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Bioactive compounds in seaweeds: An overview of their biological properties and safety

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ABSTRACT

Seaweeds are among the significant currently exploited marine plant resources which are gaining full applications in culinary, cosmetic, pharmaceutical, and biotechnological processes. Much attention has been devoted to seaweeds based on their proven health benefits and is considered as a rich source of structurally different bioactive metabolites for the discovery of novel functional food-based pharmacophores/drugs. Nonetheless, there is still a dearth of updated compilation and analysis of the in-depth pharmacological activities of these compounds. This review, therefore, aims to provide a piece of up-to-date detailed information on the major compounds isolated from various seaweed species together with their in-vitro and in-vivo biological properties. These compounds were found to possess broad pharmacological properties and inhibitory enzyme activities against critical enzymes involved in the aetiology of noncommunicable diseases. However, their toxicity, clinical efficacy, mechanisms of action, and interaction with conventional foods, are still less explored and require more attention in future studies.

1. Introduction

The importance of dietary food habits was already mentioned in the earlier quote by Hippocrates in 460 BC that "*Let food be thy medicine and medicine be thy food*". The improper dietary habits or unhealthy diet is a critical concern for the currently alarming health disorders including diabetes, obesity, cancer, and cardiovascular diseases. The intake of unhealthy foods and the low intake of fruits and vegetables causes about 2.7 million deaths including 14% of gastrointestinal cancer deaths (14%), ischaemic heart disease deaths (11%) and nearly stroke deaths (9%) (WHO Fact Sheet, accessed on June 19, 2018, http://www.who.int/dietphysicalactivity/fruit/en/index2.html). It is well known that vegetables and fruits are important sources of phytocompounds which perform a key role in the prevention of a panoply of diseases. The global phytonutrients/nutraceutical market value, regarding value, is projected to reach $4.63 Billion in 2020, at a CAGR of 7.2% from 2015 to 2020 (Markets and Markets, 2015). Likewise, the global market for the botanical and plant-derived drug was estimated $29.4 billion in 2017 and is projected to escalate to 39.6 billion in 2022 with a compound annual growth rate (CAGR) of 6.1% (Research, 2017). For the past decades, researchers have shown great interest towards the isolation of health-promoting substances from these fruits and vegetables. Both the Natural Health Products (NHP) and Nutraceuticals and Functional Foods (NFF) focused much research on bioactive foods from natural resources to develop healthy foods (Goldberg, 2012; Nice, 1997).

Marine life offers 70% of earth's surface with the vast diversity of life and biodiversity in the seas is only partially explored although marine represents a rich source of novel metabolites with various applications includes cosmeceutical, nutraceuticals, agrochemicals, pharmaceuticals and other industrially relevant chemicals (Faulkner, 2012). Recent research emphasises that drug discovery from marine resources is increasing alarmingly and various biomolecules are in the clinical pipeline.

2. Global trends in marine biodiscovery

In 2018, the world market for drugs derived from marine sources

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Table 1
Seaweed polysaccharides and their biological properties.

Polysaccharide	Source	Biological properties	Model used	Findings	Reference
Fucoidan (**1**)	Ascophyllum nodosum, Cladosiphon okamuranus, Fucus spiralis, F. distichus, F. evanescens, F. vesiculosus, F. serratus, Laminaria digitata, L. saccharina	Anticoagulant, anti-inflammatory, antiadhesive and antiangiogenic	In-vitro and in-vivo	Inhibits the leucocyte recruitment in an inflammation model in rats. In In-vitro, P-selectin-mediated neutrophil adhesion to platelets showed that only fucoidans from A. nodosum, F. distichus, F. evanescens, F. serratus, F. spiralis, L. digitata and L. saccharina could serve as P-selectin inhibitors. Besides, all fucoidans, except that from C. okamuranus, displayed anticoagulant activity by APTT while fucoidans from F. distichus, F. evanescens, F. serratus, L. digitata and L. saccharina, showed strong antithrombin action in the platelet aggregation assay. These fucoidans also inhibited HUVEC tubulogenesis. Lastly, fucoidans from F. distichus, and F. vesiculosus, F. serratus, L. digitata and L. saccharina, blocked MDA-MB-231 breast carcinoma cell adhesion to platelets.	Cumashi et al. (2007)
	Kelp	Tyrosinase inhibition	In-vitro	Showed competitive inhibition of tyrosinase toward L-tyrosine (IC_{50} = 0.82 mg/mL), and the inhibitory constant K_i obtained from double-reciprocal plots was 0.99 mg/mL.	Yu and Sun (2014)
	Fucus vesiculosus	Anti-atopic dermatitis	In vivo	Ameliorated atopic dermatitis, accompanied by the decreased inflammatory cell infiltration, splenocytes proliferation, and $CD4^+$ T cell response	Tian et al. (2019)
	F. evanescens	Antitumor	In-vivo	Administration of fucoidan at 10 mg/kg, displayed moderate antimetastatic and antitumor activities. It also potentiates the antimetastatic effects of cyclophosphamide in C57Bl/6 mice with transplanted Lewis lung adenocarcinoma.	Alekseyenko et al. (2007)
	Sargassum fusiforme	Anti-angiogenic	In-vitro	Inhibits the migration of HMEC-1 and tube formation dose-dependently.	Cong et al. (2016)
	S. fusiforme	Anti-cancer	In-vitro and In-vivo	Inhibited lung cancer cell growth through the disruption of angiogenesis via blocking VEGFR2/Erk/VEGF signalling and targeting VEGFR2/VEGF.	Chen et al. (2016)
	Sargassum hornery, Eclonia cava, Costaria costata	Anti-cancer	In-vitro	Blocks colony formation in colon cancer cells cell line and human melanoma.	Ermakova et al. (2011)
	Cladosiphon okamuranus	Anti-cancer	In-vitro and In-vivo	In ATL patients, fucoidan inhibits the growth of HTLV-1-infected T-cell lines and peripheral blood mononuclear cells.	Haneji et al. (2005)
	Adenocystis utricularis	Antiretroviral	In-vitro	Inhibitor of anti-HIV-1 activity against both drug-resistant and wild-type HIV-1 strains by blocking of viral entry and revealed no virucidal activity.	Trinchero et al. (2009)
	A. utricularis	Antiviral	In-vitro	Galactofucans potentially inhibited HSV 1 and 2, without any cytotoxic effect, while the uronofucoidans displayed no antiviral activity.	Ponce et al. (2003)
	C. okamuranus	Cardioprotective	In-vivo	Cardioprotective effect was noticed with Fucoidan against isoproterenol-induced myocardial infarction in rats. Fucoidan also improved lactate dehydrogenase, creatinine phosphokinase, aspartate transaminase and alanine transaminase. Also, fucoidan enhanced the antioxidant defence system in treated rats by reducing oxidative stress induced by isoproterenol. Moreover, fucoidan treatment reverses the effects of isoproterenol by decreasing total cholesterol, triglycerides, LDL cholesterol and increasing HDL cholesterol.	Thomes et al. (2010)
	C. okamuranus	Anti-proliferative	In-vitro	Oversulfated fucoidan dose-dependently reduced the U937 cell proliferation, induces the apoptosis by an activation-dependent pathway of caspase-3 and -7. On the other hand, the weak activity of native fucoidan suggests that the sulfate group substitution and sulfate content influence the anti-proliferative activity in U937 cells.	Teruya et al. (2007)
	C. okamuranus	Gastric protection	In-vitro	Protect the gastric mucus layer and stimulate ulcer healing power owing to its anti-peptic and basic fibroblast growth factor (bFGF) stabilising activity.	Shibata et al. (2000)
	C. okamuranus	Antiprion	In-vivo	Dietary fucoidan, administered orally for six days after infection, delays the disease onset thoroughly in infected mice with scrapie, but not when given before the infection.	Doh-ura et al. (2007)
	F. evanescens	Anticoagulant	In-vitro & In-vivo	Showed anticoagulant activity through plasma antithrombin III mediated. Thrombin inhibition.	Kuznetsova et al. (2003)
	F. vesiculosus	Anti-inflammatory	In-vitro	Fucoidan inhibits the excess PGE2 and NO production in LPS-stimulated BV2 microglia. Also diminished the iNOS, MCP-1, COX-2, MCP-1, TNF-α and L-1β	Park et al. (2011a)

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Table 1 (*continued*)

Polysaccharide	Source	Biological properties	Model used	Findings	Reference
				expression. Besides, fucoidan suppresses the NF-κB activation and down-regulation of an extracellular JNK, MAPK, ERK and AKT pathways.	
	F. vesiculosus	Anti-obesity	In-vitro	Fucoidan reduced lipid accumulation by stimulating lipolysis via increasing HSL and by expression of phosphorylated HSL and reduction of glucose uptake into adipocytes.	Park et al. (2011b)
	Undaria piaantifida	Immunostimulatory	In-vitro	Fucoidan enhanced the probiotic properties of lactic acid bacteria on immune functions by enhancing the production of IL-12 in response to a strain of LAB, Tetragenococcus halophilus KK221, disseminating production of IFN-γ. In in-vivo study with ovalbumin immunized mice, the enhanced immunobalance of T helper type 1/type 2 (Th1/Th2) was observed.	Kawashima et al. (2012)
	L. japonica	Antioxidant	In-vitro	Exhibited scavenging effects on hypochlorous acid and superoxide radical and inhibition of LDL oxidation induced by Cu^{2+}.	(Zhao et al., 2005)
	L. japonica	Anti-inflammatory	In-vitro & In-vivo	In an In-vivo air pouch inflammation model, coadministration of fucoidan or Cistanche tubulosa extract synergistically suppressed nitric oxide production, carrageenan-induced vascular exudation, prostaglandin E2 concentrations.	Kyung et al. (2012)
	Lessonia vadosa	Anticoagulant and elicitor	In-vitro	Native fucoidan showed good anticoagulant activity and activation of defence enzyme activities of PAL, LOX and GST in tobacco plants.	Chandía and Matsuhiro (2008)
	U. pinnatifida	Antiplasmodial	In-vitro & In-vivo	Fucoidan fractions inhibited the P. falciparum merozoites mediated erythrocytes invasion and IC_{50} values againt chloroquine sensitive P. falciparum 3D7 stain for the three fucoidan fractions were 9.17, 7.28, and 1.95 μg/ml and 7.03, 4.74, and 2.21 μg/ml in chloroquine resistant P. falciparum K1 strain. About 37% suppressive effect against the control group and a delay in death associated with anemia was observed in P. berghei-infected mice with fucoidan.	Chen et al. (2009)
	U. pinnatifida	Anti-allergy	In-vivo	The suppressive effect of Th2 cytokines production in bronchoalveolar lavage fluid wa snoticed, and IFN-γ amount was not increased in fucoidan treated mice.	Maruyama et al. (2005)
	U. pinnatifida	Antitumor	In-vitro & In-vivo	Fucoidan mediated tumor destruction via the response of Th1 and NK cells.	Maruyama et al. (2006)
	U. pinnatifida	Antitumor	In-vitro	Displayed antitumor activity against PC-3, HeLa, A549, and HepG2 cells.	Synytsya et al. (2010)
Alginate (**2**)	Commercial sodium alginate	Inhibition of putrefactive compound	In-vitro & In-vivo	In human fecal culture and rat cecum, inhibited the putrefactive compound formation.	Kuda et al. (2005)
	Eucheuma cottonii and Sargassum polycystum	Antidiabetic	In-vitro	IC_{50} of (0.075–0.103) mg/ml, also a mixed-type inhibition.	Zaharudin et al. (2018)
	Commercial sodium alginate	Antibacterial	In-vitro & In-vivo	Approximately 70–90% inhibition againt L. monocytogenes V. parahaemolyticus and S. typhimurium to human enterocyte-like HT-29-Luc cells was observed with sodium alginate (0.1%). In addition, sodium alginate potentially inhibited 70% of S. typhimurium invasion. Incubation with sodium alginate for 18 h also Increased transepithelial electrical resistance of HT-29-Luc monolayer cells was also observed with 18 h incubation of sodium alginate. Moreover, decreased liver pathogen count was noticed in alginate fed mice.	Kuda et al. (2015)
	Commercial sodium alginate	Antibacterial	In-vivo	Alginate-based coating containing lactate and diacetate was effective in controling The controlled growth of L. monocytogenes and enhanced microbial safety of sliced and filleted smoked salmon was reported with alginate coated lactate and diacetate.	Neetoo et al. (2010)
	Commercial sodium alginate	Antibacterial	In-vivo	Alginate-based antimicrobial coatings enhanced the microbiological safety of poached and deli turkey products by controling L. monocytogenes growth.	Juck et al. (2010)
	–	Gastroesophageal reflux disease treatment	Systematic review & meta-analysis	Effective in the treatment of symptomatic gastroesophageal reflux disease and were superior to placebo and antacids. Compared to proton pump inhibitors or histamine-2 receptor antagonists, alginates appear less effective.	Leiman et al. (2017)
	Commercial sodium alginate	Anticancer	In-vitro		Markeb et al. (2016)

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Table 1 (*continued*)

Polysaccharide	Source	Biological properties	Model used	Findings	Reference
				The novel paclitaxel-loaded alginate nanoparticle promoted decreased viability, cell-cycle arrest and induced apoptosis in patient's breast cancer cells superior to those of paclitaxel alone.	
	Commercial sodium alginate	Anti-inflammatory	In-vivo	Amelioration of mRNA expression in inflammation-related molecules and protected indomethacin-induced mucin depletion in the small intestine was reported in mice pretreated with sodium alginate prior to the administration of indomethacin.	Horibe et al. (2016)
	Commercial sodium alginate	Anti-inflammatory	In-vivo	Prevention of methotrexate-induced small intestinal mucositis and decreased hemoglobin, hematocrit levels and red blood cell counts in rats.	Yamamoto et al. (2013)
	Commercial sodium alginate	Anti-inflammatory	In-vivo	Sodium alginate prevented the increase in SOD, GPx, catalase activity and microvascular permeability and also prevented decreases in white and red blood cells in small intestinal damage induced by indomethacin.	Yamamoto et al. (2014)
	Commercial	Antioxidant	In-vitro	Low molecular weight alginates produced by thermal treatment of alginate polymer showed scavenging activity against ABTS and superoxide radicals.	Kelishomi et al. (2016)
	L. hyperborean	Wound healing	In-vivo	Calcium alginate enhanced skin collagen I expression from day 3 to day 14 with higher collagen I/III in alginate-group ratio than vaseline (control)-group at day 7 and 14. In addition, higher level of hydroxyproline in skin homogenate of alginate-group than the vaseline (control)-group from day 3 to day 14.	Wang et al. (2015)
Laminarin (**3**)	Laminaria spp.	Anti-inflammatory	In-vivo	Combined laminarin and fucoidan treatment enhanced diarrhoeal scores, body-weight loss, and clinical variables linked with a dextran sodium sulfate experiment in pigs, together with s decrease in colonic IL-6 mRNA abundance.	O'Shea et al. (2016)
	Eisenia bicyclis	Antibacterial	In-vitro	Laminarin (0.1%) inhibited the adhesion About 70–90% inhibition of L. monocytogenes, S. typhimurium and V. parahaemolyticus adhesion to human enterocyte-like HT-29-Luc cells with laminarin (0.1%).	Kuda et al. (2015)
	Commercial	Hepatoprotective	In-vivo	The increase in serum ALT, AST and LDH activities - reflecting hepatic alterations - was reduced after lipopolysaccharides injection in laminarin-treated rats than control groups. Laminarin also decreased serum monocytes number, TNF-α and nitrite.	Neyrinck et al. (2007)
	NI	Immunostimulatory	In-vitro	Showed immunostimulatory effect through the transcription factor pathway in macrophages by increasing the release of H_2O_2, NO, calcium, MCP-1, LIF, VEGF, and G-CSF with enhancing expression of STAT1, STAT3, c-Fos, c-Jun, and COX-2 mRNA in RAW 264.7 cells.	Lee et al. (2012a)
	Commercial	Anticancer	In-vitro	Through mitochondrial pathway, induces the apoptosis of human colon cancer LOVO cells.	Ji et al. (2012)
	Commercial	Anticancer	In-vitro	Induce apoptosis of LoVo cells. The TRAIL, DR4, DR5, Bid, tBid, FADD and Bax expression levels were upregulated, while the Bcl-2, pro-caspase-3 and 8, expression levels were downregulated. Moreover, the casapse-8, -3, -6 and -7 activities were increased.	Ji and Ji (2014)
	E. bicyclis	Anticancer	In-vitro	The colony formation of human melanoma SK-MEL-28 and colon cancer DLD-1 cells were inhibited by laminarin and its enzymatic hydrolysed products.	Menshova et al. (2014)
	Laminaria digitata	Anticancer	In-vitro	In HT-29 colon cancer cells, laminaric induces apoptosis through ErbB signaling pathway.	Park et al. (2013)
Carrageenan (**4**)[‘]	Commercial	Anti-inflammatory	In-vitro	Carrageenan did not induce IL-6, IL-8, or MCP-1 (CCL2) in HT-29 and HCT-8 cell lines at 0.1, 1.0, and 10.0 mg/mL.	McKim et al. (2016)
	Commercial	Anticancer	In-vitro & In-vivo	In B16–F10 and 4T1 bearing mice, carrageenan inhibited tumor growth in and enhanced immune response by increasing the number of tumor-infiltrating dentritic cells, M1 macrophages, and additional stimulated $CD4^+CD8^+$ T lymphocytes in spleen.	Luo et al. (2015)
	Commercial	Anti-allergic	In-vivo	λ-Carrageenan was identified as potentially new ligand for TLR4/MyD88 which triggers innate immunity, induced Th1-cytokines, PRRs recognised λ-carrageenan, and suppression of IgE production via reduced histamine release.	Tsuji et al. (2003)

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Table 1 (*continued*)

Polysaccharide	Source	Biological properties	Model used	Findings	Reference
	Chondrus ocellatus	Antitumor	In-vitro & In-vivo	From the histopathological in λ-carrageenan-treated mice indicated that λ-carrageenan was the causative agent for tumor cell pycnosis and necrosis in different degree. In H22 and S180 tumor cells, λ-carrageenan showed antitumor activity in-vitro.	(Zhou et al., 2004)
	C. ocellatus	Antitumor	In-vivo	λ-carrageenan enhances antitumor activities of Fluorouracil (5-Fu) and progress the immunocompetence damaged by 5-Fu.	Zhou et al. (2006)
	Gigartinaceae and Tichocarpaceae algae	Antioxidant	In-vitro & ex vivo	Exhibited reducing power and inhibition of hydroxyl radicals and superoxide anion radicals.	Sokolova et al. (2011)
	Gigartina skottsbergii	Anti-viral	In-vitro	Reduced infectivity of the viruses BoHV-1 strain Cooper and SuHV-1 strain Bartha; this effect was more pronounced against BoHV-1.	Diogo et al. (2015)
	Stenogramme interrupta	Anti-viral	In-vitro	Showed anti-viral activity against herpes simplex virus	Cáceres et al. (2000)

A549, alveolar carcinoma; AKZ; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, Aspartate transaminase; ATL, Adult T-cell leukemia; BoHV-1, bovine herpesvirus type 1; ERK, signal-regulated kinase; G-CSF, Granulocyte colony-stimulating factor; GPx, glutathione peroxidase; GST, glutathione-S-transferase; HeLa, cervical cancer; HepG2, hepatocellular carcinoma; HIV, human immune deficiency virus; HMEC-1, human microvascular endothelial cells; HSL, hormone sensitive lipase; HSV, herps simples virus; HTLV-1, human T-cell leukemia virus type 1; HUVEC, human umbilical vein endothelial cell; JNK, c-Jun N-terminal kinase; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LIF, Leukemia Inhibitory Factor; LOX, lipoxygenase; MAPK, p38 mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; NK cells, nature killer cells; PAL, phenylalanine-ammonia lyase; PC-3, prostate cancer 3; PRRs, pattern recognition receptors; STAT, Signal Transducer and Activator of Transcription; SuHV-1, suid herpesvirus type 1; VEGF, Vascular endothelial growth factor.

was around $ 10,486.8 billion, which is forecasted to touch $21,955.6 billion by 2025 at a CAGR of 11.25% for the five-year period of 2019–2025 (Infinium Global Research, 2019). Marine-based US FDA approved drugs mainly consist of marine metabolites or their synthetic analogues. Also, most of the marine-derived medicines isolated from various marine resources, but the contribution of marine algae is only about 30% (Blunt et al., 2007).

3. Recent developments in algal drug research

Seaweeds or marine macroalgae reside in the littoral zone and are now considered as primary resources of the oceans in terms of economic and ecological significance (Dhargalkar and Pereira, 2005). Taxonomically, seaweeds are grouped into three major phyla: (i) Phaeophyceae (brown algae), which are primarily brown in color due to its fucoxanthin content – xanthophyll pigment fucoxanthin (ii) Chlorophyceae (green algae) - primarily dominated by chlorophyll 'a' and 'b', and other specific xanthophyll pigments; and (iii) Rhodophyceae (red algae) primarily comprised of phycocyanin and phycoerythrin (O'Sullivan et al., 2010). Approximately more than 1500 brown, 900 green and 4000 red seaweeds are available worldwide (Dawes, 1998). The subtropical and tropical waters are entirely occupied by red and green seaweeds, while cold temperate waters are predominantly occupied by brown seaweeds (Khan and Satam, 2003).

The interest in the discovery of health-promoting substances of marine origin is increasing especially from marine plants such as seaweeds, seagrass and mangroves for the past decades (El Gamal, 2010; Rengasamy et al., 2014b). Among these, seaweeds or marine macroalgae have much attracted functional food researchers. Recent shreds of evidence suggest that seaweeds have been regularly consumed as food in East Asian countries including Korea, China, Japan, and this dietary habit as widespread throughout Europe, North America and, Southern American countries (McHugh, 2003). Noticeably, long-life expectancy and the lower rate of cardiovascular diseases among the Japanese people are likely to be associated with their dietary habits including their regular consumption of seaweeds (Shimazu et al., 2007).

