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Review

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Medicinal and Pharmaceutical Applications of Seaweeds

Mostafa El-Sheekh[(1)#], Alaa A. Fathy [(2,3)], Hani Saber[(4)], Abdullah A. Saber[(5)]
[(1)]Botany Department, Faculty of Science, Tanta University, Tanta 31527, Egypt; [(2)]Botany and Microbiology Department, Faculty of Science, Alexandria University, Alexandria, Egypt; [(3)]Department of Biology, College of Sciences and Arts, Qassim University, Unaizah, Saudi Arabia; [(4)]Botany and Microbiology Department, Faculty of Science, South Valley University, Qena 83523, Egypt; [(5)]Botany Department, Faculty of Science, Ain Shams University, Cairo 11566, Egypt.

SEAWEEDS are an indispensable natural source of bioactive metabolites characterized by multifunctional biomedical and pharmaceutical applications. For instance, seaweed-derived polyphenolics are potentially distinguished by their pivotal antioxidant effects in the treatment and/or prevention of several diseases. Moreover, pigments, fatty acids, terpenes, and terpenoids have been characterized by their potent antioxidant, anti-inflammatory, and anti-obesity properties, besides their highly effective hepatoprotective activities. Several seaweed-extracted polysaccharides, such as alginates, ulvans, and carrageenans, have been reported to exert various medicinal effects such as immunoinflammatory, antioxidant, antitumor, antiviral, and anticoagulant activities. Furthermore, seaweed-derived minerals have been widely utilized as food supplements and cosmeceuticals. This review discusses and emphasizes the biomedical and pharmaceutical applications of seaweeds and the future perspectives for their large-scale applications to develop novel, safe, and high-valued pharmaceutical constituents.

Keywords: Bioactive metabolites, Medicinal and pharmaceutical uses, Natural therapy, Seaweeds.

Introduction

Seaweeds are considered an invaluable source of potential natural bioactive metabolites exerting several biomedical and pharmaceutical effects, in addition to their valuable nutraceutical and other multifunctional applications (e.g., Pangestuti & Kim, 2011; Catarino et al., 2018; El-Sheekh et al., 2020; Ismail et al., 2020a; Metwally et al., 2020; Rosa et al., 2020; Ibrahim et al., 2022). Although there is extensive pharmaceutical research on different species of seaweeds, particularly in Europe, Asia, and North America, further in-depth in vitro and in vivo investigations on seaweed-derived bioactive compounds are required to identify and characterize their novelty and the biomedical potential of hidden bioactive constituents. Moreover, people are currently showing high interest in valuable pharmaceuticals of natural origins, such as seaweeds, to minimize the risks and immense, diverse effects associated with the administration of chemical analogs (Cornish & Garbary, 2010; Carocho et al., 2014, 2015; García-Poza et al., 2022). The medical and pharmaceutical benefits of seaweeds are well known since several centuries, and they have been commonly used in folk medicine (Liu et al., 2012). They are also utilized as natural ingredients in several recipes and supplements to treat a broad spectrum of ailments and illnesses (Tannoury et al., 2017; Cotas et al., 2020).

Pigments, fatty acids (saturated and polyunsaturated), polyphenols, terpenes, polysaccharides, amino acids and proteins, vitamins, sterols, and minerals are some of the natural compounds present in seaweeds distinguished on the basis of highly important biomedical and pharmaceutical values. The chemical structures, contents, and biological

#Corresponding author email: mostafaelsheikh@science.tanta.edu.eg
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effects of these compounds vary significantly within the different taxonomic algal groups and also the included species (e.g., Stengel et al., 2011; Al-Saif et al., 2014; Michalak & Chojnacka, 2015; Korzeniowska et al., 2018; Sathasivam et al., 2019; Rushdi et al., 2022). These natural bioactive compounds attract significant consumer attention due to their lack of toxicity, excellent biocompatibility, and biodegradability into environmentally harmless byproducts (García-Poza et al., 2022). Considering the context of rapid advancements in technology and the development of seaweed-derived pharmaceutical products, we believe that more novel and interestingly valuable compounds will be discovered in the future. This review summarizes the pharmaceutical and therapeutic applications of the abovementioned bioactive metabolites and compounds present in seaweeds.

Polyphenolics (phenolic acids and flavonoids)

Polyphenols are one of the most known natural bioactive compounds for their antioxidant potential. They are found in several phytoplankton species (Agatonovic-Kustrin & Morton, 2018; Zolotareva et al., 2019; Pereira, 2020; Ibrahim et al., 2022). The antioxidant activity of polyphenolic compounds depends primarily on (1) Combining with free radicals, stabilizing, and deactivating them, (2) Regulating the expression and metabolic pathways of certain enzymes involved in balancing the intracellular antioxidant levels, and (3) Chelating metal ions such as copper and iron through their powerful abilities to donate hydrogen atoms and/or electrons (Li et al., 2011; Nimse & Pal, 2015; Ismail et al., 2020b). All biological systems contain active free radicals, among which the most common are nitrogen and oxygen species that exert oxidative effects. This type of stress is mediated through programmed actions of apoptotic enzymes and proinflammatory cytokines, causing numerous metabolic disorders (Collin, 2019). These free radicals may be produced in response to different external environmental drivers such as pollution, tobacco smoking, pesticides, alcohol, industry-derived chemicals, and certain drugs such as paracetamol, halothane, and UV irradiation or generated inside the human body through various metabolic pathways organized in peroxisomes, mitochondria, endoplasmic reticulum, and phagocytic cells (Abrescia & Golino, 2005; Pham-Huy et al., 2008; Phaniendra et al., 2015; Collin, 2019). They exert a negative impact on the functionality of several significant biological molecules, such as proteins, carbohydrates, lipids, and nucleic acids, by destroying their typical structures, followed by an alteration in the intracellular redox status and subsequent incidence of oxidative stress. The most common signs associated with oxidative stress include overexpression of proinflammatory markers and decreases in the levels of cellular enzymes, especially those possessing antioxidant activity, such as catalase, superoxide dismutase, and peroxidases, and overexpression of proinflammatory markers, which eventually induce numerous diseases such as inflammation, hepatotoxicity, cancers, ischemia, asthma, AIDS, gastric ulcers, skin disorders, aging, emphysema, atherosclerosis, cardiovascular disorders, hemochromatosis, and neurological disorders (Abrescia & Golino, 2005; Pham-Huy et al., 2008; Muriel, 2009; Ríos-Arrabal et al., 2013; Phaniendra et al., 2015; Hayyan et al., 2016; Boukhenouna et al., 2018; Liguori et al., 2018; Malekmohammad et al., 2019).

Polyphenolics are classified into two subgroups, phenolic acids and flavonoids, on the basis of the structure of their carbon skeletons and functional groups. Polyphenols comprise a diverse group of natural phytochemicals containing more than 8000 well-known compounds (Abbas et al., 2017; Zolotareva et al., 2019; Shanab & Shalaby, 2021). Algal extracts have been documented as an indispensable resource of valuable phenolics and flavonoids with health-promoting benefits in terms of their potent antioxidant and free radical scavenging properties (Carocho et al., 2015; Wells et al., 2017; Catarino et al., 2018; Leandro et al., 2020; Semaida et al., 2022).

Members of Phaeophyta contain higher levels of phenolic and flavonoid compounds than species of Chlorophyta (Moubayed et al., 2017; Korzeniowska et al., 2018). In particular, phlorotannins (Fig. 1) are considered as a primarily predominant marine-exclusive polyphenol in Phaeophyceae (Lopes et al., 2016; Catarino et al., 2017; Rosa et al., 2020), and bromophenols and other common phenolics and flavonoids constitute the primary antioxidant bulk of polyphenols in green and red macroalgae (Al-Saif et al., 2014; Korzeniowska et al., 2018; Ibrahim et al., 2021). However, the different types of polyphenols are qualitatively and quantitatively affected by the time of algal sampling and geographical

distribution, quality of the solvents used, the protocols followed, and the environmental conditions, in particular the nutrients and pollutants in the investigated habitats (Pérez et al., 2016, Shannon & Abu-Ghannam, 2016; Mansur et al., 2020). Phlorotannins are biopolymers linked to each other and have molecular sizes ranging from 126 to 650kD (Li et al., 2011). These natural polymers are formulated in the acetate–malonate (polyketide) pathway (Martínez & Castañeda, 2013) and may be present in free forms or in combination with other cell wall components, constituting 5%–30% of algal dry weight (Korzeniowska et al., 2018). The physiological activity of phlorotannins primarily depends on the degree of their polymerization. This interesting group of polyphenols is also classified as potent chelators of heavy metals and can control the metabolic pathways of several enzymes. Table 1 lists some types of phlorotannins, their original algal sources, and pivotal pharmaceutical effects.

