude extracts of Chlorophyta (*Ulva lactuca* and *Codium tomentosum*), Phaeophyta *(Cystoseira crinita, C. stricta,* and *Sargassum vulgare)*, and Rhodophyta *(Gelidium latifolium, Hypnea musciformis*, and *Jania rubens)*. Phlorotannins is a group of phenolic compounds found in brown seaweed and extensively used as a functional ingredient in food products, pharmaceuticals, and cosmeceuticals. Previous experiments by Wang et al. (2012) emphasized the antioxidant activity of phlorotannins from the brown algae of *F. vesiculosus*. In an independent investigation, the phlorotannin-enriched fraction from *A. nodosum* showed potent radical scavenging activity, which correlated with the phenol content (Breton, Cérantola, and Ar Gall 2011). Sathya et al. (2017) reported the antioxidant activity of the crude extracts and different fractions of the brown seaweeds of *C. trinodis*, and isolated and purified phlorotannins from their extracts. It is thought that the strong antioxidant activity of phlorotannins might be related to their unique molecular structure (Ahn et al. 2007). Park et al. (2019) showed the beneficial effects of Phloroglucinol from *Ecklonia cava* (an edible brown alga belonging to the Laminariaceae family), which protected cells from oxidative stress and apoptosis via the stimulation of the Nrf2/HO-1 signaling pathway in HaCaT human keratinocytes. Phloroglucinol

significantly inhibited the viability of HaCaT cells induced by H_2O_2, which was allied with increased expression of heme oxygenase-1 (HO-1) by the triggering of nuclear factor erythroid 2-related factor-2 (Nrf2). Phloroglucinol significantly reduced H_2O_2-induced excessive production of ROS, DNA damage, and apoptosis.

Diphlorethohydroxycarmalol (DPHC), a polyphenol isolated from *Ishige okamurae*, an edible seaweed, is a possible therapeutic agent for the inhibition of diabetic nephropathy (Cha et al. 2018). Here, the researchers examined the protective effect of DPHC on methylglyoxal-induced oxidative stress in HEK (human embryonic kidney cell line) cells. The treatment utilizing DPHC inhibited cytotoxicity and ROS production, activated the Nrf2 transcription factor and increased the mRNA expression of antioxidant and detoxification enzymes of glyoxalase-1 mRNA expression, and reduced MGO-induced advanced glycation end product formation in HEK cells (Cha et al. 2018).

b. Pigments

Pigments are used to impart antioxidant, antidiabetic, immunomodulatory, antiangiogenic, and anti-inflammatory activities among other desired bioactive outcomes. Chlorophyll, carotenoids such as β-carotene, and xanthophylls (fucoxanthin, violaxanthin, antheraxanthin, zeaxanthin, lutein, neoxanthin) are considered seaweed pigments (Pangestuti and Kim 2011). These pigments are widely used in the food and beverages industries, animal feed, cosmetics, as well as pharmaceutical products. The demand for natural food colors is growing significantly. The food color market is projected to reach 5.12 billion dollars by 2023, and natural food colors are expected to be the greatest part of this projection (MarketsandMarkets 2019).

In recent work, four brown seaweeds of *Dictyota dentate, Padina australis, Sargassum crassifolium,* and *Turbinaria conoides*, all gathered from Panjang Island, Indonesia, were shown to share the same pigment composition (Heriyanto et al. 2017). Chlorophyll *a*, fucoxanthin, and β-carotene were the main pigments in all four, but the relative concentrations of the pigments differed across the species. Eleven pigments (i.e., chlorophyllide *a*, chlorophyll *c*1, fucoxanthin, violaxanthin, 13- and 13′-*cis* isomers of fucoxanthin, antheraxanthin, zeaxanthin, chlorophyll *a*, chlorophyll *a*′, pheophytin *a*, and β-carotene) were identified. *Dictyota dentata* contained the most chlorophyll *a* and total carotenoids (Heriyanto et al. 2017). Chlorophylls from seaweeds have been considered for their biological activities and health benefits. Various chlorophyll derivatives extracted from seaweeds are applied in the food, cosmetic, and pharmacology sectors (MarketsandMarkets 2019). Interestingly, Chen et al. (2017) identified seven chlorophyll derivatives from aonori (*Enteromorpha* spp.), sea lettuce (*Ulva* spp.), nori (*Porphyra umbilicalis*), wakame (*Undaria pinnatifida*), and kombu (*Laminaria ochroleuca*) for the first time.

c. Carotenoids

Carotenoids are yellow–orange tetra-terpenoid pigments produced from C4 isoprenoid units. They are synthesized only in plants, algae, fungi, and bacteria, but not in animals.