The recent review by Rengasamy et al. (2014a) compiled various bioactive compounds isolated from seaweeds and their role as enzyme inhibitors to treat multiple diseases including cancer, diabetes, inflammation, dementia and others. Seaweeds are not only targeted for drug development to treat various human health illness, but also play a significant part as plant growth regulators, fungicides, pesticides, and in part in plant growth such as auxin, cytokinin, gibberellins, betains (Stirk et al., 2014), oligosaccharides, and phenolic compounds (Rengasamy et al., 2014b, 2015). The biological properties of various bioactive metabolites from marine algae have been recently extensively reviewed by many researchers including enzyme inhibitors (Rengasamy et al., 2014a), phlorotannins (Karadeniz and Kim, 2015; Sanjeewa et al., 2016) polysaccharides (Wang et al., 2014), protein hydrolysates and bioactive peptides (Harnedy and FitzGerald, 2013; Samarakoon and Jeon, 2012), alkaloids (Güven et al., 2010), halogenated terpenoids (Wang et al., 2013) and pigments (D'Orazio et al., 2012; Dumay et al., 2015; Kim and Pangestuti, 2011). In this context, this review mainly focuses on the bioactive compounds isolated from seaweeds and their in-depth biological properties (see detailed activities in Tables 1–6 and Fig. 5).

4. The primary bioactive compound in seaweeds

4.1. Polysaccharides

Polysaccharides are carbohydrate biopolymers consisting of simple sugars linked by glycoside bonds and are classified into structural polysaccharides, mucopolysaccharides and storage polysaccharides. The study of the structure, biosynthesis and functions of sugar molecules including polysaccharides are known as glycobiology and has

Table 2
Seaweed phlorotannins and their biological properties.

Phlorotannins	Source	Biological activity	Model used	Findings	Reference
Phloroglucinol (5)	*E. cava*	Antioxidant	*In-vitro*	Showed scavenging effects against free radicals: DPPH, HO• and O_2• − and protect against H_2O_2-mediated DNA damage.	Ahn et al. (2007)
	E. maxima	Antioxidant	*In-vitro*	Potent DPPH radical scavenger at 0.13 μM	Rengasamy et al. (2013)
	E. maxima	Anti-Alzheimer's	*In-vitro*	Inhibits acetylcholinesterase (AChE) at 50% at a concentration of 579.32 μM.	Kannan et al. (2013)
	E. maxima	Antidiabetic	*In-vitro*	Inhibited 50% of α-glucosidase at a concentration of 1991 μM.	Rengasamy et al. (2013)
	E. kurome	Antibacterial	*In-vitro*	Displayed an MBC (Minimum bactericidal concentration) value of 0.79 of μmol/mL against *Campylobacter jejuni.*	Nagayama et al. (2002)
	-	Anti-cancer	*In vitro*	Phloroglucinol engineered Ag nanoparticles displayed cytotoxic effect and morphological features of apoptotic cell death in MCF-7 cell lines	Kumar et al. (2018)
Dibenzo [1,4] dioxine-2,4,7,9-tetraol (6)	*E. maxima*	Antioxidant	*In-vitro*	Displayed an EC_{50} value of 0.01 μM against DPPH radical.	Rengasamy et al. (2013)
	E. maxima	Anti-Alzheimer's	*In-vitro*	Caused a 50% inhibition of AChE at a concentration of 84.48 μM.	Kannan et al. (2013)
	E. maxima	Antidiabetic	*In-vitro*	Exhibited α-glucosidase inhibition with an IC_{50} value of 33.69 μM.	Rengasamy et al. (2013)
Eckol (7)	E. cava	Anti-influenza	In-vitro	Showed inhibitory effects on Influenza Virus NA (rvH1N1) with IC50 value of 89.5 μM and A/Chicken/Korea/MS96/96 (H9N2, with IC50 value of 152.1 μM.	Ryu et al. (2011)
	E. cava	Skin protective	*In vitro*	Inhibition of $PM_{2.5}$-induced cell apoptosis by eckol was through MAPK signaling pathway	Zhen et al. (2019)
	E. stolonifera	Anti-tyrosinase	*In vitro*	Reduced cellular melanin content and tyrosinase activity, Also downregulated melanogenesis enzymes expression such as tyrosinase, tyrosinase-related protein (TRP)-1, and TRP-2 in B16F10 melanoma cells	Manandhar et al. (2019)
	E. bicyclis, *E. cava* and *E. kurome*	Antioxidant	*In-vitro*	Exerted scavenging effect against DPPH and superoxide anion with EC_{50} value of 26 μM and 107 μM, respectively.	Shibata et al. (2008)
	E. stolonifera	Antioxidant	*In-vitro*	Exerted DPPH scavenging effect (EC_{50} = 10.6 μM) and also inhibited ROS production in tacrine-treated HepG2 cells.	Lee et al. (2012b)
	E. maxima	Antioxidant	*In-vitro*	Potent DPPH radical scavenger at 0.01 μM EC_{50} value.	Rengasamy et al. (2013)
	E. cava	Antibacterial	*In-vitro*	Displayed antibacterial activity against *Staphylococcus aureus* at MIC values varying from 125 to 250 μg/mL and against Salmonella strains at MIC values of 125–250 μg/mL. The combinations of eckol and ampicillin exhibited a synergistic or additive effect.	Choi et al. (2010)
	E. kurome	Antibacterial	*In-vitro*	Showed bactericidal activity against *S. aureus*, *Bacillus cereus*, *Escherichia coli*, *C. jejuni*, *S. typhimurium*, *S. enteritidis*, and *Vibrio parahaemolyticus* with MBC values in the range 0.08–1.08 μmol/mL.	Nagayama et al. (2002)
	E. stolonifera	Anti-hypertension	*In-vitro*	Exhibited marked inhibitory activity against ACE with an IC_{50} value of 70.82 μM.	Jung et al. (2006)
	E. stolonifera	Hepatoprotective	*In-vitro*	In tacrine-treated HepG2 cells, eckol potentially inhibits the Fas-mediated cell-death protein expression and also inhibit the cytochrome *c* release from the mitochondria to cytosol.	Lee et al. (2012b)
	E. maxima	Anti-Alzheimer's	*In-vitro*	Caused a 50% inhibition of AChE at a concentration of 76.70 μM.	Kannan et al. (2013)
	E. stolonifera	Anti-photoaging	*In-vitro*	Caused a reduced expression of MMP-1 human dermal fibroblasts by inhibiting AP-1 dependent reporter gene activity and NF-κB.	Joe et al. (2006)
	E. cava	Anti-photoaging	*In-vitro*	Showed photoprotective effect against UV-B -induced cell damage.	Heo and Jeon (2009b)
	E. bicyclis	Anti-diabetic	*In-vitro*	Exhibited α-amylase inhibition (87.5% inhibition) and antiglycation activity (96.2% inhibition) at 1 mM.	Okada et al. (2004)
	E. maxima	Anti-diabetic	*In-vitro*	Displayed α-glucosidase inhibition at 11.163 μM IC_{50} value.	Rengasamy et al. (2013)
Dieckol (8)	*E. cava*	Immunomodulatory	*In-vivo*	The ionising radiation suppressed immune cell differentiation and proliferation was enhanced. Dieckol increased thymidine incorporation by splenocytes as much as 8.8-fold above that in irradiated mice without dieckol treatment. Also, the number of $CD4^+$ helper T cells, $CD8^+$ cytolytic T cells, $CD45R/B220^+$ pan B cells, and $CD11b^+$ macrophages showed a marked increase in dieckol-treated irradiation group compared with irradiation-only control group at three days after irradiation.	Park et al. (2010)
	E. stolonifera	Anti-photoaging	*In-vitro*	Caused a reduced expression of MMP-1 human dermal fibroblasts by inhibiting AP-1 dependent reporter gene activity and NF-κB.	Joe et al. (2006)
	E. cava	Anti-photoaging	*In-vitro*	Displayed photoprotective effect against UV-B -induced cell damage.	Heo et al. (2009)
	E. cava	Anti-allergy	*In-vitro*		Le et al. (2009)

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Table 2 (*continued*)

Phlorotannins	Source	Biological activity	Model used	Findings	Reference
				Histamine release was inhibited dose-dependently from both KU812 and RBL2H3 cell lines.	
	E. stolonifera	Antibacterial	*In-vitro*	Exhibited antibacterial activity against MSSA and MSRA *S. aureus* with MIC values ranged from 32 to 128 μg/mL. The combination of dieckol with ampicillin or penicillin displayed a synergistic activity against MRSA.	Lee et al. (2008)
	E. bicyclis	Anti-diabetic	In-vitro	Exhibited inhibitory activity on glycation (86.7% inhibition) and α-amylase (97.5% inhibition) at 1 mM.	Okada et al. (2004)
	E. cava	Anti-diabetic	*In-vitro*	Showed inhibitory activity against α-glucosidase (IC_{50} = 10.8 μmol/L) and α-amylase (IC_{50} = 124.9 μmol/L). It also displayed a non-competitive type of inhibition against α-glucosidase.	Lee et al. (2009)
	E. cava	Matrix metalloproteinases inhibition	*In-vitro*	In human osteosarcoma cell, dieckol Inhibits the mRNA gene and protein levels of iNOS, COX-2, MMP-1, MMP-3, and MMP-13. Dieckol also inhibits the JNK and p38 MAPK phosphorylation.	Ryu et al. (2009)
	E. cava	Anti-inflammatory	*In-vivo*	The PGE_2, NO, and HMGB-1 production significantly inhibited in the serum of mice with LPS-induced septic shock.	Yang et al. (2016)
	E. cava	Cytoprotective	*Ex vivo*	In neonatal mouse cochlea, dieckol showed a dose dependent partial protective effect against gentamicin-induced hair cell.	Chang et al. (2016)
	E. bicyclis, *E. cava* and *E. kurome*	Antioxidant	*In-vitro*	Exerted scavenging effect against DPPH and superoxide anion with EC_{50} value of 13 μM and 7.6 μM, respectively.	Shibata et al. (2008)
2-Phloroeckol (9)	*E. stolonifera*	Hepatoprotective	*In-vitro*	In tacrine-treated HepG2 cells, eckol potentially inhibits the Fas-mediated cell-death protein expression and also inhibit the cytochrome *c* release from the mitochondria to cytosol.	Lee et al. (2012b)
	E. stolonifera	Antioxidant	*In-vitro*	Exerted DPPH scavenging effect (EC_{50} = 35.2 μM) and also inhibited ROS production in tacrine-treated HepG2 cells.	Lee et al. (2012b)
	E. stolonifera	Anti-inflammatory	*In-vitro*	Showed inhibition of NO production (EC_{50} = 85.3 μmol/L) in LPS-stimulated RAW 264.7 cells.	Wei et al. (2016)
Dioxinodehydroeckol (10)	*E. Cava*	Anti-cancer	*In-vitro*	In MCF-7 human breast cancer cells, Dioxinodehydroeckol significantly induced proliferative inhibition and apoptosis.	Kong et al. (2009)
	E. stolonifera	Antioxidant	*In-vitro*	Showed DPPH scavenging activity (EC_{50} = 8.8 μM) which is more effective than L-ascorbic acid (EC_{50} = 10.3 μM).	Kim et al. (2009)
	E. cava	UV protective	*In-vitro*	Protects the human keratinocyte cells from UVB-induced apoptosis.	Ryu et al. (2015)
6,6′ Bieckol (11)	*E. cava*	Anti-HIV	*In-vitro*	Displayed inhibition against lytic effects, HIV-1 induced syncytia formation and viral p24 antigen production at EC_{50} values of 1.23, 1.72 and 1.26 μM respectively. Also, selective inhibition against HIV-1 RT enzyme (EC_{50} = 1.07 μM).	Artan et al. (2008)
	E. cava	Anti-inflammatory	*In-vitro*	Through negative regulation of the NF-κB pathway, 6,6′ Bieckol down-regulated COX-2, iNOS, and pro inflammatory cytokines in LPS-stimulated macrophages.	Yang et al. (2012)
	E. stolonifera	Anti-inflammatory	*In-vitro*	Showed inhibition of NO production (EC_{50} = 63.9 μmol/L) in LPS-stimulated RAW 264.7 cells.	Wei et al. (2016)
	E. stolonifera	Anti-inflammatory	*In-vitro*	Down-regulated NF-κB activation in LPS-stimulated microglial cells through JNK, p38 MAPK and Akt.	Kim et al. (2016)
	E. cava	Anti-allergy	*In-vitro*	Histamine release was inhibited dose-dependently from both KU812 and RBL2H3 cell lines.	Le et al. (2009)
8,8′-Bieckol (12)	*E. cava*	Anti-HIV	*In-vitro*	Displayed HIV-1 RT and protease inhibition at IC_{50} = 0.51 and 81.5 μM respectively.	Ahn et al. (2004)
	E. kurome	Antibacterial	*In-vitro*	Showed bactericidal activity against *S. aureus*, *Bacillus cereus*, *Escherichia coli*, *C. jejuni*, *S. typhimurium*, *S. enteritidis*, and *Vibrio parahaemolyticus* with MBC values in the range 0.03–0.54 μmol/mL.	Nagayama et al. (2002)
	E. bicyclis, *E. cava* and *E. kurome*	Antioxidant	*In-vitro*	Exerted scavenging effect against DPPH and superoxide anion with EC_{50} value of 15 μM and 6.5 μM, respectively.	Shibata et al. (2008)
7-Phloroeckol (13)	*E. cava*	Anti-influenza	*In-vitro*	Exhibited inhibitory effects on Influenza Virus NA (rvH1N1), A/Hong Kong/8/68 (H3N2), A/Chicken/Korea/MS96/96 (H9N2) and, A/PR/8/34 (H1N1), with IC_{50} values of 44.2 μM, 37.4 μM, 32.2 μM and 41.2 μM, respectively.	Ryu et al. (2011)
Phlorofucofuroeckol-A (14)	*E. kurome*	Antibacterial	*In-vitro*		Nagayama et al. (2002)

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Table 2 (*continued*)

Phlorotannins	Source	Biological activity	Model used	Findings	Reference
				Showed bactericidal activity against *S. aureus*, *Bacillus cereus*, *Escherichia coli*, *C. jejuni*, *S. typhimurium*, *S. enteritidis*, and *Vibrio parahaemolyticus* with MBC values in the range 0.08–0.66 μmol/mL.	
	E. kurome	Algicidal	*In-vitro*	Showed anti-algicidal activity against red tide dinoflagellates such as K. mikimotoi and C. polykrikoides.	Nagayama et al. (2003)
	E. stolonifera	Anti-hypertension	*In-vitro*	Exhibited ACE inhibition with an IC_{50} value of 12.74 μM.	Jung et al. (2006)
	E. stolonifera	Anti-diabetic	*In-vitro*	Exerted inhibition against AGE (IC_{50} = 165.20 μM) and aldose reductase (IC_{50} = 125.45 μM).	Jung et al. (2008)
	E. stolonifera	Anti-inflammatory	*In-vitro*	Inhibited LPS-induced NO and PGE_2 production and by down-regulating inducible NO synthase and COX- 2 protein expressions.	Kim et al. (2009)
	E. stolonifera	Anti-inflammatory	*In-vitro*	In LPS-stimulated RAW 264.7 cells, Phlorofucofuroeckol-A inhibits the production of NO (EC_{50} = 6.95 μmol/L).	Wei et al. (2016)
	E. bicyclis, *E. cava* and *E. kurome*	Antioxidant	*In-vitro*	Exerted scavenging effect against DPPH and superoxide anion with EC_{50} value of 15 μM and 6.5 μM, respectively Exerted scavenging effect against DPPH and superoxide anion with EC_{50} value of 12 μM and 8.4 μM, respectively	Shibata et al. (2008)
	E. stolonifera	Antioxidant	*In-vitro*	Showed radical scavenging activities against DPPH (EC_{50} = 4.7 μM). Also suppressed the intracellular ROS concentration in LPS-induced RAW 264.7 cells	Kim et al. (2009)
Phlorofucofuroeckol B (15)	*E. stolonifera*	Antioxidant	*In-vitro*	Exerted DPPH scavenging effect (EC_{50} = 4.9 μM) and also inhibited the intracellular ROS in tacrine-treated HepG2 cells.	Lee et al. (2012b)
	E. stolonifera	Anti-inflammatory	*In-vitro*	Displayed anti-inflammatory activity based on the inhibition of NO production (EC_{50} = 12.1 μmol/L) in LPS-stimulated RAW 264.7 cells.	Wei et al. (2016)
	E. arborea	Anti-allergy	*In-vitro*	Exhibited dose-dependent inhibition of histamine release from rat basophile leukemia-2H3 cells ($IC_{50=}$7.8 μM).	Sugiura et al. (2006)
Triphlorethol-A (16)	*E. cava*	Antioxidant	*In-vitro*	Showed scavenging effect against intracellular ROS and DPPH radical and prevented lipid peroxidation.	Kang et al. (2005)
	E. cava	Antioxidant	*In-vitro*	Increased cellular antioxidant defense by inducing HO-1 via ERK–NF–E2 related factor 2(Nrf2)-ARE signaling pathway, thereby protecting cells from oxidative stress.	Kang et al. (2007)
	E. cava	Sedative	*In vivo*	50 mg/kg dose decreased sleep latency) in C57BL/6N mice and increased the amount of non-rapid eye movement sleep (NREMS, without affecting rapid eye movement sleep	Yoon and Cho (2018)
Trifucodiphlorethol A (17)	*F. vesiculosus* L.	Chemopreventive	*In-vitro*	Exerted scavenging effect against DPPH (IC_{50} = 14.4 μg/ml) and peroxyl radicals (IC_{50} = 3.5 μg/ml). Also inhibited cytochrome P450 1A (IC_{50} = 20.0 μg/ml) and aromatase (Cyp19) activity (IC_{50} = 3.3 μg/ml).	Parys et al. (2010)
Trifucotriphlorethol A (18)	*F. vesiculosus* L.	Chemopreventive	*In-vitro*	Exerted scavenging effect against DPPH (IC_{50} = 13.8 μg/ml) and peroxyl radicals (IC_{50} = 3.2 μg/ml). Also inhibited aromatase (Cyp19) activity (IC_{50} = 5.6 μg/ml) and cytochrome P450 1A (IC_{50} = 17.9 μg/ml).	Parys et al. (2010)
Fucotriphlorethol A (19)	*F. vesiculosus* L.	Chemopreventive	*In-vitro*	Exerted scavenging effect against DPPH (IC_{50} = 10.0 μg/ml) and peroxyl radicals (IC_{50} = 3.3 μg/ml). Also inhibited cytochrome P450 1A (IC_{50} = 33.7 μg/ml) and aromatase (Cyp19) activity (IC_{50} = 1.2 μg/ml).	Parys et al. (2010)
Diphlorethohydroxycarmalol (20)	*Ishige okamurae*	Anti-diabetic	*In-vitro*	Diphlorethohydroxycarmalo inhibits the high glucose-induced glucotoxicity and apoptosis at 10 or 50 μg/mL. Diphlorethohydroxycarmalol also decreases NO level, intracellular ROS generation and thiobarbituric acid reactive substances increased by high glucose.	Lee et al. (2012c)
	I. okamurae	Anticancer	*In-vitro*	In human promyelocytic leukemia (HL60) cells, Diphlorethohydroxycarmalol induces the apoptosis in via a reduction in the Bcl-2 levels and simultaneous mitochondrial signaling through Bax, ultimately leading to mitochondrial dysfunction.	Kang et al. (2012)
	I. okamurae	Radioprotective	*In-vitro* & *In-vivo*	Protected cells from apoptosis through ROS scavenging effect and also protects bone marrows cells and intestinal progenitor cells.	Ahn et al. (2011)
	I. okamurae	Antioxidant	*In-vitro*	Displayed scavenging effect on ABTS radical and intracellular ROS, and also prevents H_2O_2-induced cell damage.	Heo and Jeon (2009a)
	I. okamurae	Photoprotective	*In-vitro*	Prevents UV-B radiation-induced cell damage in human fibroblast cell line.	Heo et al. (2010a)
	I. okamurae	Antityrosinase	*In-vitro*	Showed potent inhibitory effect against tyrosinase with an IC_{50} value of 142.20 μM compared to the positive control arbutin (IC_{50} = 384.82 μM).	Heo et al. (2010a)
	I. okamurae	Antimelanogenic	*In-vitro*		Heo et al. (2010a)

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Table 2 (*continued*)

Phlorotannins	Source	Biological activity	Model used	Findings	Reference
				Exerted a melanin inhibition with an IC_{50} value of 37.73 μM and the inhibition was potent than retinol, a positive control (IC_{50} = 50.25 μM).	
	I. okamurae	Neuroprotective	*In-vitro*	Prevents H_2O_2-induced damage in neuronal cells and reduces the Bax expression.	Heo et al. (2012)
2-(4-(3,5 dihydroxyphenoxy)-3,5-dihydroxyphenoxy) benzene-1,3,5-triol (DDBT) (21)	*S. patens*	Anti-diabetic	*In-vitro*	Suppressed the hydrolysis of amylopectin by human salivary and pancreatic α-amylases. Displayed inhibitory effects against α-amylase (IC_{50} = 3.2 μg/mL), α-glucosidase from rat intestinal (IC_{50} = 25.4 μg/mL) and sucrase and maltase (IC_{50} = 114 μg/mL).	Kawamura-Konishi et al. (2012)
Octoplorethol A (22)	*I. foliacea*	Anti-diabetic	*In-vivo*	In type 2 diabetic db/db mice, Octoplorethol A significantly improves hyperinsulinemia and impaired glucose.	Lee et al. (2016)

ACE, angiotensin-converting enzyme; AGE, advanced glycation endproducts; ARE, antioxidant response element; DPP- IV, dipeptidyl peptidase IV; DPPH, 1,1-diphenyl-2-picrylhydrazyl; FRAP, ferric reducing antioxidant power; HO•, hydroxy; KU812, human basophilic leukemia; LPS, lipopolysaccharide; MIC, minimum inhibitory concentration; MSRA, methicillin resistant; MSSA, methicillin-susceptible; O2•−, superoxide anion radical; ORAC, oxygen radical absorbance capacity; RBL2H3, rat basophilic leukemia; ROS, reactive oxygen species.

offered enormous untapped potential in the discovery of new drug targets. The high molecular weight polysaccharides and their degradation products of low molecular weight oligosaccharides are economically very important owing to the numerous biological properties with minimal toxicity. Most polysaccharides are used as stabilisers, thickeners, and emulsifiers in food industries (Tseng, 2001). Seaweeds or marine macroalgae contain a wide range of polysaccharides which are described to possess a plethora of pharmacological activites including anticancer, antiinflammatory, and excellent antioxidant activities. The significant polysaccharides found in marine algae are alginates, agarans, carrageenan, fucoidan, laminarin, and ulvans (Rengasamy et al., 2014b). Although polysaccharides have potential biological properties, their viscosity and poor solubility make them inefficient for pharmaceutical applications. This problem has been overcome with the discovery of oligosaccharides which are derived from hydrolysis of polysaccharides either by using acid hydrolysis or enzyme hydrolysis method. Recent research emphasises the importance of oligosaccharides such as alginate oligosaccharides (derived from alginate), fucoidan oligosaccharides (derived from fucoidan), laminarin oligosaccharides (derived from Laminarin) and carrageenan oligosaccharides (derived from carrageenan). The polysaccharides and oligosaccharides prepared from seaweeds or marine macroalgae and their biological properties are summarised in Table 1 and the chemical structures of important polysaccharides are shown in Fig. 1.

