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A Review on Seaweeds and Seaweed-Derived Polysaccharides: Nutrition, Chemistry, Bioactivities, and Applications

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ABSTRACT

In recent studies, marine macroalgae (seaweeds) have been highlighted as excellent sources of acquiring many bioactive polymers and metabolites with vast chemical and biological values, which has attracted increasing research interests in seaweeds. Among a diversity of seaweed-derived bioactive constituents, polysaccharides have been affirmed to possess an extensive array of bioactivities, such as antioxidant, antimicrobial, anticarcinogenic, immune-enhancing and anti-inflammatory activities. Due to the exhibition of these bioactivities, seaweed polysaccharides have been promised great application potential in food, feed, pharmaceutical, nutraceutical, and cosmeceutical industries. As discovered, these bioactivities were mainly contributed by the complex polymeric structural features and chemical compositions of seaweed-derived polysaccharides and were highly associated with the extraction methods. This study has comprehensively reviewed the current and prospective applications of seaweeds and their polysaccharides from nutritional and bioactive perspectives, with further shedding light on the insight into the structure-bioactivity relationship of seaweed-derived polysaccharides.

KEYWORDS

Marine algae (seaweeds); food sustainability; seaweed-derived polysaccharides; bioactivities

Overview of seaweeds and seaweed-derived polysaccharides

Seaweeds, also known as marine macroalgae, are one of the most essential and valuable marine source commodities. Classified by pigmentation, there are three taxonomic groups, including red algae (Rhodophyta), brown algae (Ochrophyta, Phaeophyceae), and green algae (Chlorophyta).[1] For decades, seaweeds have been widely cultivated in 61 countries and territories, contributing over fifty percent of global marine and coastal aquaculture production.[2] As an example, seaweeds were traditionally harvested and further processed for food purposes in many Asian countries (such as China, Japan, and South Korea).[3,4] Globally, over 200 species of seaweeds are cultured or wild-harvested for multiple industries.[5] Specifically, 32 green seaweeds, 64 brown seaweeds and 125 red seaweeds are commercially used.[6] Among these 221 species of algae, 145 species (66%) are directly used for food purposes, including 28 green seaweeds (20%), 38 brown seaweeds (26%), and 79 red seaweeds (54%).[5,6] As for the rest, 101 species are used for making hydrocolloids, 24 are used in traditional medicine, and 25 are used in agriculture.[6,7] From the world's farmed seaweed production perspective, *Laminaria*, *Eucheuma/Kappaphycus*, *Gracilaria*, *Undaria* and *Porphyra* are the five leading genera, which represent around 93% of the total output.[2] The

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culture of seaweeds is increasingly recognized for its biological, agricultural, nutritional, medicinal values, and ecosystem services. In fact, global seaweed production has been boosted by the increasing demand from different industries over the past two decades. As an earlier report from FAO[4] suggested, the international algae production volume reached 12 million tonnes in 2000, including aquaculture and capture fisheries. While according to FAO's latest state of world fisher and aquaculture,[2] this number has tripled and climbed to 36 million tonnes in 2020, with 98% contributed by seaweed aquaculture. Except for the spikes in demand, recent significant progress in aquaculture technologies, especially algal cultivation, made this dramatic increase possible.[8] There is a range of factors that affect seaweed growth and production. These include biotic factors such as seed size, genetic material and disease infection, and abiotic factors such as sunlight, seawater temperature, oxygen level, nutrients, sedimentation, salinity and acidity level.[9] Therefore, seaweed production varies from place to place. Notably, China, South Korea and Indonesia are the three largest seaweed-producing countries, contributing 77.32, 6.55 and 5.96% to this 16.5-billion-USD seaweed market.[2,10] Among these seaweeds, most are used in the food industry sector for direct consumption or as functional food ingredients and polysaccharide additives.[4,11] The non-food industry uses some of them as hydrocolloid products in pharmaceuticals, cosmetics and nutraceuticals, or raw materials for health supplement making,[6,12] but only a tiny proportion as bioplastics, biofuels, animal feed ingredients/additives, fertilizers, and other industrial products.[7,13]

