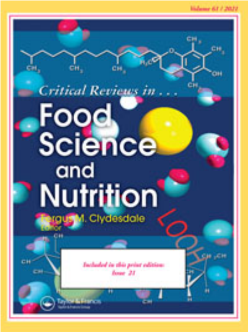

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REVIEW

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Recent advances in industrial applications of seaweeds

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ABSTRACT

Seaweeds have been generally utilized as food and alternative medicine in different countries. They are specifically used as a raw material for wine, cheese, soup, tea, noodles, etc. In addition, seaweeds are potentially good resources of protein, vitamins, minerals, carbohydrates, essential fatty acids and dietary fiber. The quality and quantity of biologically active compounds in seaweeds depend on season and harvesting period, seaweed geolocation as well as ecological factors. Seaweeds or their extracts have been studied as innovative sources for a variety of bioactive compounds such as polyunsaturated fatty acids, polyphenols, carrageenan, fucoidan, etc. These secondary metabolites have been shown to have antioxidant, antimicrobial, antiviral, anticancer, antidiabetic, anti-inflammatory, anti-aging, anti-obesity and anti-tumour properties. They have been used in pharmaceutical/medicine, and food industries since bioactive compounds from seaweeds are regarded as safe and natural. Therefore, this article provides up-to-date information on the applications of seaweed in different industries such as pharmaceutical, biomedical, cosmetics, dermatology and agriculture. Further studies on innovative extraction methods, safety issue and health-promoting properties should be reconsidered. Moreover, the details of the molecular mechanisms of seaweeds and their bioactive compounds for physiological activities are to be clearly elucidated.

KEYWORDS
Bioactive compounds; functional properties; health benefits; industrial utilization; seaweeds

Introduction

Seaweeds are taxonomically classified as algae and categorized as microalgae and macroalgae (El Gamal 2012). Seaweeds are divided into three distinct groups that are red algae (Rhodophyta), green algae (Chlorophyta) and brown algae (Ochrophyta, Phaeophyceae) (MacArtain et al. 2007; Guiry and Guiry 2021) (Figure 1). They have been used as food, fertilizer as well as pharmaceutical purposes for a long time and recently they have been utilized in wide range applications. They have been utilized as food and alternative medicine sources in Asian countries since ancient times. In Japan marine algae have been used as a raw material for wine, cheese, soup, tea and noodles (Nisizawa et al. 1987) while in Europe seaweeds have been utilized as a food and a source of polysaccharides (alginates, agar and carrageenans) for pharmaceutical and food applications (Kolanjinathan, Ganesh, and Saranraj 2014). The high vitamin and mineral contents of seaweeds make them nutritionally valuable (Rupérez 2002; MacArtain et al. 2007). In addition, seaweeds are potentially good resources of proteins, indigestible carbohydrates, essential fatty acids and dietary fiber (Rupérez and Toledano 2003; Sánchez-Machado et al. 2004).

In contrast to the terrestrial plants, seaweed is rich in health-promoting materials such as essential amino acids, polyunsaturated fatty acids, vitamins (especially A, B, C, and E), antioxidants and invaluable compounds widely used in immune system (Kim and Wijesekara 2010). Most of the marine organisms are exposed to extreme conditions of the surrounding environment. While adapting themselves to these new conditions, they generate various secondary metabolites known as biologically active, which do not exist in other organisms. For instance, pigments, phycobiliproteins from algae, are indigenous and certainly not found in land plants (Cornish and Garbary 2010; Berthon et al. 2017). Therefore, seaweeds are considered as promising sustainable marine resources as well as having comprehensive advantages in nutrition and economy.

More recently, seaweeds or their extracts have been considered as novel sources for a number of bioactive constitutes and functional carbohydrates, including terpenoids, polyphenols, phlorotannins, sulfated polysaccharides, polyunsaturated fatty acids, carrageenan, and fucoidan. These secondary metabolites have complex chemical structures and have been shown to have antioxidant (Benslima et al. 2021; Rajauria et al. 2021), antimicrobial (Martelli et al. 2020;

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Figure 1. Possible applications of algae.

Ristivojević et al. 2021), anticancer (Gutiérrez-Rodríguez et al. 2018; Smyrniotopoulos et al. 2020), antidiabetic (Zhong et al. 2020; Kim et al. 2021; Gheda et al. 2021), antiviral (Cirne-Santos et al. 2020, Wang, Wang, et al. 2020), anti-inflammatory (Cui et al. 2019; Chakraborty and Dhara 2020), anti-photoaging (Pangestuti, Shin, and Kim 2021), anti-aging (Cao et al. 2020), anti-obesity (Lu et al. 2020, Lee et al. 2020), anti-quorum sensing (Tang, Wang, and Chu 2020), anti-leukemic (Almeida et al. 2020), anti-tumor (Yan, Lin, and Hwang 2019) and cardio-protective properties (Pereira 2018b). Seaweed polysaccharides, particular fucoidan, ulvan, and their derivatives have been indicated to be effective for the treatment of Alzheimer and other neurodegenerative diseases (Bauer et al. 2021). Bioactive compounds obtained from seaweeds are regarded as safe and natural. They can also be utilized as food supplements or food ingredients (Khalid et al. 2018; Nicol et al. 2020).

Although there are numerous reviews available on the nutritional, pharmaceutical, and health benefits aspects of seaweeds (Miyashita, Mikami, and Hosokawa 2013; Sanjeewa et al. 2018; Carina et al. 2021; Saeed et al. 2021; Nielsen, Rustad, and Holdt 2021), this article provides up-to-date information on the applications of seaweed in different industries such as pharmaceutical, biomedical, cosmetics, dermatology and agriculture.

Biologically active compounds in seaweeds

While various constituents of seaweeds occur ubiquitously, some compounds are unique in certain algae classes, species, or the combination of certain bioactive compounds is unusual and synergistically enhances the overall effect. The quality and quantity of biologically active compounds in seaweeds depend on different factors, such as season, harvesting period, geographic location, abiotic (salinity, pH, temperature, water nutrient composition) and biotic factors (herbivory or direct competition with other benthic organisms) (Cotas et al. 2020; Pacheco et al. 2020). With the occurrence of extreme changes nowadays in the environment due to *global climate change*, the seaweed habitats are characterized by complex and dynamic factors. All these factors greatly affect the concentration and quality of the chemical compounds produced. Therefore, all these affect the chemical compounds concentration and composition produced greatly or only the quality (Leandro, Pereira, and Gonçalves 2019; Gaubert et al. 2019).

The nutritional ingredient of seaweed is very important and has several health benefits, as all contain primary metabolites such as polysaccharides, proteins and lipids. Polysaccharides act as prebiotics, non-digestible fibers that feed the healthy bacteria in the digestive tract. Besides these, they have many antioxidants in the form of certain vitamins (A, C, and E) and protective pigments, a number of vitamins and minerals essential for health, a great amount of iodine as well as trace mineral as health-promoting compounds. Seaweeds are a unique source of bioactive compounds and may act as a nutritional pillar to a vegan diet as well (Hayes 2015; Peñalver et al. 2020).

Structural polysaccharides

The unique polysaccharides found in various types of seaweeds have been of industrial importance. The polysaccharides from seaweeds are found principally in sulfated and non-sulfated forms (Gullón et al. 2020). Seaweeds polysaccharides are classified upon their provenience called reserve (storage) polysaccharides (starch, laminarin (β-(1→3)-d-glucans, floridean starch) and parietal polysaccharides. The later are composed of matrix polysaccharides (agars, alginates, carrageenan, fucoidans, galactans, xylans, ulvans) and skeletal polysaccharides (Hentati et al. 2020b). Green seaweeds (Chlorophyta) are rich in ulvans (kind of water-soluble polysaccharides) and cellulose while brown seaweeds (Phaeophyceae) contain alginic acids (or alginates), laminarans (or laminarins) and fucoidans (water-soluble polysaccharides). Red seaweeds (Rhodophyta) are characterized by their carrageenans (the major components of cell walls), agars, xylogalactans (especially in the Corallinales order), sulfated galactans, xylans, porphyran and floridean starch (Table 1).

Agar-agar, alginic acids or their salts (alginates) and carrageenan are obtained by extraction with hot water or an alkali solution and are most important polysaccharides for industrial applications. The predominant building blocks of agar-agar are β-d- and 3,6-anhydro-l-galactose, which are linked alternately via (1→4) and (1→3)-β-glycosidic bonds. Alginic acid is built up from β-d-mannuronic acid and α-l-guluronic acid via (1→4)-glycosidic bonds. Carrageenan is a mixture of unbranched polysaccharides consisting of partially sulfate-esterified d-galactose and 3,6-dehydrogalactose residues. All of them are hydrocolloids (also known as phycocolloids), and widely used in food production as stabilizers, thickeners, gelling agents and

Table 1. Bioactive compounds in seaweeds.

			Pigments		Phenolic compounds		
Phylum/Class	Common name	Cell wall components	Carotenoids	Chlorophylls including pigments (excl. Carotenoids)	Group	Compounds	References
Rhodophyta	Red seaweeds	starch-like polysaccharides: floridean starch (consists of highly branched amylopectin without amylose) sulfated polysaccharide: carrageenan	α- and β-carotene xanthophylls: anteraxanthin, zeaxanthin or lutein	chlorophylls *a* and *d* Phycocyanin, Phycoerythrin phycobilins (phycocyanobilin, phycoerythrobilin, phycourobilin and phycobiliviolin)	Phenolic acids Flavonoids Phenolic terpenoids Mycosporine-like amino acids	Benzoic acid, p-hydroxybenzoic acid, salicylic acid, gentisic acid, protocatechuic acid, vanillic acid, gallic acid, and syringic acid Isoflavones; daidzein or genistein Catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate, or epigallocatechin gallate Bromophycolides Palythine, shinorine, asterina-330, palythinol, and porphyra-334 Palythine and shinorine	(Agregán et al. 2017; Xu et al. 2015; Farvin et al. 2013; Souza et al. 2011)
Chlorophyta	Green seaweeds	starch	*alpha-*,*beta-*, *gamma*-carotin, lutein, neoxanthin, violaxanthin, zeaxanthin	chlorophylls *a* and *b*	Flavonoids Phenolic acids Flavonoids	Catechin, Coumarin, epicatechin, catechin gallate, epigallocatechin, epicatechin gallate, or epigallocatechin gallate Coumarin Vanillic acid C-glycosides	
Phaeophyceae	Brown seaweeds	Laminaran Cellulose, alginates, methylated mucopolysaccharides	*beta*-Carotin, Fucoxanthin, Violaxanthin	chlorophylls *a* and *c*	Phenolic acids Phlorotannins Flavonoids Phenolic terpenoids	Rosmarinic acid; quinic acid Dieckol, Eckol, Fucophloroethol-type Diphlorethohydroxycarmalol, Fucaphlorethol-type, Tetrafuhalol B Catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate, epigallocatechin gallate C-glycosides Daidzein or genistein Plastoquinones, chromanols, and chromenes Stypofuranlactone; 10,18-dihydroxy-5′a-desmethyl-5′-acetylatomaric acid; 10-keto-10-deisopropyliden-5′a-desmethyl-5′-acetylatomaric acid; 10-keto-10-deisopropyliden-atomaric acid HBAs, rosmarinic acid, and quinic acid	

emulsifiers. Agar-agar is also used for the production of culture media in microbiology (Hentati et al. 2020a; Rusu et al. 2020; Wang et al. 2017; Trif et al. 2019).

So far, fucoidans have not been found in other seaweeds than brown seaweeds, or in terrestrial plants. They are composed primarily of sulfated l-fucose (6-deoxy-l-galactose) and less than 10% of other monosaccharides. A characteristic structural feature of the fucoidans are α-1,4-bonded l-fucose-4-O-sulfate units, which can be branched, acetylated or substituted by a second sulfate group in position 2. However, there are considerable differences in terms of molecular mass, the degree of sulfation and its pattern. There are also numerous variations in the glycosidic bonds and the sugar composition.