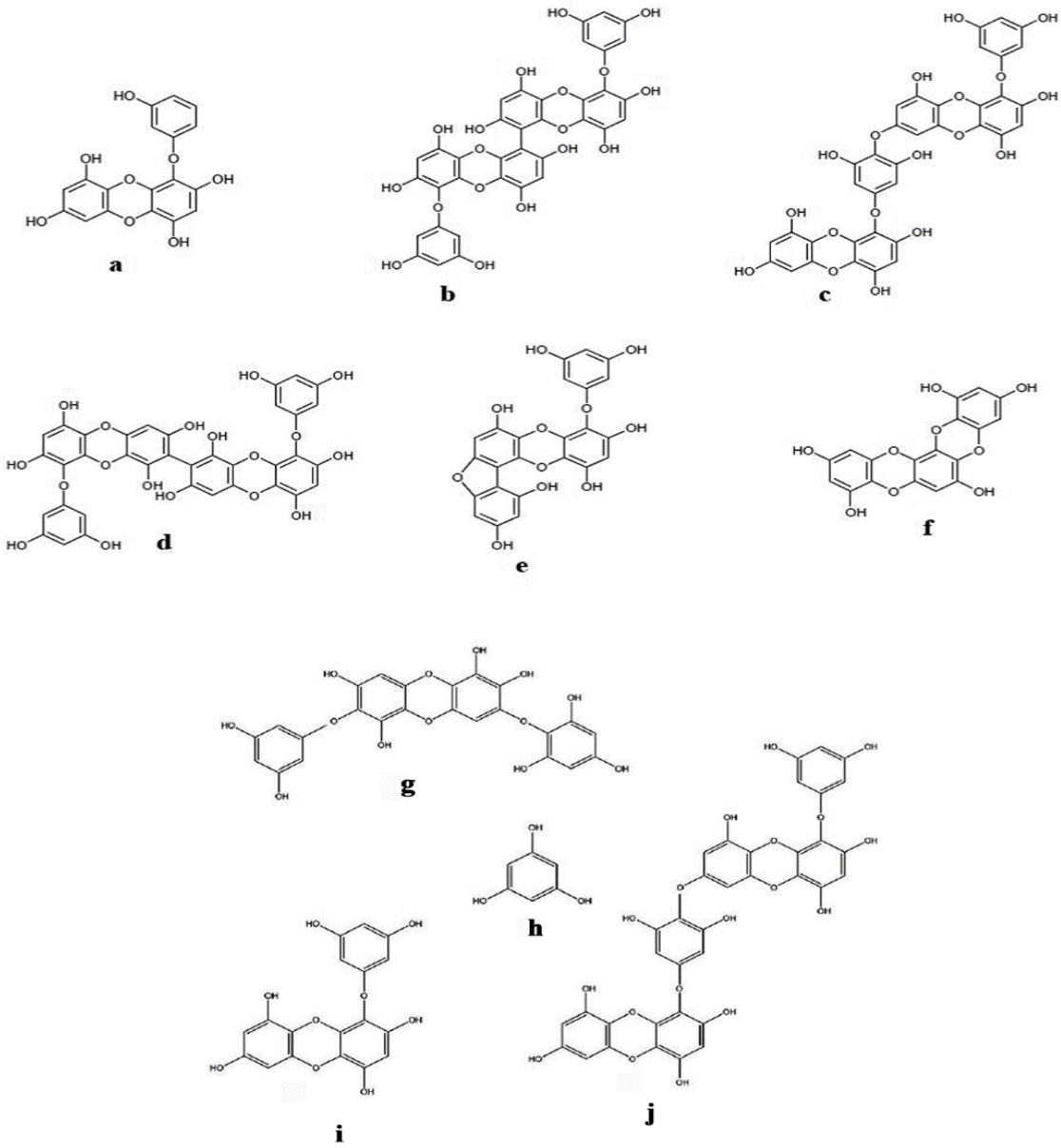

Fig. 1. Chemical compositions of some pharmaceutically important phlorotannins: (a) Eckol, (b) 6,6′-bieckol, (c) Dieckol, (d) 8,8′-bieckol, (e) Fucofuroeckol-A, (f) Dioxynodehydroeckol, (g) Diphlorethohydroxycarmalol, (h) Phloroglucinol, (i) Eckol, (j) Dieckol (Thomas & Kim, 2013)

TABLE 1. Some interesting phlorotannins with description of their algal origins and different pharmaceutical activities

Phlorotannins	Seaweeds	Potential biomedical effects	References
Eckol	*Ecklonia cava, E. kurome, E. stolonifera, Eisenia arborea* & *E. bicyclis*	Antihypertensive, antimicrobial, antioxidant, antiallergic, enzyme inhibitory action, anti-inflammatory, anticancer, photoprotective skin therapy, and anti-diabetic	Eom et al. (2012), Thomas & Kim (2013), Lopes et al. (2016), Manandhar et al. (2019), and Besednova et al. (2022)
Phloroglucinol	*Ecklonia cava, E. kurome, E. stolonifera, Eisenia bicyclis* & *lshige okamurae*	Antimicrobial, antihypertensive, antioxidant, anticoagulant, skin whitening and anti-diabetic	Li et al. (2011), Eom et al. (2012), Thomas & Kim (2013), Lopes et al. (2016), and Catarino et al. (2022)
6,8′ -bieckol	*Eisenia arborea*	Antiallergic and anti-inflammatory	Besednova et al. (2022)
Phlorofucofuroeckol	*Eisenia arborea, E. bicyclis, Ecklonia cava, E. kurome* & *E. stolonifera*	Antimicrobial, antiallergic, enzyme inhibitory, anticancer, anti-inflammatory, anti-diabetic, and prevention of noise-induced hearing loss	Li et al. (2011), Lopes et al. (2016), and Woo et al. (2021)
2-phloroeckol	*Ecklonia stolonifera*	Antidiabetic and chemo-preventive agent against UVB-induced skin cancer	Lopes et al. (2016) and Manandhar et al. (2019)
7-phloroeckol	*Eisenia bicyclis* & *Ecklonia cava*	Cosmeceutical, antimicrobial, and antiviral	Thomas & Kim (2013), Manandhar et al. (2019)
Dioxinodehydroeckol	*Eisenia bicyclis, Ecklonia cava* & *E. stolonifera*	Anti-diabetic, anti-adipogenic, antimicrobial, and anticancer	Kim & Kong (2010), Li et al. (2011), and Lopes et al. (2016)

Considerable literature has already documented the biomedical and pharmaceutical advantages of phlorotannins. They can also be used as cosmeceuticals, dietary supplements, and nutraceuticals. Shibata et al. (2002) demonstrated the in vitro inhibitory characterization of some phlorotannins extracted from *Eisenia bicyclis* (presently considered as a synonym of *Ecklonia bicyclis*) and *Ecklonia kurome* against the physiological activity of hyaluronidase. This enzyme largely contributes to the initiation of cancers and inflammatory diseases and causes diverse allergic reactions. They emphasized that these phlorotannins are primarily distinguished by their highly effective inhibitory activities on hyaluronidase compared with common inhibitors such as sodium cromoglycate (DSCG) and catechins.

Furthermore, Shibata et al. (2002) emphasized that 8,8′-bieckol has the strongest inhibition against hyaluronidase, about seven times more potent than DSCG, confirming its potential therapeutic application in the production of valuable natural anti-allergic and anticancer drugs from the edible brown seaweeds *E. bicyclis* and *E. kurome*. Sugiura et al. (2006b) suggested that methanolic extracts of Phaeophycean species collected from the Ise-Shima region of Japan distinctly have significant amounts of phlorotannins with noteworthy anti-allergic activities. Later, the interesting novel anti-allergic phlorotannin, phlorofucofuroeckol-B, was discovered in *E. arborea* (Sugiura et al., 2006a). Recently, Yu et al. (2015) tested the anti-allergic activities of ethanolic extracts of the brown seaweeds *Laminaria japonica* (nowadays regarded as a synonym of *Saccharina japonica*) and *Scytosiphon* sp., and the red macroalga *Porphyra* sp. The highest total polyphenol content was detected in *Scytosiphon* sp., and its anti-allergic activity (IC_{50}) using the hyaluronidase inhibition approach was found to be 0.67mg/mL. This concentration was significantly higher than that