4.2. Phlorotannins

Phlorotannins, more commonly known as algal polyphenols, are polymers of phloroglucinols which comprise up to 15% of dry weight of brown algae. Laminariacea have been documented to be the most abundant source of phlorotannins in marine algae. The molecular weight of phlorotannins ranges from 126 kDa to 650 kDa. In the past two decades, there have been a considerable literature on the isolation and pharmacological properties of phlorotannins from brown algal species such as *Eisienia bycycles*, *Ecklonia cava*, *E. stolonifera* and *E. maxima* (Kannan et al., 2013; Rengasamy et al., 2013; Rengasamy et al., 2014a, b). Phlorotannins have also been found to possess numerous biological/pharmacological properties such as antimicrobial (Nagayama et al., 2002), antioxidant (Kim et al., 2009), anti-HIV (Artan et al., 2008), antiproliferative (Kong et al., 2009), anticancer (Parys et al., 2010), anti-inflammatory (Kim et al., 2009), antidiabetes (Kannan et al., 2013; Rengasamy et al., 2013, 2014a), anti-Alzheimer disease (Kannan et al., 2013), antihypersensitive (Jung et al., 2006), anticoagulant (Li et al., 2007), and radioprotective (Moon et al., 2008). Further comprehensive evidence on the isolation and pharmacological properties of brown algal phlorotannins are listed in Table 2 and the chemical structures of important phlorotannins are shown in Fig. 2A and B.

4.3. Protein hydrolysates

Protein hydrolysates are mixtures of amino acids generally recognised as peptides or peptones, which are made from purified protein by acid hydrolysis or using proteolytic enzymes and further subjected to purification. To date, various protein hydrolysates have been reported from seaweeds with potent pharmacological properties. Lately much consideration has been diverted to the seaweed proteins and protein hydrolysates. Seaweed protein hydrolysates have been presented to possess many biological potential such as antibacterial activity (Beaulieu et al., 2016), anti-hypertension (Pan et al., 2016; Qu et al., 2010; Sai-kun et al., 2012; Sheih et al., 2009; Suetsuna et al., 2004), anticoagulant (Indumathi and Mehta, 2016), antiplatelet aggregation (Cian et al., 2012), antioxidant (Beaulieu et al., 2016; Cian et al., 2012, 2013) and chelating properties (Cian et al., 2016). Wakeme jelly peptide and Peptide Nori S are the commercially available anti-hypersensitive peptides from the Japanese seaweed *Undaria finnatifida*

Table 3
Biological properties of seaweed protein hydrolysates.

Source	Biological properties	Model	Findings	Reference
Palmaria palmate	Antioxidant	*In-vitro*	Hydrolysed fractions post-treatment with either chymotrypsin or trypsin, showed DPPH scavenging, FRAP, and ORAC.	Bondu et al. (2015)
	Antioxidant	*In-vitro*	Showed antioxidant effect with ORAC value of 45.17–467.54 and FRAP value of 1.06–21.59 μmol trolox equivalents/g.	Harnedy and FitzGerald (2013b)
	Antihypertensive	*In-vitro*	< 10-kDa fraction hydrolysed with chymotrypsin showed ACE inhibition with an IC_{50} of 460.05 mg/mL.	Bondu et al. (2015)
	Antihypertensive	*In-vivo*	The tridecapeptide IRLIIVLMPILMA derived from papain hydrolysate of *P. palmata* exhibited renin inhibitory activity. In spontaneously hypertensive rats, seaweed protein hydrolysate showed a drop-in blood pressure.	Fitzgerald et al. (2014)
	Cardioprotective and antidiabetic	*In-vitro*	Showed inhibition against ACE (IC_{50} = 0.19–0.78 mg/mL) and DPP-IV (IC_{50} = 1.65–4.60 mg/mL).	Harnedy and FitzGerald (2013a)
	Renin inhibitory	*In-vitro*	Fraction obtained from *P. palmata* protein hydrolysate exhibited 58.97% renin inhibition at 1 mg/mL.	Fitzgerald et al. (2012)
Undaria pinnatifida	Antihypertensive	*In-vitro* & *In-vivo*	Showed inhibition against ACE *In-vitro*. Four tetrapeptides administrated orally into spontaneously hypertensive rats displayed antihypertensive activity.	Suetsuna and Nakano (2000)
	Antihypertensive	*In-vitro* & *In-vivo*	Decreased blood pressure was observed with synthetic Phe-Tyr, and Ile-Tyr Tyr-His, Lys-Tyr, Ile-Tyr and Phe-Tyr in spontaneously hypertensive rats when administrated orally.	Suetsuna et al. (2004)
Porphyra yezoensis	Antihypertensive	*In-vitro*	About 55% of ACE inhibition was noticed with an IC_{50} value of 1.6 g/L.	Qu et al. (2010)
	Anticoagulant	*In-vitro*	The purified peptide derived from pepsin hydrolysate displayed prolonged APTT l 35 s–320 s with an IC_{50} of 0.3 μM.	Indumathi and Mehta (2016)
Porphyra columbina	Antioxidant	*In-vitro*	The residual cake hydrolysate exhibited ABTS and DPPH radical scavenging activity with IC_{50} value of 1.01 and 0.91 g/L, respectively. High copper chelating activity (≈97.5%) was also noticed.	Cian et al. (2013)
	Antihypertensive	*In-vitro*	Residual cake hydrolysate showed 45.65% inhibition against.	Cian et al. (2013)
	Antihypertensive	*In-vitro*	Hydrolysates showed ACE inhibition by uncompetitive mechanism, the highest activity being IC_{50}%, 1.2 g/L.	Cian et al. (2015)
	Antioxidant	*In-vitro*	Displayed ABTS and DPPH scavenging, β-carotene bleaching, and copper-chelating activity	Cian et al. (2015)
	Antiplatelet aggregation	*In-vitro*	The peptides showed antiplatelet aggregation activity, and the activity of peptides produced from alkaline protease was increased after simulated digestion process.	Cian et al. (2015)
	Chelating agent and anticariogenic	*In-vitro*	*P. columbina* hydrolysate showed high iron-chelating activity (33%), copper-chelating activity (β-carotene oxidation rate: R_o; 0.7 min^{-1}), and inhibition of phosphorus and Ca^{2+} release (87 and 81%, respectively).	Cian et al. (2016)
	Immunomodulation, Antihypertensive, Antioxidant	*In-vitro* and ex vivo	Both cold-water protein extract (PF) and PF hydrolysates (PFH) displayed immunosuppressive properties on rat splenocytes by enhancing IL-10 production and inhibiting the production of TNF-α and IFN-γ. PFH also showed > 35% of ACE inhibition and antioxidant effect (DPPH, TEAC, ORAC and copper-chelating activity).	Cian et al. (2012)
Enteromorpha clathrata	Antihypertensive	*In-vitro*	Alcalase was found to be more suitable for the preparation of ACE inhibitory peptides from *E. clathrata* proteins than alkaline protease and trypsin. Under optimum condition, a hydrolysate with ACE inhibition (IC_{50} = 0.66 mg/mL) was obtained.	Sai-kun et al. (2012)
	Antihypertensive	*In-vitro*	Fractions less than −10 kDa exhibited higher ACE inhibition than > 10 kDa fraction. The identified active peptide namely Pro-Ala-Phe-Gly showed ACE inhibition (IC_{50} = 35.9 μM).	Pan et al. (2016)
Ulva rigida	Antihypertensive	*In-vitro*	The hydrolysate produced under optimal proteolysis with pepsin plus bromelain, showed ACE inhibiton (IC_{50} = 0.483 mg/mL). Fraction < 1 kDa fraction exhibited the highest ACE inhibition (IC_{50} = 0.095 mg/mL). Purification by chromatographic techniques followed by Edman degradation yielded Ile-Pro (IP) and Ala-Phe-Leu (AFL) and these two peptides potentially inhibited ACE, with IC_{50} values of 0.020 and 0.023 mg/mL, respectively.	Paiva et al. (2016)

Table 4
Biological properties of seaweed terpenoids.

Terpenoids	Source	Biological activity	Model used	Findings	References
Udoteafuran (**23**)	*Udotea flabellum*	Antibacterial	*In-vitro*	Growth inhibition of *S. aureus*.	Fenical and Paul (1984)
Udoteatrial (**24**)	*U. flabellum*	Antibacterial	*In-vitro*	Growth inhibition of *S. aureus*.	
Flexilin (**25**)	*U. conglutinata*	Antimicrobial	*In-vitro*	Inhibited *S. aureus*, *Vibrio splendida*, *Dreschleria haloides*, and *Candida albicans*.	
	U. conglutinata	Cytotoxic	*In-vitro*	Inhibition of cell division in the sea urchin egg first cleavage (ED_{100} = 16 μg/ml).	
Halimedatrial (**26**)	*Halimeda* spp.	Antimicrobial	*In-vitro*	Inhibited *S. aureus*, *Bacillus subtilis*, *Serratitia marinorubra*, *Vibrio splendida*, *V. harvevi*, *V. leiognathi*, *Lulworthia* sp…, *Alternaria* sp…, *D. haloides*, *C. albicans*.	
	Halimeda spp…	Cytotoxic	*In-vitro*	Inhibition of cell division in the sea urchin egg first cleavage (ED_{100} = 1 μg/ml).	
Elatol (**27**)	*Laurencia dendroidea*	Acaricidal and repellent activity		Exhibited strong repellent activity against *T. urtica* with moderate toxicity.	Born and Bianco (2012)
	L. dendroidea	Larvicidal		Potent larvicidal effect with an LC_{50} value of 10.7 ppm.	Bianco et al. (2013)
	L. dendroidea	Antileishmanial activity	*In-vitro*	In *Leishmania amazonensis,* elatol inhibits promastigote and intracellular amastigote forms with an IC_{50} of 4.0 μM and 0.45 μM, respectively.	Santos et al. (2010)
	L. microcladia	Anti-tumor	*In-vitro* and *In-vivo*	Prompted cell cycle arrest in the G1 and the sub-G1 phases, leading cells to apoptosis. Elatol also decreased the expression of cyclin-D1, cyclin-E, cyclindependent kinase (cdk)2 and cdk4. A decrease in bcl-xl and an increase in bak, caspase-9 and p53 expression was also observed. Treatment *in-vivo* with elatol also decreased tumor growth in C57Bl6 mice.	Campos et al. (2012)
Diterpenoid seco-dolastane (4R,9S,14S)-4alpha-acetoxy-9beta, 14alpha-dihydroxydolast-1 (15),7-diene (**28**)	*C. cervicornis*	Acaricidal and repellent activity		Exhibited moderate toxicity, but a high degree of repellent activity against *T. urticae*.	
Mertensene (**29**) and violacene (**30**) and two derivatives (dibromomertensene (**31**) and dihydromertensene (**32**)	*Plocamium cartilagineum*	Insecticidal activity		Toxicity of violacene to *Schizaphis graminum* aphids was higher than other compounds, causing 92% mortality of aphid after 48 h. It was similar to insecticides used as aphicides. Violacene, dibromomertensene, and dihydromertensene decreased the reproduction index of aphids. Also, dibromomertensene and violacene protected tomato plants against the tomato moth Tuta absolute.	Argandona et al. (2000)
	Pterocladiella capillacea	Anti-cancer	*In vitro*	Mertensene induced G2/M cell cycle arrest and caspase dependent apoptosis of Human Colon Adenocarcinoma HT29 cell line via the modulation of ERK-1/-2, AKT and NF-kB signaling.	Tarhouni-Jabberi et al. (2017)
Telfairine (**33**)	*P. telfairiae*	Insecticidal activity		Exhibited 100% larvicidal activity against *Culex pipiens* pallens at 10 ppm in solution.	Watanabe et al. (1989)
Isoparguerol (**34**), isoparguerol-16-acetate (**35**), isoparguerol-7,16-diacetate (**36**), parguerol-16-acetate (**37**), deoxyparguerol (**38**), parguerol-7,16-diacetate (**39**), deoxyparguerol-7-acetate (**40**)	*Jania rubens*	Anti-tumor	*In-vitro*	The isolated compounds inhibited viability of Ehrlich carcinoma tumor cells (90, 90, 100, 80, 90, 70, 80% inhibition, respectively). Isoparguerol derivatives displayed slightly greater efficacy than parguerol derivatives.	Awad (2004)
	J. rubens	Anthelmintic	*In-vitro*	Anthelmintic activities (against earthworms -*Allolobophora caliginosa*). Isoparguerol and parguerol derivatives were more effective than deoxyparguerol series. These compounds displayed high anthelmintic activity when compared with the same concentration (10%) of the reference anthelmintic drug mebendazole.	Awad (2004)

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Table 4 (*continued*)

Terpenoids	Source	Biological activity	Model used	Findings	References
Neoirietetraol (**41**)	*Laurencia yonaguniensis*	Toxicity	*In-vivo*	Displayed toxicity to the *Artemia salina* (brine shrimp) with an LC_{50} of 40.1 μM.	Takahashi et al. (1998)
	L. yonaguniensis	Antibacterial	*In-vitro*	Displayed least antibacterial activities against *Alcaligenes aquamarinus* and *Escherichia coli*.	Takahashi et al. (2002)
Stypoquinonic acid (**42**)	*Stypopodium zonale*	Tyrosine Kinase Inhibitor	*In-vitro*	Showed inhibitory effect on tyrosine kinase (IC_{50} = 79.7 μg/mL).	Wessels et al. (1999)
	S. zonale	Antibacterial	*In-vitro*	Inhibited the growth of *Bacillus megaterium* and E. coli.	Wessels et al. (1999)
Dehydrothyrsiferol (**43**)	*Laurencia viridis*	Antitumor	*In-vitro*	Inhibited human breast cancer cell lines, viz. ZR-75-1, Hs578T and T47D with IC50 of 16.0, 18.9 and 13.5 μM, respectively.	Pec et al. (1999)
Stypolactone (**44**)	*S. zonale*	Antitumor	*In-vitro*	Showed weak cytotoxic property against A-549 (human lung carcinoma) and HT-29 and H-116 (human colon carcinoma) cell lines, with IC_{50} values of > 25.0 μg/ml, in each case.	Dorta et al. (2002)
Aplysiaterpenoid A (**45**)	*Plocamium telfairiae*	Insecticidal		Displayed strong insecticidal activities against the mosquito larvae (*Anopheles gambiae*) and German cockroach (*Blatella germanica*).	Watanabe et al. (1990)
Telfairine (**46**)	*P. telfairiae*	Insecticidal		Displayed strong insecticidal activities against the mosquito larvae (*Anopheles gambiae*) and German cockroach (*Blatella germanica*).	Watanabe et al. (1990)
Dictyterpenoid A (**47**) and B (**48**)	*Dilophus okamurae*	Feeding-deterrent		Displayed feeding-deterrent activity against abalone *Haliotis discus* hannai.	Suzuki et al. (2002)
Scopariol (**49**), isorigidol (**50**), (+)-3-(Z)-bromomethylidene-10β-bromo-β-chamigrene (**51**)	*Laurencia scoparia*	Anthelmintic	*In-vitro*	Showed anthelmintic effect against *Nippostrongylus brasiliensis*	Davyt et al. (2001)
2β,3α-epitaondiol (**52**), flabellinol (**53**), flabellinone (**54**), stypotriolaldehyde (**55**), stypohydroperoxide (**56**)	*Stypopodium flabelliforme*	Neurotoxic	*In-vitro*	Moderate toxicity to murine neuro-2a cells (LC_{50} = 2–25 μM) was observed for alln the compounds. 2β,3α-epitaondiol, flabellinol, and flabellinone possessed potent sodium channel blocking activity. In addition, stypotriolaldehyde displayed a biphasic effect on the concentration of intracellular Ca^{2+} in rat cerebellar granule neurons.	Sabry et al. (2005)
2β,3α-epitaondiol (**52**), flabellinol (**53**), flabellinone (**54**)	*S. flabelliforme*	Antitumor	*In-vitro*	Exhibited moderate cytotoxic effect with NCI–H460 human lung cancer cell line.	Sabry et al. (2005)
(6R)-6-hydroxydichotoma-3,14-diene-1,17-dial (**57**)	*Dictyota menstrualis*	Feeding-deterrence		Displayed feeding-deterrent properties against the amphipod *Parhyale hawaiensis* Dana.	Pereira et al. (2000)
3,7-dihydroxy-dihydrolaurene (**58**)	*Laurencia obtusa*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of > 300, 201.7, 182.3, 121.3, 176.4, 234.7 μM, respectively.	Kladi et al. (2006)
Perforenol B (**59**)	*L. obtusa*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of 67.4, 28.2, 54.8, 50.9, 73.2, 80.2 μM, respectively.	Kladi et al. (2006)
(1S*, 2R*, 6R*, 8S*, 9R*)-8-bromo2,5,6,9-tetramethyltricyclo-[7.2.0.0]undec-4-en-3-one (**60**)	*L. obtusa*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of > 300, > 300, 126.2, 111.3, 137.1, > 300 μM, respectively.	Kladi et al. (2006)
7-hydroxylaurene (**61**)	*L. obtusa*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of 64.2, 15.8, 18.1, 40.5, 23.9, 78.2 μM, respectively.	Kladi et al. (2006)

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Table 4 (*continued*)

Terpenoids	Source	Biological activity	Model used	Findings	References
Isolaurenisol (**62**)	*L. obtusa*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of 127.4, 95.5, 103.2, 88.6, 122.0, 165.5 μM, respectively.	Kladi et al. (2006)
(E)-2-tridecyl-2-heptadecenal (**63**)	*L. obtusa* and *L. microcladia*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of 82.7, 51.4, 71.6, 51.8, 45.8, 107.6 μM, respectively.	Kladi et al. (2006)
Perforenone A (**64**)	*L. obtusa*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of >300, >300, 138.3, 117.7, 105.1, >300 μM, respectively.	Kladi et al. (2006)
3-epi-perforenone A (**65**)	*L. obtusa*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of >300, >300, 144.4, 154.2, 151.9, >300 μM, respectively.	Kladi et al. (2006)
Laurinterol (**66**)	*L. microcladia*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of 128.3, 67.2, 76.6, 83.9, 74.6, 165.8 μM, respectively.	Kladi et al. (2006)
Bromolaurenisol (**67**)	*L. microcladia*	Cytotoxicity	*In-vitro*	Displayed cytotoxic effect on K562, MCF7, PC3, HeLa, A431, and CHO cell lines, with IC_{50} values of 112.7, 78.3, 92.4, 105.8, 81.6, >200 μM, respectively.	Kladi et al. (2006)
Amijiol (**68**)Amijiol acetate (**69**) Dolabellatrienol (**70**), Dolastane mijiol-7-10-diacetate (**71**), Pachydictyol A (**72**), Isopachydictyol A (**73**), 8b-hydroxypachydictyol A (**74**),Isodictyohemiacetal (**75**), and Dictyol C (**76**)	*Dictoyota dichotoma*	DNA protective, cytotoxicity, antioxidant	*In-vitro*	Showed DNA protective effect, and cytotoxicity against HepG2, WI-38 and MCF-7 cell lines. Also displayed antioxidant effect by means of ABTS and erythrocytes hemolysis.	Ayyad et al. (2011)
Capisterone A (**77**) and B (**78**)	*Penicillus capitatus*	Antifungal	*In-vitro*	Showed effective antifungal activity against the marine fungi (*Lindra thallasiae)*.	Puglisi et al. (2004)
(1S,2S,4R,5R,1′E)- 2-bromo-1-bromomethyl-1,4-dichloro-5-(2′-chloroethenyl)-5-methylcyclohexane (**79**)	*Plocamium hamatum*	Antifungal, antibacterial and antialgal	*In-vitro*	Showed potent antialgal activity towards *Chlorella fusca*, antinfungal effect on *Ustilago violacea* and *Mycotypha microspora*, and antibacterial effect against Bacillus megaterium.	König et al. (1999)
Labda-14-ene-8-ol (**80**), Labda-14-ene3α,8α-diol (**81**), ent-Labda-13 (16),14-diene-3-one (**82**),Labda-14-ene-8α,9α-diol (**83**), ent-Labda-13 (16),14-diene-3α-ol (**84**), ent-Labda-13 (16),14-diene (**85**)	*Ulva fasciata*	Antibacterial	*In-vitro*	Inhibited the growth of *Vibrio alginolyticus*, V. parahaemolyticus and V. vulnificus and with MIC values ranging from 30 to 250 μg/ml.	Chakraborty et al. (2010)
Peyssonoic acid A (**86**)	*Peyssonnelia* sp.	Antimicrobial and antineoplastic	*In-vitro*	Inhibited the growth of the bacterial pathogen of marine algae, *Pseudoalteromonas bacteriolytica* (IC_{50} = 799 μM), and *Lindra thalassiae* (IC_{50} = 506 μM), and also showed least antineoplastic activity against ovarian cancer cells (IC_{50} = 34.5 μM).	Lane et al. (2010)
Peyssonoic acid B (**87**)	*Peyssonnelia* sp.	Antimicrobial and antineoplastic	*In-vitro*	Inhibited the growth of *P. bacteriolytica* (IC_{50} = 377 μM), and *L. thalassiae* (IC_{50} = 331 μM), and also showed least antineoplastic activity against ovarian cancer cells (IC_{50} = 13.5 μM).	Lane et al. (2010)
2,5,5-Trimethyl-4-(4-methylpent-3-enyl)-2-cyclohexen-1-ol (**88**)	*Ulva fasciata*	Antioxidant	*In-vitro*	Displayed DPPH and ABTS scavenging effect (IC_{50} = 13.74 mM and 66.8% inhibition at 50 μM, respectively).	Chakraborty and Paulraj (2010)
4- Isopentyl-3,4,5,5-tetramethyl-2-cyclohexen-1-ol (**89**)	*U. fasciata*	Antioxidant	*In-vitro*	Displayed DPPH scavenging effect (IC_{50} = 23.60–20.83 mM).	Chakraborty and Paulraj (2010)
6-Isopentyl-1,5,5,6-tetramethyl-1-cyclohexene (**90**)	*U. fasciata*	Antioxidant	*In-vitro*	Displayed DPPH and ABTS scavenging effect (IC_{50} = 80.56 mM and 12.8% inhibition at 50 μM, respectively).	Chakraborty and Paulraj (2010)
3,4,5,5-Tetramethyl-4-(3-oxopentyl)-2-cyclohexene-1-one (**91**)	*U. fasciata*	Antioxidant	*In-vitro*	Displayed DPPH and ABTS scavenging effect (IC_{50} = 10.24 mM and 78% inhibition at 50 μM, respectively).	Chakraborty and Paulraj (2010)