Indeed, the multiple applications of seaweeds benefit from their abundance of functional ingredients and bioactive compounds.[14] From a nutritional point of view, seaweeds are an excellent resource of saccharides, proteins, phenolic compounds, unsaturated fatty acids, vitamins and minerals.[14–17] The nutrient compositions of seaweeds vary by not only their species, age, size, reproductive status and surrounding ecology but also the seawater pH, depth, temperature, salinity, nutrient enrichment, oxygen content, ultraviolet radiation, light intensity exposure and the intensity of herbivory.[6,16,18] In general, on a dry weight (DW) basis, saccharide content, the largest constituent, varies between 237 and 557 g kg^{-1} DW.[19] Even though the ash content varies between 118 and 419 g kg^{-1} DW, making it the second largest constituent, the ash content contained in seaweed biomass has been considered unsuitable for biorefining.[19] The relative protein, polyphenol, and lipid contents are generally low in all species, which account for up to 470 g kg^{-1} DW of *Palmaria palmata* (Rhodophyta),[20] 61 g kg^{-1} DW of *Alaria esculenta*,[21] and 57 g kg^{-1} DW of *Spatoglossum macrodontum* (Phaeophyceae),[22] respectively. These bioactive constituents in marine macroalgae have been proven to possess numerous beneficial properties, such as antioxidant, antimicrobial,[23] anti-inflammatory, anti-arthritic,[24] and antidiabetic activities.[25]

As a large constitution of seaweeds, polysaccharides have attracted today's scientists' intense research interests. Due to their complex chemical structure and diversity of functional groups, seaweed-derived polysaccharides display various physicochemical properties,[26] exhibit an extensive array of biological activities,[27] and can interact with numerous chemical compounds, lipids, cellular proteins and microbiota.[28] Therefore, seaweed-derived polysaccharides are commonly believed to be promising biopolymers with a wide range of applications. For illustration, Zhang et al.'s[29] recent study found the sulphated polysaccharides extracted from *Undaria pinnatifida* (Phaeophyceae) can modulate the gut microbiota, thereby inhibiting weight gain and lipid metabolism, which could become a potential solution to high-fat diet-induced obesity. The functional properties of seaweed polysaccharides are mainly contributed by their complex polymeric structures, such as glycosidic linkages, chain conformation, molecular weight,[30] degree of sulphation, percentage of uronic acid, and monosaccharide composition.[27] Therefore, it is essential and necessary to understand the chemistry of seaweed polysaccharides to investigate further the linkage between their structural features and the relevant bioactivities. Besides, the variation in extraction methods is another affecting factor on the presentence of bioactivities of seaweed-derived polysaccharides.[27] Although seaweeds and seaweed-derived polysaccharides have been assigned promising bioactivities and applications, the triggered food safety issue has raised grave concerns for their consumers. Pogozhykh et al.'s[31] experiment results indicated that the oral intake of edible carrageenan could deteriorate the gut inflammation manifested by both systemic and tissue effects. Therefore, this study aims to comprehensively review the current and prospective applications of seaweeds and seaweed-derived polysaccharides from nutritional and bioactive perspectives, with further emphasis on the effects of polysaccharide structural features on their expression of biological activities.

Nutritional values of seaweeds

Blue Transformation, a far-sighted vision proposed by FAO[32] in 2022, aims to secure and maximize the contribution of aquatic food systems to nutrition, food security and affordable healthy diets by following sustainable approaches. This vision is compatible with United Nations (UN) Sustainable Development Goals (SDGs).[33] As illustrated in Fig. 1, seaweeds have an excellent nutritional profile with high macro- and micro-nutrients.[16] Meanwhile, seaweed aquaculture accounts for over half of the worldwide mariculture production and has sustained an average of 6.2% annual growth in the past two decades.[2,52] Considering these nutrients are associated with a variety of bioactivities and nutritional values, seaweeds have a vast potential to make a constructive contribution to people's health, food security, and components of affordable healthy diets.