of the commonly used anti-allergic medication disodium cromoglycate (IC_{50}= 1.13mg/mL), thus, *Scytosiphon* sp. has been proposed as a promising natural source of polyphenols with alleviating allergy potential. Antitumor and anticancer properties of polyphenols from brown algae have also been extensively investigated. In the evaluation of the algal cytotoxic potential of *Fucus vesiculosus*, the most predominant brown seaweed in the Baltic Sea, against human pancreatic cancer cells using a bioassay-guided fractionation approach, Zenthoefer et al. (2017) attributed the antioxidant and pharmaceutical effects of its extracts to two similar bioactive polyphenolic compounds belonging to phlorotannins. Kim et al. (2015) also documented the inhibitory activity of phloroglucinol towards breast cancer cells by hampering the epithelial-mesenchymal cell transition and without inducing any cytotoxic symptoms. Mansur et al. (2020) recently proposed in vitro the potency of several polyphenols extracted from *Cystoseira tamariscifolia* (now identified as *Carpodesmia tamariscifolia*) against certain types of human cancer such as leukemia and prostate cancer. As regards anticancer characteristics of green macroalgae, Kosanić et al. (2015) investigated the anticancer potential of extracts of two chlorophycean species, *Ulva lactuca* and *Enteromorpha intestinalis* (currently regarded as a synonym of *Ulva intestinalis*), against four human cancer cell lines Fem-x, A549, LS174, and K562, and highlighted that the latter algal species exhibited the strongest cytotoxic activity against all the cell lines. In addition, they related this highly effective activity to phenols and flavonoids. Members of Rhodophyta also have interesting anticancer characterizations in virtue of their potent polyphenols. Zubia et al. (2009) examined the antioxidant activities of 24 different Rhodophyte species sampled from the Brittany coasts of France and found that *Asparagopsis armata, Brongniartella byssoides* (nowadays classified as *Vertebrata byssoides*), and *Heterosiphonia plumosa* have the strongest cytotoxicities against Daudi and Jurkat human cancer cell lines due to their high total phenolic contents and remarkable radical-scavenging activities.

Regarding their anti-inflammatory effects, phlorotannins-rich brown macroalgae, such as *Ascophyllum nodosum* and *Fucus vesiculosus*, are well characterized by their significant anti-inflammatory properties. According to Dutot et al. (2012), phlorotannins isolated from *Ascophyllum nodosum* are primarily responsible for reductions in lipopolysaccharide levels, which has been shown to induce the expression of tumor necrosis factor and interleukin 6 in U937 macrophages. Yuan et al. (2019) also confirmed that polyphenol-rich ethanolic and ethyl acetate extracts of *Sargassum muticum* exert excellent antioxidant and anti-inflammatory effects against UV-B-irradiated HaCaT cells and 2,2′-azobis-2-methyl-propanimidamide (AAPH)-induced Vero cells. Subsequently, this brown seaweed has been recommended for developing compounds of tremendous biomedical and medicinal importance.

In the context of skin diseases, phlorotannins such as eckol and dieckol isolated from *Ecklonia stolonifera* possess the ability to positively regulate the gene expression of collagenase involved in dermal collagen degradation (Joe et al., 2006). Such findings have supported the nutraceutical benefits of this brown alga and its highly valuable medicinal properties for skincare. The production of melanin pigment is controlled by a key enzyme known as tyrosinase, and natural algal inhibitors of this enzyme could be used in pharmaceutical and cosmetic industries to prevent and/or treat excessive production of melanin. In this regard, one study investigated the in vitro antityrosinase and in vivo antimelanogenic activities of the methanolic extracts of three red macroalgae, *Digenea simplex, Laurencia papillosa,* and *L. paniculata* (the last two species are currently known as *Palisada papillosa* and *P. paniculata,* respectively) from the Persian Gulf (Namjoyan et al., 2019). The latter *Laurencia* species are the first to be described for their remarkable antityrosinase activity (43.18%) and the ability to decrease total melanin content by 47.27% in zebrafish (in vivo model tested), indicating that such ability supports their use as whitening agents to treat hyperpigmentation diseases. The antidiabetic activities of phlorotannins have also been evaluated in the extracts of several phaeophycean algal species such as *Ascophyllum nodosum, Fucus distichus, F. vesiculosus, Ecklonia cava, E. stolonifera, Ishige okamurae, Padina pavonica, Sargassum aquifolium, S. polycystum, S. ringgoldianum, Spatoglossum asperum*, and *Turbinaria ornata* (Lopes et al., 2016; Catarino et al., 2017; Rushdi et al.,

2020). In particular, the phenolic extracts of *A. nodosum* and *Fucus* spp., for instance, were found to exert favorable effects in treating type 2 diabetes mellitus by inhibiting α-amylase and α-glucosidase enzymes (Thilagam et al., 2013). It was observed that 50% ethanolic extract of *A. nodosum* distinctly inhibited α-glucosidase activity, which was associated with its valuable content of phlorotannins (Zhang et al., 2007). Another study by Liu et al. (2016) compared the inhibitory activities of *Fucus vesiculosus* and *A. nodosum* with those of the standard antidiabetic drug "acarbose". Results showed that the ethanolic and acetone extracts of *A. nodosum* exhibited IC_{50} concentrations of 4.4 and 0.34µg/mL, respectively, whereas those of *F. vesiculosus* exhibited IC_{50} concentrations of 8.9 and 0.72µg/mL, respectively, compared to an IC_{50} concentration of 720µg/mL for acarbose. Therefore, they confirmed—that these two seaweeds are primarily distinguished by their potent inhibitory activities that are approximately 160–2000 times much stronger than that of acarbose. Finally, Ohta et al. (2002) also reported similar observations where they highlighted that 70% methanolic extract of phlorotannins-rich *Pelvetia siliquosa* (currently identified as *Silvetia siliquosa*) exerted a remarkable inhibitory effect against α-glucosidase.

Regarding the biological control of several bacterial diseases using polyphenols of algal origin, Nagayama et al. (2002), for example, investigated the antimicrobial activity of phlorotannins extracted from *Ecklonia kurome* and reported a broad spectrum of effectiveness against 25 strains of foodborne pathogenic bacteria, 9 strains of methicillin-resistant *Staphylococcus aureus*, and 1 strain of *Streptococcus pyogenes*. Among the bacterial strains tested, *Campylobacter* spp. have been identified as the most susceptible strains to such phlorotannins. The bactericidal characteristics of these phlorotannins have also been distinguished by their much higher antibacterial effects than those of standard catechins. Kim et al. (2018) also detected the antilisterial potential of phlorotannins extracted from the brown seaweed *Eisenia bicyclis* against the gram-positive bacterium *Listeria monocytogenes*. Similarly, Moubayed et al. (2017) suggested the major functional constituents present in *Sargassum latifolium* and *S. platycarpum* that are characterized by their excellent antimicrobial potential of primarily phenolic nature. Recently, El-Sheekh et al. (2020) demonstrated the antibacterial potential of several phaeophycean species, including *Cystoseira myrica, Padina boergesenii*, and *Sargassum cinereum,* against several gram-positive and gram-negative species. They concluded that the inhibitory activities of the antibacterial compounds of these seaweeds are most likely related to the synergistic effect of their pivotal natural compounds, including polyphenols. They emphasized that chloroform is the most efficient solvent for extracting interesting antibacterial polyphenols, such as the flavonoids rutin, quercetin, and kaemferol, from these algal taxa, followed by ethanol, petroleum ether, and water. Moreover, they suggested that *Gracilaria dendroides* had the most potent activity against all the investigated bacterial strains, followed by *Ulva reticulata* and *Dictyota ciliolata.*

Polyphenols derived from seaweeds have been extensively characterized by their potent molluscicidal activities. Within their recently published data on the in vivo experiment performed on the possible molluscicidal activity of the ethanolic extract of *Cystoseira barbata* (currently named as *Treptacantha barbata*) against the host snails *Biomphalaria alexandrina* and their related disease schistosomiasis. Ibrahim & Abdel-Tawab (2020) emphasized that this polar seaweed extract could be a powerful molluscicidal agent against *B. alexandrina* snails at a dose of LC_{50} 175.04mg.L^{-1} after the exposure for 48h. Furthermore, they identified polyphenols of this seaweed extract using high-performance liquid chromatography analysis and characterized forty different phenolic and flavonoid compounds. Among these bioactive polyphenols, acacetin, kaempferol 3-(2-p-comaroyl) glucose, and rosmarinic were the most predominant flavonoids with concentration values of 1677.17, 462.66, 128.14ppm, respectively, whilst vanillic and benzoic acids constituted the major phenolics with concentration values of 139 and 128ppm, respectively. They reasoned that this algal polyphenols-derived molluscicidal activity is most likely due to their detergent effects on the epithelial tissues of the snails and also by inhibiting their detoxification system.