(*continued on next page*)

Table 4 (*continued*)

Terpenoids	Source	Biological activity	Model used	Findings	References
Crinitol (**92**)	*Sargassum tortile*	Antibacterial	*In-vitro*	Showed inhibition against *Bacillus subtilis* (MIC = 50 μg/ml), *Brevibacterium ananoniagenes* (MIC = 100 μg/ml), *Streptococcus mutans* (MIC = 50 μg/ml), *Staphylococcus aureus* (MIC = 400 μg/ml), *Propionibacterium acnes* (MIC = 25 μg/ml), *Trichophyton mentagrophytes* (MIC = 25 μg/ml).	Kubo and Smith (1998)
Racemobutenolid A (**93**) and B (**94**)	*Caulerpa racemosa*	Cytotoxicity	*In-vitro*	Exhibited moderate cytotoxic effect on HL-60 (IC_{50} = 49.3 μM).	Yang et al. (2015)
4′,5′-dehydrodiodictyonema A (**95**)	*C. racemosa*	Enzyme inhibitory activities	*In-vitro*	Showed inhibitory effects against protein tyrosine phosphatase 1B (PTP1B), T-cell PTPase (TC-PTP) and cell division cycle 25 homolog B (CDC25B) with IC_{50} values 2.30, 12.56, and 42.92 μM, respectively.	Yang et al. (2015)

and *Porphyra yasoensis*, respectively (Harnedy and FitzGerald, 2013). Although protein hydrolysates possess various biological properties, isolation of anti-hypertension inhibitory peptides from seaweed is now getting much momentum among researchers worldwide. The detailed information on the proteins, peptides, and other protein hydrolysates isolated from seaweeds are given in Table 3.

4.4. Terpenoids

Terpenoids, sometimes referred to as terpenes, are a huge group of natural products commonly found in plants. They are a unique class of hydrocarbon moiety comprising of terpenes attached to an oxygen-containing group. In the current market, more than 60–75% drugs are employed for the treatment/management of infectious diseases and cancer, among these more than 23000 molecules belong to the class of terpenoid (Wang et al., 2005). For instance, the currently available commercial antimalarial drug Artemisinin and the anticancer drug paclitaxel (Taxol®) are terpenoid biomolecules, and many terpenoid molecules are in the clinical pipeline. Terpenoids are commonly classified as monoterpenoids, sesquiterpenes, diterpenes, sesterterpenes based on their chemical structure. Marine organisms are well-known to be a reservoir of these four categories of terpenes which have been documented to have numerous pharmacological properties. Seaweeds or marine macroalgae are a vast source of structurally diverse terpenoids especially red seaweeds, which are reported to have high amount of terpenoids. Among the seaweeds, the family Rhodomelaceae is considered as a terpenoid pool due to its vast chemical diversity and structurally different terpenoids. More than 1058 molecules harnessed naturally have been identified and characterised from this family which accounts to 20% of the total halogenated compounds characterised from all marine organisms (Wang et al., 2013). The comprehensive information on the pharmacological properties of terpenoids from seaweeds are shown in Table 4 and the chemical structures of important terpenoids are shown in Fig. 3A–C.

4.5. Alkaloids

In 1819 Meissner proposed the term “alkaloid” which originated from the Arabic words “al kaly” and the Greek “eidos”, meaning alkali-like. Alkaloids are heterocyclic nitrogenous compounds having Br-, I-, Cl-, and S- in their structure (Güven et al., 2010, 2013). Alkaloids are well known diverse group of natural biomolecules reported to have enormous health benefits and biological potential. The well-known example is Galanthamine; a commercially available anticholinesterase inhibitor used to treat dementia over the years. A more recent book written by Aniszewski (2015) described the applications of alkaloids in pharmaceutical and agricultural industries. Although alkaloids are extensively studied, research on marine algal-based alkaloids is still under-explored. The first alkaloid molecule was isolated from marine red algae Phyllophora nervosa is hordenine in 1969 (Güven et al., 1969, 1970). The alkaloids isolated from various marine algae and its pharmacological properties are listed in Table 5 and the chemical structures of important alkalaoids are shown in Fig. 4.

4.6. Photosynthetic pigments

Plants possess various photosynthetic pigments such chlorophylls, carotenoids, anthocyanins, betains, and research on the biological properties of these colourful pigments is gaining much attention due to its health-promoting effects. Like other terrestrial plants seaweeds, marine macroalgae are listed as one of the primary resources of these beneficial health pigments including carotenoids, fucoxanthin (xanthophyll pigments found in brown seaweeds), phycocyanin and phycoerythrin (found in red seaweeds). The importance of carotenoids especially β-carotene, α-carotene, β-cryptoxanthin, lycopene, lutein and zeaxanthin has already been well documented (Rodriguez-Amaya,

Table 5
Biological properties of seaweed alkaloids.

Alkaloid	Source	Biological activity	Model used	Findings	References
Caulerpin (**96**)	Caulerpa racemosa	Antinociceptive	In-vivo	In the abdominal constriction test, the alkaloid exerted a reduction in the acetic acid-induced nociception at 0.0945 μmol (0.0103–1.0984). Caulerpin also caused a favourable nociception inhibition in the hot plate test at 100 μmol/kg, p.o.	De Souza et al. (2009)
	C. racemosa	Anti-inflammatory	In-vivo	100 μmol/kg, p.o og caulerpin showed a high anti-inflammatory activity. This effect was further established on (i) capsaicin-induced ear edema model (% inhibition of 55.8) and (ii) the carrageenan-induced peritonitis (number of recruit cells decreased by 48.3%)	
	C. racemosa	Anti-viral	In-vitro	Showed antiviral activity against bovine viral diarrhea virus (EC_{50} = 2.0 μM).	Pinto et al. (2012)
	Caulerpa sp.	Spasmolytic	Ex vivo using guinea pig ileum	Repressed phasic contractions induced by carbachol, histamine, and serotonin in a non-selective manner. A dose-dependent inhibition against serotonin-induced cumulative contractions. It also relaxed KCl-pre-contracted ileum and carbachol in a dose-dependent manner.	Ayyad and Badria (1994)
	Caulerpa lentilifera, C. racemosa, Caulerpa microphysa and Caulerpa sertularoides	Antibacterial	In-vitro	Presented moderate antibacterial action against 8 bacterial species isolated from algal surface.	Vairappan (2004)
Almazole C (**97**)	Haraldiophylum sp.	Antibacterial	In-vitro	Showed antibacterial activity against Gram-negative pathogens.	Fresneda et al. (2007)
Lophocladine A (**98**) and B (**99**)	Lophocladia sp.	Anticancer	In-vitro	Exhibited cytotoxicity to MDAMB-435 breast cancer and NCI–H460 human lung tumor cell lines. The activity was correlated with microtubule inhibition.	Gross et al. (2006)
	Lophocladia sp.	Neuroprotective	In-vitro	Showed affinity for NMDA receptors and found to be a δ-opioid receptor antagonist.	
4. Martefragin A (**100**)	Martensia fragilis	Antioxidant	Ex vivo	In in rat liver microsomes, Martefragin A inhibited NADPH-dependent lipid peroxidation (IC_{50} = 2.8 μM).	Takahashi et al. (1998)
5. Racemosin A (**101**)	Caulerpa racemosa	Neuroprotective	In-vitro	Reduced the Aβ25–35-induced SH-SY5Y cell damage with a 14.6% increase in cell viability at 10 μM compared to the positive control EGCG (16.57% increaseat 10 μM).	Liu et al. (2013)
6. Racemosin C (**102**)	Caulerpa racemosa	Tyrosine phosphatase-1B inhibitory activity	In-vitro	Exhibited significant PTP1B (human protein tyrosine phosphatase-1B) inhibitory activity with IC_{50} values of 5.86 μM compared to the positive control oleanolic acid (IC_{50} = 3.03 μM).	Yang et al. (2014)
7. Azocinyl morpholinone (**103**) [3-(2-ethyl-6-((3Z,7Z)-1,2,5,6-tetrahydroazocin-5-yl)hexyl) morpholin6-one] (**104**)	Gracilaria opuntia	Antioxidant	In-vitro	Showed scavenging effect against DPPH radicals (IC_{50} = 0.086 mg/mL).	Makkar and Chakraborty (2018)
	G. opuntia	Anti-inflammatory	In-vitro and In-vivo	Inhibited COX-2 (IC_{50} = 0.84 mg/mL) and 5-lipoxidase (IC_{50} = 0.85 mg/mL).	Makkar and Chakraborty (2018)

Table 6
Biological properties of fucoxanthin from seaweeds.

Source	Biological activity	Model used	Findings	Reference
Eisenia bicyclis and Undaria pinnatifida	Antidiabetic	In-vitro	Displayed inhibitory activity against AGE formation (IC_{50} = 86.48 μM), HRAR (IC_{50} = 108.31 μM), RLAR (IC_{50} = 264.67 μM), and PTP1B activity (IC_{50} = 4.80 μM).	Jung et al. (2012)
U. pinnatifida	Antidiabetic	In-vivo	Fucoxanthin improved hyperglycemia in diabetic/obese KK-A^y mice. It enhanced the insulin signaling pathway, with translocation of GLUT4, and by stimulating expression of GLUT4 in the soleus and extensor digitorum longus muscles, respectively.	Nishikawa et al. (2012)
U. pinnatifida	Antioxidant	In-vitro	Decreased TBARS values on day 1 and 6 in ground chicken breast meat during chilled storage after cooking.	Sasaki et al. (2008)
Halocynthia roretzi	Anticancer	In-vitro	Fucoxanthinol significantly decreased viability of HL-60 human leukemia cells at 12.5 μM.	Konishi et al. (2006)
U. pinnatifida	Anticancer	In-vitro	Fucoxanthin significantly decreased the viability of Caco-2 (human colorectal carcinoma), HCT116 (human colorectal adenocarcinoma) and PC-3 human prostate cancer cells at 10 μM.	Kotake-Nara et al. (2005)
U. pinnatifida	Anticancer	In-vitro	Strong inhibitory effect was noticed 13-cis and 13′-cis fucoxanthin on Caco-2 cells and HL-60 cells.	Nakazawa et al. (2009)
Hijikia fusiforme	Anticancer	In-vivo	In C3H/He male mice, fucoxanthin suppressed liver tumorigenesis. Besides, in the skin of ICR mice, antitumor-promoting effect was noticed with fucoxanthin in a two-stage carcinogenesis experiment.	Nishino (1998)
H. fusiforme	Anticancer	In-vivo	In $B6C3F_1$ male mice, drinking water mixed with 0.01% fucoxanthin for 7 weeks significantly decreased the number of putative preneoplastic aberrant crypt foci (ACF)/mouse from 63.3 for the control group to 47.1 value.	Kim et al. (1998)
Laminaria japonica	Neuroprotective	In-vitro	Pre-treatment with fucoxanthin reduced β-amyloid protein (Aβ)-induced cell death in cortical cultured neurons or PC12 cells.	Zhao et al. (2015)
L. japonica	Anti-pigmentary	In-vitro and In-vivo	Inhibited melanogenesis in melanoma, UVB-induced skin pigmentation and tyrosinase. The application of 1% fucoxanthin topically also suppressed mRNA expression of COX-2, NTR, endothelin receptor A, EP1, MC1R and tyrosinase-related protein 1.	Shimoda et al. (2010)
L. japonica	Anti-osteoporosis	In-vitro	Suppression of osteoclastogenesis by inhibiting differentiation of osteoclast and apoptosis induction through caspase-3 activation in osteoclast-like cells.	Das et al. (2010)
Myagropsis myagroides	Anti-inflammatory	In-vitro	Inhibited NO production, inducible nitric oxide synthase (iNOS), COX-2 protein expressions and slightly reduced the PGE_2 production. Fucoxanthin also dose-dependently reduced the release of TNF-α, IL-1β, and IL-6.	Heo et al. (2010b)
Petalonia binghamiae	Anti-obesity	In-vitro	Promotion of 3T3-L1 adipocyte differentiation was noticed with fucoxanthin treatment during the early stage of differentiation (D0-D2) and it was proved by the increased accumulation of tryglycerides. Besides, fucoxanthin dose-dependently increased protein expression of PPARγ, C/EBPα, SREBP1c, aP2, and adiponectin mRNA expression. Fucoxanthin reduced the expression of PPARγ, C/EBPα, and SREBP1c during the intermediate (D2–D4) and late stages (D4–D7) of differentiation.	Kang et al. (2011)
U. pinnatifida	Anti-obesity	In-vivo	Lowered body weight and viscerafat-pads weights in diet-induced obesity mice fed a high-fat diet without altering food intake.	Woo et al. (2009)
U. pinnatifida	Anti-obesity	In-vivo	In diabetic/obese KK-A^y mice, fucoxanthin effectively regulated the mRNA expression of inflammatory adipocytokines involved in iNOS, insulin resistance and COX-2 in white adipose tissue.	Hosokawa et al. (2010)
U. pinnatifida	Anti-obesity	In-vitro and In-vivo	Inhibited lipase enzyme in the gastrointestinal lumen and suppressed absorption of triglyceride in rats. Moreover, fucoxanthin was further converted to fucoxanthinol in the intestine and finally released into the lymph.	Matsumoto et al. (2010)
U. pinnatifida	Anti-obesity	In-vivo	Dietary fucoxanthin caused an increase in serum HDL, non-HDL-cholesterol levels, total cholesterol levels via the activation of SREBP signaling and by suppressing serum cholesterol uptake in the liver via decreasing LDLR and SR-B1 expression in KK-A^y mice. Fucoxanthin also promoted LDLR degradation through up-regulation of PCSK9 and leads to increased non-HDL-cholesterol levels.	Beppu et al. (2012)
Sargassum heterophyllum	Antiplasmodicidal	In-vitro	Displayed excellent antiplasmodial effect against chloroquine-sensitive strain (D10) of Plasmodium falciparum with an IC_{50} value of 1.5 μM.	Afolayan et al. (2008)
Sargassum siliquastrum	Cytoprotective	In-vitro	Inhibited DNA damage, apoptosis induced by H_2O_2 and intracellular ROS formation,	Heo et al. (2008)
S. siliquastrum	Photoprotective	In-vitro	Fucoxanthin treatment effectively decreased generation of Intracellular ROS by exposure to UV-B radiation. In addition, the protective effect of fucoxanthin was also confirmed through Hoechst 33342/PI staining.	Heo and Jeon (2009b)
U. pinnatifida	Anti-angiogenic	In-vitro and ex vivo	Suppressed proliferation and tuve formation of HUVEC at more than 10 μM, but showed no significant effect on HUVEC chemotaxis. Moreover, fucoxanthin suppressed microvessel outgrowth, using a rat aortic ring, in a dose-dependent manner.	Sugawara et al. (2006)

C/EBPα, CCAAT/enhancer-binding protein α; EP1, prostaglandin E receptor 1; HRAR, human recombinant aldose reductase; HUVEC, human umbilical vein endothelial cells; iNOS, inducible nitric oxide synthase; LDLR, low-density lipoprotein receptor; MC1R, melanocortin 1 receptor; NTR, p75 neurotrophin receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; PGE2, prostaglandin E2; PPARγ, protein expression of peroxisome proliferator-activated receptor γ; RLAR, rat lens aldose reductase; SR-B1, scavenger receptor class B type 1; SREBP, sterol regulatory element binding protein; SREBP1c, sterol regulatory element-binding protein 1c; TBARS, thiobarbituric acid reactive substances.

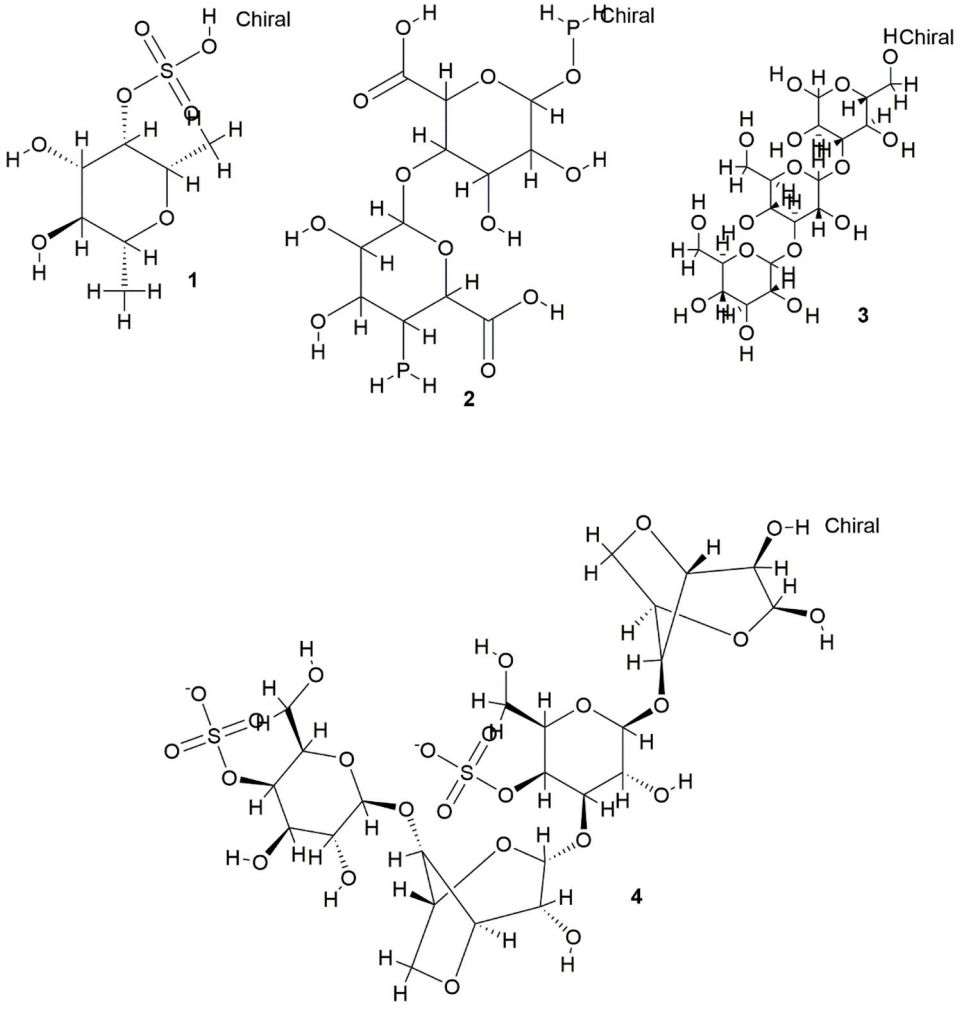
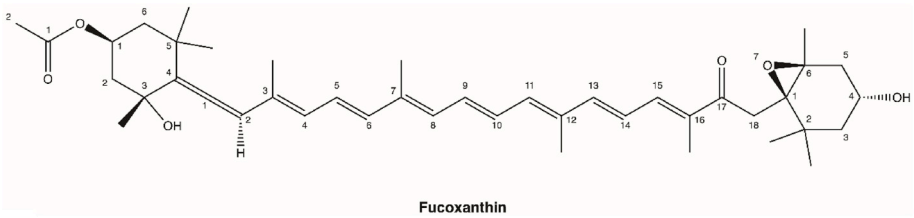


Fig. 1. Chemical structures of biological active polysaccharides from seaweeds.