Carotenoids perform a multitude of functions in the human body (Nisar et al. 2015; Eggersdorfer and Wyss 2018). In most red seaweeds, the major carotenoids are α-carotene, β-carotene, lutein, and zeaxanthin (Nisar et al. 2015). It is established that the carotenoids from seaweeds show multiple biological activities. Lopes-Costa et al. (2017) treated two human colorectal cancer cell lines with the carotenoid fucoxanthin and polyphenol phloroglucinol, alone and in combination with 5-fluorouracil, and suggested these compounds are promising anticancer agents. *Pyropia yezoensis*, belonging to Bangiales (Rhodophyta), is one of the most economically valuable marine foods in East Asia and contains many nutrients and health-promoting compounds. Koizumi et al. (2018) determined lutein, zeaxanthin, α-carotene, and β-carotene as key carotenoids in both the thallus and conchocelis stages of *P. yezoensis*. Fucoxanthin is one of the most prevalent carotenoids in brown seaweeds and belongs to the group of xanthophylls, exhibiting several biological properties such as antioxidant, antimicrobial, anti-obesity, and anticancer activities (D'Orazio et al. 2012). Fucoxanthin showed a greater antioxidant potential than alpha-carotene, inhibiting lipid peroxidation caused by retinol deficiency in rats (Sangeetha, Bhaskar, and Baskaran 2009). Fucoxanthin also proved protective against oxidative stress induced by UVB radiation in human fibroblast cells (Heo and Jeon 2009). Defensive effects of fucoxanthin and fucoxanthinol against tributyltin-induced oxidative stress in HepG2 cells was determined by Zeng et al. (2018). The treatment utilizing fucoxanthinol significantly decreased the ROS and malondialdehyde (MDA); further, both fucoxanthin and fucoxanthinol clearly increased the expression level of Bcl-2/Bax in tributyltin induced HepG2 cells.

d. Polysaccharides

Polysaccharides isolated from seaweeds exhibit noticeable antioxidant activity and are effectively used to decrease oxidative damage to the human body (Wu et al. 2013; Xu, Huang, and Cheong 2017). The water-soluble polysaccharides fraction from the brown alga *Hizikia fusiformis* showed free radical scavenging activities against hydroxyl radicals and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical in vitro and defended against oxidative stress in the carbon tetrachloride-induced liver injury model (Xu, Huang, and Cheong 2017). According to Sousa et al. (2016), the antioxidant activity of the polysaccharide fraction from *Solieria filiformis* demonstrates a dose-dependent DPPH radical scavenging effect. Similarly, the polysaccharides extracted from *Saccharina latissima* scavenged 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonate; ABTS) radicals and exhibited strong antioxidant reducing power in vitro (Jiménez-Escrig, Gómez-Ordóñez, and Rupérez 2015). Wang et al. (2013) highlighted the antioxidant activities and intestinal functions of *Sargassum fusiforme* polysaccharides, by demonstrating their significant role in the development of intestinal function in cyclophosphamide-induced immune-suppressed mice.

Sulfated polysaccharides such as fucans, fucoidans, carrageenans, galactans, and laminarin, are a major component in the cell wall of seaweeds (Deniaud-Bouët et al. 2017) Sulfated polysaccharides have been at the forefront of pharmaceutical research due to their

varying biological efficacy and potent antioxidant properties (Wijesekara, Pangestuti, and Kim 2011). Fucoidan is a complex sulfated polysaccharide present in brown seaweeds with a variety of beneficial biological effects (Anastyuk et al. 2012). The antioxidant activities of crude extracts of fucoidan isolated from *Sargassum glaucescens* have also been documented (Huang et al. 2016). Fucoidan extracted from *S. glaucescens* showed antioxidant activities by scavenging DPPH and ABTS radicals (Huang et al. 2016). Chen et al. (2015) found low molecular weight fucoidan (LMF) from *S. hemiphyllum* suppressed tumor angiogenesis via the suppressing of HIF-1/VEGF signaling in hypoxia-stimulated human bladder cancer cells (T24) and athymic nude mice (BALB/c). In addition, fucoidan was purified from *Turbinaria conoides* and found that fucoidan significantly inhibited the proliferation of lung carcinoma (A549) cells (Alwarsamy, Gooneratne, and Ravichandran 2016). Other findings by Han et al. (2017) reported that fucoidan induces ROS-dependent apoptosis in 5637 human bladder cancer cells and reduced telomerase expression via suppressing the PI3K/Akt signaling pathway. In support of these findings, van Weelden (2019) announced fucoidan as an effective candidate in the future treatment of cancer. Further, Wang et al. (2018) found fucoidan suppressed acetaminophen-induced hepatotoxicity via oxidative stress inhibition and Nrf2 translocation. Fucoidan changed the expression of alanine aminotransferase (ALT), aspartate aminotransferase (AST), ROS, MDA, and related proteins levels (CYP2E1, pJNK, and Bax) in mice liver. Wang et al. used the human hepatocyte HL-7702 cell line to clarify the potential molecular mechanism of fucoidan. Fucoidan pretreatment reduced the levels of ALT, AST, ROS, and MDA by increasing the levels of glutathione, SOD, and catalase activities. It further reduced the oxidative stress-induced phosphorylated c-Jun N-terminal protein kinase and matrix metalloproteinase and stimulated the translocation of Nrf2 from the cytoplasm into the nucleus (Wang et al. 2018).

Laminarin is a small glucan isolated from brown seaweeds. The biological properties of laminaran are essentially related to the antioxidant activities that are essential to prevent oxidative damage caused by reactive oxygen species. Laminaran and three fucoidan fractions were obtained from the brown seaweeds of *Alaria marginata* and *A. angusta* and their anticancer activities were determined in carcinoma cells (HT-29) (Usoltseva Menshova 2016). Laminaran was subsequently isolated from the marine brown seaweed *Cystoseira barbata* and was investigated for its structural features, as well as its antioxidant and antibacterial activities (Sellimi et al. 2018).