Terpenes and terpenoids

Terpenes are a major secondary metabolite

produced by several seaweeds, which are well known for their high potential functioning in the treatment of numerous diseases (Fernando et al., 2016). Chemically, they are hydrocarbons synthesized from the building blocks of five-carbon "isoprene units", which are attached in a specific manner. Terpenoids are terpene-derived compounds with specifically modified chemical groups, such as the presence of oxidized methyl groups at various positions, in addition to other certain functional groups (Balboa et al., 2013). However, these two related terms are most often used interchangeably. Terpenoids are categorized into hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes, tetraterpenes, and polyterpenes (Singh & Sharma, 2015). According to Bedoux et al. (2014) and Yang et al. (2015), Chlorophyceae species typically contain cyclic and linear sesquiterpenes, diterpenes, and triterpenes, whereas Rhodophyceae members are distinguished by a high structural composition of halogenated terpenes, with polyhalogenated monoterpenes being primarily involved in several antimicrobial treatments. Furthermore, Gaysinski et al. (2015) and Joung et al. (2017) emphasized that brown macroalgae are importantly excellent resource-rich in terpenoids, particularly diterpenes and meroditerpenes, characterized by ecologically and biologically different structures compared with their similar analogs of terrestrial plants. In general, seaweed-derived terpenoids have a wide niche of potential biomedical and pharmaceutical applications.

Lim et al. (2019) showed that the brown marine alga *Sargassum serratifolium* is a promising antioxidant, containing significant amounts of the meroterpenoids sargahydroquinoic acid, sargaquinoic acid, and sargachromanol, and hence could be used in the prevention of various diseases caused by oxidative stress, as well as in food production as nutraceutical supplements. Joung et al. (2017) had confirmed that these meroterpenoids are well distinguished by their anti-inflammatory properties. In an in vivo study conducted by Kwon et al. (2018) to evaluate the effects of *S. serratifolium* ethanolic extract rich in the aforementioned meroterpenoids on obesity in high-fat-diet–fed mice, it was observed that supplementing these valuable algal-derived terpenoids distinctly reduced high-fat-diet–induced obesity and hepatic steatosis without any noticeable changes in food consumption, improved blood lipid profiles, and increased circulating adiponectin levels. The lipid-reducing activities and antiobesity characteristics exerted by these meroterpenoids were attributed to their potent pharmaceutical effects on activating the signaling pathways of AMPK-related fatty acid oxidation and suppressing the signaling crosstalks of SREBP1c-related lipogenesis in the liver and adipose tissues. In another more interesting study conducted by Lim et al. (2018), they concluded that *S. serratifolium*-extracted terpenoid compounds could be considered as excellent hepatoprotective agents against oxidative damage mediated by the prooxidant tert-butyl hydroperoxide in the human hepatoma cell line HepG2. They observed a significant increase in the activity of the endogenous antioxidant enzymes superoxide dismutase and catalase, as well as a noticeable increase in the metabolic biosynthesis of some other essential detoxifying enzymes with hepatoprotective properties, and attributed all these significantly positive cascades to the meroterpenoids of *S. serratifolium*. Shimizu et al. (2015) emphasized that the novel sesquiterpene "zonarol" isolated from the cosmopolitan brown seaweed *Dictyopteris undulata* exhibits neuroprotection in terms of activating the Nrf2/ARE pathway, promoting phase-2 enzymes, and eventually protecting the neuronal cells from the related oxidative damage. Regarding the antiviral activity of terpenoid compounds derived from brown seaweeds, Abrantes et al. (2010) investigated the in vivo effects of two diterpenes respectively extracted from the Brazilian seaweeds *Dictyota pfaffii* (currently considered as a synonym of *D. friabilis*) and *D. menstrualis* to suppress herpes simplex type-1 infection in Vero cells. They obtained promising results with a remarkable inhibitory effect against herpes simplex type-1 infection, indicating the feasibility of exploiting these natural antioxidant compounds for manufacturing strong antiviral drugs with no toxic effects.

Rhodophyte species are also characterized by their highly effective pharmaceutical in vivo and in vitro terpenoid compounds and in particular, the halogenated ones. For instance, Águila-Ramírez et al. (2012) tested in vitro the antibacterial efficacy of *Laurencia johnstonii*, and other marine seaweeds belonging to other taxonomic groups, against five specific human pathogenic bacterial strains and found that the ethyl ether

extract of this red seaweed has markedly been distinguished by its high potential antibacterial activity against *Staphylococcus aureus* where diameters of the inhibition zones produced were more or less the same as those obtained by the commercial antibiotic erythromycin (18.7±1.5mm *vs*. 20mm, respectively). They ascribed the antibacterial characteristics of the *L. johnstonii* ethyl ether extract to its sesquiterpene compounds. A more recently published paper by Daskalaki et al. (2019) proved in a mice model experiments that the Laurencia-derived diterpenes can promote an anti-inflammatory M2-like phenotype in macrophages by activating the expression of the enzyme "Arginase1", the transcription factor C/EBPβ, and mediator's miR-146a. Additionally, gene expression of the proinflammatory cytokine mediators tumor necrosis factor-α and nitric oxide synthase have significantly been suppressed. Hence, these halogenated diterpenes are considered promising lead molecules with significant pharmaceutical advantages for the manufacture of anti-inflammatory drugs that target macrophage polarization mechanisms. Concerning the antiviral properties of the halogenated terpenes extracted from the red macroalgae, Soares et al. (2012) investigated the antiviral activity of the crude dichloromethane: methanol (1:1) extracts of thirty-six different seaweed species, including six red algal taxa, from the Brazilian coasts against herpes simplex viruses and pointed out that *Laurencia dendroidea* has good antiviral activity against acyclovir-resistant Herpes simplex (HSV-1-ACVr) with a percentage inhibition value of 97.5%. Using ^{1}H-NMR and ^{13}C-NMR spectroscopy, the halogenated sesquiterpenes "(-)-elatol and obtusol" were identified as the main bioactive components with distinctly antiviral characteristics in this seaweed extract (Fig. 2).

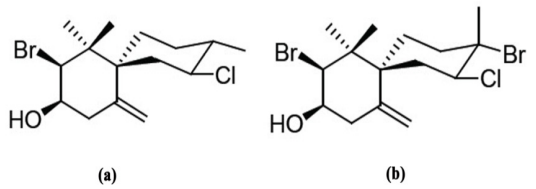

Fig. 2. The halogenated sesquiterpenes (-)-elatol (a) and obtusol (b) identified in the red seaweed *Laurencia dendroidea* and characterized by their antiviral activity against acyclovir-resistant Herpes simplex (HSV-1-ACVr) (Soares et al., 2012)

The subtropical and tropical green seaweed *Caulerpa racemosa* has also been studied and showed promising neuroprotective activities due to its biomedical constituents mainly the three diterpenoids racemobutenolids A and B, and 4',5'-dehydrodiodictyonema (Yang et al., 2015).

Pigments

Seaweed pigments are classified into three basic categories, chlorophylls, carotenoids, and phycobiliproteins. Chlorophylls are fat-soluble compounds that contain a porphyrin ring distinguished by their green color. They are present in all higher plants, macroalgae and microalgae, and cyanobacteria (Ferruzzi & Blakeslee, 2007). Carotenoids are accessory pigments in the form of linear polyenes, as they enhance the light-harvesting properties by passing on light excitation energy to chlorophyll (Larkum & Kühl, 2005). Carotenoids are fat-soluble, yellow-colored pigments and are subdivided into unsaturated hydrocarbons, carotenes, and xanthophylls, which are the oxygen derivatives of carotenes (Sousa et al., 2006). Fucoxanthin, a brown pigment produced by brown seaweeds and diatoms, is one of the most abundant carotenoids, accounting for approximately 10% of total carotenoids produced in nature (Matsuno, 2001). Phycobiliproteins are water-soluble fluorescent proteins found primarily in Rhodophyta, Cyanobacteria, and Cryptomonads. They are accessory pigments that participate in the photosynthetic light-harvesting system by absorbing light energy in the visible spectrum (450–650nm) (Glazer, 1994; Sousa et al., 2006). Phycocyanins, allophycocyanins, and phycoerythrins represent the three major groups of phycobiliproteins found in Rhodophyta (Bogorad, 1975; Glazer, 1994).