2016). The global fucoxanthin production market was about 500 tons in 2015 and is expected to grow at a CAGR of 5.3% from 2016 to 2021 (ResearchnReports, 2016). In seaweeds, fucoxanthin and astaxanthin are the two primary available carotenoid pigments. Fucoxanthin ($C_{42}H_{58}O_6$) is contributing to 10% of the total carotenoid production globally (Dembitsky and Maoka, 2007). In recent years, scientific research on fucoxanthin have attracted considerable interest owing to their potential pharmacological properties including antimicrobial, antimalarial activities, antioxidant, anti-obese, antidiabetic, anti-inflammatory, anticancer, antiangiogenic, and its protective effects on the various organs (D'Orazio et al., 2012; Gammone and D'Orazio, 2015; Kim and Pangestuti, 2011; Peng et al., 2011; Rengasamy et al., 2014b). The other essential seaweed pigments are phycocyanin and phycoerythrin which are predominantly available in microalgae and red seaweeds. Phycocyanin comprises of two similar α and β subunits of proteins with molecular weight of 17000 and 19500 Da, respectively. The importance of phycocyanin was critically reviewed by Romay et al. (2003) followed by many other researchers. Phycoerythrins are made up of two peptides such as α and β subunits with 160–180 amino acids (Anwer et al., 2015; Sonani et al., 2017). The detailed information on the isolation and bioactivity of fucoxanthin, phycocyanin and phycoerythrin are listed in Table 6.



4.7. Polyunsaturated fatty acids (PUFA)

PUFA, consist of long hydrocarbon chains which terminate with hydroxyl groups. They are also commonly termed as long-chain PUFA (LC-PUFA). Depending on the position of the first carbon-carbon double bond (C═C), it is classified into omega 3 or omega six fatty acids.

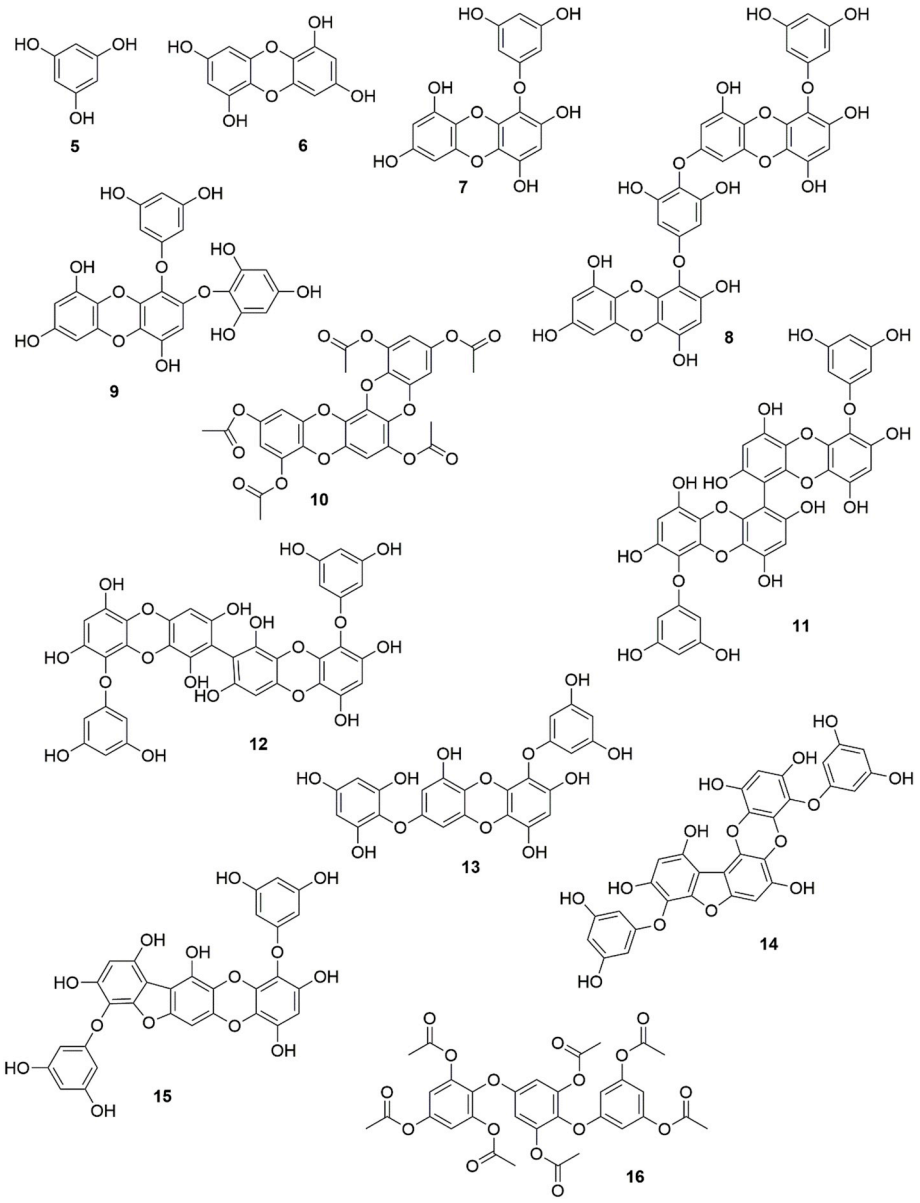


Fig. 2A. Chemical structures of biological active phlorotannins from seaweeds.

Alpha-linolenic acid (18 carbons and three double bonds), EPA (20 carbons and five double bonds) and DHA (22 carbons and six double bonds) are three main omega three fatty acids which play a crucial role in healthy human physiology (Rengasamy et al., 2014b). Among these, EPA and DHA are now gaining much attention from the marine functional food researchers due to their health beneficial effects including the reduction of the risk factors linked to fetal development, assisting visual and neurodevelopment, cardiovascular disorders, Alzheimer's disease hypertension, and improving conditions such as coronary artery disease and arthritis (Swanson et al., 2012). Nearly half of the total fatty acid content in various seaweeds are comprised of EPA (C20:5, n-3) (Dawczynski et al., 2007; MURATA and Nakazoe, 2001). The other interesting point to note is that seaweeds are the only source for n-3 PUFA 18:4, n-3 (Rengasamy et al., 2014). Owing to the high concentrations of PUFA, especially omega three fatty acids, seaweeds are excellent candidates for the development of nutracetuticals/dietary supplements for human health.

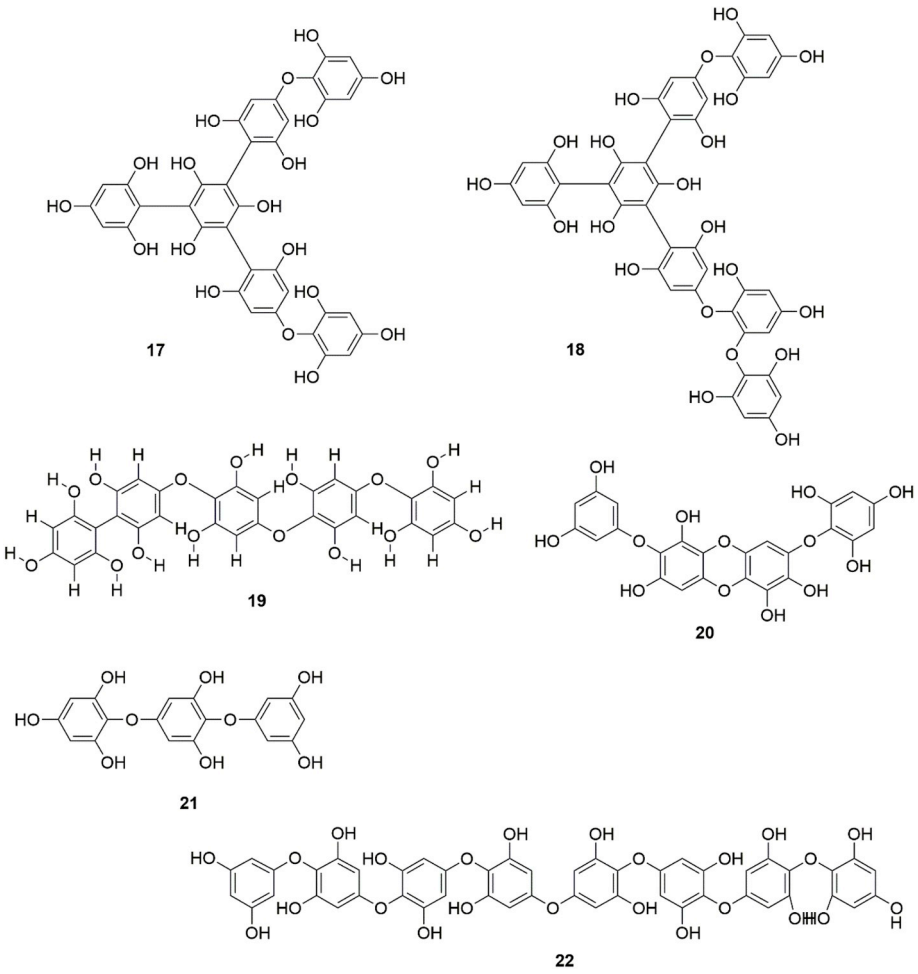


Fig. 2B. Chemical structures of biological active phlorotannins from seaweeds.

4.8. Polyamines

Polyamines are low molecular weight water-soluble aliphatic compounds consists of two or more amino groups which are least studied bioactive natural compounds available in all the living organisms including bacteria, fungi, plants and mammalian cells. The first polyamine, spermine, was isolated from human semen in 1678. Three known vital polyamines were putrescine (1,4-butane diamine or tetramethylenediamine), spermidine (N-(3-aminopropyl)-1,4-butane diamine or aminopropyl-tetramethylenediamine), spermine (N, N0-bis(3-aminopropyl)-1,4-butane diamine or diaminopropyl-tetramethylenediamine) and agmatin, a polyamine derivative derived from arginine. Spermine and spermidine are reported to have anti-glycation effect, and it is well documented that glycation has an essential role in the genesis of diabetes complications (Gugliucci and Menini, 2003). Polyamines are also reported to have various biological importance in cancer prevention, inflammation, and their role as antioxidants, anti-aging effect, and their effect on gut maturation (Larqué et al., 2007). Apart from human health benefits, polyamines also have a beneficial impact on plant growth and development. However, research on the discovery of polyamines from various natural resources, including seaweeds or marine macroalgae, is still in infancy stage.

5. Safety and toxicity of seaweed compounds

Although seaweeds have gained much interest in food industrial applications for their nutritive values, it is important to determine their toxicological profile for the safety of consumers. Few studies have probed into the safety profile of seaweeds compounds. For instance, the toxicity of fucoidan in Sprague-Dawley rats was tested by Kim et al.

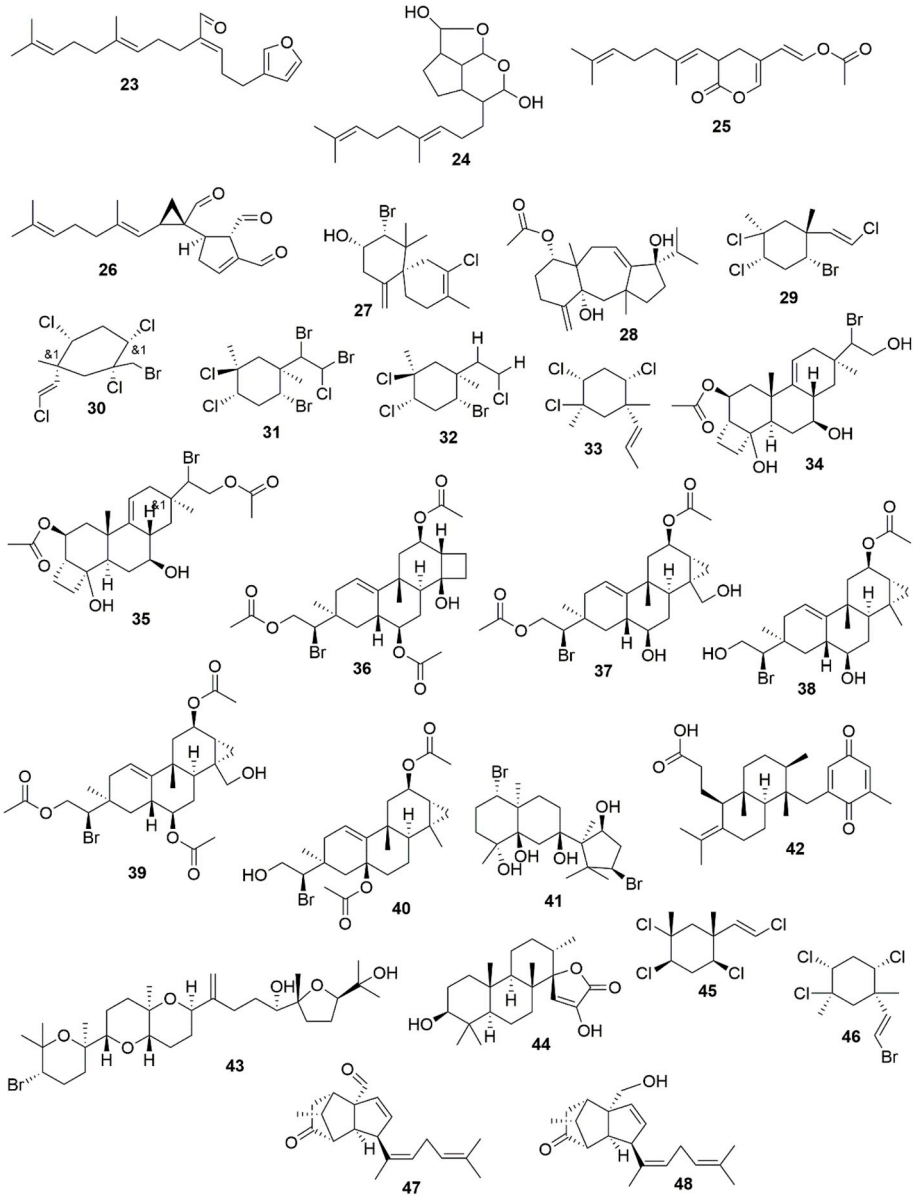


Fig. 3A. Chemical structures of terpenoids from seaweeds.

(2010). Fucoidan (1350 mg/kg bw/day) for 4 weeks) did not cause significant differences in groups matched by gender with respect to body weight, ophthalmoscopy, urinalysis, hematology, and histopathology. Also, Fucoidan did not affect prothrombin time or activated partial thromboplastin time, which indicates an inability to change blood clotting. Moreover, Vidal et al. (1984) carried out toxicity studies on two metabolites present in *Caulerpa* species, caulerpin and caulerpicin, and demonstrated that these two substances are not toxic. Food-grade carrageenan has also been shown to be relatively non-toxic by oral, dermal and inhalation routes of exposure in animal species, mutagenicity studies and reproductive toxicity studies (Weiner, 1991). It is also important to point out that many bioactive compounds, especially the terpenoids, have not been tested in toxicological studies. Considering the fact that some of these compounds are known to possess insecticidal properties such as mertensene, violacene (Argandona et al., 2000), telfairine (Watanabe et al., 1989), aplysiaterpenoid A

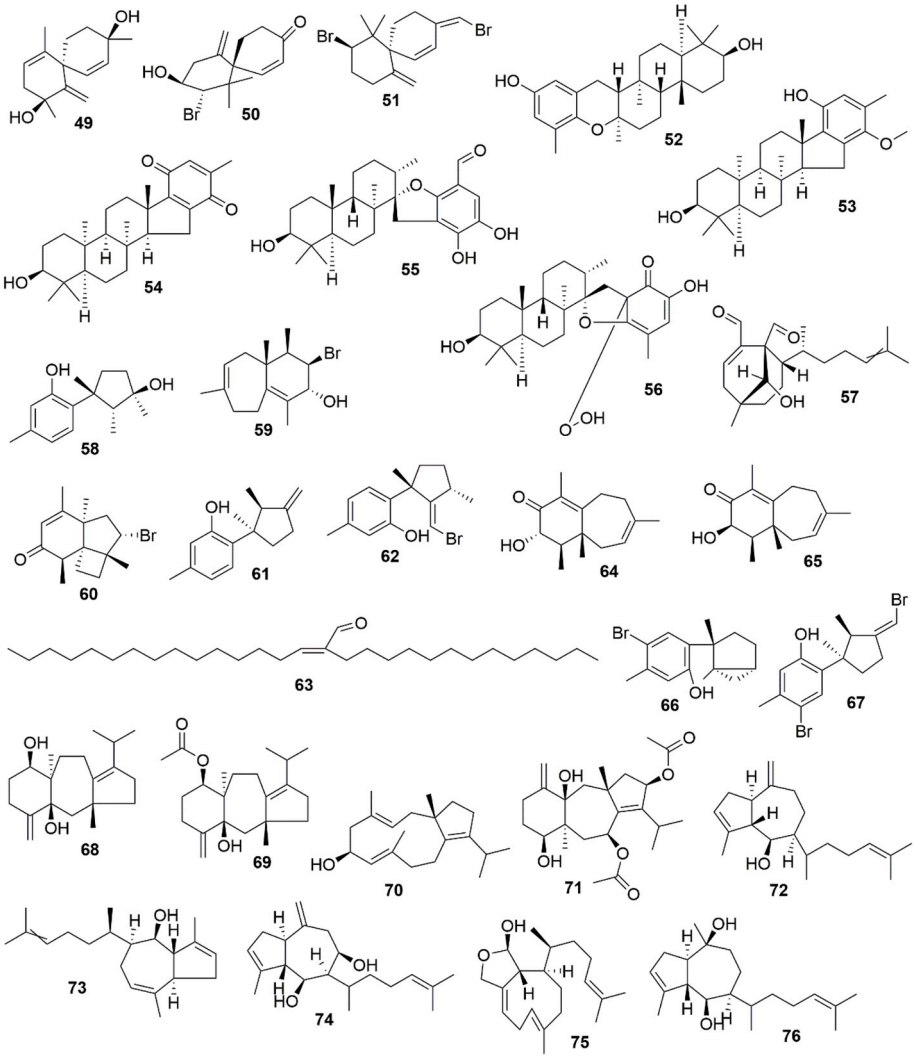


Fig. 3B. Chemical structures of terpenoids from seaweeds.

(Watanabe et al., 1990), elatol (Bianco et al., 2013), it is necessary that future studies aim to determine their safety profile *in vitro* and on animal species.

6. Concluding remarks and future prospects

Marine macroalgae or seaweeds are considered as one among the economically important biological resources which offer an extensive assortment of phytonutrients and phytochemicals comprising of vitamins, proteins, micro and macro elements, poly- and oligosaccharides, polyunsaturated fatty acids, terpenoids, alkaloids, polyphenols especially phlorotannins and polyamines with potential pharmacological properties. Among these bioactive compounds, research on alkaloids and polyamines still in infancy stage; it might be due to inadequate knowledge on isolation and structural chemistry with seaweed biologist. Recent evidences suggest that dietary polyamines not only possess health benefits but also possess significant role in plant growth and development, nonetheless, not much information is available on seaweed polyamines. Marine algae have been frequently reported for their potential as enzyme inhibitors against various health illness including cancer, diabetes, inflammation, gout, dementia, and others (Rengasamy et al., 2014). Therefore, it is necessary to initiate algal drug discovery research platform to focus on enzyme inhibitors which is now a hot topic of research among both the natural product chemists as well as commercial drug market.

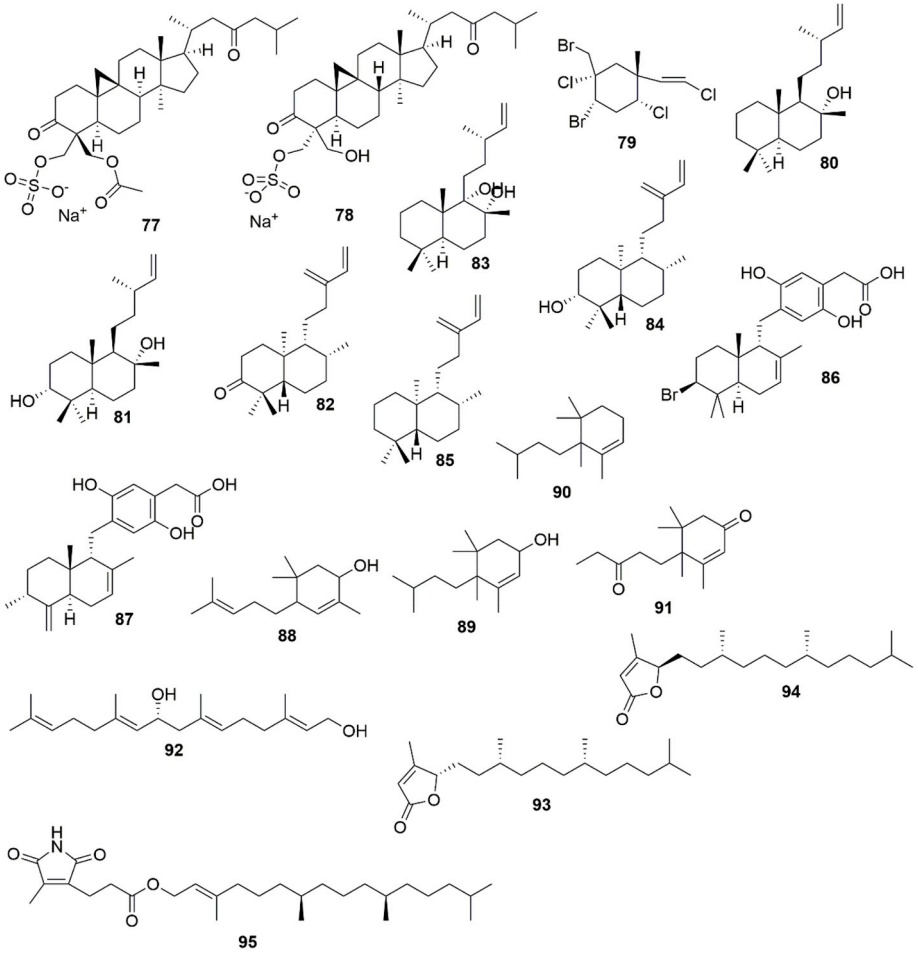


Fig. 3C. Chemical structures of terpenoids from seaweeds.