The antioxidant activities of seaweeds have been largely studied in vitro using crude extracts, rather than pure compounds. Various brown algae, especially *Hydroclathrus clathratus* and *Padina arborescens*, have also been found to inhibit the human and monkey cancer cell lines (Wang et al. 2008). For instance, the phenolic-rich extracts from three common edible seaweeds of *Palmaria*, *Ascophyllum*, and *Alaria* (found in the United Kingdom) showed potential anti-proliferative activity against colon cancer cells (Nwosu et al. 2011). *Sargassum muticum*,a brown seaweed with strong antioxidant properties, showed cytoprotective mechanisms against oxidative stress on a human cell (Pinteus et al. 2017). Accordingly, Park et al. (2018) investigated the mechanism of the antioxidative effect of ethanol

extract of *Sargassum serratifolium* (EESS) on DNA damage and apoptosis in SW1353 human chondrocytes stimulated by H_2O_2. Further, Kim et al. (2018) reported the inhibitory property of EESS on receptor activator of nuclear factor-κB ligand (RANKL)-stimulated osteoclastogenesis and oxidative stress via the suppression of NF-κB and stimulation of the Nrf2/HO-1 signaling pathway. Recently, Silva et al. (2019) described the antioxidant and neuroprotective potential of the *Bifurcaria bifurcata* in an in vitro Parkinson's disease model. Their ongoing research isolated diterpenes eleganolone and eleganonal, which showed antioxidant potential, could be interesting for future study. Ethanol extracts of *Ecklonia cava* (an edible marine brown algae) showed the inhibitory effects on RANKL-stimulated osteoclast differentiation and oxidative stress through mitogen-activated protein (MAP) kinase/NF-κB pathway reduction and heme oxygenase-1 induction reported by Kim et al. (2019).

4. Excessive use of antioxidant

ROS have positive effects on immune reactivity, controlling anti-microbial and anti-tumoral activities in the body. The excess deactivation of such oxidants by antioxidants may hinder these vital functions and enhance cellular survival by abating apoptotic pathways or increase energy production from glycolysis. Therefore, we conclude that a critical balance of oxidants and antioxidants should be present in the human body. This balance can be disrupted by the consumption of excessive antioxidants, which may result in "antioxidant stress" in the body and may correspond to the enhanced growth of cancer cells and to compromised immunity (Villanueva and Kross 2012).

5. Clinical trials with seaweeds compounds

The production of both ROS and reactive nitrogen species (collectively known as RS) is associated with various diseases that include cancer, cardiovascular diseases, atherosclerosis, hypertension, ischemia, diabetes mellitus, and neurodegenerative diseases (Borek 1993; Cadenas and Davies 2000). It is reported that the extracts of various seaweeds, such as brown algae *Hydroclathrus clathratus* and *Padina arborescences*, can inhibit human and monkey cancer cells (Wang et al. 2008). Corona et al. (2016) examined the gastrointestinal modifications and bioavailability of seaweed phlorotannins from *Ascophyllum nodosum* as well as their effect on inflammatory markers in healthy participants. The majority of the metabolites in both urine and plasma samples suggested colonic metabolism of high-molecular-weight phlorotannins. The increase of cytokine IL-8 content was observed by Corona et al., which might suggest a possible target for phlorotannin bioactivity. LMF is widely used as a food supplement for cancer patients. The effectiveness of LMF was conducted by Tsai et al. (2017) as a supplemental therapy to chemotarget agents in metastatic colorectal cancer patients. In this study, patients were recruited ($N = 54$) and divided into two groups: a study group ($n = 28$) and a control group ($n = 26$). Each patient received 4 g of fucoidan twice in a day for 6 months. Tsai et al. found that LMF combined with chemotarget agents significantly improved the disease control rate.

Takahashi et al. (2018) performed a clinical study for advanced cancer patients ($N = 20$) to observe the efficacy of fucoidans, especially focusing on inflammation in relation to quality of life (QOL) scores. The patients were treated with 400 mL/d fucoidan (10 mg/mL) orally for at least 4 weeks. Inflammatory biomarkers, protein and various cytokines, and QOL scores were observed before treatment and again after 2 weeks and after 4 weeks of fucoidan administration. After 2 weeks of fucoidan ingestion, the interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α were significantly reduced and the QOL scores (e.g., fatigue) were stable without noteworthy changes. Another study reported the effects of phenol extract from brown seaweeds (*Ascophyllum nodosum)* on DNA damage, oxidative stress, and inflammation in vivo (Baldrick et al. 2018). Participants ($N = 80$) received either a 400 mg capsule containing 100 mg seaweed (poly)phenol and 300 mg maltodextrin or a 400 mg maltodextrin placebo control capsule daily. After the experimental period of 8 weeks, Baldrick et al. found modest reduction in basal DNA damage in only patients who were obese; there were no significant changes in C-reactive protein, antioxidant status, or inflammatory cytokines (Table 2).

6. Conclusions

A variety of essential antioxidant compounds are derived from marine seaweeds. The nutritional value of some edible seaweeds is of interest because of their antioxidant potentials. However, therapeutic applications of these compounds in vivo using both animal models and human subjects need to be fully explored. There are potential markets for such seaweeds and their products as excellent natural sources of nutrients with high antioxidant activity in the food, drug, and cosmetics industries. Therefore, the systematic study of marine seaweeds will continue to attract tremendous attention as a vast natural source of essential nutrients and pharmaceuticals.