The recent applications of fucoidans include nanomedicine (Chollet et al. 2016), pharmacological, and pharmaceutical, and it is considered a hot topic in recent decades (Zhao et al. 2018; Fitton et al. 2019; Van Weelden et al. 2019; Wang, Cui, et al. 2019; Luthuli et al. 2019). Fucoidan has antibacterial (e.g. against *Helicobacter pylori* infection) (Tomori, Nagamine, and Iha 2020), antioxidant (e.g. against oxidative stress) (Jayawardena et al. 2020), anticancer activities via inducing apoptosis of cancer cells (Bai et al. 2020; Fernando et al. 2020), with implications in metastasis and drug resistance (Reyes et al. 2020), or effective on improving skin psoriasis (Takahashi et al. 2020).

Polyunsaturated fatty acids (PUFA)

Seaweeds usually contain a low level of lipids, ranging from 1 to 5%, and are therefore considered a low-fat food. The highest concentration of lipid is 7.8% (dw) in the brown seaweed (*Bellotia eriophorum*). Further components of great importance for health are the essential fatty acids (EFA), particularly polyunsaturated fatty acids (PUFA) and the omega-3 fatty acids including EPA, DPA and DHA, which are found in fish, comes originally from seaweeds (Rosemary et al. 2019; Schmid et al. 2018). Omega-3 and omega-6 fatty acids are abundant in red and brown seaweeds, varying from 34 to 74% of total lipid content. The monounsaturated fatty acid (MUFA) is usually oleic acid (C18:1), reaching up to 21% of total lipids in brown seaweed (Pereira 2018a; Afonso et al. 2021). The brown seaweeds have high concentrations of oleic acid, linoleic acid and α-linolenic acid while they possess low EPA. The red seaweeds have higher EPA, palmitic acid, oleic acid, and arachidonic acid contents than brown seaweeds. Green seaweeds have in greater quantity of linoleic acid and α-linolenic, palmitic, oleic and DHA (Kumari et al. 2010; Peñalver et al. 2020).

Proteins

Protein content of seaweeds may change according to the species. Protein mean content ranges from 10 to 30% of dry matter, with red seaweeds showing the highest content with up to 47%. The protein content of seaweeds is comparable well with high-protein foods, such as soybean that averages 43.3% protein of dry matter, and higher than that of a schnitzel or egg (Fleurence et al. 2012; Raposo, De Morais, and De Morais 2016).

The most abundant amino acids in seaweeds are aspartic and glutamic acid, which can reach up to 40% of total amino acid content, as well as asparagine, serine, histidine, arginine, lysine, valine, leucine, and isoleucine. Red seaweeds have the highest average proportion of total essential amino acids (EAA), as well as lysine, when compared to brown and green seaweeds (Vieira et al. 2018).

Pigments

Pigments are polyenes soluble in lipids exerting strong antioxidant activities and determine the color of seaweeds. Seaweeds can synthesize three kinds of pigments: chlorophylls (a, b, c1, and c2), carotenoids and phycobiliproteins (water-soluble pigments: phycoerythrin and phycocyanin) (Table 2). Phycobiliproteins are water-soluble pigment protein complex that mainly found in red and blue-green algae. Carotenoids are also effective antioxidant compounds present in seaweeds and different species of seaweeds contain different kinds of carotenoids such as β-carotene, fucoxanthin and tocopherol. The content of β-carotene in seaweeds ranges from 36 to 4500 mg/kg dry weight. Fucoxanthin contains up to 70% of the total carotenoid content and is the pigment that gives the color to brown seaweeds. The concentration of the main pigments may change due to seasonal and environmental conditions as well as the physiological status of seaweed species (Pérez, Falqué, and Domínguez 2016; Wang et al. 2017; Westermeier et al. 2020).

Phenolic compounds

Phenolic compounds, as secondary metabolites of seaweeds, can be produced in high quantity and/or quality, due to the direct impact of environmental extrinsic factors (Cotas et al. 2020). Polyphenols known as phlorotannin are common tannins found in brown seaweeds, and categorized into six categories: (1) fucols (aryl–aryl bonds), (2) phloretols (aryl–ether bonds), (3) eckols (dibenzo-1,4-dioxin bonds), (4) fucophloretols (ether or phenyl linage), (5) carmalols (dibenzodioxin moiety), and (6) fuhalols (ortho-/para- arranged ether bridges containing an additional hydroxyl group on one unit) (Table 1) (Lomartire et al. 2021; Santos et al. 2019; Imbs and Zvyagintseva 2018). Phlorotannins are produced by polymerization of phloroglucinol. They are important components of the cell wall and are responsible for the UV protection. Recent studies have shown neuroprotective, antidiabetic, anticancer, antioxidant, anti-inflammatory, antimicrobial potentials of phlorotannins (Shrestha, Zhang, and Smid 2021). The other type of dieckol found in the species *Ecklonia cava* (Phaeophyceae), is the most exploited phlorotannin, due to its biotechnological properties (Yoon et al. 2017).

Terpenoids

Active metabolites among the carotenoids, polyphenols and alkaloids, including terpenoids that can be found in

Table 2. Vitamin and minerals in seaweeds.

Component	Amount / 100g seaweed	Daily dose recommended*
Vitamins		
Vitamin A (Retinol)	67 µg	1,200 mcg
Vitamin B1 (Thiamin)	220 µg	mg/1.4 mg/ 1.5 mg (women over 18 years/women/ breast-feeding)
Vitamin B2 (Riboflavin)	340 µg	1300 µg
Vitamin B3 (Niacin)	1200 µg	14–16 mg
Vitamin B5 (Pantothenic acid)	325 µg	5 mg/6 mg/7 mg (men and women 14 years and older/pregnant women/breast-feeding women)
Vitamin B6 (Pyridoxine)	34 µg	1.3 mg/1.7 mg/ 1.2 mg/ 1.3 mg/1.5 mg/1.9 mg/ 2 mg (males 14–50 years/ males over 50 years/ females 14–18 years/ females 19-50 years/ females over 50 years/ pregnant women/ breast-feeding women)
Vitamin B7 (Biotin)	0,2 µg	25–40 µg
Vitamin B9 (Folic acid)	180 µg	300 µg/ 450 µg/ 550 µg (healthy adult/ breastfeeding women/ during pregnancy)
Vitamin C	900 µg	75–90 mg 115 mg – pregnancy and lactation: age 18 or younger
Minerals		
Calcium	70 mg	1,000 mg/1,200 mg age 19–50/women age 51+ and men age 71+ 1,200 mg/day
Kalium	127 mg	
Magnesium	100 mg	400 mg/420 mg/310 mg/320 mg men age 19–30/ men age 31 and up/women age 19–30/women age 31 and up
Natrium	98 mg	>2 g
Phosphor	11 g	700 mg

*Estimated values for adequate intake (D-A-CH, 2020), German Nutrition Society (DGE) and Adequate intake (EFSA, 2014).

seaweeds. Phenolic terpenoids are secondary metabolites that have already been identified in seaweeds. Red seaweeds synthesize phenolic terpenoids, such as diterpenes and sesquiterpenes (Stengel, Connan, and Popper 2011; Lomartire et al. 2021). The most prolific source of terpenes in the marine environment are recognized to be a red seaweed species *Laurencia,* well known as halogenated secondary metabolites producers, especially terpenoids mainly sesquiterpenoids, sterols and acetogennins (de Oliveira et al. 2015; Rocha, Seca, and Pinto 2018).

The meroditerpenoids are partially derived from terpenoids and are characterized for having a polyprenyl chain linked to a hydroquinone ring moiety were found in brown seaweeds, mainly from the family Sargassaceae (Phaeophyceae). This group includes plastoquinones, chromanols, and chromenes. The biosynthesis of terpenoid precursors can occur through the mevalonate (MVA) pathway and the methylerythritol phosphate (MEP) pathway (Stout et al. 2010).

Vitamins

Seaweeds are an excellent source of vitamins (Table 2). The wide range of vitamins includes vitamins A, C and E as well as the vitamin B complex, including vitamin B12, which is otherwise only found in animal products. These components are of particular importance for the immune system as well as for skin, hair, nails and connective tissue. Very rich in folic acid (vitamin B9), from an amount of 100 g seaweed up to 180 µg of the vitamin can be absorbed.

Large amounts of vitamins B1, B2 and B12 present in seaweeds. The vitamin B2 is required for several biochemical processes in the body, such as energy production from proteins. Seaweeds are one of the few non-animal sources of Vitamin B12 that is important for the production of red blood cells and cell division.

Minerals

The incomparably high mineral content makes seaweeds important for food supplements (Table 2). In addition to calcium, magnesium, iron and potassium, they contain the trace elements iodine, copper, zinc and selenium, as well as manganese, strontium, molybdenum and germanium. The elements are bound to the polysaccharides and are bioavailable in this form.

Seaweed is an important source of iodine that is essential for the production of thyroid hormone (Smyth 2021). The daily iodine requirement of 0.2 mg (nutritional recommendation of the German Nutrition Society, DGE) can often not be covered by iodized table salt. The edible seaweeds have different but generally very high contents of this element; therefore, caution is required with certain types of seaweeds. Depending on the type of seaweeds, 1–5 g of dried seaweed per day is safe and recommended for healthy people. The iodine content is well above the maximum tolerable upper limit of 20 milligrams per kilogram. Because of the potentially high iodine content of algae, experts' advice only buying products that have the iodine content stated on the packaging. Soaking the algae in water before preparation can reduce the iodine content. Pregnant women, the elderly people with a weakened immune system or a thyroid disease should clarify with their doctor whether they can eat algae despite the high iodine content.

Dulse (*Palmaria palmata,* Rhodophyta) is one of the most consumed red seaweed, and is a source of iodine, protein, magnesium and calcium (MacArtain et al. 2007). A 150 ug/day requirement of iodine can be obtained from a single gram of red seaweed. Seaweed is also high importance due to content of other elements such as copper, manganese, molybdenum, silicon or germanium, which usually are inadequately contained in a usual diet.

Industrial application of seaweed in food

The modern consumers are very much aware of the food's nutritive value and the adverse effect that synthetic preservatives may have on their health, thus it is not surprising that their preference is fresh and lightly-preserved foods, free of chemical preservatives but containing natural compounds that may contribute to their health (Petruzzi et al. 2017). In this context, a group of functional products, that carry more than just nutritive value, has been developed. Some food products (meat, fish, chicken, etc.) are susceptible to spoilage and more easily contaminated thus the focus of today's research and food industry has been intensified in finding natural sources of antimicrobial and antioxidant compounds that would replace the synthetic ones to apply for them.

Algal constitutes such as polysaccharides, phenolic compounds, bioactive peptides, pigments, omega-3 fatty acids, terpenoids, and vitamins, recently came under the spotlight for their strong biological effects (Gullón et al. 2020; Šimat et al. 2021). Besides antihypertensive, antioxidant, antithrombotic, antimicrobial, and immunomodulatory effect (Lafarga, Acién-Fernández, and Garcia-Vaquero 2020), these components showed a wide range of possible applications in food, therapeutic, and drug industry, also in the formation of functional ingredients. The use of seaweeds as a source of new natural antioxidant and antibacterial substances with a possible role as nutraceutical agents may contribute to both food quality and food safety. However, several issues need to be addressed before the application of seaweeds at the industrial level. The seaweeds phytochemical profile and content are significantly affected by factors such as species, season, age, geographical location, and environmental conditions (Generalić Mekinić et al. 2019). The availability of the biomass for extraction of particular compounds is often unknown (Jacobsen et al. 2019) thus, the standardization of the raw material preparation and extraction methods is needed (Čagalj et al. 2021) as well as identification of the compounds and expressing the results using the same standard compound (Generalić Mekinić et al. 2019) and safety risks assessment such as heavy metals or toxins (Banach, Hoek-van den Hil, and Fels-Klerx 2020).

Antioxidant properties

The classification of primary and secondary antioxidants has been done based on their antioxidant mechanisms. The primary antioxidants react directly with free radicals by transforming them to more stable, non-radical products a reaction that plays an important role in preventing the lipid oxidation. The secondary antioxidants prevent or limit the lipid oxidation by mechanisms such as the chelation of transition metals, singlet-oxygen quenching (in photooxidation), and oxygen scavenging (Decker 2002; Hermund 2018).