Carbohydrates

Carbohydrates are essential macro-nutrients mainly responsible for energy supply to maintain bodily functions and support physical activities. Seaweeds are an excellent source of acquiring carbohydrates. As the latest SR Legacy data released by the U.S. department of agriculture[53] indicated, the carbohydrate content of edible seaweeds is about 81% on a DW basis. Specifically, in Table 1, the carbohydrate contents of red, green and brown seaweeds are within the ranges 8.3–68.2%, 4–79.9% and 12.8–81% of their DW, respectively. Depending on the complexity and length of molecules, carbohydrates can be classified as monosaccharides, disaccharides, oligosaccharides, and polysaccharides.[108] Regarding the monosaccharides, mannose, glucose, fructose, galactose, fucose, xylose, and arabinose can be commonly identified in seaweed hydrolysates.[109] Moreover, recent bioactive findings on disaccharides and oligosaccharides have attracted intense research interest. For instance, Calvo et al.'s[110] study found κ-carrabiose exhibited high cytotoxic responses against LM2 tumoral cells, suggesting a vast potential for this red seaweed-derived disaccharide become a promising antitumor agent. Besides, Yang et al.[25] found out that the oligosaccharides from *Sargassum confusum* (Phaeophyceae) can regulate JNK-IRS1/PI3K signalling pathways and stimulate insulin secretion, thereby boosting glucose tolerance. Whereas Padam et al.'s[111] experiment affirmed the extraordinary prebiotic activity of oligosaccharides from *Eucheuma denticulatum* (Rhodophyta) by showing their abilities to restrain five different probiotics. Polysaccharides (~50% and up to 76% on a DW basis) are the main contributor to seaweeds' considerably high carbohydrate content.[112] The significant polysaccharides discovered in red seaweeds are carrageenans and agars, whereas fucoidans, alginates and laminarins are the polysaccharides mainly distributed in brown seaweeds.[113] Besides, ulvans are unique polysaccharides that can be extracted from the cell walls of the genus *Ulva* (green seaweeds).[114] As eco-friendly and sustainable polymers, seaweed-derived polysaccharides have been subjected to multidisciplinary research fields due to their diverse bioactivities and unique physiochemical properties.[113] The promising applications and limitations of seaweed-derived polysaccharides will be focused on and critically discussed based on their structural features and bioactive properties.

Proteins

Proteins are large biomolecules consisting of one or more long chains of amino acid residues.[115] Proteins play an indispensable role in the human body. In general terms, proteins can help build and repair human body tissues, facilitate metabolic reactions, and coordinate numerous bodily