Seaweed pigments are valuable candidates in pharmaceutical research because of their effective, nontoxic substances characterized by potent antioxidant activities. In this context, Pangestuti & Kim (2011) mentioned that seaweeds have a variety of natural pigments with potential antioxidant activities, including fucoxanthins, phycoerythrobilins, chlorophyll a, and their derivatives. Chlorophyll a and other related derivatives extracted from several phaeophycean species have demonstrated powerful antioxidant activities (Le Tutour et al., 1998), and porphyrin ring, in particular, is an essential structure for

this activity (Endo et al., 1985a, b). Cahyana (1993) reported that the derivatives of chlorophyll lacking central Mg^{2+} and phytyl chain exhibit more effective antioxidant activity than normal chlorophyll. For instance, Lanfer-Marquez et al. (2005) investigated the antioxidant activities of different chlorophyll derivatives and found that chlorophyll b derivatives exhibit stronger antioxidant activity than chlorophyll a derivatives. Cho et al. (2011) also examined the antioxidant activity of the green macroalga *Enteromorpha prolifera* (currently considered as a synonym of *Ulva prolifera*) and attributed its antioxidant activity to the chlorophyll a derivative pheophorbide a. Cahyana et al. (1992) confirmed that pyropheophytin a of the phaeophycean seaweed *Eisenia bicyclis* possesses more potent antioxidant property than the commercially used antioxidants such as α-tocopherol and butylated hydroxytoluene (BHT). Yan et al. (1999) verified that fucoxanthins extracted from *Hijikia fusiformis* exhibit strong radical scavenging activity. Sachindra et al. (2007) characterized the two novel fucoxanthin metabolites fucoxanthinol and halocynthiaxanthin from the brown seaweed *Undaria pinnatifida* and found that the order of scavenging activity followed a pattern of fucoxanthin > fucoxanthinol > halocynthiaxanthin. Similarly, Sasaki et al. (2008) succeeded in decreasing the formation of secondary oxidation products by mixing fucoxanthin with 200mg/kg of ground chicken meat. Sasaki et al. (2010) also reported that oral administration of fucoxanthin to broiler chicks can improve plasma antioxidant status and meat color. Furthermore, fucoxanthins extracted from *Padina tetrastromatica* demonstrated more antioxidant activity than β-carotene in adjusting the physiological action of the enzymes found in the plasma and liver of retinol-deficient rats (Ravi Kumar et al., 2008; Sangeetha et al., 2009). Finally, Yabuta et al., (2010) investigated and confirmed the antioxidant activity of phycoerythrobilin derived from the red seaweed *Porphyra* sp.

Seaweed-derived pigments are strong candidates for developing new anticancer products as novel chemopreventive agents for cancer therapy (Pangestuti & Kim, 2011). Chlorophylls and their derivatives have been extensively investigated for their antimutagenic effects in vitro against various dietary and environmental mutagens (Ferruzzi & Blakeslee, 2007). Moreover, the pigments of marine seaweeds have been examined for their antimutagenic/antigenotoxic activities. For instance, lutein, β-carotene, and chlorophyll a extracted from the red seaweed *Porphyra tenera* (presently considered as a synonym of *Neopyropia tenera*) have demonstrated an antimutagenic activity in the bacterial strain *Salmonella typhimurium* (Okai et al., 1996). Furthermore, pheophytin a extracted from *Enteromorpha prolifera* (currently considered as a synonym for *Ulva prolifera*) exhibited greater suppressive activity on mouse skin tumorigenesis than chlorophyll a extracted from *S. typhimurium* (Hiqashi-Okai et al., 1999). These findings suggest that porphyrin derivatives, extracted from seaweed, exert an effective and potent chemopreventive activity against carcinogenesis. The carotenoid fucoxanthin and its metabolite fucoxanthinol demonstrated favorable effects against adult T-cell leukemia. Ishikawa et al. (2008) suggested that the inhibitory activities of fucoxanthin and fucoxanthinol are more effective than those of β-carotene and astaxanthin. Fucoxanthin has also been demonstrated to induce apoptosis in human leukemia cells (HL-60) (Kotake-Nara et al., 2005). In addition, siphonaxanthin extracted from Codium fragile tissues inhibited HL-60 cells more significantly than fucoxanthin (Ganesan et al., 2011). Fucoxanthin also exerted antiproliferative and suppressive effects on some types of cancers in humans, such as colon cancer cell lines (Caco-2, HT-29, and DLD-1) (Hosokawa et al., 2004) and prostate cancer cells (PC-3, DU 145, and LNCaP) (Kotake-Nara et al., 2001).

Secondary metabolites obtained from several seaweeds have also been confirmed to exhibit promising anti-inflammatory activities (Abad et al., 2008). Pheophytin isolated from *Enteromorpha prolifera* suppressed inflammatory responses in mouse macrophages (Okai & Hiqashi-Okai, 1997). Fucoxanthin also possesses anti-inflammatory properties comparable to those of the widely used steroid prednisolone (Shiratori et al., 2005). Heo et al. (2010) evaluated the inhibitory effect of nitric oxide (NO) production from nine different brown seaweeds and attributed this ability to their fucoxanthin contents.

Considering the increasing demand for safe antiobesity agents, there exists a need for alternative natural antiobesity sources. Algal pigments have the potential to be used in the treatment or prevention of obesity because they

may act as a regulator of lipid metabolism in fat tissues. Fucoxanthins, which are natural pigments derived from seaweeds, are commonly used in food supplements, slimming supplements, and pharmaceuticals for the management and prevention of obesity (Pangestuti & Kim, 2011). Treatments with fucoxanthin and neoxanthin also exerted significant suppressive effects, indicating that the allenic bond found in their chemical structure plays a significant role in antiobesity characterization (Okada et al., 2008). Other studies have found that oral fucoxanthin treatments significantly reduced abdominal white adipose tissue weight in obese mice fed on a high-fat diet (Maeda et al., 2005, 2007a, b, 2008). All these and other studies suggest that fucoxanthin can specifically suppress adiposity in obese mice. A clinical study conducted by Abidov et al. (2010) confirmed that the pigment xanthigen enhanced weight loss and liver fat content and improved liver function tests in obese nondiabetic women.

The pigments extracted from seaweed tissues are an excellent natural source of neuroprotective agents for the treatment and/or prevention of neurodegenerative diseases and thus could be used as an alternative to synthetic ingredients used in neuroprotection (Pangestuti & Kim, 2011). There have been studies on the neuroprotective properties of seaweed-derived pigments. For instance, in a study on stroke-prone spontaneously hypertensive rats, Ikeda et al. (2003) discovered that fucoxanthin extracted from *Undaria pinnatifida* reduced cell damage in cortical neurons during hypoxia and oxygen reperfusion. Pheophytin and its analog, vitamin B12 derived from *Sargassum fulvellum*, have been demonstrated to promote neurite outgrowth in PC12 cells (Ina & Kamei, 2006; Ina et al., 2007).

Sugawara et al. (2006) discovered that fucoxanthin effectively inhibited the differentiation of endothelial progenitor cells into endothelial cells, leading to the formation of new blood vessels. In vivo and ex vivo angiogenesis assays using a rat aortic ring demonstrated that fucoxanthin and fucoxanthinol inhibited microvessel outgrowth (Sugawara et al., 2006). Furthermore, the antiangiogenic activity of siphonaxanthin, derived from the green macroalga Codium fragile, was found to be comparable to that of fucoxanthin (Ganesan et al., 2010).

Das et al. (2010) investigated the effects of fucoxanthin on osteoclastogenesis using cells from the macrophage cell line RAW264.7, which can differentiate into osteoclast-like cells when stimulated by the receptor activator of the NF-kB ligand. Furthermore, dietary fucoxanthin may be beneficial in the prevention of bone diseases such as osteoporosis and rheumatoid arthritis, both of which are associated with bone resorption. In diabetic/obese KK-Ay mice, dietary fucoxanthin has been shown to reduce insulin levels and hyperglycemia (Hosokawa et al., 2010; Maeda et al., 2007a, b, 2009). Fucoxanthin has the potential to act as an inhibitor in the regulation of proinflammatory adipocytokines, insulin, and hyperglycemia. Fucoxanthin isolated from *Laminaria japonica* has been shown to inhibit tyrosinase activity in UVB-treated guinea pigs and melanogenesis in UVB-treated mice. In addition, fucoxanthin has been shown to have photoprotective properties in human fibroblast cells by inhibiting DNA damage and increasing antioxidant activity (Heo & Jeon, 2009). Based on the findings, oral administration of fucoxanthin can be used to avoid or reduce the negative effects of UV radiation.