Over the last years, the phytochemical content of seaweed extracts has been extensively studied as a source of natural antioxidants. A distinct groups of compounds, phlorotannins have been found to carry a high antioxidant activity (Generalić Mekinić et al. 2019; Hermund et al. 2018; Jacobsen et al. 2019). The phlorotannins have been suggested to scavenge free radicals, namely, superoxide, peroxide and nitric radicals and chelate ferrous ions (Generalić Mekinić et al. 2019; Roohinejad et al. 2017). The high complexity of phlorotannin structures makes their characterization and identification difficult and rarely reported (Hermund et al. 2018). Still, there are many examples of their successful application in foods (Table 3). According to studies reviewed in this paper, seaweeds show a great potential for industrial applications as natural antioxidants due to their possibility to slow down lipid oxidation and prolong shelf-life of many food types.

Antimicrobial activity

In recent years, the food industries are on the lookout for finding novel natural antimicrobials for producing safe foods and prolong its shelf life. However, these natural compounds have to perform equally or better than synthetic, traditional preservatives, while preserving or improving the sensory properties of the product in order to be acceptable for industrial production (Cabral et al. 2021). Besides, the consumers need to be educated on the use of the new antimicrobials for the new food products.

The results of various research studies have shown that seaweeds crude extracts have antimicrobial potential against foodborne pathogens and spoilage bacteria (Pérez, Falqué, and Domínguez 2016). However, only a few studies reported the application of extracts or seaweed powder in food models (Table 4). Usually, these studies investigate the microbial quality and antimicrobial effect via changes in total viable count (TVC) whether the total microbial population is able to grow in the presence of oxygen at the ambient temperature. Issues to be considered for future research that will enable the use of seaweeds in the industry. The safety issues and the performance of challenge tests on foodborne pathogens to establish their role in food safety. Application of whole seaweed powder in food products without extraction or purification should be reconsidered due to heavy metals, pesticide residues, dioxins, pharmaceuticals or marine bio-toxins (Banach, Hoek-van den Hil, and Fels-Klerx 2020; Cabral et al. 2021; Pérez, Falqué, and Domínguez 2016). Most studies lack chemical identification or purification of used crude extracts that are needed for their industrial applications. Despite that, extracts' antimicrobial activity cannot be disputed. Phlorotannins, polysaccharides, pigments, proteins, fatty acids, halogenated compounds and other minor compounds contribute to antimicrobial activity of seaweeds (Pérez, Falqué, and Domínguez 2016). Different groups of compounds have divergent antimicrobial mechanisms of action, however, most of them are yet unclear (Cabral et al. 2021).

Identification of antimicrobial compounds in extracts is rather complex and difficult, and the synergy effect of

Table 3. Recent studies on application of seaweed and seaweed extracts in food models.

Food model	Seaweed or extract used in the experiment	Investigated parameters in foods to determine antimicrobial (AM) and/or antioxidant (AO) properties	Salient findings	References
Chicken breast	Films incorporated with *Fucus vesiculosus* extract	AO: TBARS*	AO: Chicken breast packaged in films with seaweed extract had lower TBARS values for 25 days of storage.	Andrade et al. (2021)
Farmed freshwater catfish (*Pangasius pangasius*) fillet	Fillets dipped in *Padina tetrastromatica* extract solutions	AM: APC AO: FFA, TVB-N, TBARS	AM: Fillets treated with seaweed extract had lower APC values than control. AO: Fillets dipped in seaweed extract solutions had lower FFA, TVB-N and TBARS values than control.	Deepitha et al. (2021)
Rainbow Trout (*Oncorhynchus mykiss*) fillets	Fillets dipped in *Ulva ohnoi* and *Crassiphycus corneus* extract solutions	AM: Total viable psychrophilic bacteria AO: TBARS	AM: Seaweed extracts inhibited bacterial growth in fillets when compared to control. AO: Fillets dipped in seaweed extract solutions had lower TBARS values than control.	Sáez et al. (2021)
White shrimp (*Penaeus vannamei*)	Edible coating with *Gracilaria gracilis* extract	AM: TVC, psychotropic bacteria count and *Enterobacteriaceae*, TVB-N, TMA-N AO: PV, TBARS, PPO activity	AM: Increase of TVC, psychotropic bacteria count and *Enterobacteriaceae* in treated shrimps was slower. Shrimps coated with seaweed extract had lower TVB-N and TMA-N than control. AO: Coated white shrimps had lower PV and TBARS values, and weaker PPO activity than control.	Balti et al. (2020)
Frankfurters (pork sausages)	*Palmaria palmata*, *Porphyra umbilicalis*, *Himanthalia elongata* and *Undaria pinnatifida* powders	AM: TVC AO: TBARS	AM: TVC of *H. elongata*, *P. palmata* and *P. umbilicalis* sausages was similar to control sample. However, TVC of sausage with added *U. pinnatifida* was higher. AO: Frankfurters with added seaweeds had higher TBARS values than control.	Vilar et al. (2020)
Rainbow trout (*Oncorhynchus mykiss*) burgers	Bio-based *Himanthalia elongata* and *Palmaria palmata* (seaweed or seaweed extracts) edible films	AM: Total aerobic mesophilic and total psychrotrophic bacteria AO: TBARS	AM: *H. elongata* most effectively reduced microbial growth. AO: Films with seaweed extracts had lower TBARS values than films with seaweeds. All films had lower TBARS values than control, except film with *P. palmata* at the end of the storage.	Albertos et al. (2019)
Fish fingers made with silver carp surimi	*Ulva intestinalis* powder and extract	AO: PV, TBARS	AO: Fish finger with seaweed powder and extract both showed lower PV and TBARS values at the end of storage time.	Jannat-Alipour et al. (2019)
Pork patties	*Fucus vesiculosus* extracts	AO: TBARS	AO: Pork patties with seaweed extracts had lower TBARS values than control at the end of the storage.	Agregán et al. (2019)
Pork liver pâté	*Ascophyllum nodosum*, *Fucus vesiculosus* and *Bifurcaria bifurcata* extracts	AM: TVC, LAB counts, *Pseudomonas spp.*, molds and yeasts AO: CD, TBARS	AM: TVC was <3 log CFU/g at the end of the storage for all batches. LAB count was <1 log CFU/g. *Pseudomonas* spp., molds and yeasts were not found. AO: pork liver pâtés produced with extracts had lower CD and TBARS values than control.	Agregán et al. (2018)
Indian mackerel (*Rastrelliger kanagurta*)	*Gracilariopsis longissima* (formerly *Gracilaria verrucosa*) extracts in two concentrations in icing medium	AM: Total viable mesophilic count (TVMC) and total viable psychrophilic count (TVPC), TVB-N, TMA-N, biogenic amines	AM: Extracts significantly reduced microbial growth (TVMC – 6.5 and 5.23 log CFU/g, TVPC – 6.56 and 6.3 log CFU/g at day 15 of storage) and prolonged the shelf-life of Indian mackerel. Lower TVB-N, TMA-N and biogenic amines values were found in Indian mackerel when seaweed was incorporated in the icing medium.	Arulkumar, Paramasivam, and Miranda (2018)
Turkey meat sausages	*Gongolaria barbata* (formerly *Cystoseira barbata*) extract	AO: TBARS	AO: TBARS values were significantly lower in sausages formulated with seaweed extracts.	Sellimi et al. (2018)

Table 3. (Continued)

Food model	Seaweed or extract used in the experiment	Investigated parameters in foods to determine antimicrobial (AM) and/or antioxidant (AO) properties	Salient findings	References
Yellowfin tuna (*Thunnus albacares*) fillets	Edible coating with *Codium* spp. and *Fucus vesiculosus* extracts	AM: TVC, TVB-N AO: TBARS	AM: Shelf-life was prolonged for 3 days, coated fillets and control ones had 2 log cycles difference. *F. vesiculosus* extract showed higher antimicrobial activity. Coatings with extracts had lower TVB-N values than control. Only control exceeded TVB-N recommended limit at the end of storage. AO: Coatings with extracts had lower TBARS values than control.	Vala et al. (2017)
Chicken meat sausages	*Kappaphycus alvarezii* powder	AO: TBARS	AO: Sausages with seaweed powder had lower TBARS than control.	Pindi et al. (2017)
Pacific white shrimp (*Litopenaeus vannamei*)	Shrimps dipped in *Neopyropia yezoensis* (formerly *Porphyra yezoensis*) extracts	AM: TVC, TVB-N AO: TBARS, PPO activity	AM: Microbial growth was significantly reduced and shelf-life was prolonged. The control group TVC was 6.23 log CFU/g at day 4, while treated shrimps had similar results at day 8. Seaweed extracts inhibited the increase of TVB-N. AO: Seaweed extracts inhibited the increase of TBARS and PPO activity.	Li, Liu, et al. (2017)
Tuna jerky	*Sargassum wightii* extract	AM: APC, yeast and mold count, and *E. coli*/ coliform count	AM: APC was lower in tuna jerky when seaweed extracts were used. No *E. coli*, yeast or mold was found in all samples.	Hanjabam et al. (2017)
Yogurt	*Ascophyllum nodosum* and *Fucus vesiculosus* extracts	AM: *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* counts AO: TBARS	AM: tested bacteria were not affected by adding seaweeds extracts. AO: Yogurts containing seaweed extracts had significantly lower TBARS values than control.	O'Sullivan et al. (2016)
Fuji apples	Apple wedges immersed in *Fucus spiralis*, *Bifurcaria bifurcata*, *Codium tomentosum* and *Codium vermilara* extracts solutions	AO: PPO and POD activity	AO: The highest inhibition effect in PPO and POD activity was found for *C. tomentosum* extract coating.	Augusto et al. (2016)

*TBARS – 2-thiobarbituric acid-reactive substances; FFA – free fatty acids; APC – aerobic plate count; TVC – total viable counts; LAB – lactic acid bacteria; CFU – colony-forming unit; TVB-N – total volatile basic nitrogen; TMA-N – trimethylamine; PV – peroxide value; CD – conjugated dienes; PPO – polyphenol oxidase; POD – peroxidas.

purified compounds should also be considered (Skroza et al. 2019). Moreover, attention should be given to choosing the best drying and extraction methods with optimal parameters for each seaweed to produce extracts with the highest antimicrobial activity (Čagalj et al. 2021).

Dietary fiber

Dietary fiber consists of a mixture of plant carbohydrate polymers, both oligosaccharides and polysaccharides that may be associated with lignin and other non-carbohydrate components such as polyphenols. There are two fractions of dietary fiber, a soluble fiber that forms viscous gels in contact with water and insoluble fiber that retains water and increases fecal mass (Elleuch et al. 2011; Peñalver et al. 2020). Seaweeds are considered a good source of dietary fiber, as most of their structural polysaccharides can be considered as fiber since humans cannot digest them (Gomez-Zavaglia et al. 2019). The average content of soluble and insoluble fiber in seaweed is 24.5 g/100 g and 21.8 g/100 g, respectively (Peñalver et al. 2020). Due to the high content of dietary fiber, seaweeds can be a rich source of prebiotics (Gomez-Zavaglia et al. 2019), however, further research is necessary for their incorporation in functional foods.

Other applications in food industry

Besides antioxidants and antimicrobials, seaweeds' bioactive compounds (minerals, hydrocolloids, mannitol, and pigments) are applied in functional food products as nutritional supplements of minerals (calcium, iodine, selenium, iron, etc.) and vitamins, food coatings, and gelling, thickening, emulsifying, and film-forming agents (Qin 2018). Seaweed hydrocolloids are applied in ice cream, beer, fruit drinks, puddings, wine, jelly candies, and other foods as additives because of their numerous functional properties such as inhibition of crystallization, clarifying, flocculating, suspending and clouding agents, etc. (Qin 2018). Carrageenan, agar, and alginate are being used to produce edible coatings and films, active packaging materials, and intelligent packaging concepts (Perera et al. 2021). However, due to their high production costs, researchers are currently investigating the production of edible

Table 4. Some sulfated polysaccharides isolated from seaweed and their pharmacological effects.