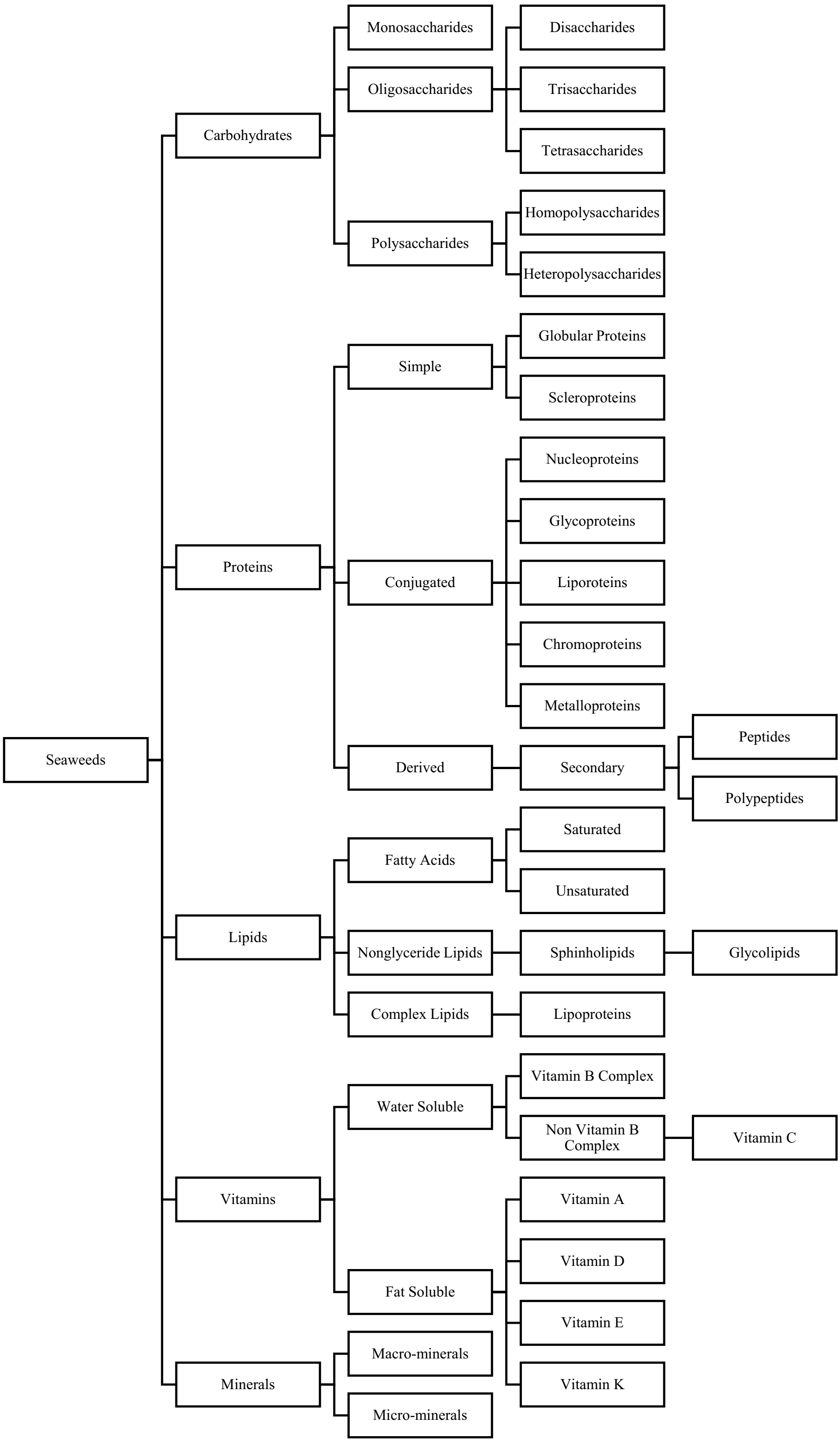

Figure 1. Nutritional compounds identified in seaweeds.[6,34–51]

Table 1. Macronutrient contents of seaweeds (% DW).

Species	Carbohydrate	Dietary Fibre	Protein	Lipid	References
		Chlorophyta (Green Seaweeds)			
Caulerpa lentillifera	**4*** – 72.9	17.5–37.2	**0.4*** – 19.4	0.5–14	[54–57]
C. racemosa	32.1–71.7	**64.9****	11.4–20.4	1.1–4.5	[6,58–60]
Codium fragile	43.5–50.5	5.1	4.3–17.3	0.7 – **15****	[6,61,62]
C. galeatum	-	5.26–5.31	12.9–15.6	3.5–5.1	[63]
C. isthmocladum	16.7–35.6	**1.1*** – 22.1	3.5–5.1	0.5	[64,65]
Ulva compressa	14.5 - **79.9****	33.7–41	15.7 - **32.1****	1–1.7	[66,67]
U. intestinalis	35.5–57	4.2	9–10.5	2.9	[19,67–69]
U. lactuca	34.7–76.8	53.1–55	9.3–17.1	**0.2*** – 3.6	[19,68,70,71]
		Phaeophyta (Brown Seaweeds)			
Ascophyllum nodosum	31.7–59	42.6	5.9–8.5	2–2.65	[19,72,73]
Colpomenia sinuosa	32.1–40.4	20.1	9.2–10.8	1.5–4.35	[68,74]
Cystophora polycystidea	55	6–6.1	5.1–6.6	5.7–9.2	[63,75]
Dictyopteris jolyana	**81****	65.8	12.5	-	[64]
Durvillaea potatorum	-	3–4.3	**3.1*** – 5.1	0.4–0.7	[63]
Ecklonia radiata	65.4	12.7–15.8	6.4–8.5	1.1–2.2	[63,76,77]
Eisenia bicyclis	60.6	10 – **75****	7.5	**0.1***	[6]
Fucus serratus	**12.8*** – 28.7	40.4–52.3	7.1	4.4 – **11.5****	[19,78]
F. vesiculosus	26.6–34.53	45–59	7.1 – **42.1****	1.47–1.74	[19,79,80]
Hormosira banksii	57.6–68.23	4.4–22	**3.1*** – 8.8	0.7–3.81	[63,77]
Laminaria digitata	21.7–57	60.5	6.6–26.8	0.77–1.9	[19,72,81–83]
Saccharina latissima	40–55.7	27.8	6.1–8.1	1.6–2.3	[19,84,85]
Sargassum fusiforme	26	3.7	3.2	0.7	[63,75]
S. ilicifolium	26–32.9	-	8.9	2	[68,75]
Spatoglossum schroederi	40.1–59.3	4.28–59.2	5.21–21.5	3.1	[64,86]
Undaria pinnatifida	55.9	**2.9***	12.5–15.7	2.2	[63,76]
		Rhodophyta (Red Seaweeds)			
Ahnfeltia plicata	30.2–59.1	-	20.1–31.1	1.1	[19,87]
Botryocladia occidentalis	31.4	25	10.3	-	[64]
Ceramium virgatum	35.2	-	15.8	9 – **12****	[19,88]
Chondrus crispus	52.6	-	10.3–12.4	**0.4*** – 5.8	[19,89,90]
Delesseria sanguinea	25.9 - **68.2****	5.45	9.44–21.8	<1	[19,91,92]
Dilsea carnosa	41.8–47.7	-	15.2–22.8	0.6–2.1	[19,83]
Furcellaria lumbricalis	25.6–55.4	-	**3.5*** – 27.9	**0.4*** – 4.3	[19,90,93]
Gracilaria changii	41.1–42	63.9 - **65.6****	11.3–13.9	<1.1	[94,95]
G. corticata	**8.3*** – 43	-	19.3–22.8	1.3–7.1	[68,96,97]
G. domingensis	47.9	45.9	6.2–16.8	1.2–1.4	[64,98]
Halymenia brasiliana	58.1	46.8	8.2	-	[64]
Hypnea valentiae	31.8	-	9.3–16.5	2.8–6.8	[68,99]
Laurencia filiformis	-	14.4–15.1	11.1–18.3	4.9–6.4	[63,98]
Palmaria palmata	38–47	-	10.9–12.7	1.2–2.5	[84,100]
Porphyra tenera	36.6–37	**3.3*** – 32	36.6 – **47****	3.1	[63]
P. umbilicalis	21.4–25	2.6–44.3	5.1–21.7	1.1	[101–103]
P. yezoensis	43.8–46.2	27.2–34.9	37.8–40	1.5–2.6	[104,105]
Rhodomela confervoides	34–47.6	-	12.5–25.5	0.9	[19,106,107]