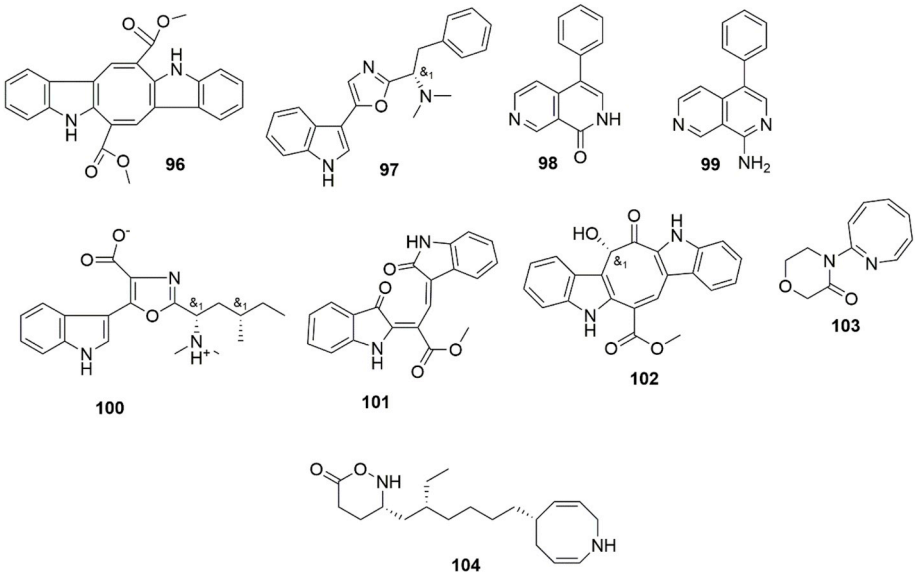


Fig. 4. Chemical structures of alkaloids from seaweeds.

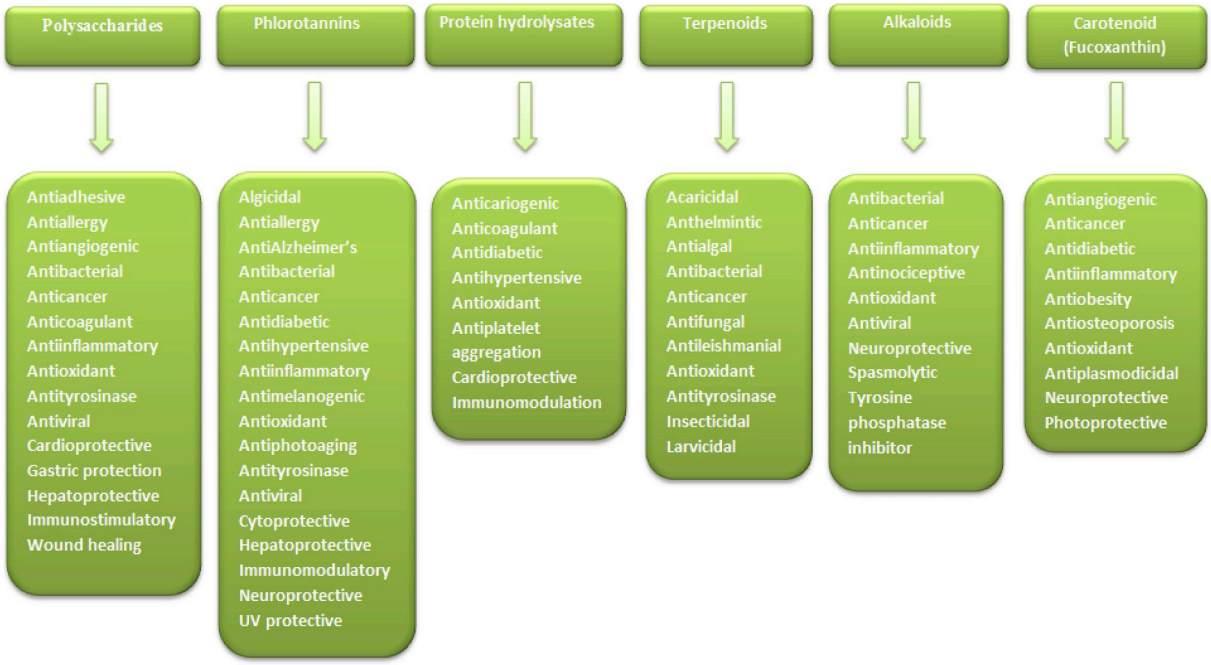


Fig. 5. Biological properties of different classes of seaweed compounds.

Author contributions

K.R.R.R and M.F. conceptualized the study. K.R.R.R, M.F and MZA conducted the literature collection, and prepared the first draft. All authors were involved in improving and polishing the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Afolayan, A.F., Bolton, J.J., Lategan, C.A., Smith, P.J., Beukes, D.R., 2008. Fucoxanthin, tetraprenylated toluquinone and toluhydroquinone metabolites from Sargassum heterophyllum inhibit the in vitro growth of the malaria parasite Plasmodium falciparum. Z. Naturforschung C 63, 848–852.

Ahn, M.-J., Yoon, K.-D., Min, S.-Y., Lee, J.S., Kim, J.H., Kim, T.G., Kim, S.H., Kim, N.-G., Huh, H., Kim, J., 2004. Inhibition of HIV-1 reverse transcriptase and protease by phlorotannins from the brown alga Ecklonia cava. Biol. Pharm. Bull. 27, 544–547.

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., 2007. Antioxidant activities of phlorotannins purified from Ecklonia cava on free radical scavenging using ESR and H2O2-mediated DNA damage. Eur. Food Res. Technol. 226, 71–79.

Ahn, M., Moon, C., Yang, W., Ko, E.-J., Hyun, J.W., Joo, H.G., Jee, Y., Lee, N.H., Park, J.W., Ko, R.K., 2011. Diphlorethohydroxycarmalol, isolated from the brown algae Ishige okamurae, protects against radiation-induced cell damage in mice. Food Chem. Toxicol. 49, 864–870.

Alekseyenko, T., Zhanayeva, S.Y., Venediktova, A., Zvyagintseva, T., Kuznetsova, T., Besednova, N., Korolenko, T., 2007. Antitumor and antimetastatic activity of fucoidan, a sulfated polysaccharide isolated from the Okhotsk Sea Fucus evanescens brown alga. Bull. Exp. Biol. Med. 143, 730–732.

Aniszewski, T., 2015. Alkaloids: Chemistry, Biology, Ecology, and Applications. Elsevier.

Anwer, K., Sonani, R., Madamwar, D., Singh, P., Khan, F., Bisetty, K., Ahmad, F., Hassan, M.I., 2015. Role of N-terminal residues on folding and stability of C-phycoerythrin: simulation and urea-induced denaturation studies. J. Biomol. Struct. Dyn. 33, 121–133.

Argandona, V., Del Pozo, T., San-Martín, A., Rovirosa, J., 2000. Insecticidal activity of Plocamium cartilagineum monoterpenes. Bol. Soc. Chil. Quim. 45, 371–376.

Artan, M., Li, Y., Karadeniz, F., Lee, S.-H., Kim, M.-M., Kim, S.-K., 2008. Anti-HIV-1 activity of phloroglucinol derivative, 6, 6′-bieckol, from Ecklonia cava. Bioorg. Med. Chem. 16, 7921–7926.

Awad, N.E., 2004. Bioactive brominated diterpenes from the marine red alga Jania Rubens (L.) Lamx. Phytother Res. 18, 275–279.

Ayyad, S.-E., Badria, F., 1994. Caulerpine: an antitumor indole alkaloid from Caulerpa racemosa. Alexandria. J. Pharm. Sci. 8 217-217.

Ayyad, S.-E.N., Makki, M.S., Al-kayal, N.S., Basaif, S.A., El-Foty, K.O., Asiri, A.M., Alarif, W.M., Badria, F.A., 2011. Cytotoxic and protective DNA damage of three new diterpenoids from the brown alga Dictoyota dichotoma. Eur. J. Med. Chem. 46, 175–182.

Beaulieu, L., Sirois, M., Tamigneaux, É., 2016. Evaluation of the in vitro biological activity of protein hydrolysates of the edible red alga, Palmaria palmata (dulse) harvested from the Gaspe coast and cultivated in tanks. J. Appl. Phycol. 28, 3101–3115.

Beppu, F., Hosokawa, M., Niwano, Y., Miyashita, K., 2012. Effects of dietary fucoxanthin on cholesterol metabolism in diabetic/obese KK-A y mice. Lipids Health Dis. 11, 112.

Bianco, E.M., Pires, L., Santos, G.K., Dutra, K.A., Reis, T.N., Vasconcelos, E.R., Cocentino, A.L., Navarro, D.M., 2013. Larvicidal activity of seaweeds from northeastern Brazil and of a halogenated sesquiterpene against the dengue mosquito (Aedes aegypti). Ind. Crops Prod. 43, 270–275.

Blunt, J.W., Copp, B.R., Hu, W.-P., Munro, M., Northcote, P.T., Prinsep, M.R., 2007. Marine natural products. Nat. Prod. Rep. 24, 31–86.

Bondu, S., Bonnet, C., Gaubert, J., Deslandes, É., Turgeon, S.L., Beaulieu, L., 2015. Bioassay-guided fractionation approach for determination of protein precursors of proteolytic bioactive metabolites from macroalgae. J. Appl. Phycol. 27, 2059–2074.

Born, F.S., Bianco, E.M., 2012. Acaricidal and repellent activity of terpenoids from seaweeds Collected in Pernambuco, Brazil. Nat. Prod. Commun. 7, 463–466.

Cáceres, P.J., Carlucci, M.a.J., Damonte, E.B., Matsuhiro, B., Zúñiga, E.A., 2000. Carrageenans from chilean samples of Stenogramme interrupta (Phyllophoraceae): structural analysis and biological activity. Phytochemistry 53, 81–86.

Campos, A., Souza, C.B., Lhullier, C., Falkenberg, M., Schenkel, E.P., Ribeiro-do-Valle, R.M., Siqueira, J.M., 2012. Anti-tumour effects of elatol, a marine derivative compound obtained from red algae Laurencia microcladia. J. Pharm. Pharmacol. 64, 1146–1154.

Chakraborty, K., Paulraj, R., 2010. Sesquiterpenoids with free-radical-scavenging properties from marine macroalga Ulva fasciata Delile. Food Chem. 122, 31–41.

Chakraborty, K., Lipton, A., Raj, R.P., Vijayan, K., 2010. Antibacterial labdane diterpenoids of Ulva fasciata Delile from southwestern coast of the Indian Peninsula. Food Chem. 119, 1399–1408.

Chandía, N.P., Matsuhiro, B., 2008. Characterization of a fucoidan from Lessonia vadosa (Phaeophyta) and its anticoagulant and elicitor properties. Int. J. Biol. Macromol. 42, 235–240.

Chang, M.Y., Byon, S.-H., Shin, H.-C., Han, S.E., Kim, J.Y., Byun, J.Y., Lee, J.D., Park, M.K., 2016. Protective effects of the seaweed phlorotannin polyphenolic compound dieckol on gentamicin-induced damage in auditory hair cells. Int. J. Pediatr. Otorhinolaryngol. 83, 31–36.

Chen, J.-H., Lim, J.-D., Sohn, E.-H., Choi, Y.-S., Han, E.-T., 2009. Growth-inhibitory effect of a fucoidan from brown seaweed Undaria pinnatifida on Plasmodium parasites. Parasitol. Res. 104, 245–250.

Chen, H., Cong, Q., Du, Z., Liao, W., Zhang, L., Yao, Y., Ding, K., 2016. Sulfated fucoidan FP08S2 inhibits lung cancer cell growth in vivo by disrupting angiogenesis via targeting VEGFR2/VEGF and blocking VEGFR2/Erk/VEGF signaling. Cancer Lett. 382, 44–52.

Choi, J.-G., Kang, O.-H., Brice, O.-O., Lee, Y.-S., Chae, H.-S., Oh, Y.-C., Sohn, D.-H., Park, H., Choi, H.-G., Kim, S.-G., 2010. Antibacterial activity of Ecklonia cava against methicillin-resistant Staphylococcus aureus and Salmonella spp. Foodborne. Pathogens. Disease. 7, 435–441.

Cian, R.E., Martínez-Augustin, O., Drago, S.R., 2012. Bioactive properties of peptides obtained by enzymatic hydrolysis from protein byproducts of Porphyra columbina. Food Res. Int. 49, 364–372.
Cian, R.E., Alaiz, M., Vioque, J., Drago, S.R., 2013. Enzyme proteolysis enhanced extraction of ACE inhibitory and antioxidant compounds (peptides and polyphenols) from Porphyra columbina residual cake. J. Appl. Phycol. 25, 1197–1206.
Cian, R.E., Garzón, A.G., Ancona, D.B., Guerrero, L.C., Drago, S.R., 2015. Hydrolyzates from Pyropia columbina seaweed have antiplatelet aggregation, antioxidant and ACE I inhibitory peptides which maintain bioactivity after simulated gastrointestinal digestion. LWT-Food Sci. Technol. 64, 881–888.
Cian, R.E., Garzón, A.G., Ancona, D.B., Guerrero, L.C., Drago, S.R., 2016. Chelating properties of peptides from red seaweed Pyropia columbina and its effect on iron bioaccessibility. Plant Foods Hum. Nutr. 71, 96–101.
Cong, Q., Chen, H., Liao, W., Xiao, F., Wang, P., Qin, Y., Dong, Q., Ding, K., 2016. Structural characterization and effect on anti-angiogenic activity of a fucoidan from Sargassum fusiforme. Carbohydr. Polym. 136, 899–907.
Cumashi, A., Ushakova, N.A., Preobrazhenskaya, M.E., D'incecco, A., Piccoli, A., Totani, L., Tinari, N., Morozevich, G.E., Berman, A.E., Bilan, M.I., 2007. A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds. Glycobiology 17, 541–552.
Das, S.K., Ren, R., Hashimoto, T., Kanazawa, K., 2010. Fucoxanthin induces apoptosis in osteoclast-like cells differentiated from RAW264. 7 cells. J. Agric. Food Chem. 58, 6090–6095.
Davyt, D., Fernandez, R., Suescun, L., Mombrú, A.W., Saldana, J., Domínguez, L., Coll, J., Fujii, M.T., Manta, E., 2001. New sesquiterpene derivatives from the red alga laurencia s coparia. Isolation, structure determination, and anthelmintic activity. J. Nat. Prod. 64, 1552–1555.
Dawczynski, C., Schubert, R., Jahreis, G., 2007. Amino acids, fatty acids, and dietary fibre in edible seaweed products. Food Chem. 103, 891–899.
Dawes, C.J., 1998. Marine Botany. John Wiley & Sons.
De Souza, É.T., Pereira de Lira, D., Cavalcanti de Queiroz, A., Costa da Silva, D.J., Bezerra de Aquino, A., Campessato Mella, E.A., Prates Lorenzo, V., De Miranda, G.E.C., De Araújo-Júnior, J.X., De Oliveira Chaves, M.C., 2009. The antinociceptive and anti-inflammatory activities of caulerpin, a bisindole alkaloid isolated from seaweeds of the genus Caulerpa. Mar. Drugs 7, 689–704.
Dembitsky, V.M., Maoka, T., 2007. Allenic and cumulenic lipids. Prog. Lipid Res. 46, 328–375.
Dhargalkar, V., Pereira, N., 2005. Seaweed: Promising Plant of the Millennium.
Diogo, J.V., Novo, S.G., González, M.J., Ciancia, M., Bratanich, A.C., 2015. Antiviral activity of lambda-carrageenan prepared from red seaweed (Gigartina skottsbergii) against BoHV-1 and SuHV-1. Res. Vet. Sci. 98, 142–144.
Doh-ura, K., Kuge, T., Uomoto, M., Nishizawa, K., Kawasaki, Y., Iha, M., 2007. Prophylactic effect of dietary seaweed fucoidan against enteral prion infection. Antimicrob. Agents Chemother. 51, 2274–2277.
Dorta, E., Cueto, M., Díaz-Marrero, A.R., Darias, J., 2002. Stypolactone, an interesting diterpenoid from the brown alga Stypopodium zonale. Tetrahedron Lett. 43, 9043–9046.
Dumay, J., Morançais, M., Nguyen, H.P.T., Fleurence, J., 2015. Extraction and purification of R-phycoerythrin from marine red algae. Nat. Prod. Mar. Algae.: Method. Protocol. 109–117.
D'Orazio, N., Gemello, E., Gammone, M.A., de Girolamo, M., Ficoneri, C., Riccioni, G., 2012. Fucoxantin: a treasure from the sea. Mar. Drugs 10, 604–616.
El Gamal, A.A., 2010. Biological importance of marine algae. Saudi Pharm. J. 18, 1–25.
Ermakova, S., Sokolova, R., Kim, S.-M., Um, B.-H., Isakov, V., Zvyagintseva, T., 2011. Fucoidans from brown seaweeds Sargassum hornery, Eclonia cava, Costaria costata: structural characteristics and anticancer activity. Appl. Biochem. Biotechnol. 164, 841–850.
Faulkner, D., 2012. Marine Natural Products Chemistry. Springer Science & Business Media.
Fenical, W., Paul, V.J., 1984. Antimicrobial and Cytotoxic Terpenoids from Tropical Green Algae of the Family Udoteaceae, Eleventh International Seaweed Symposium. Springer, pp. 135–140.
Fitzgerald, C.n., Mora-Soler, L., Gallagher, E., O'Connor, P., Prieto, J., Soler-Vila, A., Hayes, M., 2012. Isolation and characterization of bioactive pro-peptides with in vitro renin inhibitory activities from the macroalga Palmaria palmata. J. Agric. Food Chem. 60, 7421–7427.
Fitzgerald, C., Aluko, R.E., Hossain, M., Rai, D.K., Hayes, M., 2014. Potential of a renin inhibitory peptide from the red seaweed Palmaria palmata as a functional food ingredient following confirmation and characterization of a hypotensive effect in spontaneously hypertensive rats. J. Agric. Food Chem. 62, 8352–8356.
Fresneda, P.M., Castaneda, M., Blug, M., Molina, P., 2007. Iminophosphorane-based preparation of 2, 5-disubstituted oxazole derivatives: synthesis of the marine alkaloid almazole C. Synlett 2007, 0324–0326.
Gammone, M.A., D'Orazio, N., 2015. Anti-obesity activity of the marine carotenoid fucoxanthin. Mar. Drugs 13, 2196–2214.
Goldberg, I., 2012. Functional Foods: Designer Foods, Pharmafoods, Nutraceuticals. Springer Science & Business Media.
Gross, H., Goeger, D.E., Hills, P., Mooberry, S.L., Ballantine, D.L., Murray, T.F., Valeriote, F.A., Gerwick, W.H., 2006. Lophocladines, bioactive alkaloids from the red alga Lophocladia sp. J. Nat. Prod. 69, 640–644.
Gugliucci, A., Menini, T., 2003. The polyamines spermine and spermidine protect proteins from structural and functional damage by AGE precursors: a new role for old molecules? Life Sci. 72, 2603–2616.
Güven, K., Bora, A., Sunam, G., 1969. Alkaloid content of marine algae: I. Hordenine from Phyllophora nervosa. Eczacılık Bülteni 11, 177–184.
Güven, K., Bora, A., Sunam, G., 1970. Hordenine from the alga Phyllophora nervosa. Phytochemistry 9, 1893.
Güven, K.C., Percot, A., Sezik, E., 2010. Alkaloids in marine algae. Mar. Drugs 8, 269–284.
Güven, K.C., Coban, B., Sezik, E., Erdugan, H., Kaleağasıoğlu, F., 2013. Alkaloids of marine macroalgae. In: Ramawat, K.G., Mérillon, J.-M. (Eds.), Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 25–37.
Haneji, K., Matsuda, T., Tomita, M., Kawakami, H., Ohshiro, K., Uchihara, J.-N., Masuda, M., Takasu, N., Tanaka, Y., Ohta, T., 2005. Fucoidan extracted from Cladosiphon okamuranus Tokida induces apoptosis of human T-cell leukemia virus type 1-infected T-cell lines and primary adult T-cell leukemia cells. Nutr. Cancer 52, 189–201.
Harnedy, P.A., FitzGerald, R.J., 2013. Cardioprotective peptides from marine sources. Curr. Protein Pept. Sci. 14, 162–172.
Harnedy, P.A., FitzGerald, R.J., 2013a. Cardioprotective peptides from marine sources. Curr. Protein Pept. Sci. 14, 162–172.
Harnedy, P.A., FitzGerald, R.J., 2013b. In vitro assessment of the cardioprotective, antidiabetic and antioxidant potential of Palmaria palmata protein hydrolysates. J. Appl. Phycol. 25, 1793–1803.
Heo, S.-J., Jeon, Y.-J., 2009a. Evaluation of diphlorethohydroxycarmalol isolated from Ishige okamurae for radical scavenging activity and its protective effect against H2O2-induced cell damage. Process Biochem. 44, 412–418.
Heo, S.-J., Jeon, Y.-J., 2009b. Protective effect of fucoxanthin isolated from Sargassum siliquastrum on UV-B induced cell damage. J. Photochem. Photobiol. B Biol. 95, 101–107.
Heo, S.-J., Ko, S.-C., Kang, S.-M., Kang, H.-S., Kim, J.-P., Kim, S.-H., Lee, K.-W., Cho, M.-G., Jeon, Y.-J., 2008. Cytoprotective effect of fucoxanthin isolated from brown algae Sargassum siliquastrum against H2O2-induced cell damage. Eur. Food Res. Technol. 228, 145–151.
Heo, S.-J., Ko, S.-C., Cha, S.-H., Kang, D.-H., Park, H.-S., Choi, Y.-U., Kim, D., Jung, W.-K., Jeon, Y.-J., 2009. Effect of phlorotannins isolated from Ecklonia cava on melanogenesis and their protective effect against photo-oxidative stress induced by UV-B radiation. Toxicol. In Vitro 23, 1123–1130.
Heo, S.-J., Ko, S.-C., Kang, S.-M., Cha, S.-H., Lee, S.-H., Kang, D.-H., Jung, W.-K., Affan, A., Oh, C., Jeon, Y.-J., 2010a. Inhibitory effect of diphlorethohydroxycarmalol on melanogenesis and its protective effect against UV-B radiation-induced cell damage. Food Chem. Toxicol. 48, 1355–1361.
Heo, S.-J., Yoon, W.-J., Kim, K.-N., Ahn, G.-N., Kang, S.-M., Kang, D.-H., Oh, C., Jung, W.-K., Jeon, Y.-J., 2010b. Evaluation of anti-inflammatory effect of fucoxanthin isolated from brown algae in lipopolysaccharide-stimulated RAW 264.7 macrophages. Food Chem. Toxicol. 48, 2045–2051.
Heo, S.-J., Cha, S.-H., Kim, K.-N., Lee, S.-H., Ahn, G., Kang, D.-H., Oh, C., Choi, Y.-U., Affan, A., Kim, D., 2012. Neuroprotective effect of phlorotannin isolated from Ishige okamurae against H 2 O 2-induced oxidative stress in murine hippocampal neuronal cells, HT22. Appl. Biochem. Biotechnol. 166, 1520–1532.
Horibe, S., Tanahashi, T., Kawauchi, S., Mizuno, S., Rikitake, Y., 2016. Preventative effects of Sodium Alginate on indomethacin-induced small-intestinal injury in mice. Int. J. Med. Sci. 13, 653.
Hosokawa, M., Miyashita, T., Nishikawa, S., Emi, S., Tsukui, T., Beppu, F., Okada, T., Miyashita, K., 2010. Fucoxanthin regulates adipocytokine mRNA expression in white adipose tissue of diabetic/obese KK-Ay mice. Arch. Biochem. Biophys. 504, 17–25.
Indumathi, P., Mehta, A., 2016. A novel anticoagulant peptide from the Nori hydrolysate. J. Funct. Foods. 20, 606–617.
Infinium Global Research, 2019. Marine-derived drugs market (type - phenol, steroid, ether, peptide, and other; source - algae, invertebrates, and microorganisms; mode of delivery - anti-microbial, anti-tumor, anti-cardiovascular, anti-viral, anti-inflammatory, and others): global industry analysis, trends, size, share and forecasts to 2025. Release date: 11th July 2019. https://www.medgadget.com/2019/07/marine-derived-drugs-market-growing-at-a-cagr-of-11-20-and-expected-to-reach-21955-6-million-by-2025-exclusive-report-by-infinium-global-research.html.
Ji, C.F., Ji, Y.B., 2014. Laminarin-induced apoptosis in human colon cancer LoVo cells. Oncol. Lett. 7, 1728–1732.
Ji, Y.B., Ji, C.F., Zhang, H., 2012. Laminarin induces apoptosis of human colon cancer LOVO cells through a mitochondrial pathway. Molecules 17, 9947–9960.
Joe, M.-J., Kim, S.-N., Choi, H.-Y., Shin, W.-S., Park, G.-M., Kang, D.-W., Kim, Y.K., 2006. The inhibitory effects of eckol and dieckol from Ecklonia stolonifera on the expression of matrix metalloproteinase-1 in human dermal fibroblasts. Biol. Pharm. Bull. 29, 1735–1739.
Juck, G., Neetoo, H., Chen, H., 2010. Application of an active alginate coating to control the growth of Listeria monocytogenes on poached and deli Turkey products. Int. J. Food Microbiol. 142, 302–308.
Jung, H.A., Hyun, S.K., Kim, H.R., Choi, J.S., 2006. Angiotensin-converting enzyme I inhibitory activity of phlorotannins from Ecklonia stolonifera. Fish. Sci. 72, 1292–1299.
Jung, H.A., Yoon, N.Y., Woo, M.-H., Choi, J.S., 2008. Inhibitory activities of extracts from several kinds of seaweeds and phlorotannins from the brown alga Ecklonia stolonifera on glucose-mediated protein damage and rat lens aldose reductase. Fish. Sci. 74, 1363–1365.
Jung, H.A., Islam, M.N., Lee, C.M., Jeong, H.O., Chung, H.Y., Woo, H.C., Choi, J.S., 2012. Promising antidiabetic potential of fucoxanthin isolated from the edible brown algae Eisenia bicyclis and Undaria pinnatifida. Fish. Sci. 78, 1321–1329.
Kang, K.A., Lee, K.H., Chae, S., Koh, Y.S., Yoo, B.-S., Kim, J.H., Ham, Y.M., Baik, J.S., Lee, N.H., Hyun, J.W., 2005. Triphlorethol-A from Ecklonia cava protects V79-4 lung fibroblast against hydrogen peroxide induced cell damage. Free Radic. Res. 39, 883–892.
Kang, K.A., Lee, K.H., Park, J.W., Lee, N.H., Na, H.K., Surh, Y.J., You, H.J., Chung, M.H., Hyun, J.W., 2007. Triphlorethol-A induces heme oxygenase-1 via activation of ERK