Species	Pharmacological effect	References
Sulfated polysaccharide isolated from Monostroma nitidum	Antiviral activities against viruses (human immunodeficiency virus type 1 (HIV-1) and herpes simplex viruses (HSVs))	(Lee, Koizumi, et al. 2010)
Fucoidan isolated from Sargassum sp. and Fucus vesiculosus	Lung and skin cancer-preventive effect	Ale et al. (2011)
Sulfated polysaccharides isolated from Saccharina japonica	Antitumor activity breast cancer melanoma cell lines	Vishchuk, Ermakova, and Zvyagintseva (2011)
Sulfated polysaccharide isolated from Solieria filiformis	Analgesic activity	De Araújo et al. (2011)
Sulfated polysaccharide isolated from Ecklonia cava	Anticoagulant activity	Wijesinghe, Athukorala, and Jeon (2011)
Sulfated polysaccharide isolated from *Crassiphycus birdiae* (formerly *Gracilaria birdiae*)	Anti-inflammatory activity	De Sousa Oliveira Vanderlei et al. (2011)
Sulfated polysaccharide isolated from Ulva clathrate (formerly Enteromorpha clathrate)	Anticoagulant activity	Qi et al. (2012)
Sulfated polysaccharides isolated from Saccharina japonica	Anticoagulant activity	Jin et al. (2013)
Sulfated polysaccharides isolated from Ulva lactuca (formerly Ulva fasciata), Gloiopeltis furcata, and Sargassum henslowianum	Antitumor activities	Shao, Chen, and Sun (2013)
Sulfated polysaccharide, fucans, isolated from Sargassum vulgare	Anticoagulant, anti-inflammatory, antithrombotic effects	Dore et al. (2013)
Polysaccharides isolated from green Ulva linza (formerly Enteromorpha linza)	Anticoagulant activity	Wang et al. (2013)
A phlorotannin derivative isolated from *Ecklonia cava*	Anti-diabetic activity	Kang et al. (2013)
Sulfated polysaccharides isolated from *Monostroma nitidum*	Hypolipidemic, and anti-inflammatory activities	Hoang et al. (2015)
Rhamnan sulfate isolated from Monostroma nitidum	Obesity prevention and for reducing the prevalence of obesity-related diseases.	Zang et al. (2015)
Sulfated polysaccharide isolated from Gayralia oxysperma (formerly Monostroma oxyspermum)	Anticoagulant activity	Seedevi et al. (2015)
Sulfated Polysaccharide isolated from Turbinaria conoides	Anticancer activity	Delma et al. (2015)
Sulfated polysaccharide isolated from the Codium subtubulosum (formerly Codium divaricatum)	Anticoagulant activity	N. Li et al. (2015)
Phlorotannin	Anti-tumor activity	Yang et al. (2015)
Ecklonia cava phlorotannins	Cytotoxic effect	Ahn et al. (2015)
Dieckol-rich extract	Anti-diabetic activity	Lee and Jeon (2015)
Native carrageenan extracted from Kappaphycus alvarezii	Anticancer activity inhibition on the growth of breast, colon, liver, and osteosarcoma cell	Suganya et al. (2016)
Sulfated Polysaccharide isolated Sargassum ilicifolium (formerly Sargassum cristaefolium)	Anti-inflammatory activity	Wu et al. (2016)
Sulfated polysaccharide isolated from Sargassum horneri	Anti-inflammatory activity	Sanjeewa et al. (2017)
Sulfated polysaccharide isolated from Sargassum fusiforme	Antitumor activity HepG-2 cell proliferation inhibition	Yu et al. (2017)
Sulfated polysaccharide isolated from *Monostroma angicava*	Anticoagulant activity	N. Li et al. (2017)
Sulfated polysaccharide isolated from *Neo*porphyra *haitanensis* (formerly *Porphyra haitanensis*)	The immunoregulatory activity	Q. M. Liu et al. (2017)
Sulfated polysaccharide isolated from *Ericaria crinite* (formerly *Cystoseira crinita*)	Antidiabetic and antihypertensive effect	Ben Gara et al. (2017)
Sulfated polysaccharide fractions extracted from *Saccharina japonica* (formerly *Laminaria japonica*)	The renal protective effect	X. Li et al. (2017)
Phlorotannin derivatives obtained from *Ecklonia cava*	Anti-diabetic activity	Park et al. (2018)
Bioactive peptides	Anti-hypertensive activity	(Admassu et al. 2018; Qu et al. 2010)
Sulfated polysaccharide isolated from *Monostroma angicava*	Anticoagulant activity	X. Liu et al. (2018)
Fucoidans isolated from Saccharina japonica (formerly Laminaria japonica)	Anticancer activity	Zhao, Xu, and Xu (2018)
Sulfated polysaccharide isolated from Gelidium pacificum	Anti-inflammatory activity	Cui et al. (2019)
Polysaccharides isolated from Ecklonia maxima, Gelidium pristoides, and Ulva rigida	Neuroprotective potentials *-inhibitory potentials against pathological processes involved in the development and progression of Alzheimer's disease*	Olasehinde et al. (2019)
Phlorotannin-rich seaweed extracts	Anti-diabetic activity	Catarino et al. (2019)
Sulfated polysaccharides of seaweeds Portieria hornemannii, Spyridia hypnoides, Asparagopsis taxiformis, Centroceras clavulatum and Padina pavonica	Inhibiting HeLa cell line	Arunkumar et al. (2021)
Cystoseira compressa phlorotannin extract	Anti-diabetic activity	Gheda et al. (2021)

films directly from raw seaweeds without hydrocolloids extraction (Lim et al. 2021). In relation to harvesting location and part of the algal tallus used, seaweeds can be applied as flavor enhancers. They contain several volatile and nonvolatile compounds, such as monosodium glutamate, monosodium aspartate, nucleotides, peptides and organic acids, that generate the *umami* flavor (Figueroa, Farfán, and Aguilera 2021). This segment is still under research and it has no large industrial application so far.

Pharmaceuticals application

The burden of non-communicable diseases is constantly increasing globally (Erpel et al. 2020). According to World Health Organization (WHO), cardiovascular diseases (CVDs) are the most common causes of death worldwide, and it is estimated that 17.9 million people have died due to CVDs. Cancer is the second leading cause of death globally. About 422 million people suffer from diabetes (WHO 2021). Scientists are focused to explore the natural bioactive compounds that can prevent or treat diseases (Erpel et al. 2020). Natural products called non-pharmaceutical materials have been used to prevent or treatment of several health problems. The use of natural products as pharmaceutical ingredients has been attracting great interest since ancient times (Sang, Hung, and Se-Kwon 2019). Seaweed is a good candidate for preventing or curing the above-mentioned diseases because of biological activities (Brown et al. 2014; Sang, Hung, and Se-Kwon 2019). Epidemiological studies comparing the relation between seaweed consumption and the incidence of chronic diseases such as cancer, hyperlipidemia, and CVDs is demonstrated that the incidence of these diseases is lower in the Japanese population consuming seaweed in their diets compared to Western diets (Brown et al. 2014). Seaweeds containing pharmaceutical agents are among the natural products used for the preparation of pharmaceuticals (Sang, Hung, and Se-Kwon 2019). Whole seaweed or their extracts have traditionally been used to treat joint pain, inflammation, as well as burns (Sutapa, Dhruti, and Gopa 2017).

In recent years, interest in marine organisms, including seaweed, has increased by pharmaceutical companies for novel drug delivery systems from natural products. The excellent hydrogel-forming capacity and hypoallergenic nature of seaweed offer a wider usage area for medical purposes, especially in drug delivery and tissue engineering. A significant part of seaweed-derived pharmaceutical agents is used for potential applications in the pharmaceutical industry. Particularly, polysaccharides have numerous biological activities. Seaweed polysaccharides contain hydrophilic groups such as carboxyl, sulfate, and hydroxyl groups that can easily interact with biological tissues. Sulfated polysaccharides with anionic sulfate groups prevent aggregation during blood circulation due to reduced interaction with serum proteins (Abdul Khalil et al. 2017). These polysaccharides naturally occur or can be synthesized artificially due to their various chemical and biological functions (Wang et al. 2013). The biological activity of sulfated polysaccharides depends on their chemical composition, molecular weight, monosaccharide composition, sulfate content, and the position of the sulfate group (Lopes et al. 2017; Wang et al. 2013; Zhao et al. 2018). The main sulfated polysaccharides found in seaweed are carrageenan, ulvan, fucoidan, and alginic acid isolated from red algae, green algae, and brown algae, respectively (Cunha and Grenha 2016; Sutapa, Dhruti, and Gopa 2017). They act as nanocarriers in nanoencapsulation systems (Ceylan, Sengor, and Yilmaz 2017; Ceylan et al. 2018). These polymers used in industrial applications are derived from only a few specific types of seaweed. These sulfated polysaccharides have a variety of biological activities and immunomodulatory activities (Zhong et al. 2020; Arunkumar et al. 2021). For example, it has been stated carrageenan derived from red seaweeds shows antitumor, antiviral, and anticoagulant activities (Cunha and Grenha 2016; Eccles et al. 2010). Experimental findings from previous studies revealed that the replication of some enveloped viruses is inhibited by carrageenan due to interference with virus adsorption. Also, some steps of a virus life cycle in host cells are inhibited by carrageenan (Wang et al. 2011), which demonstrated that replication, mRNA expression, and protein production of influenza A (H1N1) virus are inhibited by carrageenan.

Eccles et al. (2010) determined the effect of carrageenan nasal spray on the severity of common cold symptoms. For this purpose, a randomized, double-blind, placebo-controlled exploratory trial was done, and 35 human subjects exhibiting the early symptoms of common cold received carrageenan (0.12%) found in a saline solution (three times daily and four days). As a result, it was stated that carrageenan nasal spray application reduced the symptoms of the common cold and the viral load. Lopes et al. (2017) analyzed the activity of polysaccharides isolated from *Ulva compressa* (Chlorophyta) against the herpes simplex virus (HSV). They revealed that the inhibitory effect of a sulfated heteroglycuronan was maintained until 4 h post-treatment and it was obtained the 100% of viral inhibition at 100 µg/ml.

In addition to sulfated polysaccharides, it has been demonstrated by numerous studies that phlorotannins, a polyphenol obtained from brown algae, have numerous bioactivities such as anti-cancer, anti-viral, inflammatory, anti-diabetes, and anti-obesity activities (Sang, Hung, and Se-Kwon 2019; Zhong et al. 2020). Phlorotannins protect seaweed from natural enemies including chemicals, pathogen microorganisms as well as UV radiation and digestive inhibitors (Abdelhamid et al. 2019; Liu et al. 2020). The pharmaceutical values of phlorotannins are related to their structure and, the degree of polymerization. Phlorotannins having a wide variety of biological activities are believed to be one of the most promising candidates which can be developed as pharmaceuticals (Kim and Himaya 2011). In this sense, it has been stated that dieckol and phloroglucinol classified as phlorotannins can improve the effects of anticancer drugs and provide protection against the cytotoxicity of irradiation and chemotherapy (Erpel et al. 2020). It was evidenced that phenolic compounds composed of a large group such as phlorotannins inhibited α-amylase and α-glucosidase (Catarino et al. 2019; Park et al. 2018; Firdaus and Awaludin Prihanto 2014; Lordan et al. 2013; Pantidos et al. 2014).

Seaweed contains many bioactive peptides which have anti-hypertensive activity (Admassu et al. 2018; Qu et al. 2010). A cytotoxic compound Kahalalide F (KF) is a marine-derived cyclic depsipeptide produced by the green alga *Bryopsis pennata*. It entered phase II clinical trials in Spain (PharmaMar) (Alves et al. 2018). The bioactive marine-derived molecules have anti-obesity, antidiabetic (Catarino et al. 2019), antihypertensive (Admassu et al. 2018), anticoagulant (Liu et al. 2018), anti-inflammatory (Wu et al. 2016), antiviral (Lopes et al. 2017), and antitumor (Zhao et al. 2018; Shao, Chen, and Sun 2013) properties. The species studied for biological activities in the last decade are presented in Table 4.