* Lowest content identified in the seaweed group; ** Highest content identified in the seaweed group.

functions.[115] As Table 1 indicates, the protein contents of green, brown and red seaweeds are within the ranges 0.4–32.1%, 3.1–42.1% and 3.5–47% of their DW, respectively. What is noteworthy is that some seaweed species can be considered excellent protein-acquiring sources, such as *Fucus vesiculosus* (Phaeophyceae) (up to 42.1% DW) and *Neopyropia tenera* (formerly *Porphyra tenera*) (Rhodophyta) (up to 47% DW). This application potential has been further supported by a recent study conducted by Healy et al.[116] about the seaweed protein and amino acid content. It stated that the essential amino acid, methionine, contained in *Alaria esculenta*, *Laminaria digitata* and *Saccharina latissima* (Phaeophyceae) were three times higher than in soy. Similar opinion has been posed in Machado et al.'s[117] research, which indicated *Porphyra* spp. protein content was even higher than some common protein-rich foods like fish, eggs, soybeans and cereals. At the same time, their study also revealed three abundant amino acids (aspartic acid, glutamic acid, and alanine) in seaweed proteins were highly associated with the umami flavour of seaweeds, which explored the possibility of extracting seaweed protein for flavour enhancer purposes. Furthermore, seaweed proteins contain all amino acids essential for the human body.[16,117] Specifically, alanine, arginine, glycine, aspartic, and glutamic acid are the standard amino acids identified in proteins extracted from different seaweed species, but less of cystine, lysine and tryptophan.[16] Significantly, the total essential amino acid contents of seaweeds are sufficient for the dietary requirements as per FAO and WHO standards.[118]

Lipids

As summarized in Table 1, the lipid contents of brown, red and green seaweeds are within the ranges 0.1–11.5%, 0.4–12% and 0.2–15% of their DW, respectively. Meanwhile, many of these lipid contents are made up of polyunsaturated fatty acids (PUFAs), which are usually in the form of omega-6 (*n-6*) and omega-3 (*n-3*) lipids.[119] Investigated by recent studies, 20:4 *n-6* arachidonic acid (ARA), 18:2 *n-6* linoleic acid (LNA), 22:6 *n-3* docosahexaenoic acid (DHA), 20:5 *n-3* eicosapentaenoic acid (EPA), and 18:3 *n-3* ɑ-linolenic acid (ALA) were identified in seaweed lipids.[15,63,120] Omega-6 (*n-6*) and omega-3 (*n-3*) fatty acids are essential for the human diet.[119] However, the omega-3:omega-6 ratio will significantly affect the balance of ensuing eicosanoids.[119] As a result, the unbalanced ratio will lower vitamin E concentration and increase lipid peroxidation.[121] Therefore, omega-3 and omega-6 fatty acids should be consumed in a balanced ratio, ideally from 1:3 to 1:5.[119] In today's human diet, most PUFA-rich foods, such as legumes, seeds, cereals, and terrestrial animal products, contain more omega-6 fatty acids.[63] Therefore, it is necessary to increase the intake of an alternative food rich in *n-3* PUFAs to fill the vacancy of omega-3 fatty acids and balance the omega-3:omega-6 ratio. While seaweeds can meet this demand due to their low *n-3:n-6* PUFA ratio.[120] Proven by previous studies, the DHA, ARA and EPA contained in seaweeds are highlighted for their potential to benefit brain health, modulate inflammatory diseases, and prevent cardiovascular diseases.[63,119,120]