Fatty acids

The fatty acid profiles of seaweeds are typically characterized by a mixture of C16 and C18 saturated and unsaturated fatty acids, as well as longer carbon-chain lengths containing several omega fatty acids. Saturated fats are generally stored in neutral lipid bodies, whereas unsaturated fatty acids play a significant role in cellular and tissue metabolism, such as membrane fluidity regulation, electron and oxygen transport, and thermal adaptation (Funk, 2001; Williams & Laurens, 2010). Seaweeds produce essential fatty acids, particularly long-chain PUFAs (Ratledge, 2010; Borowitzka, 2013). These compounds are hydrocarbon chains distinguished by the number and position of their double bonds, which allows their classification into two groups, n-3 and n-6 PUFAs (or omega-3 and omega-6 PUFAs). The essential fatty acid precursor linoleic acid (LA, 18:2) is used to produce n-6 PUFAs, whereas n-3 PUFAs are produced from the essential fatty acid α-linolenic acid (ALA, 18:3). LA and ALA are referred to as "essential" because they cannot be synthesized in mammals due to a genetic predisposition and thus must be obtained through diet (Robertson et al., 2013). Dietary long-chain PUFAs have been demonstrated to possess cardioprotective (Adkins & Kelley, 2010), anti-

inflammatory (Calder, 2006), immunomodulatory (Sijben & Calder, 2007), cognitive (Dangour et al., 2009), neurobehavioral (Boucher et al., 2011), and anticancer (Gleissman et al., 2010; Gheda et al., 2018; El Shafay et al., 2021) properties. Consequently, these bioactive fatty acids may be used in the treatment or prevention of certain chronic diseases (Kelley et al., 2007). As PUFAs are potent inhibitors of platelet aggregation, they may be useful in preventing the formation of atherosclerotic lesions (Phang et al., 2009). PUFAs exert a variety of health benefits due to their unique structural and metabolic functions. They play a significant role in obesity (Wellen & Hotamisligil, 2003), type 2 diabetes mellitus (T2DM) (Pradhan et al., 2001), rheumatoid arthritis (Choy & Panayi, 2001), Alzheimer's disease (Akiyama et al., 2000), and inflammatory bowel disease, all of which have been linked to low-grade chronic inflammation (Fiocchi, 1998). Omega-3 and omega-6 PUFAs have been demonstrated to protect against age-related neuroinflammation and cognitive impairment (Labrousse et al., 2012) and thus may play a role in the prevention of Alzheimer's disease. Algal fatty acids have also been demonstrated to be beneficial in the treatment of inflammation and a variety of cardiovascular diseases (e.g., hypertension, cardiac arrhythmia, myocardial infarction, and thrombosis) (Nauroth et al., 2010; Adarme-Vega et al., 2014). Moreover, fatty acids and their derivatives have been demonstrated to exhibit antimicrobial and antifouling activity (Agoramoorthy et al., 2007; El-Zamkan et al., 2021).

Unsaturated fatty acids reduce the risk of heart disease and atherosclerosis by lowering lipid levels such as cholesterol and triglycerides. The phytochemical composition of the brown marine alga *Dictyota* sp. revealed a diverse range of saturated and polyunsaturated fatty acids. These valuable metabolites contribute to various biomedical and pharmaceutical applications, such as antiproliferative, antimicrobial, antiviral, antioxidant, anti-inflammatory, and anti-hyperpigmentation properties (Rushdi et al., 2022). Long-chain PUFAs, such as EPA and DHA, are beneficial in various inflammatory pathologies, including Alzheimer's disease, arthritis, and lupus (Yates et al., 2014). Vo et al. (2011) discovered that PUFAs derived from the brown seaweed Ishige okamurae reduced inflammation caused by an allergic response by decreasing the release of histamine and moderating the production of inflammatory cytokine in human basophilic KU812F cells. Polyunsaturated fatty acids (PUFAs) with a wide range of biological functions are abundant in marine macroalgae (Khan et al., 2008). Arachidonic acid, an n-6 polyunsaturated fatty acid, is a precursor of well-known inflammatory regulators such as prostaglandins and leukotrienes (Calder, 2005; Shanab et al., 2018). On the other hand, n-3 PUFAs, such as eicosapentaenoic acid and docosahexaenoic acid, are well known for inhibiting the synthesis of eicosanoids such as proinflammatory prostaglandin E2 (James et al., 2000).

In the context of the anticancer activities of seaweed-derived fatty acids, Salem et al. (2020) conducted an in vitro study on the red seaweed *Gracilaria dendroides* and discovered that it has a potential effect on the liver cancer cell line (HepG-2) due to its distinctive fatty acid constituents. Fucosterol is the most abundant sterol in brown seaweeds, while cholesterol is the most abundant sterol in red seaweeds, whereas the sterol composition of green macroalgae is a complex mixture of 28-isofucosterol, ergosterol, -sitosterol, poriferasterol, cholesterol, and others (Bhakuni & Rawat, 2006; Bogie et al., 2019; Meinita et al., 2021a, b). These compounds are claimed to have antioxidant, antidiabetic, anti-inflammatory, anticancer, hepatoprotective, and anti-disease Alzheimer's activity (Hannan et al., 2020). Fucosterol and 24-methylenecholesterol extracted from the brown seaweeds, such as *Sargassum fusiforme* and *Undaria pinnatifida*, have been linked to a number of health benefits in humans (Vane & Botting, 1995).

Polysaccharides

Polysaccharides are a long chain of monosaccharide units held together by glycosidic bonds (Kalimuthu & Kim, 2015). Polysaccharides extracted from seaweeds can be incorporated into the algal cell wall or accumulated in different algal tissues (Chandini et al., 2008; Kalimuthu & Kim, 2015). There are several types of seaweed-extracted polysaccharides such as alginates, agar, and carrageenan, which are widely used on an industrial scale as gelling agents (Ferdouse et al., 2018). Sulfated polysaccharides exhibit remarkable medicinal properties such as immunoinflammatory (Mohamed et al., 2012), antioxidant (de Souza et al., 2007), antitumor

(Moghadamtousi et al., 2014), antiviral (Jiao et al., 2011), anticoagulant (Jin et al., 2013), and antifungal (El Fayoumy et al., 2022) activities. They are a complex group of macromolecules with high structural diversity and different molecular weights, disaccharide formation, and sulfation (Himaya & Kim, 2015).

Agar-agar

The chemical structure of agar consists of a mixture of polysaccharides with a comparable backbone chemical structure with a variety of substitutions of hydroxyl group residues (Fig. 3) (Lahaye & Rochas, 1991). It consists of linked disaccharides, namely agarobioses and neoagarobioses, forming the backbone of the chemical structure (Duckworth et al., 1971). Several rhodophycean genera such as Gelidium, Gracilaria, Pterocladia, and Gelidiella have been reported to contain variable amounts of agar (e.g., Alba & Kontogiorgos, 2018). The extraction process of agar is a sensitive technique that is significantly affected by several factors such as the algal species, environmental conditions, collecting time, and post-collection handling (Abraham et al., 2018).

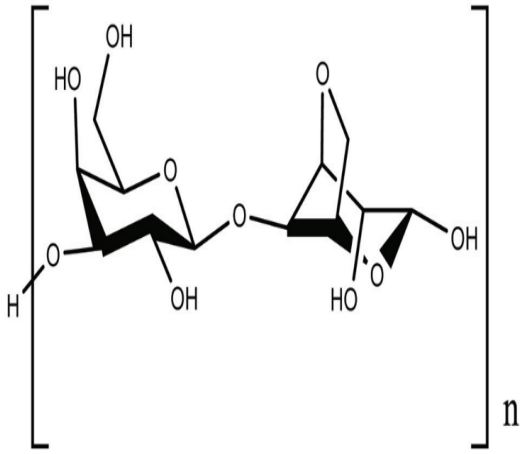

Fig. 3. Generalized chemical structure of agar (Shahidi & Rahman, 2018)

Carrageenan

Carrageenan is a polysaccharide containing up to 40% ester–sulfate groups (Li et al., 2014). It is generally composed of repeated disaccharide sugars (Fig. 4). The following five types of carrageenans have been identified: Kappa (κ), iota (ι), lambda (λ), mu (μ), nu (ν), and theta (θ) (Fig. 5) (De Ruiter & Rudolph, 1997; Campo et al., 2009).

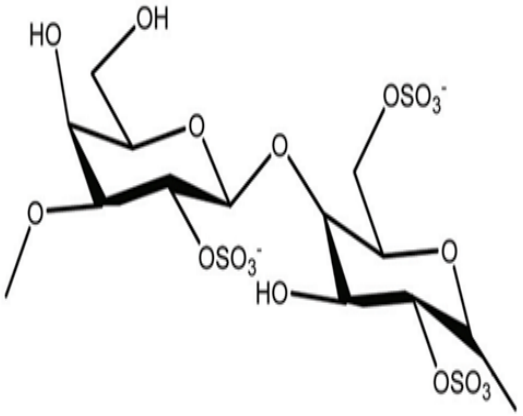

Fig. 4. General chemical structure of carrageenan (Shahidi & Rahman, 2018)

Carrageenan is commercially used in food industries for its gelling, thickening, and emulsifying properties (de Velde et al., 2002). Its sulfate and hydroxyl content exerts a significant effect on its hydrophilic properties (Alba & Kontogiorgos, 2018). Regarding its biological activity, Necas & Bartosikova (2013) reported that carrageenan exhibited anti-HIV activity. In addition, several studies have reported that carrageenan exhibits antiproliferative cancer activity as well as tumor growth inhibition (Yuan & Song, 2005; de Souza et al., 2007). The content of sulfate groups in carrageenan defines its bioactivity. Carrageenan can prevent the binding or entry of viral molecules into cells, wherein its bioactivity is comparable to that of heparan sulfate (Grassauer et al., 2008). Moreover, the mechanism of action of carrageenan activity involves blocking the interaction between cancer cells and the basement membrane, which inhibits the spread and adherence of tumor cells (Yuan et al., 2004; Yuan & Song, 2005). For instance, it has been reported that the red marine macroalga *Gracilaria lemaneiformis* (currently considered as a synonym of *Gracilariopsis lemaneiformis*) contains sulfated polysaccharides with remarkable anticancer and immunomodulatory activity, inhibiting tumor growth, promoting splenocyte proliferation, and enhancing macrophage phagocytosis (Fan et al., 2012).