Marine organisms provide an important contribution to the drug development process. Traditionally, research on marine organisms has mainly focused on macro-organisms including algae, sponges, corals, and other marine invertebrates. However, although a large number of biologically active compounds are isolated from marine organisms, compounds marketed or formalized are relatively few (Calado et al. 2018). The main reasons limiting the usage of marine organisms are as follows: in addition to the challenges in any drug discovery process, other factors include the limitations in continuous supply of compounds due to seasonality of algae, difficulties in harvesting, isolation and purification procedures, and insufficient investments by pharmaceutical companies (Calado et al. 2018; Martins et al. 2014; Pereira and Costa-Lotufo 2012). Marine-derived drugs on the market began in the early 1950s with Bergmann, who isolated and identified two nucleosides, called spongouridin and spongotimidine, from the sponge *Cryptotethya crypta*, formerly known as *Tethya crypta*. In the last 50 years, more than 30,000 new compounds of marine-derived have been isolated and more than 300 patents have been approved. The drugs contain marine-derived compounds approved by FDA and EMA, namely Cytarabine, Ziconotide, Omacor, Trabectedin, Lurbinectedin, Eribulin Mesylate, Brentuximab Vedotin, and Iota Carrageenan. Iota Carrageenan is approved as an over-the-counter (OTC) drug. Iota-carrageenan (Carragelose®) is the first commercial product obtained from algae. The company Marinomed Biotechnologie GmbH, produced the Carragelose® using the iota-carrageenan found in the Rhodophyceae seaweed. The spray is effective against the early symptoms of the common cold and many respiratory viruses. The function of nasal spray is to create a physical barrier and prevent the attachment of viruses to the host cells (Alves et al. 2018; Calado et al. 2018; Gallimore 2017; Martins et al. 2014).

Various biological properties including antioxidant, anti-obesity, anti-diabetic, anticancer, and antimicrobial activities of fucoxanthin have been investigated for a long time (Karpiński and Adamczak 2019) and commercial preparations of fucoxanthin have been prepared. Xanthigen® is the commercial formulation of fucoxanthin having anti-obesity activity and serving as a nutraceutical (Wan-Loy and Siew-Moi 2016).

Although the marine-derived active and inactive ingredients are used in drugs, the number of drugs derived from seaweed is limited. Most of the studies have focused on the potential biological activities of components found in seaweed. Especially sulfated polysaccharides including alginate and carrageenan have been used as inactive ingredients in drug formulation. They act as encapsulating and gel formation agents, taste maskers, and release control agents. Also, alginate usually contains bicarbonate salt converting to carbon dioxide. Thus, it provides the polymer to float on the surface of the gastric juice (Liu et al. 2015; Szekalska et al. 2016). The list of commercialized drugs containing algae-derived ingredients is presented in Table 5.

There are many compounds obtained from seaweed, but few of these compounds are used as pharmaceutical agents. Among them, sulfated polysaccharides and phlorotannins are the most important group of biologically active substances that determine the pharmacological value of algae. Therefore, the use of seaweed components is recommended for pharmacological applications.

Biomedicals applications

In recent years, researchers are looking for new active ingredients, particularly in marine organisms especially in the very large and heterogeneous group of seaweeds. Some isolated ingredients from seaweed such as alginates or carrageenan have been used medicinally for a long time (Table 6).

Seaweeds-based biomaterials

The natural active biomaterials are gaining more and more interest in the field of modern medicine due to their abundance, low cost and biocompatibility (Song et al. 2018). Besides, seaweeds are rich in chlorophyll. The chlorophyll is absorbed at 650 nm and has the ability of fluorescence and photoacoustic imaging. Therefore, seaweeds-based biomaterials are recognized as potential photoacoustic contrast agents (Rahmati, Alipanahi, and Mozafari 2019). In many areas, alginic acid and alginates are used because of their characteristic sol and gel properties, their emulsion and suspension stabilizing effect as well as film formers and cation exchangers.

Magnetized seaweeds as micro-robots for medicine

The micro-robots used in medicine are able to place active substances in a targeted manner, even in inaccessible tissues and body cavities, or for imaging processes. The robots should be specifically controlled, biodegradable and usable as often as required without harming the patient and the treatment with them to be of minimally invasive medical interventions. Biohybrid micro-swimmers for biomedical applications have been developed integrating seaweeds species with special shape or structure. For developing biohybrid magnetic micro-robots, diatoms, intact three-dimensional (3D) spiral morphology, is a perfect candidate for micro-nano medicine.

Seaweeds have a strong adsorption capacity to certain micro-molecules and nanoparticles or metal ions. They can be used to produce membranes for medical devices, besides

Table 5. Commercial drug list containing the seaweed-derived active or inactive ingredient.

Brand name	Active-inactive ingredient	Indications	References
Aricept ODT	Carrageenan,	Aricept ODT is used in the treatment of Alzheimer's disease	(Sozio et al. 2012; Sutthapitaksakul, Dass, and Sriamornsak 2021; Takeuchi et al. 2017)
Bromocriptine Mesylate	Carrageenan	Bromocriptine is used in the treatment of hyperprolactinemia; diabetes, type 2	Oshige et al. (2019)
Dexilant	Carrageenan	Dexilant is used in the treatment of Barrett's esophagus; GERD; erosive esophagitis	
Cardura	Carrageenan	Doxazosin is used in men to treat the symptoms of an enlarged prostate	(FDA 2021)
Jalyn	Carrageenan	5-alpha-reductase inhibitors, Antiadrenergic agents, peripherally acting	(FDA 2021)
Donepezil Hydrochloride	Carrageenan	Donepezil is used to treat dementia in people who have Alzheimer's disease	(FDA 2021; MedlinePlus, 2021)
Dutasteride and Tamsulosin Hydrochloride	Carrageenan	It used to treat benign prostatic hyperplasia	(FDA 2021; MedlinePlus, 2021)
Carragelose®	iota-carrageenan	It is to create a physical barrier and prevent the attachment of viruses to the host cells	(Alves et al. 2018; Calado et al. 2018; Gallimore 2017; Martins et al. 2014)
Gaviscon	Sodium alginate	Gaviscon is used for the treatment of reflux symptoms	Rohof et al. (2013)
Metaxalone	Alginic acid	It is used with rest, physical therapy, and other measures to relax muscles	(Anonymous 2021; FDA 2021; MedlinePlus, 2021)
Glyburide	Sodium alginate	Glyburide lowers blood sugar	(Anonymous 2021; FDA 2021; MedlinePlus, 2021)
Tarka	Sodium alginate	Tarka is a prescription medicine used to treat the symptoms of High Blood Pressure (Hypertension)	(Anonymous 2021; FDA 2021; MedlinePlus, 2021)
Gastrotuss® baby sirup	Magnesium alginate,	It is used reflux treatment in children and infants	Szekalska et al. (2016)
Xanthigen	Fucoxanthin,	Anti-obesity effects, weight control	(Wan-Loy and Siew-Moi 2016)

being considered micro-transporters for a wide variety of substances. The medical membrane devices are optimized for contact with body fluids, for the separation of toxins or the reduction of fouling. In this way, the membrane surfaces can be improved to enable the colonization and growth of cells or to reduce the adherence of undesirable microbes (Delasoie and Zobi 2019).

Micro 3D prints for biomedical cell culture

Shrinking 3D printing to micro-format will enable completely new applications in biomedical research, in preclinical studies or new approaches in regenerative medicine – the behavior of cells can be better studied in a 3D environment. Cells need ideal conditions to feel comfortable and develop normally. 3D structures require an exact interaction of software and hardware in combination with newly developed printing materials, as special organic inks. The material must be very reactive and cure with pinpoint accuracy, but it must not be harmful to the cells. The cells can be mixed into the printing material and printed directly or placed on sterile, prefabricated structures. The complex structures reflect the natural microenvironment of the cell and thus influence its behavior. If cells are completely embedded in the material, this must also be permeable to nutrients in order to ensure the survival and reproduction of the cells. Different seaweeds polysaccharides with gelling capacity can be adapted to serve as either 2-D or more physiologically relevant 3-D culture systems (Lee and Mooney 2012).

These kind of structures can also be manufactured directly in a microfluidic chip. The new production possibilities enable completely new approaches in in vitro research. The technology allows the production of semipermeable membranes for the investigation of transport mechanisms. The permeability of the structure depends on the selected pressure parameters and can therefore be adapted to the properties of the tissue to be examined. Living cells of choice can be mixed into the polymeric seaweeds-based the material and printed directly. Cells embedded in a corresponding matrix can be used for 3D in vitro cell tests, which are becoming increasingly important in cell culture, tissue regeneration and pharmaceutical research (Edmondson et al. 2014). The corresponding matrix can be out of a hybrid hydrogel seaweeds-derived polysaccharides: agarose or alginate (also alginic acid and algin). (Stock et al. 2016; Langhans 2018; Jönsson et al. 2020).

Regenerative medicine and in tissue engineering

Regenerative medicine is based on the patient's own regeneration mechanisms, which are stimulated by a combination of compatible cells, stimulation factors and so-called scaffolds. The framework enables a higher cell density at the time of implant insertion, supports the defect area mechanically during the healing process and increases the possibility of tissue self-organization. Tissue engineering for an array of therapeutic applications is a multidisciplinary field dedicated to engineering for malfunctioning tissues, repairing injured or organs as a substitute to whole organ transplantation. For the development of ideal natural polymer-derived bioengineered scaffolds, some requirements have to be considered: high porosity with huge specific surface area, designable surface chemistry sufficient structural integrity, appropriate distribution of pore size

Table 6. Seaweeds polysaccharides for biomedical applications.

Seaweed polysaccharide	Product name	Application	Mode of action	Reference
Betaphycus gelatinus (formerly Eucheuma gelatininum), Saccharina japonica (formerly Laminaria japonica), degraded Gracilariopsis lemaneiformis (formerly Gracilaria lemaneiformis), Neopyropia yezoensis (formerly Porphyra yezoensis), Undaria pinnatifida and Sargassum fusiforme polysaccharides		oxalate-triggered injured human kidney epithelial cells (HK-2)	cell morphology and viability bioassay	Bhadja et al. (2016)
k-Carrageenan	human adipose stem cells (hASCs) encapsulated	cartilage tissue damages	proliferation, viability, and chondrogenic differentiation of human stem cells	Popa et al. (2015)
Laminaran		matrix deposition and accelerate the tissue-generation process	produce a dermis by culturing monolayer human skin fibroblasts in the presence of collagen-I deposition increasement	Ayoub et al. (2015)
Fucoidan		mineral deposition in the bone matrix	increase the expression of type-I collagen, osteocalcin, and the activity of alkaline phosphatase enzyme	Cho et al. (2009)
		osteoarthritis treatment	collagen-triggered arthritis	Park et al. (2010)
	polycaprolactone-fucoidan containing biocomposites	substitute to commercial bone -> foster the bone tissue-regeneration capability	promote human osteoblastic proliferation, and type-I collagen expression enhanced ALP activity with efficient mineralization of bone tissue	Changotade et al. (2008) Jin and Kim (2011) Lee et al. (2012)
	fucoidan containing chitosan-alginate (Chi-Alg-fucoidan)	substitute for bone implantation		
Fucoidan and laminarin	polysaccharides incorporated electrospun polycaprolactone (PCL) nanofibrous mat	modulate astrocyte activities nanoscaffold for the treatment of injuries in central nervous system	increase astrocytes	Jung et al. (2012)
Cellulose	seaweed cellulose-based scaffolds	tissue engineering	in-vitro mammalian cell growth	(Hickey and Pelling 2019; Bar-Shai et al. 2021)
	cellulose acetate	cardiac scaffolds cartilage tissue engineering		Entcheva et al. (2004)
Agarose	hydrogels	cartilage tissue neural tissue engineering	pro-chondrogenic	Awad et al. (2004) (Lynam et al. 2015; Zarrintaj et al. 2017)
	chitosan-agarose (CHAG scaffold)	cartilage extracellular matrix	Well attach and grow of Human Wharton's Jelly-Mesenchymal Stem Cells and L929 cells	Merlin Rajesh Lal, Suraishkumar, and Nair (2017)
Alginate		reconstruct lost bone treat various organ defects regeneration of bone and cartilage stem-cell transplantation		
	chitosan-alginate gel/bone morphogenetic protein-2/mesenchymal stem cells blended chitosan/alginate hybrid scaffolds	injectable biomaterial for new bone tissue regeneration	accelerated vascularization and promoted osteogenesis following embedment in the bone	Park et al. (2005) Li et al. (2005)
	porous 3D matrix composed of calcium phosphate cement in combination with alginate	novel scaffold for bone-tissue engineering and drug-delivery applications		Lee et al. (2011)
	alginate, chitosan, collagen and hydroxyapatite-based composite	bone tissue regeneration		Yu et al. (2013)
	alginates-based gel modified with proline-histidine-serine-arginine-asparagine	bone-tissue engineering		Nakaoka et al. (2013)
	hitosan-alginate (Chi-Alg)	substitute for bone implantation	greater cell proliferation, promising compatibility toward MG-63, and increased secretion of alkaline phosphatase mineralization and adsorption of protein	Venkatesan, Bhatnagar, and Kim (2014)
	scaffold combining alginate, gelatin and 2-hydroxyethyl methacrylate	proliferation of chondrocytes		Singh et al. (2019)
	alginate scaffolds	cartilage tissue engineering		Gharravi et al. (2012)
	3D alginate scaffolds	co- administration of PRP and/or chondrogenic supplements	differentiation of ADSCs into mature cartilage	Beigi et al. (2018)