Vitamins

Vitamins are essential micronutrients for organisms to maintain life and good health.[122] Basically, vitamins can be classified into two groups by their solubilities, including water-soluble vitamins and fat-soluble vitamins.[122] Referring to Fig. 1, water-soluble vitamins, including vitamin B complex and vitamin C, and fat-soluble vitamins, including vitamin A, vitamin D, vitamin E and vitamin K, were identified in seaweeds. Even though various types of vitamins were identified in seaweeds, referring to Table 2, seaweeds cannot be considered a good source for acquiring vitamins B_5, B_6, B_8, B_9 and E.[6,119] While what is noteworthy is that there were abundant vitamin B_{12} contents discovered in many species, such as *Pylaiella littoralis*, *Fucus vesiculosus* (Phaeophyceae) and *Ulva lactuca* (Chlorophyta).[123,127] Identifying vitamin B_{12} in seaweeds was regarded as a breakthrough because nature vitamin B_{12} was only found in animal-based foods previously but is essential for brain functions of the human body.[123] Uchida et al.'s[128] study indicated the average B_{12} content in *Neopyropia yezoensis* (formerly *Pyropia yezoensis*) (Rhodophyta) samples was 14 μg/100 g DW, which was much higher than that contained in anchovy. Undoubtedly, this great discovery has broadened today's vegetarians' non-meat food choices to acquire vitamin B_{12} and have a balanced intake of vitamins.

Minerals

Minerals are essential micronutrients necessary for the living body to maintain cell functions and metabolism.[16] Seaweeds are an abundant source of acquiring minerals due to their marine habitat, which gives seaweed the possibility to absorb a diversity of minerals.[119,129] The mineral content of seaweeds is up to 30% of their DW.[6] Referring to Table 3, seaweed minerals, including sodium (Na), potassium (K), phosphorous (P), magnesium (Mg), calcium (Ca), zinc (Zn), iron (Fe), copper (Cu), manganese (Mn) and iodine (I) were identified in previous studies.[6,51] Among these elements, it was found that the Na, Ca, K, Mg and Cu contents in seaweeds presented higher levels than that in

Table 2. Vitamin contents of seaweeds (mg/100 g DW).

Species		Vit. B Complex								Vit. C	Vit. D	Vit. E	Vit. K	References
	Vit. A	B_1	B_2	B_3	B_5	B_6	B_8	B_9	B_{12}					
						Chlorophyta (Green Seaweeds)								
Caulerpa lentillifera	-	0.05	0.02	1.09	-	-	-	-	-	1	-	2.22	-	[6]
Codium fragile	0.527	0.223	0.558	-	-	-	-	-	-	<0.22	-	-	-	[6]
Ulva lactuca	0.017	<0.02	0.533	-	-	-	-	-	0.024	<0.24	-	-	-	[6,123,123]
U. pertusa	-	-	-	-	-	-	-	-	-	-	-	-	-	[6]
U. rigida	0.958	0.47	0.199	<0.5	1.7	<0.1	0.012	6	-	9.42	-	19.70	-	[6,16]
						Phaeophyta (Brown Seaweeds)								
Fucus vesiculosus	0.307	0.02	0.035	-	-	-	-	-	-	14.12	-	-	-	[6]
Himanthalia elongata	0.079	0.02	0.02	-	-	-	-	-	-	28.56	-	-	-	[6]
Laminaria digitata	-	1.25	0.138	61.2	-	6.41	6.41	0.005	-	35.5	-	3.43	-	[6]
L. ochroleuca	0.041	0.058	0.212	-	-	-	-	-	-	0.356	-	-	-	[6]
Saccharina japonica	0.481	0.2	0.85	1.58	-	0.09	-	-	-	-	-	-	-	[6]
S. latissima	0.04	0.05	0.21	-	-	-	-	0.0003	-	0.35	-	1.6	-	[6]
Sargassum muticum	-	-	-	-	-	-	-	-	-	-	0.09	-	-	[124]
Undaria pinnatifida	0.22	0.3	1.4	2.56	-	0.18	-	0.0036		5.29	<0.05	2.5	-	[6,124]
						Rhodophyta (Red Seaweeds)								
Gracilaria changii	-	-	-	-	-	-	-	-	0.0002	28.5	-	-	-	[6,125]
Palmaria palmata	1.59	1.56	1.91	1.89	-	8.99	-	0.009	-	34.5	-	13.9	-	[6]
Phorphyra umbilicalis	3.65	0.144	0.36	-	-	-	-	0.029	-	4.214	-	-	-	[6]
P. yezoensis	-	0.129	0.382	11	-	-	-	0.052	-	-	-	-	0.0114	[6,126]

Table 3. Mineral contents of seaweeds (mg/100 g DW).