Porphyran

Porphyran is a characteristic sulfated polysaccharide commonly extracted from the red seaweed *Porphyra* (Villarroel & Zanlungo, 1981; Liu et al., 2019). It consists of two sugars linked together (Fig. 6) (Morrice et al., 1983).

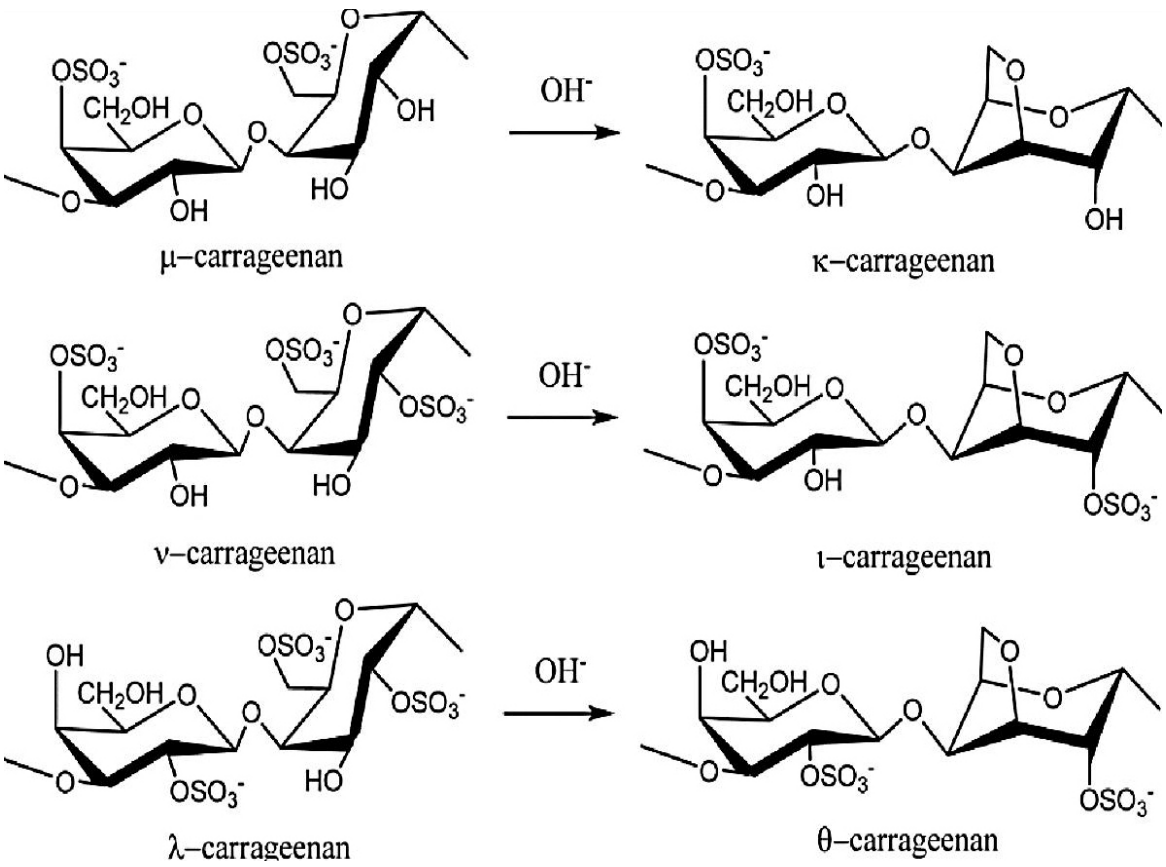

Fig. 5. Diverse types of carrageenan (after Du et al., 2016)

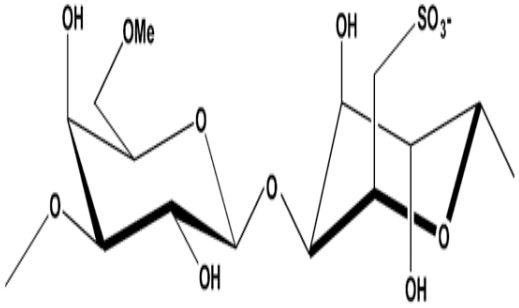

Fig. 6. Chemical structure of porphyran (Delattre et al., 2011)

Porphyra is well known for its nutritional value as it contains proteins, polysaccharides, vitamins, and minerals, and the characteristic component is the polysaccharide porphyran. It has been recognized for its medicinal potential, such as antioxidant, antitumor, immunostimulant, adsorption ability, anticoagulant, and antimicrobial properties, in addition to its prebiotic activity (Zhang et al., 2005; Kwon & Nam, 2007; Cotas et al., 2020).

Ulvans

Ulvan is a water-soluble sulfated polysaccharide with significant physiochemical and biological characteristics and is therefore considered as an important natural compound for numerous pharmaceutical applications (Lahaye & Robic, 2007; Jiao et al., 2011). *Ulvan* is composed of repeated sulfated sugars (Fig. 7) (Percival & McDowell, 1967; Pereira, 2018).

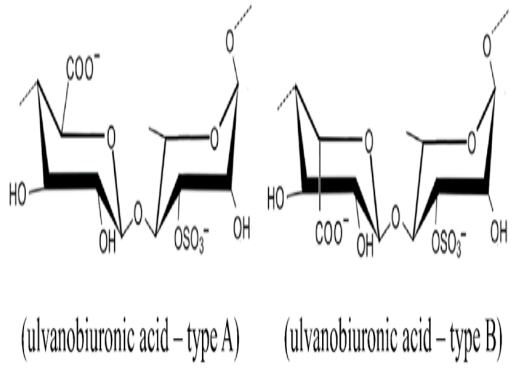

Fig. 7. Typical structure of chemical units of ulvan (Pereira, 2018)

The content and chemical structure of ulvans vary within different species of the genus *Ulva* and according to the conditions of cultivation and extraction methods (Zhao et al., 2018). The content of ulvans ranges from 38% to 54% of the total extracted polysaccharides of dried algal cell wall (Costa et al., 2010). The amount of hydroxyl (-OH) groups in ulvans is responsible for its hydrophilic tendency and water solubility. It can also form rigid and stiff intrachain H-bond networks, and hence, ulvans are considered as a good thickener and gelatinating agent in several food industries (Pereira, 2018). Ulvans are characterized by a number of medicinal and pharmaceutical applications such as probiotic, antibacterial, anticancer, antiviral, and immunostimulating agents (Jiao et al., 2011) and strong antioxidant (Qi et al., 2005, 2006), antitumor (Kaeffer et al., 1999), immunostimulatory (Leiro et al., 2007), anti-inflammatory (Lerio, et al., 2007; Chiellini & Morelli, 2011), antihypercholesterolemic (Rizk et al., 2016), antihyperlipidemic (Taboada et al., 2010), and anticoagulant/antithrombin (Zhang et al., 2008) agents.

Alginates

Alginic acid or alginate is a chain of linked sulfated sugars (Fig. 8). Alginate is the primary component in numerous marine brown algae, such as *Turbinaria, Ascophyllum, Durvillaea, Ecklonia, Laminaria, Lessonia, Macrocystis*, and *Sargassum*, present in the form of insoluble alginate salts (Guo et al., 1998; Vera et al., 2011; Abraham et al., 2018). Alginate is an indigestible polysaccharide and thus may reduce the glycemic load on the body (Jenkins et al., 2000); consequently, it has been used as a source of dietary fiber since several years (Bonithon-Kopp et al., 2000; Goodlad, 2001; Levi et al., 2001; Terry et al., 2001; Brownlee et al., 2005). Studies on rats fed on diets with high total cholesterol and fat content, compared with other algal polysaccharides, have shown that Na-alginates reduced the total cholesterol content and blood cholesterol levels significantly better than fucoidan and agar (Ren et al., 1994; Jimenez-Escrig & Sanchez-Muniz, 2000).