and NF-E2 related factor 2 transcription factor. FEBS Lett. 581, 2000–2008.
Kang, S.-I., Ko, H.-C., Shin, H.-S., Kim, H.-M., Hong, Y.-S., Lee, N.-H., Kim, S.-J., 2011. Fucoxanthin exerts differing effects on 3T3-L1 cells according to differentiation stage and inhibits glucose uptake in mature adipocytes. Biochem. Biophys. Res. Commun. 409, 769–774.
Kang, S.-M., Kim, A.-D., Heo, S.-J., Kim, K.-N., Lee, S.-H., Ko, S.-C., Jeon, Y.-J., 2012. Induction of apoptosis by diphlorethohydroxycarmalol isolated from brown alga, Ishige okamurae. J. Funct. Foods. 4, 433–439.
Kannan, R.R., Aderogba, M.A., Ndhlala, A.R., Stirk, W.A., Van Staden, J., 2013. Acetylcholinesterase inhibitory activity of phlorotannins isolated from the brown alga, Ecklonia maxima (Osbeck) Papenfuss. Food Res. Int. 54, 1250–1254.
Karadeniz, F., Kim, S.-K., 2015. Antitumor and Antimetastatic Effects of Marine Algal Polyphenols, Handbook of Anticancer Drugs from Marine Origin. Springer, pp. 177–183.
Kawamura-Konishi, Y., Watanabe, N., Saito, M., Nakajima, N., Sakaki, T., Katayama, T., Enomoto, T., 2012. Isolation of a new phlorotannin, a potent inhibitor of carbohydrate-hydrolyzing enzymes, from the brown alga Sargassum patens. J. Agric. Food Chem. 60, 5565–5570.
Kawashima, T., Murakami, K., Nishimura, I., Nakano, T., Obata, A., 2012. A sulfated polysaccharide, fucoidan, enhances the immunomodulatory effects of lactic acid bacteria. Int. J. Mol. Med. 29, 447–453.
Kelishomi, Z.H., Goliaei, B., Mahdavi, H., Nikoofar, A., Rahimi, M., Moosavi-Movahedi, A.A., Mamashli, F., Bigdeli, B., 2016. Antioxidant activity of low molecular weight alginate produced by thermal treatment. Food Chem. 196, 897–902.
Khan, S.I., Satam, S., 2003. Seaweed mariculture: scope and potential in India. Aquacult. Asia. 8, 26–29.
Kim, S.-K., Pangestuti, R., 2011. Biological Activities and Potential Health Benefits of Fucoxanthin Derived from Marine Brown Algae. Adv. Food Nutr. Res. Elsevier, pp. 111–128.
Kim, J.M., Araki, S., Kim, D.J., Park, C.B., Takasuka, N., Baba-Toriyama, H., Ota, T., Nir, Z., Khachik, F., Shimidzu, N., 1998. Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1, 2-dimethylhydrazine initiation. Carcinogenesis 19, 81–85.
Kim, A.-R., Shin, T.-S., Lee, M.-S., Park, J.-Y., Park, K.-E., Yoon, N.-Y., Kim, J.-S., Choi, J.-S., Jang, B.-C., Byun, D.-S., 2009. Isolation and identification of phlorotannins from Ecklonia stolonifera with antioxidant and anti-inflammatory properties. J. Agric. Food Chem. 57, 3483–3489.
Kim, K.-J., Lee, O.-H., Lee, H.-H., Lee, B.-Y., 2010. A 4-week repeated oral dose toxicity study of fucoidan from the Sporophyll of *Undaria pinnatifida* in Sprague–Dawley rats. Toxicology 267, 154–158.
Kim, A.-R., Lee, B., Joung, E.-J., Gwon, W.-G., Utsuki, T., Kim, N.-G., Kim, H.-R., 2016. 6, 6′-Bieckol suppresses inflammatory responses by down-regulating nuclear factor-κB activation via Akt, JNK, and p38 MAPK in LPS-stimulated microglial cells. Immunopharmacol. Immunotoxicol. 38, 244–252.
Kladi, M., Xenaki, H., Vagias, C., Papazafiri, P., Roussis, V., 2006. New cytotoxic sesquiterpenes from the red algae Laurencia obtusa and Laurencia microcladia. Tetrahedron 62, 182–189.
Kong, C.-S., Kim, J.-A., Yoon, N.-Y., Kim, S.-K., 2009. Induction of apoptosis by phloroglucinol derivative from Ecklonia cava in MCF-7 human breast cancer cells. Food Chem. Toxicol. 47, 1653–1658.
König, G.M., Wright, A.D., Linden, A., 1999. Plocamium hamatum and its monoterpenes: chemical and biological investigations of the tropical marine red alga. Phytochemistry 52, 1047–1053.
Konishi, I., Hosokawa, M., Sashima, T., Kobayashi, H., Miyashita, K., 2006. Halocynthiaxanthin and fucoxanthinol isolated from Halocynthia roretzi induce apoptosis in human leukemia, breast and colon cancer cells. Comp. Biochem. Physiol. C Toxicol. Pharmacol. 142, 53–59.
Kotake-Nara, E., Sugawara, T., Nagao, A., 2005. Antiproliferative effect of neoxanthin and fucoxanthin on cultured cells. Fish. Sci. 71, 459.
Kubo, I., Smith, L., 1998. Crinitol, an acyclic diterpene diol from marine algae. In: Atta-ur-Rahman (Ed.), Studies in Natural Products Chemistry: Structure and Chemistry (Part F). Elsevier Science, pp. 25–40.
Kuda, T., Yano, T., Matsuda, N., Nishizawa, M., 2005. Inhibitory effects of laminaran and low molecular alginate against the putrefactive compounds produced by intestinal microflora in vitro and in rats. Food Chem. 91, 745–749.
Kuda, T., Kosaka, M., Hirano, S., Kawahara, M., Sato, M., Kaneshima, T., Nishizawa, M., Takahashi, H., Kimura, B., 2015. Effect of sodium-alginate and laminaran on Salmonella typhimurium infection in human enterocyte-like HT-29-Luc cells and BALB/c mice. Carbohydr. Polym. 125, 113–119.
Kumar, P., Yuvakkumar, R., Vijayakumar, S., Vaseeharan, B., 2018. Cytotoxicity of phloroglucinol engineered silver (Ag) nanoparticles against MCF-7 breast cancer cell lines. Mater. Chem. Phys. 220, 402–408.
Kuznetsova, T., Besednova, N., Mamaev, A., Momot, A., Shevchenko, N., Zvyagintseva, T., 2003. Anticoagulant activity of fucoidan from brown algae Fucus evanescens of the Okhotsk Sea. Bull. Exp. Biol. Med. 136, 471–473.
Kyung, J., Kim, D., Park, D., Yang, Y.-H., Choi, E.-K., Lee, S.-P., Kim, T.-S., Lee, Y.-B., Kim, Y.-B., 2012. Synergistic anti-inflammatory effects of Laminaria japonica fucoidan and Cistanche tubulosa extract. Lab. Anim. Res. 28, 91–97.
Lane, A.L., Mular, L., Drenkard, E.J., Shearer, T.L., Engel, S., Fredericq, S., Fairchild, C.R., Prudhomme, J., Le Roch, K., Hay, M.E., 2010. Ecological leads for natural product discovery: novel sesquiterpene hydroquinones from the red macroalga Peyssonnelia sp. Tetrahedron 66, 455–461.
Larqué, E., Sabater-Molina, M., Zamora, S., 2007. Biological significance of dietary polyamines. Nutrition 23, 87–95.
Le, Q.-T., Li, Y., Qian, Z.-J., Kim, M.-M., Kim, S.-K., 2009. Inhibitory effects of polyphenols isolated from marine alga Ecklonia cava on histamine release. Process Biochem. 44, 168–176.
Lee, D.-S., Kang, M.-S., Hwang, H.-J., Eom, S.-H., Yang, J.-Y., Lee, M.-S., Lee, W.-J., Jeon, Y.-J., Choi, J.-S., Kim, Y.-M., 2008. Synergistic effect between dieckol from Ecklonia stolonifera and β-lactams against methicillin-resistant Staphylococcus aureus. Biotechnol. Bioproc. Eng. 13, 758–764.
Lee, S.H., Karadeniz, F., Kim, M.M., Kim, S.K., 2009. α-Glucosidase and α-amylase inhibitory activities of phloroglucinal derivatives from edible marine brown alga, Ecklonia cava. J. Sci. Food Agric. 89, 1552–1558.
Lee, J.Y., Kim, Y.-J., Kim, H.J., Kim, Y.-S., Park, W., 2012a. Immunostimulatory effect of laminarin on RAW 264.7 mouse macrophages. Molecules 17, 5404–5411.
Lee, M.-S., Shin, T., Utsuki, T., Choi, J.-S., Byun, D.-S., Kim, H.-R., 2012b. Isolation and identification of phlorotannins from Ecklonia stolonifera with antioxidant and hepatoprotective properties in tacrine-treated HepG2 cells. J. Agric. Food Chem. 60, 5340–5349.
Lee, S.-H., Choi, J.-I., Heo, S.-J., Park, M.-H., Park, P.-J., Jeon, B.-T., Kim, S.-K., Han, J.-S., Jeon, Y.-J., 2012c. Diphlorethohydroxycarmalol isolated from Pae (Ishige okamurae) protects high glucose-induced damage in RINm5F pancreatic β cells via its antioxidant effects. Food Sci. Biotechnol. 21, 239–246.
Lee, S.-H., Ko, S.-C., Kang, M.-C., Lee, D.H., Jeon, Y.-J., 2016. Octaphlorethol A, a marine algae product, exhibits antidiabetic effects in type 2 diabetic mice by activating AMP-activated protein kinase and upregulating the expression of glucose transporter 4. Food Chem. Toxicol. 91, 58–64.
Leiman, D., Riff, B., Morgan, S., Metz, D., Falk, G., French, B., Umscheid, C., Lewis, J., 2017. Alginate therapy is effective treatment for gastroesophageal reflux disease symptoms: a systematic review and meta-analysis. Dis. Esophagus 30, 1–8.
Li, J., Wei, Y., Du, G., Hu, Y., Li, L., 2007. Anticoagulant activities of phlorotannins from Sargassum thunbergii. Zhong Yao Xin Yao Yu Lin Chuang Yao Li 18, 191–194.
Liu, D.-Q., Mao, S.-C., Zhang, H.-Y., Yu, X.-Q., Feng, M.-T., Wang, B., Feng, L.-H., Guo, Y.-W., 2013. Racemosins A and B, two novel bisindole alkaloids from the green alga Caulerpa racemosa. Fitoterapia 91, 15–20.
Luo, M., Shao, B., Nie, W., Wei, X.-W., Li, Y.-L., Wang, B.-L., He, Z.-Y., Liang, X., Ye, T.-H., Wei, Y.-Q., 2015. Antitumor and adjuvant activity of λ-carrageenan by stimulating immune response in cancer immunotherapy. Sci. Rep. 5, 11062.
Makkar, F., Chakraborty, K., 2018. Previously undescribed antioxidative azocinyl morpholinone alkaloid from red seaweed Gracilaria opuntia with anti-cyclooxygenase and lipoxygenase properties. Nat. Prod. Res. 32, 1150–1160.
Manandhar, B., Wagle, A., Seong, S.H., Paudel, P., Kim, H.-R., Jung, H.A., Choi, J.S., 2019. Phlorotannins with potential anti-tyrosinase and antioxidant activity isolated from the marine seaweed *Ecklonia stolonifera*. Antioxidants 8, 240.
Markeb, A.A., El-Maali, N.A., Sayed, D.M., Osama, A., Abdel-Malek, M.A., Zaki, A.H., Elwanis, M.E., Driscoll, J.J., 2016. Synthesis, structural characterization, and preclinical efficacy of a novel paclitaxel-loaded alginate nanoparticle for breast cancer treatment. Int. J. Breast Canc. 2016.
Markets and Markets, 2015. Phytonutrients Market by Type (Carotenoids, Phytosterols, Flavonoids, Phenolic Compounds, and Vitamin E), Application (Food & Beverage, Feed, Pharmaceutical, and Cosmetic); FB 3557. pp. 2015 June 2015.
Maruyama, H., Tamauchi, H., Hashimoto, M., Nakano, T., 2005. Suppression of Th2 immune responses by mekabu fucoidan from Undaria pinnatifida sporophylls. Int. Arch. Allergy Immunol. 137, 289–294.
Maruyama, H., Tamauchi, H., Iizuka, M., Nakano, T., 2006. The role of NK cells in antitumor activity of dietary fucoidan from. Undaria pinnatifida 1415–1417.
Matsumoto, M., Hosokawa, M., Matsukawa, N., Hagio, M., Shinoki, A., Nishimukai, M., Miyashita, K., Yajima, T., Hara, H., 2010. Suppressive effects of the marine carotenoids, fucoxanthin and fucoxanthinol on triglyceride absorption in lymph duct-cannulated rats. Eur. J. Nutr. 49, 243–249.
McHugh, D., 2003. A Guide to the Seaweed Industry FAO Fisheries Technical Paper 441. Food and Agriculture Organization of the United Nations, Rome.
McKim Jr., J.M., Baas, H., Rice, G.P., Willoughby Sr, J.A., Weiner, M.L., Blakemore, W., 2016. Effects of carrageenan on cell permeability, cytotoxicity, and cytokine gene expression in human intestinal and hepatic cell lines. Food Chem. Toxicol. 96, 1–10.
Menshova, R.V., Ermakova, S.P., Anastyuk, S.D., Isakov, V.V., Dubrovskaya, Y.V., Kusaykin, M.I., Um, B.-H., Zvyagintseva, T.N., 2014. Structure, enzymatic transformation and anticancer activity of branched high molecular weight laminaran from brown alga Eisenia bicyclis. Carbohydr. Polym. 99, 101–109.
Moon, C., Kim, S.H., Kim, J.C., Hyun, J.W., Lee, N.H., Park, J.W., Shin, T., 2008. Protective effect of phlorotannin components phloroglucinol and eckol on radiation-induced intestinal injury in mice. Phytother Res. 22, 238–242.
MURATA, M., Nakazoe, J.-i., 2001. Production and Use of marine aigae in Japan. Jpn. Agric. Res. Q.: JARQ 35, 281–290.
Nagayama, K., Iwamura, Y., Shibata, T., Hirayama, I., Nakamura, T., 2002. Bactericidal activity of phlorotannins from the brown alga Ecklonia kurome. J. Antimicrob. Chemother. 50, 889–893.
Nagayama, K., Shibata, T., Fujimoto, K., Honjo, T., Nakamura, T., 2003. Algicidal effect of phlorotannins from the brown alga Ecklonia kurome on red tide microalgae. Aquaculture 218, 601–611.
Nakazawa, Y., Sashima, T., Hosokawa, M., Miyashita, K., 2009. Comparative evaluation of growth inhibitory effect of stereoisomers of fucoxanthin in human cancer cell lines. J. Funct. Foods. 1, 88–97.
Neetoo, H., Ye, M., Chen, H., 2010. Bioactive alginate coatings to control Listeria monocytogenes on cold-smoked salmon slices and fillets. Int. J. Food Microbiol. 136, 326–331.
Neyrinck, A.M., Mouson, A., Delzenne, N.M., 2007. Dietary supplementation with laminarin, a fermentable marine β (1–3) glucan, protects against hepatotoxicity induced by LPS in rat by modulating immune response in the hepatic tissue. Int. Immunopharmacol. 7, 1497–1506.
Nice, D., 1997. Antioxidant Based Nutraceuticals. New Technologies for Healthy Foods