Species	Na	K	P	Ca	Mg	Fe	Zn	Mn	Cu	I	References
					Chlorophyta (Green Seaweeds)						
Caulerpa lentillifera	8917	1142	1030	1874	1650	21.4	3.5	7.9	2.2	-	[6,51]
C. racemosa	2574	318	29.71	1852	1610	81	7	4.91	0.8	-	[6,51]
Ulva lactuca	-	245	140	840	465	66	0.9	-	0.3	1.6	[6,16,51,119]
U. rigida	1595	1561	210	524	2094	283	0.6	1.6	0.5	-	[6,51]
					Phaeophyta (Brown Seaweeds)						
Fucus vesiculosus	2450	4322	315	938	994	11	3.71	5.5	<0.5	14.5	[6,51]
Himanthalia elongate	4100	8250	240	720	435	59	-	-	-	14.7	[6,51,119]
Laminaria digitata	3818	11579	-	1005	659	9	1.77	<0.5	<0.5	-	[6,51,119]
Saccharina japonica	3260	5951	300	910	757	43	1.63	0.65	0.4	690	[6,51]
S. latissimi	2620	4330	165	810	715	-	-	-	-	15.9	[6]
Sargassum fusiforme	-	-	-	1860	687	89	1.35	-	-	43.6	[6,51]
Undaria pinnatifida	7000	6810	450	1380	680	30	0.944	0.332	0.185	30	[6,51,119]
					Rhodophyta (Red Seaweeds)						
Chondrus crispus	4270	3184	135	1120	732	17	7.14	1.32	<0.5	24.5	[6,119]
Gracilaria changii	5465	3417	-	402	565	5	4.35	-	-	-	[6,51]
Palmaria palmata	2500	9000	235	1200	610	50	2.86	1.14	0.4	100	[6,51,130]
Phorphyra umbilicalis	940	2030	235	330	370	23	0.7	-	0.1	17.3	[6,51,119]
P. tenera	3627	3500	-	390	565	11	3	3	<0.63	1.7	[6,51]
P. yezoensis	570	2400	-	440	650	13	10	2	1.47	-	[6]

terrestrial foods.[119] Bayomy[131] found that every 100 g of fresh *Ulva lactuca* contained about 2200 mg Ca. As a reference, eating eight grams of *Ulva lactuca* can provide 260 mg Ca, which is about 37% of the reference nutrient intake (RNI) of calcium for an adult man. In contrast, the same portion of cheddar cheese can only provide 5% of the RNI.[119] Regarding sodium and potassium, it was estimated that the Na concentration ranged from 0.5% in *Ulva lactuca* (as *Ulva fasciata*) (Chlorophyta) to 15.8% in *Dermonema virens* (Rhodophyta), and the K concentration ranged from 0.2% in *Hypnea spinella* (Rhodophyta) to 24.7% in *Dictyota dichotoma* (Phaeophyceae).[51] The relatively higher concentration of potassium is reasonable. This is because the accumulation of potassium salts can help seaweeds maintain metabolic activities and Na/K balance, essential for seaweeds to control hypertension and live in a high-pressure environment.[51,132] Simultaneously, it highlighted the potential of seaweeds becoming the raw materials for extracting edible salts.[7,51] Besides, iodine is one of the essential nutrients in growth patterns and metabolic regulations.[6] According to Andersen et al.'s study,[133] the bioavailabilities of iodine in edible seaweeds are 4.6 mg and 2.1 mg per 45 g of *Ascophyllum nodosum* (Phaeophyceae) and *Chondrus crispus*, which means a mere 1.5 or 3 mg of each corresponding edible seaweed will meet the recommended daily dietary iodine intake amount. Therefore, seaweeds can be considered as indispensable dietary iodine intake sources.