Acknowledgments. This work was supported by BB21+ Project in 2021.

REFERENCES

Agregán, R., Munekata, P. E. S., Franco, D., Carballo, J., Barba, F. J., and Lorenzo, J. M. 2018. Antioxidant potential of extracts obtained from macro- (*Ascophyllum nodosum*, *Fucus vesiculosus* and *Bifurcaria bifurcata*) and micro-algae (*Chlorella vulgaris* and *Spirulina platensis*) assisted by ultrasound. Medicines, *5(2)*, 33. https://doi.org/10.3390/medicines5020033

Agregán, R., Munekata, P. E. S., Franco, D., Dominguez, R., Carballo, J., and Lorenzo, J. M. 2017. Phenolic compounds from three brown seaweed species using LC-DAD-ESI-MS/MS. Food Res. Int., *99(Part 3)*, 979–985. https://doi.org/10.1016/j.foodres.2017.03.043

Ahn, G.-N., Kim, K.-N., Cha, S.-H., Song C.-B., Lee, J., Heo, M-.S., Yeo, I.-K., Lee, N.-H., Jee, Y.-H., Kim, J-.S., Heu, M.-S., and Jeon Y.-J. 2007. Antioxidant activities of phlorotannins purified from *Ecklonia cava* on free radical scavenging using ESR and H_2O_2-mediated DNA damage. Eur. Food Res. Technol., *226(1–2)*, 71–79. https://doi.org/10.1007/s00217-006-0510-y

Alghazeer, R., Howell, N. K., El-Naili, M. B., and Awayn, N. 2018. Anticancer and antioxidant activities of some algae from Western Libyan Coast. Nat. Sci., *10(7)*, 232–246. https://doi.org/10.4236/ns.2018.107025

Alwarsamy, M., Gooneratne, R., and Ravichandran, R. 2016. Effect of fucoidan from Turbinaria conoides on human lung adenocarcinoma epithelial (A549) cells. Carbohydr. Polym., *152*, 207–213. https://doi.org/10.1016/j.carbpol.2016.06.112

Anastyuk, S. D., Imbs, T. I., Shevchenko, N. M., Dmitrenok, P. S., and Zvyagintseva, T. N. 2012. ESIMS analysis of fucoidan preparations from Costaria costata, extracted from alga at different life-stages. Carbohydr. Polym., *90(2)*, 993–1002. https://doi.org/10.1016/j.carbpol.2012.06.033

Baldrick, F. R., McFadden, K., Ibars, M., Sung, C., Moffatt, T., Megarry, K., Thomas, K., et al. 2018. Impact of a (poly)phenol-rich extract from the brown algae *Ascophyllum nodosum* on DNA damage and antioxidant activity in an overweight or obese population: A randomized controlled trial. Am. J. Clin. Nutr., *108(4)*, 688–700. https://doi.org/10.1093/ajcn/nqy147

Barahona, T., Chandía, N. P., Encinas, M. V., Matsuhiro, B., and Zúñiga, E. A. 2011. Antioxidant capacity of sulfated polysaccharides from seaweed: A kinetic approach. Food Hydrocoll., *25(3)*, 529–535. https://doi.org/10.1016/j.foodhyd.2010.08.004

Bocanegra, A., Bastida, S., Benedí, J., Ródenas, S., and Sánchez-Muniz, F. J. 2009. Characteristics and nutritional and cardiovascular-health properties of seaweeds. J. Med. Food, *12(2)*, 236–258. https://doi.org/10.1089/jmf.2008.0151

Boominathan, M., and Mahesh, A. 2015. Seaweed carotenoids for cancer therapeutics *in* Handbook of Anticancer Drugs from Marine Origin. S. K. Kim, ed. Cham, Switzerland: Springer International, pp. 185–203. https://doi.org/10.1007/978-3-319-07145-9_10

Borek, C. 1993 Molecular mechanisms in cancer induction and prevention. Environ. Health Perspect. *101(S3)*, 237–245. https://doi.org/10.1289/ehp.93101s3237

Breton, F., Cérantola, S., and Ar Gall, E. 2011. Distribution and radical scavenging activity of phenols in *Ascophyllum nodosum* (Phaeophyceae). J. Exp. Mar. Biol. Ecol., *399(2)*, 167–172. https://doi.org/10.1016/j.jembe.2011.01.002

Cadenas, E., and Davies, K. J. A. 2000. Mitochondrial free radical generation, oxidative stress, and aging. Free Radical Biol. Med., *29(3)*, 222–230. https://doi.org/10.1016/s0891-5849(00)00317-8

Cha, S. H., Hwang, Y., Heo, S. J., Jun, H. S. 2018.Diphlorethohydroxycarmalol attenuates methylglyoxal-induced oxidative stress and advanced glycation end product formation in human kidney cells *in* Therapeutic Potential of Natural Antioxidants, special issue, Oxid. Med. Cell. Longevity. *2018*, 3654095. https://doi.org/10.1155/2018/3654095

Chakraborty, K., Maneesh, A., and Makkar, F. 2017. Antioxidant activity of brown seaweeds. J. Aquat. Food Prod. Technol., *26(4)*, 406–419. https://doi.org/10.1080/10498850.2016.1201711