and Nutraceuticals. Science Publishers, Shrewsbury, pp. 105–123.
Nishikawa, S., Hosokawa, M., Miyashita, K., 2012. Fucoxanthin promotes translocation and induction of glucose transporter 4 in skeletal muscles of diabetic/obese KK-Ay mice. Phytomedicine 19, 389–394.
Nishino, H., 1998. Cancer prevention by carotenoids. Mutat. Res. Fundam. Mol. Mech. Mutagen. 402, 159–163.
O'Shea, C., O'Doherty, J., Callanan, J., Doyle, D., Thornton, K., Sweeney, T., 2016. The effect of algal polysaccharides laminarin and fucoidan on colonic pathology, cytokine gene expression and Enterobacteriaceae in a dextran sodium sulfate-challenged porcine model. J. Nutr. Sci. 5.
Okada, Y., Ishimaru, A., Suzuki, R., Okuyama, T., 2004. A new phloroglucinol derivative from the brown alga Eisenia bicyclis: potential for the effective treatment of diabetic complications. J. Nat. Prod. 67, 103–105.
O'Sullivan, L., Murphy, B., McLoughlin, P., Duggan, P., Lawlor, P.G., Hughes, H., Gardiner, G.E., 2010. Prebiotics from marine macroalgae for human and animal health applications. Mar. Drugs 8, 2038–2064.
Paiva, L., Lima, E., Neto, A.I., Baptista, J., 2016. Isolation and characterization of angiotensin I-converting enzyme (ACE) inhibitory peptides from Ulva rigida C. Agardh protein hydrolysate. J. Funct. Foods. 26, 65–76.
Pan, S., Wang, S., Jing, L., Yao, D., 2016. Purification and characterisation of a novel angiotensin-I converting enzyme (ACE)-inhibitory peptide derived from the enzymatic hydrolysate of Enteromorpha clathrata protein. Food Chem. 211, 423–430.
Park, E., Ahn, G., Yun, J.-S., Kim, M.J., Bing, S.J., Kim, D.S., Lee, J., Lee, N.H., Park, J.W., Jee, Y., 2010. Dieckol rescues mice from lethal irradiation by accelerating hemopoiesis and curtailing immunosuppression. Int. J. Radiat. Biol. 86, 848–859.
Park, H.Y., Han, M.H., Park, C., Jin, C.-Y., Kim, G.-Y., Choi, I.-W., Kim, N.D., Nam, T.-J., Kwon, T.K., Choi, Y.H., 2011a. Anti-inflammatory effects of fucoidan through inhibition of NF-κB, MAPK and Akt activation in lipopolysaccharide-induced BV2 microglia cells. Food Chem. Toxicol. 49, 1745–1752.
Park, M.-K., Jung, U., Roh, C., 2011b. Fucoidan from marine brown algae inhibits lipid accumulation. Mar. Drugs 9, 1359–1367.
Park, H.-K., Kim, I.-H., Kim, J., Nam, T.-J., 2013. Induction of apoptosis and the regulation of ErbB signaling by laminarin in HT-29 human colon cancer cells. Int. J. Mol. Med. 32, 291–295.
Parys, S., Kehraus, S., Krick, A., Glombitza, K.-W., Carmeli, S., Klimo, K., Gerhäuser, C., König, G.M., 2010. In vitro chemopreventive potential of fucophlorethols from the brown alga Fucus vesiculosus L. by anti-oxidant activity and inhibition of selected cytochrome P450 enzymes. Phytochemistry 71, 221–229.
Pec, M.K., Moser-Thier, K., Fernández, J.J., Souto, M.L., Kubista, E., 1999. Growth inhibition by dehydrothyrsiferol-a non-Pgp modulator, derived from a marine red alga-in human breast cancer cell lines. Int. J. Oncol. 14, 739–782.
Peng, J., Yuan, J.-P., Wu, C.-F., Wang, J.-H., 2011. Fucoxanthin, a marine carotenoid present in brown seaweeds and diatoms: metabolism and bioactivities relevant to human health. Mar. Drugs 9, 1806–1828.
Pereira, R.C., Cavalcanti, D.N., Teixeira, V.L., 2000. Effects of secondary metabolites from the tropical Brazilian brown alga Dictyota menstrualis on the amphipod Parhyale hawaiensis. Mar. Ecol. Prog. Ser. 205, 95–100.
Pinto, A.M.V., Leite, J.P.G., Ferreira, W.J., Cavalcanti, D.N., Villaça, R.C., Giongo, V., Teixeira, V.L., Paixão, I.C.N.d.P., 2012. Marine natural seaweed products as potential antiviral drugs against bovine viral diarrhea virus. Rev. Bras. Farmacognosia. 22, 813–817.
Ponce, N.M., Pujol, C.A., Damonte, E.B., Flores, M.L., Stortz, C.A., 2003. Fucoidans from the brown seaweed Adenocystis utricularis: extraction methods, antiviral activity and structural studies. Carbohydr. Res. 338, 153–165.
Puglisi, M.P., Tan, L.T., Jensen, P.R., Fenical, W., 2004. Capisterones A and B from the tropical green alga Penicillus capitatus: unexpected anti-fungal defenses targeting the marine pathogen Lindra thallasiae. Tetrahedron 60, 7035–7039.
Qu, W., Ma, H., Pan, Z., Luo, L., Wang, Z., He, R., 2010. Preparation and antihypertensive activity of peptides from Porphyra yezoensis. Food Chem. 123, 14–20.
Rengasamy, K.R., Aderogba, M.A., Amoo, S.O., Stirk, W.A., Van Staden, J., 2013. Potential antiradical and alpha-glucosidase inhibitors from Ecklonia maxima (Osbeck) Papenfuss. Food Chem. 141, 1412–1415.
Rengasamy, K.R., Kulkarni, M.G., Stirk, W.A., Van Staden, J., 2014a. Advances in algal drug research with emphasis on enzyme inhibitors. Biotechnol. Adv. 32, 1364–1381.
Rengasamy, K.R., Kulkarni, M.G., Stirk, W.A., Van Staden, J., 2014b. Bioactive Metabolites and Value-Added Products from Marine Macroalgae, Seafood Processing By-Products. Springer, pp. 423–454.
Rengasamy, K.R., Kulkarni, M.G., Stirk, W.A., Van Staden, J., 2015. Eckol-a new plant growth stimulant from the brown seaweed Ecklonia maxima. J. Appl. Phycol. 27, 581–587.
Research, B., 2017. Botanical and plant-derived drugs: global markets, code - BIO022H. https://www.bccresearch.com/market-research/biotechnology/botanical-and-plant-derived-drugs-global-markets.html.
ResearchnReports, 2016. Global fucoxanthin sales market 2016 industry, analysis, research, share, growth, sales, trends, supply. Forecast to 2021 114.
Rodriguez-Amaya, D.B., 2016. Natural food pigments and colorants. Curr. Opin. Food Sci. 7, 20–26.
Romay, C., Gonzalez, R., Ledon, N., Remirez, D., Rimbau, V., 2003. C-phycocyanin: a biliprotein with antioxidant, anti-inflammatory and neuroprotective effects. Curr. Protein Pept. Sci. 4, 207–216.
Ryu, B., Li, Y., Qian, Z.-J., Kim, M.-M., Kim, S.-K., 2009. Differentiation of human osteosarcoma cells by isolated phlorotannins is subtly linked to COX-2, iNOS, MMPs, and MAPK signaling: implication for chronic articular disease. Chem. Biol. Interact. 179, 192–201.
Ryu, Y.B., Jeong, H.J., Yoon, S.Y., Park, J.-Y., Kim, Y.M., Park, S.-J., Rho, M.-C., Kim, S.-J., Lee, W.S., 2011. Influenza virus neuraminidase inhibitory activity of phlorotannins from the edible brown alga Ecklonia cava. J. Agric. Food Chem. 59, 6467–6473.
Ryu, B., Ahn, B.-N., Kang, K.-H., Kim, Y.-S., Li, Y.-X., Kong, C.-S., Kim, S.-K., Kim, D.G., 2015. Dioxinodehydroeckol protects human keratinocyte cells from UVB-induced apoptosis modulated by related genes Bax/Bcl-2 and caspase pathway. J. Photochem. Photobiol. B Biol. 153, 352–357.
Sabry, O.M., Andrews, S., McPhail, K.L., Goeger, D.E., Yokochi, A., LePage, K.T., Murray, T.F., Gerwick, W.H., 2005. Neurotoxic meroditerpenoids from the tropical marine brown alga Stypopodium flabelliforme. J. Nat. Prod. 68, 1022–1030.
Sai-kun, P., Ming-qian, Z., Dong-rui, Y., Hui, S., 2012. Preparation of ACE inhibitory peptides by enzymatic hydrolysis of protein from Enteromorpha clathrata. Food Sci. (N. Y.) 9, 034.
Samarakoon, K., Jeon, Y.-J., 2012. Bio-functionalities of proteins derived from marine algae—a review. Food Res. Int. 48, 948–960.
Sanjeewa, K.K.A., Kim, E.-A., Son, K.-T., Jeon, Y.-J., 2016. Bioactive properties and potentials cosmeceutical applications of phlorotannins isolated from brown seaweeds: a review. J. Photochem. Photobiol. B Biol. 162, 100–105.
Santos, A.O.d., Veiga-Santos, P., Ueda-Nakamura, T., Sudatti, D.B., Bianco, É.M., Pereira, R.C., Nakamura, C.V., 2010. Effect of elatol, isolated from red seaweed Laurencia dendroidea, on Leishmania amazonensis. Mar. Drugs 8, 2733–2743.
Sasaki, K., Ishihara, K., Oyamada, C., Sato, A., Fukushi, A., Arakane, T., Motoyama, M., Yamazaki, M., Mitsumoto, M., 2008. Effects of fucoxanthin addition to ground chicken breast meat on lipid and colour stability during chilled storage, before and after cooking. Asian-Australas. J. Anim. Sci. 21, 1067–1072.
Sheih, I.-C., Fang, T.J., Wu, T.-K., 2009. Isolation and characterisation of a novel angiotensin I-converting enzyme (ACE) inhibitory peptide from the algae protein waste. Food Chem. 115, 279–284.
Shibata, H., Kimura-Takagi, I., Nagaoka, M., Hashimoto, S., Aiyama, R., Iha, M., Ueyama, S., Yokokura, T., 2000. Properties of fucoidan from Cladosiphon okamuranus tokida in gastric mucosal protection. Biofactors 11, 235–245.
Shibata, T., Ishimaru, K., Kawaguchi, S., Yoshikawa, H., Hama, Y., 2008. Antioxidant activities of phlorotannins isolated from Japanese Laminariaceae. J. Appl. Phycol. 20, 705.
Shimazu, T., Kuriyama, S., Hozawa, A., Ohmori, K., Sato, Y., Nakaya, N., Nishino, Y., Tsubono, Y., Tsuji, I., 2007. Dietary patterns and cardiovascular disease mortality in Japan: a prospective cohort study. Int. J. Epidemiol. 36, 600–609.
Shimoda, H., Tanaka, J., Shan, S.J., Maoka, T., 2010. Anti-pigmentary activity of fucoxanthin and its influence on skin mRNA expression of melanogenic molecules. J. Pharm. Pharmacol. 62, 1137–1145.
Sokolova, E., Barabanova, A., Homenko, V., Solov'eva, T., Bogdanovich, R., Yermak, I., 2011. In vitro and ex vivo studies of antioxidant activity of carrageenans, sulfated polysaccharides from red algae. Bull. Exp. Biol. Med. 150, 426–428.
Sonani, R.R., Rastogi, R.P., Singh, N.K., Thadani, J., Patel, P.J., Kumar, J., Tiwari, A.K., Devkar, R.V., Madamwar, D., 2017. Phycoerythrin averts intracellular ROS generation and physiological functional decline in eukaryotes under oxidative stress. Protoplasma 254, 849–862.
Stirk, W.A., Tarkowská, D., Turečová, V., Strnad, M., Van Staden, J., 2014. Abscisic acid, gibberellins and brassinosteroids in Kelpak®, a commercial seaweed extract made from Ecklonia maxima. J. Appl. Phycol. 26, 561–567.
Suetsuna, K., Nakano, T., 2000. Identification of an antihypertensive peptide from peptic digest of wakame (Undaria pinnatifida). J. Nutr. Biochem. 11, 450–454.
Suetsuna, K., Maekawa, K., Chen, J.-R., 2004. Antihypertensive effects of Undaria pinnatifida (wakame) peptide on blood pressure in spontaneously hypertensive rats. J. Nutr. Biochem. 15, 267–272.
Sugawara, T., Matsubara, K., Akagi, R., Mori, M., Hirata, T., 2006. Antiangiogenic activity of brown algae fucoxanthin and its deacetylated product, fucoxanthinol. J. Agric. Food Chem. 54, 9805–9810.
Sugiura, Y., Matsuda, K., Yamada, Y., Nishikawa, M., Shioya, K., Katsuzaki, H., Imai, K., Amano, H., 2006. Isolation of a new anti-allergic phlorotannin, phlorofucofuroeckol-B, from an edible brown alga, Eisenia arborea. Biosci. Biotechnol. Biochem. 70, 2807–2811.
Suzuki, M., Yamada, H., Kurata, K., 2002. Dictyterpenoids A and B, two novel diterpenoids with feeding-deterrent activity from the Brown alga dilophus o kamurae. J. Nat. Prod. 65, 121–125.
Swanson, D., Block, R., Mousa, S.A., 2012. Omega-3 fatty acids EPA and DHA: health benefits throughout life. Adv. Nutr. 3, 1–7.
Synytsya, A., Kim, W.-J., Kim, S.-M., Pohl, R., Synytsya, A., Kvasnička, F., Čopíková, J., Park, Y.I., 2010. Structure and antitumour activity of fucoidan isolated from sporophyll of Korean brown seaweed Undaria pinnatifida. Carbohydr. Polym. 81, 41–48.
Takahashi, S., Matsunaga, T., Hasegawa, C., Saito, H., Fujita, D., Kiuchi, F., Tsuda, Y., 1998. Martefragin A, a novel indole alkaloid isolated from red alga, inhibits lipid peroxidation. Chem. Pharmaceut. Bull. 46, 1527–1529.
Takahashi, Y., Daitoh, M., Suzuki, M., Abe, T., Masuda, M., 2002. Halogenated metabolites from the new Okinawan red alga Laurencia yonaguniensis. J. Nat. Prod. 65, 395–398.
Tarhouni-Jabberi, S., Zakraoui, O., Ioannou, E., Riahi-Chebbi, I., Haoues, M., Roussis, V., Kharrat, R., Essafi-Benkhadir, K., 2017. Mertensene, a halogenated monoterpene, induces G2/M cell cycle arrest and caspase dependent apoptosis of human colon adenocarcinoma HT29 cell line through the modulation of ERK-1/-2, AKT and NF-κB signaling. Mar. Drugs 15, 221.
Teruya, T., Konishi, T., Uechi, S., Tamaki, H., Tako, M., 2007. Anti-proliferative activity of oversulfated fucoidan from commercially cultured Cladosiphon okamuranus TOKIDA in U937 cells. Int. J. Biol. Macromol. 41, 221–226.
Thomes, P., Rajendran, M., Pasanban, B., Rengasamy, R., 2010. Cardioprotective activity of Cladosiphon okamuranus fucoidan against isoproterenol induced myocardial infarction in rats. Phytomedicine 18, 52–57.

Tian, T., Chang, H., He, K., Ni, Y., Li, C., Hou, M., Chen, L., Xu, Z., Chen, B., Ji, M., 2019. Fucoidan from seaweed *Fucus vesiculosus* inhibits 2, 4-dinitrochlorobenzene-induced atopic dermatitis. Int. Immunopharmacol. 75, 105823.
Trinchero, J., Ponce, N., Córdoba, O.L., Flores, M.L., Pampuro, S., Stortz, C.A., Salomón, H., Turk, G., 2009. Antiretroviral activity of fucoidans extracted from the brown seaweed Adenocystis utricularis. Phytother Res. 23, 707–712.
Tseng, C., 2001. Algal biotechnology industries and research activities in China. J. Appl. Phycol. 13, 375–380.
Tsuji, R., Hoshino, K., Noro, Y., Tsuji, N., Kurokawa, T., Masuda, T., Akira, S., Nowak, B., 2003. Suppression of allergic reaction by λ-carrageenan: toll-like receptor 4/MyD88-dependent and-independent modulation of immunity. Clin. Exp. Allergy 33, 249–258.
Vairappan, C.S., 2004. Antibacterial activity of major secondary metabolites found in four species of edible green macroalgae genus Caulerpa. Asian J. Microbiol. Biotechnol. Environ. Sci. 6, 197–201.
Vidal, J., Laurent, D., Kabore, S., Rechencq, E., Boucard, M., Girard, J., Escale, R., Rossi, J., 1984. Caulerpin, caulerpicin, *Caulerpa scalpelliformis*: comparative acute toxicity study. Bot. Mar. 27, 533–538.
Wang, G., Tang, W., Bidigare, R.R., 2005. Terpenoids as Therapeutic Drugs and Pharmaceutical Agents, Natural Products. Springer, pp. 197–227.
Wang, B.-G., Gloer, J.B., Ji, N.-Y., Zhao, J.-C., 2013. Halogenated organic molecules of Rhodomelaceae origin: chemistry and biology. Chem. Rev. 113, 3632–3685.
Wang, L., Wang, X., Wu, H., Liu, R., 2014. Overview on biological activities and molecular characteristics of sulfated polysaccharides from marine green algae in recent years. Mar. Drugs 12, 4984–5020.
Wang, T., Gu, Q., Zhao, J., Mei, J., Shao, M., Pan, Y., Zhang, J., Wu, H., Zhang, Z., Liu, F., 2015. Calcium alginate enhances wound healing by up-regulating the ratio of collagen types I/III in diabetic rats. Int. J. Clin. Exp. Pathol. 8, 6636.
Watanabe, K., Miyakado, M., Ohno, N., Okada, A., Yanagi, K., Moriguchi, K., 1989. A polyhalogenated insecticidal monoterpene from the red alga, Plocamium telfairiae. Phytochemistry 28, 77–78.
Watanabe, K., Umeda, K., Kurita, Y., Takayama, C., Miyakado, M., 1990. Two insecticidal monoterpenes, telfairine and aplysiaterpenoid A, from the red alga Plocamium telfairiae: structure elucidation, biological activity, and molecular topographical consideration by a semiempirical molecular orbital study. Pestic. Biochem. Physiol. 37, 275–286.
Wei, R., Lee, M.-S., Lee, B., Oh, C.-W., Choi, C.-G., Kim, H.-R., 2016. Isolation and identification of anti-inflammatory compounds from ethyl acetate fraction of Ecklonia stolonifera and their anti-inflammatory action. J. Appl. Phycol. 28, 3535–3545.
Weiner, M.L., 1991. Toxicological properties of carrageenan. Agents Actions 32, 46–51.
Wessels, M., König, G.M., Wright, A.D., 1999. A new tyrosine kinase inhibitor from the marine brown alga Stypopodium zonale. J. Nat. Prod. 62, 927–930.
Woo, M.N., Jeon, S.M., Shin, Y.C., Lee, M.K., Kang, M., Choi, M.S., 2009. Anti-obese property of fucoxanthin is partly mediated by altering lipid-regulating enzymes and uncoupling proteins of visceral adipose tissue in mice. Mol. Nutr. Food Res. 53, 1603–1611.
Yamamoto, A., Itoh, T., Nasu, R., Kajiwara, E., Nishida, R., 2013. Sodium alginate inhibits methotrexate-induced gastrointestinal mucositis in rats. Biol. Pharm. Bull. 36, 1528–1534.
Yamamoto, A., Itoh, T., Nasu, R., Nishida, R., 2014. Sodium alginate ameliorates indomethacin-induced gastrointestinal mucosal injury via inhibiting translocation in rats. World J. Gastroenterol.: WJG 20, 2641.
Yang, Y.-I., Shin, H.-C., Kim, S.H., Park, W.-Y., Lee, K.-T., Choi, J.-H., 2012. 6, 6′-Bieckol, isolated from marine alga Ecklonia cava, suppressed LPS-induced nitric oxide and PGE2 production and inflammatory cytokine expression in macrophages: the inhibition of NFκB. Int. Immunopharmacol. 12, 510–517.
Yang, H., Liu, D.-Q., Liang, T.-J., Li, J., Liu, A.-H., Yang, P., Lin, K., Yu, X.-Q., Guo, Y.-W., Mao, S.-C., 2014. Racemosin C, a novel minor bisindole alkaloid with protein tyrosine phosphatase-1B inhibitory activity from the green alga Caulerpa racemosa. J. Asian Nat. Prod. Res. 16, 1158–1165.
Yang, P., Liu, D.-Q., Liang, T.-J., Li, J., Zhang, H.-Y., Liu, A.-H., Guo, Y.-W., Mao, S.-C., 2015. Bioactive constituents from the green alga Caulerpa racemosa. Bioorg. Med. Chem. 23, 38–45.
Yang, Y.-I., Woo, J.-H., Seo, Y.-J., Lee, K.-T., Lim, Y., Choi, J.-H., 2016. Protective effect of brown alga phlorotannins against hyper-inflammatory responses in lipopolysaccharide-induced sepsis models. J. Agric. Food Chem. 64, 570–578.
Yoon, M., Cho, S., 2018. Triphlorethol A, a dietary polyphenol from seaweed, decreases sleep latency and increases non-rapid eye movement sleep in mice. Mar. Drugs 16, 139.
Yu, P., Sun, H., 2014. Purification of a fucoidan from kelp polysaccharide and its inhibitory kinetics for tyrosinase. Carbohydr. Polym. 99, 278–283.
Zaharudin, N., Salmeán, A.A., Dragsted, L.O., 2018. Inhibitory effects of edible seaweeds, polyphenolics and alginates on the activities of porcine pancreatic α-amylase. Food Chem. 245, 1196–1203.
Zhao, X., X, C., Cai, Y., Wang, D., Fang, Y.U., 2005. Study of antioxidant activities of fucoidan from Laminaria japonica. High Technol. Lett. 11, 91–94.
Zhao, X., Zhang, S., An, C., Zhang, H., Sun, Y., Li, Y., Pu, X., 2015. Neuroprotective effect of fucoxanthin on β-amyloid-induced cell death. J. Chin. Pharm. Sci. 24, 467–474.
Zhen, A.X., Hyun, Y.J., Piao, M.J., Fernando, P.D.S.M., Kang, K.A., Ahn, M.J., Yi, J.M., Kang, H.K., Koh, Y.S., Lee, N.H., 2019. Eckol inhibits particulate matter 2.5-induced skin keratinocyte damage via MAPK signaling pathway. Mar. Drugs 17, 444.
Zhou, G., Sun, Y., Xin, H., Zhang, Y., Li, Z., Xu, Z., 2004. In vivo antitumor and immunomodulation activities of different molecular weight lambda-carrageenans from Chondrus ocellatus. Pharmacol. Res. 50, 47–53.
Zhou, G., Sheng, W., Yao, W., Wang, C., 2006. Effect of low molecular λ-carrageenan from Chondrus ocellatus on antitumor H-22 activity of 5-Fu. Pharmacol. Res. 53, 129–134.