and controllable biodegradability with degradation rate closely matching the rate of new tissue formation (Ayoub et al. 2015; Lalzawmliana et al. 2019; Singh et al. 2019). Table 6 shows the use of the seaweeds polysaccharides for biomedical applications.

Cosmetic and dermatological applications

The skin protects the body from environmental factors including temperature, solar UV radiation and pollutants. It is in direct contact with the environment and therefore undergoes aging because of environmental factors (Fisher et al. 2002). In addition to chronological aging, factors such as UVR exposure, pollution and dietary habits contribute to skin aging (Dobos et al. 2016; Mesa-Arango, Sv, and Sanclemente 2017). Chronic exposure to UV irradiation can lead to the excessive production of reactive oxygen species (ROS), which degrade the integrity of skin (Yin, Chen, and Hamblin 2015). Moreover, exposure of the skin to particulate contaminants in air such as dust, PAHs and NO3 may cause skin aging, inflammation or allergic skin conditions (Drakaki, Dessinioti, and Antoniou 2014). Thus, the demand for skin care products has increased to delay skin aging. The use of seaweed metabolites in cosmetic and dermatological applications has increased in recent years, in terms of cosmeceutical properties, 50 brown, 35 red and 18 green algae species have been reported to have potential skin care effects (Thiyagarasaiyar et al. 2020).

Antiwrinkle activity

The major cause of skin wrinkling is loss of collagen and hyaluronic acid in dermal layer. *Matrix metalloproteinases* (MMPs), elastase and hyaluronidase are enzymes that degrades collagen, elastin and hyaluronic acid (Fernando et al. 2018; Thiyagarasaiyar et al. 2020). Thus, the compounds with hyaluronidase, collagenase and elastase inhibitory activity may have potential to be used as anti-wrinkle products (Berthon et al. 2017). Seaweed polysaccharides play a major role inhibition of collagenase and elastase activity (Jesumani et al. 2019). Antioxidant activity of the polysaccharides of five seaweed species has been investigated and it has been found that five samples had the strongest radical scavenging effect (Zhang et al. 2010) (Table 7). Fucoidans are well-known seaweed polysaccharides for their radical scavenging, antioxidant and anti-inflammatory activities. These compounds can inhibit matrix metalloproteases (MMPs) involved in the degradation of connective tissues (Fernando et al. 2018). It was stated that that fucoidan extract from *Chnoospora minima* and *Sargassum polycystum* (Phaeophyceae) suppresses collagenase and elastase activities, and has potential as antiwrinkling cosmeceutical (Fernando et al. 2018). Apart from that, polysaccharide extract of *Ulva* sp. and protein extract of *Ulva intestinalis* have shown antiaging effect by inducing hyaluronic acid and collagen synthesis (Table 7) (Adrien et al. 2017; Bodin et al. 2020). Phlorotannins, eckol and dieckol extracted from *Eisenia bicyclis, Ecklonia cava* and *E. cava* subsp. *stolonifera* (formerly *E. stolonifera*) (Phaeophyceae) have showed strong inhibition on the MMP1 expression (Joe et al. 2006). In another study, the crude phlorotannin extracts of *Eisenia bicyclis* and *E. cava* subsp. *kurome* (formerly *E. kurome*) (Phaeophyceae) inhibited hyaluronidase activity stronger than well-known commercial inhibitors such as catechins and sodium cromoglycate (Shibata et al. 2002).

Photoprotection activity

Sunlight is known to play an important role in skin aging (Farage et al. 2008). The use of photoprotection products help to avoid UV induced sunburn, photoaging, hyperpigmentation and skin cancer. The bioactive component of seaweeds included antioxidant substances such as fucoxanthin, carotenoids and phenols are capable of absorbing UVR and keep the human fibroblast cells from UV induced damage (Jesumani et al. 2019). Fucoxanthin isolated from *Sargassum siliquastrum* (Phaeophyceae) has the ability to protect against oxidative stress induced by UVB radiation (Heo and Jeon 2009). Moreover, fucoxanthin can scavenge intracellular ROS generated by UVB. Another bioactive compound, astaxanthin is a xanthophyll carotenoid, shows strong antioxidant activity and protects from peroxidation by scavenging the radicals (Jesumani et al. 2019). A phlorotannin, dieckol isolated from *Ecklonia cava* has prominent protective effects on UVB radiation-induced cell damages (Heo et al. 2009). Besides this, eckol, dieckol, dioxinodehyroeckol, and bieckol are effective for the inhibition of MMPs in human dermal fibroblast cells (Jesumani et al. 2019). Mycosporine-like amino acids are secondary metabolites produced by aquatic organisms, which protect against solar radiation. Mercurio et al. (2015) reported that the extract of *Porphyra umbilicalis* (Rhodophyta) containing mycosporine-like amino acids can act as UV filter and prevent UV-induced DNA damage and inflammation. In another study, Kim et al. (2013) reported that sargachromanol E from *Sargassum horneri* (Phaeophyceae) showed a protective effect against cell damage and inhibition of collagen degradation induced by UVA related activation of collagenases.

Wound healing functions

Skin wounds occur because of a damage or surgical procedure and provide an entry point for various infections (Baliano et al. 2016). Bioactive compounds derived from seaweeds such as tannins, triterpenoids and alkaloids have been found to affect the wound healing process and they can be potential as wound drugs (Premarathna et al. 2019; Premarathna et al. 2020). Fard et al. (2011) reported that *Kappaphycus alvarezii* (formerly *Eucheuma cottonii*) (Rhodophyta) possesses several antioxidant compounds, which may be functional for the accelerated wound healing and ethanolic extract of this species is more effective than the aqueous extract by 20% in wound healing. Baliano et al.

Table 7. The effects of bioactive compounds derived from seaweeds in dermatological and cosmetic applications.

Seaweed	Bioactive compound	Activity	Effect	References
Brown seaweeds				
Chnoospora minima	Fucoidan	Tyrosinase inhibitory activity Collagenase and elastase inhibitory activity NO, INOS, COX-2, PGE_2 inhibitory activity	Skin whitening Antiwrinkling Anti-inflammatory effects	Fernando et al. (2018)
Ecklonia cava	Phlorotannin	Tyrosinase inhibitory activity	Skin whitening	Wang et. al. (2019)
Ecklonia cava subsp. *stolonifera* (formerly *E. stolonifera*)	Phlorotannin	Tyrosinase inhibitory activity	Anti hyperpigmentation	Kang et al. (2004)
Sargassum fusiforme (formerly *Hizikia fusiforme*)	Sulfated polysaccarides	Antioxidant activity	Antiwrinkling	Wang et al. (2018)
Sargassum ilicifolium	Aqueous extract	Wound healing activity	Cell proliferation	Premarathna et al. (2019)
Sargassum polycystum	Hexan extract	Tyrosinase inhibitory activity	Skin whitening	Quah et al. (2014)
Sargassum polycystum	Fucoidan	Tyrosinase inhibitory activity Collagenase and elastase inhibitory activity NO, INOS, COX-2, PGE_2 inhibitory activity	Skin whitening Antiwrinkling Anti-inflammatory effects	Fernando et al. (2018)
Sargassum siliquastrum	Fucoxanthin	UVB induced ROS inhibitory activity	UVB protection	Heo and Jeon (2009)
Spatoglossum asperum	Metanol extract	Antifungal activity	Skin protection	Pandithurai et al. (2015)
Turbinaria conoides	Phloroglucinol	Antioxidant, tyrosinase inhibitory activity	Skin whitening	Sari et al. (2019)
Undaria pinnatifida	Fucoidan	Tyrosinase inhibitory activity	Skin whitening	Wang et. al. (2019)
Red seaweeds				
Corallina pilurifera	Methanol extract	Free radical oxidation and MMP_2 inhibition activity	Antiphotoaging	Ryu et al. (2009)
Gelidium robustum	Ethanol extract	Antibacterial activity	Acne treatment	Muñoz-Ochoa et al. (2010)
Neoporphyra haitanensis	Sulfated polysaccarides	Antioxidant	ROS scavenging affect	Zhang et al. (2010)
Neopyropia yezoensis (formerly *Porphyra yezoensis*)	Peptide	Promote collagen synthesis	Antiaging	Kim et al. (2017)
Porphyra umbilicalis	Mycosporine-like amino acids	UV induced ROS inhibitory activity	UV protective effect	Mercurio et al. (2015)
Green seaweeds				
Ulva linza (formerly *Enteromorpha linza*)	Sulfated polysaccarides	Antioxidant	ROS scavenging effect	Zhang et al. (2010)
Halimeda tuna	Metanol extract	Antibacterial and antifungal activity	Pathogen treatment	Indira et al. (2013)
Ulva intestinalis	Aqueous extract	Collagen and hyaluronic acid production activity	Antiaging	Bodin et al. (2020)
Ulva australis (formerly *Ulva pertusa*)	Sulfated polysaccarides	Antioxidant	ROS scavenging effect	Zhang et al. (2010)
Ulva sp.	Sulfated polysaccarides	Hyaluronan production activity	Antiaging	Adrien et al. (2017)

(2016) investigated the wound healing potential of seaweed *Padina gymnospora* (Phaeophyceae) in vitro and they stated that the wound repair effect of *Padina* could be related to its fatty acid composition. In another study, an aqueous extract of *Sargassum ilicifolium* (Phaeophyceae) has shown a potential therapeutic agent for wound healing by promoting fibroblast proliferation (Premarathna et al. 2019) (Table 7). Moreover, Premarathna et al. (2020) studied the wound healing activity of aqueous extracts of twenty-three seaweeds in vitro and in vivo. The findings showed that healing process was significantly fast in the mice group treated with *Sargassum ilicifolum* by enhancing epithelialization and tissue proliferation.

Calcium alginate derived from seaweeds is used as an absorbent material in wound dressings. Calcium alginates can also act as hemostatic dressings, alginate-based materials dressings are indicated for bleeding wounds (Paul and Sharma 2014).

In recent years, more attention has been devoted to medical textiles with usage to healthcare products, where hygienic conditions are required. Bioactive compounds of seaweeds may be used for medical textile production. New natural and biodegradable products may be developed from these compounds with antioxidant and antimicrobial properties (Janarthanan and Senthil Kumar 2018; Lomartire et al. 2021).