Chen, K., Ríos, J. J., Pérez-Gálvez, A., and Roca, M. 2017. Comprehensive chlorophyll composition in the main edible seaweeds. Food Chem., *228*, 625–633. https://doi.org/10.1016/j.foodchem.2017.02.036

Chen, M. C., Hsu, W. L., Hwang, P. A., and Chou, T. C. 2015. Low molecular weight fucoidan inhibits tumor angiogenesis through downregulation of HIF-1/VEGF signaling under hypoxia. Mar. Drugs, *13(7)*, 4436–4451. https://doi.org/10.3390/md13074436

Cornish, M. L., and Garbary, D. J. 2010. Antioxidants from macroalgae: Potential applications in human health and nutrition. Algae, *25(Part 4)*, 155–171. https://doi.org/10.4490/algae.2010.25.4.155

Corona, G., Ji, Y., Anegboonlap, P., Hotchkiss, S., Gill, C., Yaqoob, P., Spencer, J. P., and Rowland, I.2016. Gastrointestinal modifications and bioavailability of brown seaweed phlorotannins and effects on inflammatory markers. Br. J. Nutr. *115(7)*, 1240–1253. https://doi.org/10.1017/S0007114516000210

Deniaud-Bouët, E., Hardouin, K., Potin, P., Kloareg, B., and Hervé C. 2017. A review about brown algal cell walls and fucose-containing sulfated polysaccharides: Cell wall context, biomedical properties and key research challenges. Carbohyd. Polym., *175*, 395–408. https://doi.org/10.1016/j.carbpol.2017.07.082

de Sousa Santos, A. K. F., da Fonseca, D. V., Salgado, P. R. R., Muniz, V. M., de Arruda Torres, P., Lira, N. S., da Silva Dias, C., de Morais Pordeus, L. C., Barbosa-Filho, J. M., and de Almeida, R. N. 2015. Antinociceptive activity of *Sargassum polyceratium* and the isolation of its chemical components. Rev. Bras. Farmacogn., *25(6)*, 683–689. https://doi.org/10.1016/j.bjp.2015.07.017

D'Orazio, N., Gemello, E., Gammone, M. A., De Girolamo, M., Ficoneri, C., and Riccioni G. 2012. Fucoxantin: A treasure from the sea. Mar. Drugs, *10(3)*, 604–616. https://doi.org/10.3390/md10030604

Eggersdorfer, M., and Wyss, A. 2018. Carotenoids in human nutrition and health. Arch. Biochem. Biophys., *652*, 18–26. https://doi.org/10.1016/j.abb.2018.06.001

Han, M. H., Lee, D. S., Jeong, J. W., Hong, S. H., Choi, I. W., Cha, H. J., Kim, S., Kim, H. S., Park, C., Kim, G. Y., Moon, S. K., Kim, W. J., and Choi, Y. H. 2017. Fucoidan induces ROS-dependent apoptosis in 5637 human bladder cancer cells by downregulating telomerase activity via inactivation of the PI3K/akt signaling pathway. Drug Dev. Res., *78(1)*, 37–48. https://doi.org/10.1002/ddr.21367

Harker, M., Berkaloff, C., Lemoine, Y., Britton, G., Young, A. J., Duval, J.-C., Rmiki, N.-E., and Rousseau, B. 1999. Effects of high light and desiccation on the operation of the xanthophyll cycle in two marine brown algae. Eur. J. Phycol. *34(1)*, 35–42. https://doi.org/10.1080/09670269910001736062

Heo, S. J., and Jeon, Y.-J. 2009. Protective effect of fucoxanthin isolated from *Sargassum siliquastrum* on UV-B induced cell damage. J. Photochem. Photobiol., B, *95(2)*, 101–107. https://doi.org/10.1016/j.jphotobiol.2008.11.011

Heriyanto, H., Juliadiningtyas, A. D., Shioi, Y., Limantara, L., and Brotosudarmo. T. H. P. 2017. Analysis of pigment composition of brown seaweeds collected from Panjang Island, Central Java, Indonesia. Philipp. J. Sci., *146(3)*, 323–330.

Holdt, S. L., and Kraan, S. 2011. Bioactive compounds in seaweed: Functional food applications and legislation. J. Appl. Phycol., *23(3)*, 543–597. https://doi.org/10.1007/s10811-010-9632-5

Huang, C.-Y., Wu, S.-J., Yang, W.-N., Kuan, A.-W., and Chen, C.-Y. 2016. Antioxidant activities of crude extracts of fucoidan extracted from *Sargassum glaucescens* by a compressional-puffing-hydrothermal extraction process. Food Chem., *197(Part B)*, 1121–1129. https://doi.org/10.1016/j.foodchem.2015.11.100

Jégou, C., Kervarec, N., Cérantola, S., Bihannic, I., and Stiger-Pouvreau, V. 2015. NMR use to quantify phlorotannins: The case of *Cystoseira tamariscifolia*, a phloroglucinol-producing brown macroalga in Brittany (France). Talanta, *135*, 1–6. https://doi.org/10.1016/j.talanta.2014.11.059