Laminarin

Laminarin, also known as "laminaran" or "leucosin," is a bioactive compound extracted from brown seaweeds such as *Laminaria japonica, Ecklonia kurome, Eisenia bicyclis*, *Fucus vesiculosus, Saccharina longicruris,* and *Ascophyllum nodosum* in the form of a water-soluble polysaccharide consisting of branching 20–25 glucose units (Fig. 9) (Gupta & Abu-Ghannam, 2011).

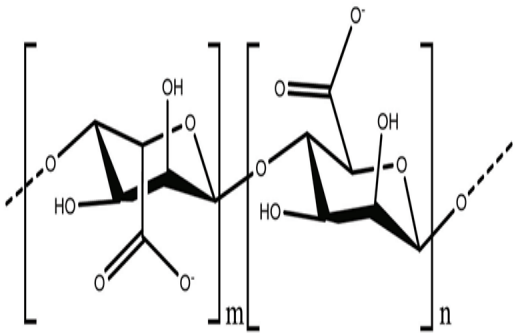

Fig. 8. Chemical structure of alginates (Abraham et al., 2018)

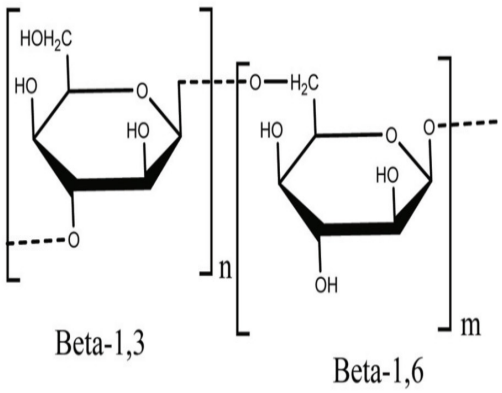

Fig. 9. Chemical structure of laminarin (after Shahidi & Rahman, 2018)

To date, two laminarin series have been identified; one is composed of glucose units (G-series), and the other is composed of D-mannitol units (M-series) (Nelson & Lewis, 1974). The ratio of laminarin series, along with their changeable structural configurations, exerted a significant effect on the biological activities of laminarin (Chizhov et al., 1998; Rioux et al., 2017). It has been shown that laminarin derived from marine algae inhibited the activity of HIV by preventing its adsorption into human-derived lymphocytes and deactivating its reverse transcriptase (Muto et al., 1988).

Furthermore, various important medicinal properties of laminarin have been confirmed, such as enhancing the function of immune system

by increasing the number of B cells and helper T cells and reducing systolic blood pressure and cholesterol levels (Hoffman et al., 1995; Miao et al., 1999; Holdt & Kraan, 2011).

Fucoidan

Another important sulfated polysaccharide is fucoidan, which is composed of sulfated L-fucose and <10% of other monosaccharides with sulfate–ester groups (Fig. 10) (Chevolot et al., 1999; Daniel et al., 2001).

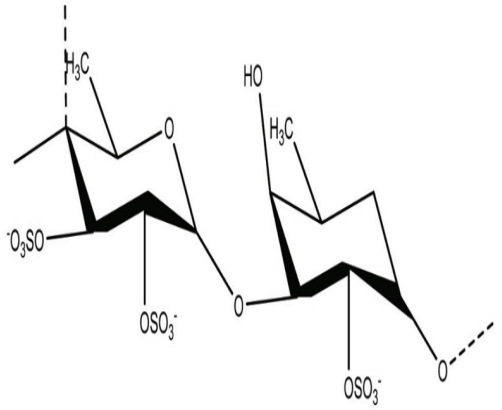

Fig. 10. General chemical structure of fucoidan (after Shahidi & Rahman, 2018)

Fucoidan exhibits a remarkable inhibition activity against several RNA and DNA viruses (Ahmadi et al., 2015). It has been observed that this inhibition activity was achieved by preventing the interaction between viral molecules and cells, which hinders the production of viral-induced syncytium (Elizondo-Gonzalez et al., 2012). Fucoidan can effectively enhance the defense mechanism of the immune system by inducing cellular and humoral immune reactions through macrophages (Wang et al., 2019). Studies have also reported that fucoidans extracted from some brown algae exhibited anticoagulant activity, which was described as heparin-like action (Li et al., 2008; Jiao et al., 2011). In general, the content and/or position of the sulfate groups of fucoidan is the primary cause of its entire recorded medicinal activity (Li et al., 2008; Fiton, 2011; Kalimuthu & Kim, 2015). In addition, their monomeric structure, type of linkage, and branching can significantly affect their biological properties (Jiao et al., 2011; Thanh-Sang & Kim, 2013; Lorbeer et al., 2013).

Minerals

Iodine, iron, copper, zinc, and some other minerals derived from marine macroalgae have been recognized as natural mineral supplements due to their efficacy (Takeshi et al., 2005; Cabrita et al., 2016). An excess or deficiency of iodine concentration in the human body can cause serious health problems (Miyai et al., 2008). Seaweeds are a potentially rich source of natural iron for humans. For instance, *Ulva, Sargassum, Porphyra,* and *Gracilariopsis* contain high iron (Fe) levels (Garcia-Casal et al., 2007, 2009). Zinc (Zn) is an essential nutrient for healthy body tissues due to its antioxidant properties, ability to regulate the immune response, and role in vitamin A metabolism (Salgueiro et al., 2000; Rink & Haase, 2007). It is also important for maintaining the functions of hormones and vitamin D involved in normal bone growth (Salgueiro et al., 2002). Copper (Cu) is a key element for enzymes responsible for hemoglobin biosynthesis (Anuradha et al., 2015). Cu and Zn are required in adequate amounts to maintain fundamental metabolic pathways (Underwood, 1977; Onianwa et al., 1999).

Conclusions and future perspectives

This review has discussed the medical and pharmaceutical values of the different bioactive compounds present in seaweeds. Today, seaweeds and their derivatives are widely used in a variety of medical applications and also included in the manufacture of natural and safe drugs. To combat pathogens, such as the new generation of viruses that pose a threat to humans, it is expected that new bioactive compounds, with highly effective pharmaceutical implications, from seaweeds will be discovered in the forthcoming years, and thus further in-depth investigations are necessary in this respect.

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Authors' contributions: All the co-authors wrote and reviewed the manuscript equally, and approved the final version of the manuscript.

Ethics approval: Not applicable.

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التطبيقات الطبية والصيدلانية للطحالب البحرية

مصطفى الشيخ[1]، علاء فتحى[2،3]، هانى صابر[4]، عبد الله عنتر صابر[5]

[1]قسم النبات - كلية العلوم - جامعة طنطا- طنطا31527 - مصر، [2]قسم النبات والميكروبيولوجى - كلية العلوم- جامعة الأسكندرية - مصر، [3]قسم الأحياء- كلية العلوم والآداب - جامعة القصيم - عنيزة - المملكة العربية السعودية، [4]قسم النبات والميكروبيولوجى - كلية العلوم - جامعة جنوب الوادي - قنا 83523 - مصر، [5]قسم النبات - كلية العلوم - جامعة عين شمس - ميدان العباسية – القاهرة 11566 - مصر

تعد الطحالب البحرية مصدرًا طبيعيًا لا غنى عنه للأيضات النشطة بيولوجيًا التي تتميز بالتطبيقات الطبية الحيوية والصيدلانية متعددة الوظائف. على سبيل المثال، تتميز مادة البوليفينول المشتقة من الأعشاب البحرية بتأثيراتها المضادة للأكسدة في علاج و/ أو الوقاية من العديد من الأمراض. علاوة على ذلك، تتميز الأصباغ والأحماض الدهنية والتربينويدات بخصائصها القوية المضادة للأكسدة والألتهابات ومضادة للسمنه، إلى جانب أنشطتها عالية الفعالية في حماية الكبد. تتميز أيضا العديد من السكريات المستخرجة من الأعشاب البحرية، مثل الألجينات والأولفان والكاراجينان، بتأثيراتها الطبية المختلفة لعلاج إلتهابات المناعة وكمضادات للأكسدة والأورام والفيروسات والتخثر. علاوة على ذلك، تم استخدام المعادن المشتقة من الطحالب البحرية على نطاق واسع كمكملات غذائية ومستحضرات تجميل. تناقش هذه الورقة المراجعية التطبيقات الطبية الحيوية والصيدلانية للطحالب البحرية ووجهات النظر المستقبلية لتطبيقاتها على نطاق واسع لتطوير مكونات صيدلانية جديدة وآمنة وذات فاعليه عالية.