Antimicrobial activity for skin problems

Microorganisms can cause problems such as acne on the skin, as well as cause infections by entering through a wound (Kumar et al. 2016). Secondary metabolites of seaweed have been known as potential sources of antibiotics, and therefore antimicrobial products of seaweed can be used to prevent acne (El-Shafay, Ali, and El-Sheekh 2016; Jesumani et al. 2019). Lee et al. (2014) reported that phlorotannin, fucofuroeckol-A isolated from *Eisenia bicyclis* showed high antibacterial activity against acne-related bacteria. Similarly, it has been reported that, methanol extracts from *Ecklonia cava, Ecklonia cava* subsp. *kurome* (formerly *Ecklonia kurome*) and *Ishige sinicola* (Phaeophyceae) may be used in the development of therapeutics for acne (Choi et al. 2011). Choi et al. (2014) found that phlorotannins dieckol and phlorofucofuroeckol-A obtained from *Ecklonia cava* have antimicrobial activity against *P. acnes*. The antibacterial activity of phlorotannins is due to inhibition of oxidative phosphorylation and their ability to bind with bacterial proteins that cause cell lysis (Shannon and Abu-Ghannam 2016).

Seaweeds also show antifungal activity owing to their secondary metabolites (Demirel et al. 2009; Freile-Pelegrín and Tasdemir 2019). This activity of seaweeds could be used in the treatment of fungal skin infections. Lee et al. (2010) found dieckol extracted from *Ecklonia cava* showed antifungal activity against *Trichophyton rubrum*. The methanolic extract of brown seaweed *Spatoglossum asperum* (Phaeophyceae) showed good antifungal activity against different dermatophytic species, *Candida albicans* and *C. tropicalis* (Pandithurai et al. 2015). In another study, extract of *Halimeda tuna* (Chlorophyta) showed antifungal activity against *Aspergillus niger, Aspergillus flavus, Alternaria alternaria, Candida albicans, Epidermophyton floccossum, Trichophyton mentagrophytes, Trichophyton rubrum, Penicillium* sp. and *Rhizopus* sp. (Indira et al. 2013) (Table 7).

It has been reported that seaweed extracts can protect cosmetic products against microbial spoilage due to their antimicrobial properties (Jesumani et al. 2019). In this context, phenolic compounds can be used as promising agents that can inhibit the growth of microorganisms and extend the shelf life of cosmetic products.

Skin whitening activity

Hyperpigmentation is caused due to excessive accumulation of melanin pigments in the skin (Bastonini, Kovacs, and Picardo 2016; Jesumani et al. 2019). Radiation from sunlight helps the synthase tyrosinase which causes the formation of melanin through melanogenesis (Joshi, Kumari, and Upasani 2018; Sari et al. 2019). Therefore, tyrosinase inhibitors are used to control hyperpigmentation or skin whitening (Jesumani et al. 2019; Sari et al. 2019). The natural tyrosinase inhibitors attract great attention in recent years for skin whitening sources. It has been reported that fucoxanthin of *Saccharina japonica* (formerly *Laminaria japonica*) (Phaeophyceae) suppressed tyrosinase activity in UVB-irradiated pigs and melanogenesis in UVB-irradiated mice (Berthon et al. 2017). Other secondary metabolite of brown seaweeds, phloroglucinol, could be involved in the control of pigmentation due to their tyrosinase inhibitory activity (Kang et al. 2004). Fernando et al. (2018) reported that fucoidans of *Chnoospora minima* and *Sargassum polycystum* (Phaeophyceae) showed skin-whitening effects. Similarly, Sari et al. (2019) found that ethanol extract of *Turbinaria conoides* showed antioxidant and tyrosinase inhibitor activity. The diphlorethohydroxycarmalol extract from *Ishige okamurae* (Phaeophyceae) and dieckol from *Ecklonia cava* showed stronger tyrosinase activity than commercial whitening agents (Heo et al. 2009; Heo et al. 2010). Quah et al. (2014) investigated the skin whitening potential of *Sargassum polycystum* and *Padina boryana* (formerly *Padina tenuis*) on human cell lines and guinea pigs, and they concluded that hexane extract *of Sargassum polycystum* is more promising as a skin whitening agent. Moreover, Wang, Cui, et al. (2019) analyzed the whitening effects of a mixture of fucoidan-rich extract of *Undaria pinnatifida* (Phaeophyceae), phlorotannin-rich extract of *Ecklonia cava*, and glycosaminoglycans from sea squirt. The mixture showed strongest whitening effect than those of each component alone. They reported that this mixture may be used as a whitening agent in the medical and cosmetic products.

Agriculture application

Increasing consumer awareness about healthy food has increased the importance of organic agriculture (Kyriacou and Rouphael 2018). Thus, organic producer/farmers have turned to using natural stimulants to increase crop yields (Bradshaw et al. 2012). In the last two decades, extracts of seaweeds (belonging to Rhodophyta, Chlorophyta and Ochrophyta) have been processed in various formulations and used in agriculture. Seaweeds are a rich source of bioactive compounds such as pigments (i.e., chlorophyll, carotenoid, and phycobiliprotein), proteins (lectins), peptides, vitamins (A, B (B1, B2, B9, B12), C, D, E and K), minerals (calcium, iron, iodine, magnesium, phosphorus, potassium, zinc, copper, manganese, selenium, and fluoride), occipins, fluorotannines, steroids, polyphenols (phenolic acid, flavonoids, cinnamon acid, isoflavon, benzoic acid, lignan, quercetin), essential fatty acids, dietary fibers, polysaccharides (i.e., galactan, fucoidan, alginate, and laminarin), phytohormone (i.e., citokynin, auxin, gibberellin, and abscisic acid) and sulfated polysaccharides. Therefore, they are increasingly used in the agriculture and food industries (Al-Juthery et al. 2020; Cotas et al. 2020; Salma et al. 2021; Patel and Mukherjee 2021). These compounds are effective in increasing seed formation and germination, plant growth-productivity, resistance to biotic/abiotic stresses and post-harvest shelf life in plants. Factors such as differences in the concentration of used compounds, light, carbon dioxide (CO_2), pH, pollutants and temperature alter their effects (Al-Juthery et al. 2020; Moga et al. 2021). Researchers and farmers have been considering various seaweeds as potential immunostimulants for aquaculture since the 1980s. Since the 2000s, many studies have been carried out in accordance with these applications. However, the obtained data show that their results to date are mixed and shown the necessity of a systematic review of the data (Thépot et al. 2021).

Seaweed extracts account for more than 33% of the global market for bio-stimulants (Eef et al. 2018). Seaweed is a sector whose global market is expanding, with an annual growth rate of 8.9%. It is currently valued at US $11.7 billion and projections point to a value of US $22.13 billion in 2024 (Cotas et al. 2020).

There are many studies on the beneficial effects of seaweed extracts on plant and crop yields (Table 8). Brown algae are the most commonly used species in agriculture and among the most studied are *Ascophyllum nodosum*, *Fucus* spp., *Sargassum* spp., *Laminaria* spp. and *Turbinaria* spp.

Table 8. Different application of seaweed extracts on plant and crop yields.

Seaweed	Usage aim	Checked specification	Treatment substance	Effect	References
Saccharina japonica (formerly Laminaria japonica)	Biostimulants	Nutritional value	Broccoli	Enhancing the concentrations of both glucosinolates and phenolic compounds. Increase in gluconasturtiin and several hydroxycinnamic derivatives. Increased both indole and aliphatic glucosinolate levels Stimulated the accumulation of kaempferol derivatives.	Flores et al. (2021)
Sargassum angustifolium	Biostimulants	Enhancing seed germination indices and salt tolerance	Calotropis procera	Seeds primed by biostimulant germinate Increased germination percentage Improved seed vigor index	Jafarlou et al. (2021)
Ulva lactuca (formerly Ulva fasciata) and Sargassum lacerifolium	Bioremediation	Heavy metal	Soil and Raphanus sativus	Biosorption of soil heavy metals by seaweeds decreased the bioaccumulated concentrations of metals in radish plant roots and/or translocated to its shoots Promoted the growth of cultivated radish and improved the germination percentage and the morphological and biochemical growth parameters Achieved soil remediation	Ahmed, Gheda, and Ismail (2021)
Gracilaria parvispora, Eisenia arborea (formerly Ecklonia arborea), and Sargassum horridum	Hormetic growth responses	Tolerating stress	Vigna radiata	High concentrations mostly caused a decrease in various morphological parameters Low concentrations stimulated some of these shoot length, root length, and dry weight responded to the seaweed concentrations in a hormetic manner	Di Filippo-Herrera et al. (2021)
Ascophyllum nodosum	Growth regulators	Tolerance to Fe deficiency	Tomato	Lowest concentration of phenolics, laminarin, and fucose compounds contributed to increasing the tolerance to Fe deficiency in tomato	Carrasco-Gil et al. (2021)
Ulva lactuca	Defense response	Reduce postharvest blue mold and gray mold	Apple	Increased also the activities of phenylalanine ammonialyase (PAL), peroxydase (POD), and polyphenoloxydase (PPO) as well as the levels of lignin and phenolic compounds. Triggered a rapid and transient accumulation of hydrogen peroxide (H_2O_2) as well as the activation of antioxidant-related enzymes	El Alaoui-Talibi et al. (2017)
Micro and macro seaweed	Wastewater treatment and crude bio-oil production	Conventional raw material	–	Bio-oil produced from pyrolysis of seaweeds usually has high contents of oxygen-, nitrogen- and sulphur-containing compounds, which should be as minimum as possible to enhance the bio-oil stability and reduce NOx and SOx emissions Autotrophic growth, seaweeds are receiving a great attention in the field of bioremediation	Wang, Zhao, et al. (2020)
Sargassum and Gracilaria	Bio-decomposer isolates and formulas	Pilot study	–	Increase the CO_2 evolution rate, humic acid content, and decrease the substrate dry weight and C/N.	Salma et al. (2021)
Laminaria pallida and Gracilariopsis funicularis	Fertilizer	Nutrient source	Bioachar	Best quality in terms of macro elements, pH and total C. G. funicularis biochar showed significantly higher nutrient concentrations, therefore has great potential in soil quality improvement	Katakula et al. (2020)
Ulva lactuca (formerly Ulva fasciata), Cystoseira compressa, and Laurencia obtusa	Growth bio-stimulant and salinity stress alleviator	Seed germination and seedling growth	Vigna sinensis and Zea mays	Enhances the growth of either V. sinensis or Z. mays under salinity stress Enhanced guaiacol peroxidase activity Exhibited remarkable tolerance for salinity stress	Hussain, Kasinadhuni, and Arioli (2021)
Kappaphycus alvarezii and Hydropuntia edulis (formerly Gracilaria edulis)	Fertilizers	Growth, yield, and tuber quality	Potato (*Solanum tuberosum* L.)	Maximum tuber bulking rate and tuber yield (accounting 32.11% and 24.87% yield enhancement over control). Maximum nutrient (N, P, and K) uptake as well as best values of quality traits in terms of ascorbic acid, reducing sugar content, and specific weight of potato tuber was recorded with economically viable treatment having 10% K sap spray	Garai et al. (2021)

Table 8. (Continued)