Jiménez-Escrig, A., Gómez-Ordóñez, E., and Rupérez, P. 2015. Infrared characterisation, monosaccharide profile and antioxidant activity of chemical fractionated polysaccharides from the edible seaweed sugar Kombu (*Saccharina latissima*). Int. J. Food Sci. Technol., *50(2)*, 340–346. https://doi.org/10.1111/ijfs.12655

Karentz, D., McEuen, F. S., Land, M. C., and Dunlap, W. C. 1991. Survey of mycosporine-like amino acid compounds in Antarctic marine organisms: Potential protection from ultraviolet exposure. Mar. Biol., *108(1)*, 157–166. https://doi.org/10.1007/BF01313484

Kim, H. J., Park, C., Kim, G. Y., Park, E. K., Jeon, Y. J., Kim, S., Hwang, H. J., and Choi, Y. H. 2018. *Sargassum serratifolium* attenuates RANKL-induced osteoclast differentiation and oxidative stress through inhibition of NF-κB and activation of the Nrf2/HO-1 signaling pathway. Biosci. Trends, *12(3)*, 257–265. https://doi.org/10.5582/bst.2018.01107

Kim, S., Kang, S. S., Choi, S. I., Kim, G. H., and Imm J. Y. 2019. Ecklonia cava extract containing dieckol suppresses RANKL-induced osteoclastogenesis via MAP Kinase/NF-κB pathway inhibition and heme oxygenase-1 induction. J. Microbiol. Biotechnol., *29(1)*, 11–20. https://doi.org/10.4014/jmb.1810.10005

Koizumi, J., Takatani, N., Kobayashi, N., Mikami, K., Miyashita, K., Yamano, Y., Wada, A., Maoka, T., and Hosokawa, M. 2018. Carotenoid profiling of a red seaweed *Pyropia yezoensis*: Insights into biosynthetic pathways in the order Bangiales. Mar. Drugs, *16(11)*, 426. https://doi.org/10.3390/md16110426

Kolsi, R. B. A., Frikha, D., Salah, H. B., Jribi, I., Patti, F. P., Allouche, N., and Belghith, K. 2017. Phenolic composition and biological activities of brown alga *Dictyopteris polypodioides.* J. Pharmacog. Phytochem., *6(2)*, 109–113.

Lemesheva, V., and Tarakhovskaya, E. 2018. Physiological functions of phlorotannins. Biol. Commun., *63(1)*, 70–76. https://doi.org/10.21638/spbu03.2018.108

Li, Y., Fu, X., Duan, D., Liu, X., Xu, J., and Gao, X. 2017. Extraction and identification of phlorotannins from the brown alga, *Sargassum fusiforme* (Harvey) Setchell. Mar. Drugs, *15*, 49. https://doi.org/10.3390/md15020049

Lohrmann, N. L., Logan B. A., and Johnson, A. S. 2004. Seasonal acclimatization of antioxidants and photosynthesis in *Chondrus crispus* and *Mastocarpus stellatus*, two co-occurring red algae with differing stress tolerances. Biol. Bull., *207(3)*, 225–232. https://doi.org/10.2307/1543211

Lopes-Costa, E., Abreu, M., Gargiulo, D., Rocha, E., and Ramos, A. A. 2017. Anticancer effects of seaweed compounds fucoxanthin and phloroglucinol, alone and in combination with 5-fluorouracil in colon cells. J. Toxicol. Environ. Health Part A., *80(13–15)*, 776–787. https://doi.org/10.1080/15287394.2017.1357297

MarketsandMarkets. 2019. Food Colors Market worth 5.12 Billion USD by 2023. Press release. Accessed 1 March 2019. https://www.marketsandmarkets.com/PressReleases/food-colors.asp

Montero, L., Sánchez-Camargo, A. P., García-Cañas, V., Tanniou, A., Stiger-Pouvreau, V., Russo, M., Rastrelli, L., Cifuentes, A., Herrero, M., and Ibáñez, E. 2016. Anti-proliferative activity and chemical characterization by comprehensive two-dimensional liquid chromatography coupled to mass spectrometry of phlorotannins from the brown macroalga *Sargassum muticum* collected on North-Atlantic coasts. J. Chromatogr. A., *1428*, 115–125. https://doi.org/10.1016/j.chroma.2015.07.053

Newman, D. J., and Cragg, G. M. 2004. Marine natural products and related compounds in clinical and advanced preclinical trials. J. Nat. Prod., *67(8)*, 1216–1238. https://doi.org/10.1021/np040031y

Nisar, N., Li, L., Lu, S., Khin, N. C., and Pogson, B. J. 2015. Carotenoid metabolism in plants. Mol. Plant, *8(1)*, 68–82. https://doi.org/10.1016/j.molp.2014.12.007

Nwosu, F., Morris, J., Lund, V. A., Stewart, D., Ross, H. A., and McDougall, G. J. 2011. Anti-proliferative and potential anti-diabetic effects of phenolic-rich extracts from edible marine algae. Food Chem., *126(3)*, 1006–1012. https://doi.org/10.1016/j.foodchem.2010.11.111

Otero, P., López-Martínez, M. I., and García-Risco, M. R. 2019. Application of pressurized liquid extraction (PLE) to obtain bioactive fatty acids and phenols from *Laminaria ochroleuca* collected in Galicia (NW Spain). J. Pharm. Biomed. Anal., *164*, 86–92. https://doi.org/10.1016/j.jpba.2018.09.057

Pangestuti, R., and Kim, S.-K. 2011. Biological activities and health benefit effects of natural pigments derived from marine algae. J. Funct. Foods, *3(4)*, 255–266. https://doi.org/10.1016/j.jff.2011.07.001

Park, C., Cha, H.-J., Hong, S. H., Kim, G. Y., Kim, S., Kim, H. S., Kim, B. W., Jeon, Y. J., and Choi, Y. H. 2019. Protective effect of phloroglucinol on oxidative stress-induced DNA damage and apoptosis through activation of the Nrf2/HO-1 signaling pathway in HaCaT human keratinocytes. Mar. Drugs., *17*, 225. https://doi.org/10.3390/md17040225

Park, C., Hong, S. H., Shin, S. S., Lee, D. S., Han, M. H., Cha, H.-J., Kim, S., et al. 2018. Activation of the Nrf2/HO-1 signaling pathway contributes to the protective effects of *Sargassum serratifolium* extract against oxidative stress-induced DNA damage and apoptosis in SW1353 human chondrocytes. *Int. J. Environ. Res. Public Health, 15(6)*, 1173. https://doi.org/10.3390/ijerph15061173

Pinteus, S., Lemos, M. F. L., Silva, J., Alves, C., Neugebauer, A., Freitas, R., Duarte, A., and Pedrosa, R. 2017. An insight into *Sargassum muticum* cytoprotective mechanisms against oxidative stress on a human cell in vitro model. Mar. Drugs, *15(11)*, 353. https://doi.org/10.3390/md15110353

Rajauria, G. 2018. Optimization and validation of reverse phase HPLC method for qualitative and quantitative assessment of polyphenols in seaweed. J. Pharm. Biomed. Anal., *148*, 230–237. https://doi.org/10.1016/j.jpba.2017.10.002

Rajauria, G., Foley, B., and Abu-Ghannam, N. 2016. Identification and characterization of phenolic antioxidant compounds from brown Irish seaweed *Himanthalia elongata* using LC-DAD–ESI-MS/MS. Innov. Food Sci. Emerg. Technol., *37(Part B)*, 261–268. https://doi.org/10.1016/j.ifset.2016.02.005

Renju, G. L., Kurup, G. M., and Bandugula, V. R. 2014. Effect of lycopene isolated from *Chlorella marina* on proliferation and apoptosis in human prostate cancer cell line PC-3. Tumor Biol., *35(11)*, 10747–10758. https://doi.org/10.1007/s13277-014-2339-5

Roberts, J. M., Wheeler, A. J., and Freiwald, A. 2006. Reefs of the deep: The biology and geology of cold-water coral ecosystems. Science, *312(5773)*, 543–547. https://doi.org/10.1126/science.1119861

Safer, A. M., and Al-Nughamish, A. J. 1999. Hepatotoxicity induced by the anti-oxidant food additive, butylated hydroxytoluene (BHT), in rats: An electron microscopical study. Histol. Histopathol. *14(2)*, 391–406. https://doi.org/10.14670/HH-14.391

Sangeetha, R. K., Bhaskar, N., and Baskaran, V. 2009. Comparative effects of β-carotene and fucoxanthin on retinol deficiency induced oxidative stress in rats. Mol. Cell. Biochem., *331(1–2)*, 59. https://doi.org/10.1007/s11010-009-0145-y

Sathya, R., Kanaga, N., Sankar, P., and Jeeva, S. 2017. Antioxidant properties of phlorotannins from brown seaweed *Cystoseira trinodis* (Forsskål) C. Agardh. Arab. J. Chem., *10(S2)*, S2608–S2614. https://doi.org/10.1016/j.arabjc.2013.09.039

Schwartz, J. L. 1996. The dual roles of nutrients as antioxidants and prooxidants: Their effects on tumor cell growth. J. Nutr., *126(S4)*, 1221S–1227S. https://doi.org/10.1093/jn/126.suppl_4.1221S

Sellimi, S., Maalej, H., Rekik, D. M., Benslima, A., Ksouda, G., Hamdi, M., Sahnoun, Z., Li, S., Nasri, M., and Hajji, M. 2018. Antioxidant, antibacterial and in vivo wound healing properties of laminaran purified from *Cystoseira barbata* seaweed. Int. J. Biol. Macromol. *119*, 633–644. https://doi.org/10.1016/j.ijbiomac.2018.07.171

Silva, J., Alves, C., Freitas, R., Martins, A., Pinteus, S., Ribeiro, J., Gaspar, H. Alfonso A., and Pedrosa R. 2019. Antioxidant and neuroprotective potential of the brown seaweed *Bifurcaria bifurcata* in an in vitro Parkinson's disease model. Mar. Drugs, *17(2)*, 85. https://doi.org/10.3390/md17020085

Sousa, W. M., Silva, R. O., Bezerra, F. F., Bingana, R. D., Barros, F. C. N., Costa, L. E. C., Sombra, V. G., et al. 2016. Sulfated polysaccharide fraction from marine algae *Solieria filiformis*: Structural characterization, gastroprotective and antioxidant effects. Carbohydr. Polym., *152*, 140–148. https://doi.org/10.1016/j.carbpol.2016.06.111