Seaweed	Usage aim	Checked specification	Treatment substance	Effect	References
Seaweeds polysaccharides	Polysaccharides	Active food packaging	Food quality	Increase in hydrophilicity and improved mechanical properties such as tensile strength and elongation at break Achieved due to the naturally occurring antioxidant properties	Carina et al. (2021)
Lithothamnion corallioides, Lithothamnion glaciale, Lithothamnion tophiforme and Phymatolithon calcareum	Plant nutrition	Conditions of abiotic and biotic stressors	Pear trees	Results demonstrate that, depending on the yearly climate conditions, it was possible to substantially reduce the primary nutrients by 35–46% and total fertilization units applied by 13% and significantly improve quantitative and qualitative production indicators (average weight of fruits (5%) and total yield (19–55%)).	Daniel and Fabio (2020)
Ascophyllum nodosum and Sargassum sp	Biostimulants	Flower bud, flower, and fruit number	Tomato	Enhanced flowering Increased the flower bud, flower, and fruit number	Dookie et al. (2021)
Gracilariopsis longissima (formerly Gracilaria verrucosa)	Bioremediation	Organic matter	Water quality for aquaculture	Total organic material (TOM) and total ammonia nitrogen(TAN) decreased	Widowati et al. (2021)
Ulva ohnoi	Bioremediation and biomass production	Water quality	Aquaculture	Good quality biomass production and efficient nutrient removal	Salvi et al. (2021)
Sargassum polycystum	Dietary Supplementation	Improved shrimp performance, health status	Litopenaeus vannamei	Significant improvement in water quality, survival, growth, and feed utilization indices Nonspecific immune responses (phagocytosis (%), lysozyme, phenoloxidase, super oxide dismutase (SOD) activity, total nitric oxide) were improved	Abdel-Rahim et al. (2021)
Asparagopsis taxiformis	Food ingredients	Reduces enteric methane	Beef steers	Carbon dioxide (CO_2) yield increased The persistent reduction of CH_4 by A. taxiformis supplementation suggests that this is a viable feed additive to significantly decrease the carbon footprint of ruminant livestock and potentially increase production efficiency.	Roque et al. (2021)
Caulerpa spp.	Dietary ingredient	Growth performance and survival	Labeo rohita	Higher growth, SGR, PER and lowest FCR The protein content of fish was significantly highest	Solanki and Joshi (2021)
Turbinaria murrayana	Ration supplementation	Optimizing performance and carcass quality characteristics	Broiler Chickens	Level of 10% in the ration can maintain performance, carcass quality, do not interfere with physiological organs, and can reduce the content of abdominal fat, liver fat and broiler liver cholesterol.	Reski et al. (2021)
Laminaria digitata	Dietary ingredient	Animal performance, intestinal microbial and transcriptome profiles	Pigs	It has positive influence on intestinal health through alterations in the gastrointestinal microbiome and increased butyrate production	Vigors et al. (2021)
Padina tetrastromatica and Sargassum ilicifolium	Immune protection	Vibrio parahaemolyticus	Penaeus monodon	Seaweeds had maximal antibacterial activity against V. parahaemolyticus with zones of inhibition ranging P. tetrastromatica improved growth performance and the immune capacity of P. monodon by increasing their phenoloxidase activity, superoxide anion concentration, and resistance against V. parahaemolyticus	Aftabuddin et al. (2021)
Sargassum ilicifolium	Biocontrol agent	Macrophomına phaseolına	Soybean	Induce resistance mechanism in plant by enhanced antioxidants scavenging potential of ROS outburst and detoxify the pathogenicity of M. phaseolina by accumulation of secondary metabolites.	Rahman et al. (2021)
Gracilaria gracilis	Dietary ingredient	Health status and pathogen resistance	Sparus aurata	Improved lysozyme plasmatic concentration protect the fish against a Photobacterium damselae subsp. piscicida infection Improve growth, health, and bacterial resistance	Passos et al. (2021)

Table 8. (Continued)

Seaweed	Usage aim	Checked specification	Treatment substance	Effect	References
Ulva clathratia (formerly Enteromorpha *clathratia*)	Bio-oil	Pilot study		Two-step reaction method can ensure a high bio-oil yield and low solid residue rate	Wang et al. (2021)
Undaria pinnatifida	Proteins extracted	Foods and nutraceuticals	Food	Excellent antioxidant, antihypertension, anticoagulant, anti-diabetes, antimicrobial and anti-cancer activities possessed by proteins of U. pinnatifida enable the use of these proteins in various nutraceutical applications	Nadeeshani, Hassouna, and Lu (2021)
Durvillaea potatorum and Ascophyllum nodosum	Biostimulants	Soil treatment and yield	Grape	Soil applications of the seaweed extract significantly increased wine grape yield	Arioli et al. (2021)
Sargassum ilicifolium (formerly Sargassum cristaefolium)	Feed supplement	Growth performance, hematological parameters, histology of hepatopancreas, and intestinal microbiota	Litopenaeus vannamei	The triglyceride level of shrimp in the S. cristaefolium diets was lower The total viable bacterial and Vibrio counts in the intestine of shrimp were gradually decreased when the level of S. cristaefolium was increased	Jahromi et al. (2021)
Ascophyllum nodosum	Biostimulation	Volatile composition	Must and wine	High doses foliar application increased the content in musts of several individual terpenoids, C_{13} norisoprenoids, esters, benzenoids, alcohols, carbonyl compounds and C_6 compounds	Gutiérrez-Gamboa et al. (2021)
Anabaena minutissima (Cyanobacteria), Ecklonia maxima, and Jania pedunculata var. adhaerens (formerly Jania adhaerens)	Agro-ecological option	Rhizoctonia solani	Tomato	Increases of germination and seedling dry weight for treated seeds without pathogen challenge were observed. The extracts reduced disease severity and increased seedling dry weight both in in vitro and greenhouse experiments at all concentrations. All extracts also increased stem seedling caliber under greenhouse conditions. The plant chitinase activity was increased by all extracts. The aromatic rings assigned to lignin changed with the treatment	Righini et al. (2021)
Fucus vesiculosus	Active coating (packaging)	Lipid oxidation	Chicken breasts	The extract was successfully incorporated into a whey protein film and successfully strengthened the thickness, tensile strength, and elastic modulus. The active film also was able to inhibit the chicken breasts lipid oxidation for 25 days of storage.	Andrade et al. (2021)

(Phaeophyceae) species are used as agricultural bio fertilizers (Al-Juthery et al. 2020). Some studies have shown that seaweed provides defence against fungal, bacterial and viral pathogens in plants. It has been reported that the defence response occurs after the detection of signal molecules, called elicitors, derived from pathogens or the host plant (Al-Juthery et al. 2020). The positive effects of seaweed and bioactive compounds that perform these activities on some factors in agricultural practices are summarized in Figure 2.

In addition to having a growth-promoting effect on plants, seaweed also provides benefits to the physical, chemical and biological properties of the soil. In fresh or dried seaweed form and seaweed concentrates stimulate the growth of beneficial soil microorganisms and improve soil health by increasing the soil's moisture-holding capacity (Kaur 2020). Containing organic components such as a wide variety of macronutrients, microelement nutrients, growth hormones, amino acids, vitamins, betaines, cytokines and sterols, seaweed extracts play an important role in environmentally sustainable agricultural production. In general, seaweed extracts can cause changes in the physiological/biochemical process associated with plant nutrient uptake and growth in agriculture.

Conclusion

The trend to utilize alternative functional marine foods based on seaweed has become popular in the usage of marine bio-resources today. Recent studies have demonstrated that some extracts and compounds from a wide variety of algae have potential applications in pharmacology/medicine (as antioxidants, antibiotic, antifungal, antiviral, anti-inflammatory, anticancer, etc.), and have utilized as food ingredients, cosmeceuticals, bioremediation, biofuels, etc.

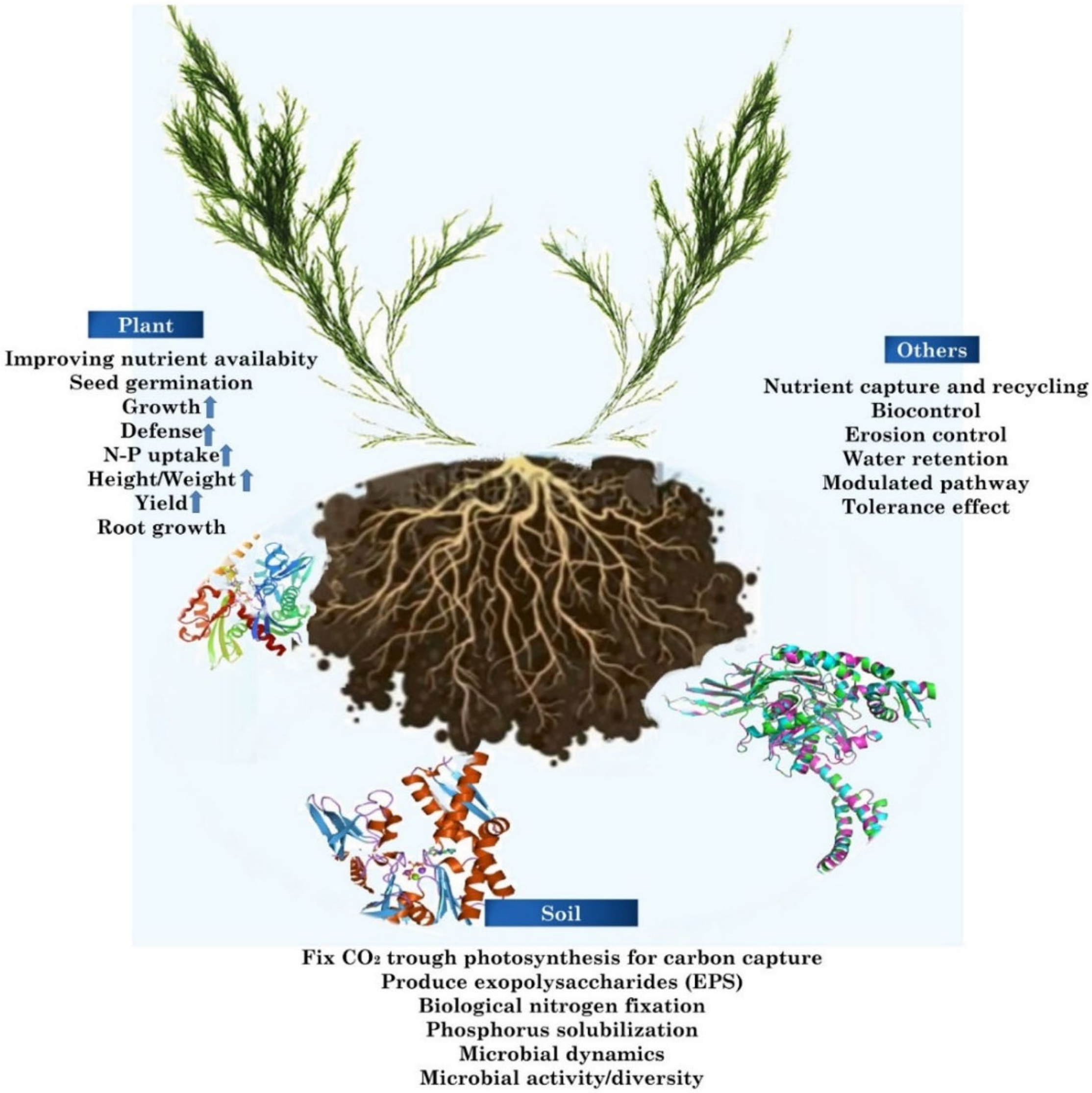

Figure 2. Overview of the seaweed's positive effect on different areas.

Few evidence has shown that seaweed and its bioactive compounds have also used to treat some neurodegenerative disorders.

Different extraction methods should be assessed to isolate and purify individual bioactive compounds for the utilization in a variety of industries. In addition, more research is required to identify the seaweed species that are available abundantly with the best source of these natural individual compounds. However, safety issues for the use of seaweed should be considered since they might contain heavy metals, pesticide residues, dioxins or marine bio-toxins. Therefore, the careful selection of suitable, clean coastal regions for their production and constant quality control are particularly important. Seaweed culture is expected to rise all over the world mainly in America and Asian countries.

In addition, the details of the molecular mechanisms of seaweeds for physiological activities are to be clearly elucidated. The structure-activity relationship will be useful in the process of exactly how these molecules perform their activities. Therefore, emphasis should be placed on understanding the details that may provide an insight into uncovered molecular-level functions in future research and applications.

In conclusion, bioactive compounds obtained from seaweeds show antioxidant, anti-pigmentation, anti-wrinkling, and antimicrobial activities, etc. Thus, number of products that are commercially produced from seaweeds are rising and the market value of these products gradually increases. Overall, seaweed is a unique sector whose global market is expanding with an annual growth rate.

Disclosure statement

The authors declare no conflict of interest.

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