Takahashi, H., Kawaguchi, M., Kitamura, K., Narumiya S., Kawamura, M., Tengan, I., Nishimoto, S., Hanamure, Y., Majima, Y., Tsubura, S., Teruya, K., and Shirahata, S. 2018. An exploratory study on the anti-inflammatory effects of fucoidan in relation to quality of life in advanced cancer patients. Integr. Cancer Ther., *17(2)*, 282–291. https://doi.org/10.1177/1534735417692097

Thomas, N. V., and Kim, S.-K. 2011. Potential pharmacological applications of polyphenolic derivatives from marine brown algae. Environ. Toxicol. Pharmacol., *32(3)*, 325–335. https://doi.org/10.1016/j.etap.2011.09.004

Tsai, H.-L., Tai, C.-J., Huang, C.-W., Chang, F.-R., and Wang, J.-Y. 2017. Efficacy of low-molecular-weight fucoidan as a supplemental therapy in metastatic colorectal cancer patients: A double-blind randomized controlled trial. Mar. Drugs, *15(4)*, 122. https://doi.org/10.3390/md15040122

Usoltseva Menshova, R. V., Anastyuk, S. D., Shevchenko, N. M., Zvyagintseva, T. N., and Ermakova, S. P. 2016. The comparison of structure and anticancer activity in vitro of polysaccharides from brown algae *Alaria marginata* and *A. angusta*. Carbohyd Polym., *153*, 258–265. https://doi.org/10.1016/j.carbpol.2016.07.103

van Weelden, G., Bobñski, M., Okła, K., Van Weelden,W. J., Romano, A., and Pijnenborg, J. M. A. 2019. Fucoidan structure and activity in relation to anti-cancer mechanisms. Mar. Drugs, *17(1)*, 32. https://doi.org/10.3390/md17010032

Villanueva, C., and Kross, R. D. 2012. Antioxidant-induced stress. Int. J. Mol. Sci. *13(2)*, 2091–2109. https://doi.org/10.3390/ijms13022091

Wang, H., Chiu, L. C. M., Ooi, V. E. C., and Ang Jr, P. O. 2008. Seaweed polysaccharides with anticancer potential. Bot. Mar., *51(4)*, 313–319. https://doi.org/10.1515/BOT.2008.041

Wang, T., Jónsdóttir, R., Liu, H., Gu, L., Kristinsson, H. G., Raghavan, S., and Ólafsdóttir, G. 2012. Antioxidant capacities of phlorotannins extracted from the brown algae *Fucus vesiculosus*. J. Agric. Food Chem., *60(23)*, 5874–5883. https://doi.org/10.1021/jf3003653

Wang, W., Lu, J.-B., Wang, C., Wang, C.-S., Zhang, H.-H., Li, C.-Y., and Qian, G.-Y. 2013. Effects of *Sargassum fusiforme* polysaccharides on antioxidant activities and intestinal functions in mice. Int. J. Biol. Macromol., *58*, 127–132. https://doi.org/10.1016/j.ijbiomac.2013.03.062

Wang, Y.-Q., Wei, J.-G., Tu, M.-J., Gu, J.-G., and Zhang, W. 2018. Fucoidan alleviates acetaminophen-induced hepatotoxicity via oxidative stress inhibition and Nrf2 translocation. Int. J. Mol. Sci., *19(12)*, 4050. https://doi.org/10.3390/ijms19124050

Wijesekara, I., Pangestuti, R., Kim, S.-K. 2011. Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae. Carbohydr. Polym., *84(1)*, 14–21. https://doi.org/10.1016/j.carbpol.2010.10.062

Wijesinghe, W. A. J. P., and Jeon, Y.-J. 2012. Biological activities and potential industrial applications of fucose rich sulfated polysaccharides and fucoidans isolated from brown seaweeds: A review. Carbohydr. Polym., *88(1)*, 13–20. https://doi.org/10.1016/j.carbpol.2011.12.029

Wu, M., Wu, Y., Qu, M., Li, W., and Yan, X. 2013. Evaluation of antioxidant activities of water-soluble polysaccharides from brown alga *Hizikia fusiformis*. Int. J. Biol. Macromol. *56*, 28–33. https://doi.org/10.1016/j.ijbiomac.2013.01.017

Xu, S.-Y., Huang, X., and Cheong, K.-L. 2017. Recent advances in marine algae polysaccharides: Isolation, structure, and activities. Mar. Drugs, *15(12)*, 388. https://doi.org/10.3390/md15120388

Yuan, Y., Zhang, J., Fan, J., Clark, J., Shen, P., Li, Y., and Zhang, C. 2018. Microwave assisted extraction of phenolic compounds from four economic brown macroalgae species and evaluation of their antioxidant activities and inhibitory effects on α-amylase, α-glucosidase, pancreatic lipase and tyrosinase. Food Res. Int., *113*, 288–297. https://doi.org/10.1016/j.foodres.2018.07.021

Zeng, J., Zhang, Y., Ruan, J., Yang, Z., Wang, C., Hong, Z., and Zuo, Z. 2018. Protective effects of fucoxanthin and fucoxanthinol against tributyltin-induced oxidative stress in HepG2 cells. Environ. Sci. Pollut. Res., *25(6)*, 5582–5589. https://doi.org/10.1007/s11356-017-0661-3

Received: *16 July 2019*; revised: *5 May 2021*.