Current and prospective applications of seaweeds

There is an enormous biorefinery potential in marine macroalgae. Contributed by their nutritional and biochemical values, seaweeds have been subjected to diverse applications among a broad range of industries. As Fig. 2 indicates, the majority of seaweeds are used in food (43.77%), hydrocolloid (18.10%), plant & soil nutrition (11.57%), personal care (7.86%), bioplastics (5.34%), feed (3.86%) and nutraceutical (1.93%) industries. While the rest of the utilizations include biorefinery, dyeing, pharmaceutical, cardboard making, wastewater treatment, construction, carbon sequestration, energy, textile, and biosorption areas which are all less than 1.5%.[134] From a sustainable perspective, seaweed aquaculture is imperative to meet UN SDGs.[52] Specifically, seaweed cultivation can not only directly benefit Zero Hunger (SDG2), Good Health and Well-Being (SDG3), Affordable and Clean Energy (SDG7), Climate Action (SDG13) and Life Below Water (SDG14), but also ulteriorly contribute to other nine SDGs.[33,52]

Food security

Seaweeds have been traditionally consumed for food purposes mainly in eastern Asian countries but are vastly underutilized in the western world. Statistically, the seaweed intake per capita of the Japanese population was 5.5 g DW d^{-1}, which was commonly believed as the highest.[135] Benefiting from their micro- and macro-nutritional elements, seaweeds can be considered and further popularized as nutritional components of the human diet. Duarte

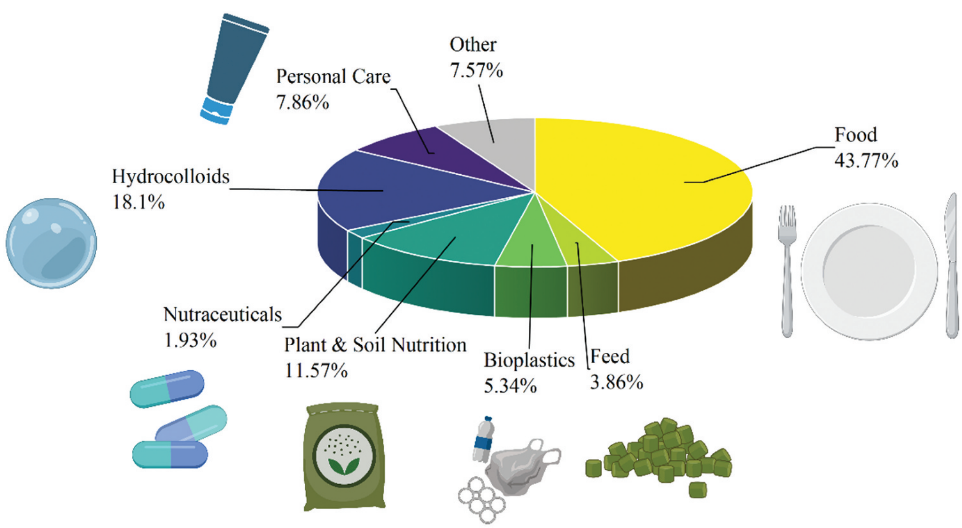

Figure 2. Current application directions of seaweeds. Raw data generated from phyconomy seaweed Database,[134] analysed by origin Pro® 2023, and visualized by BioRender.

et al.[52] believed that one of the feasible strategies to relieve the growing food supply stress induced by the climbing global population size is increasing the seaweed consumption of the worldwide population to half of the Japanese seaweed intake per capita. This might indeed contribute positively to the Zero Hunger goal; however, their view relied too heavily on quantitative analysis of the food demands from the growing population but ignored the seaweed production capacity and capacity growth rate. This is because even though the goal desires only half of the per capita Japanese intake, it requires about three times of current production by 2050,[52] which needs a 7.41% annual growth in seaweed production from now on. In comparison, seaweed production has only sustained an average of 6.2% yearly growth for the past two decades. However, to a certain extent, involving seaweeds in the human diet can relieve the boosted stress of demand for land crops and ulteriorly contribute positively to worldwide food security.

Moreover, seaweeds can help with global food security issues by promoting meat production yield. Alagan et al.[136] found that the diet containing the combination of 5% *Azolla* (aquatic plant) and 3% *Ulva lactuca* (Chlorophyta) significantly increased the 60-day chicken body weight gain from 568.7 g to 816.4 g and decreased the feed conversion ratio from 4.76 to 3.39. Therefore, the feeding diet supplemented with a specific dose of seaweed not only increased the meat production yield of chicken but also boosted the feed use efficiency. This finding can be further supported by Mohammadigheisar et al.'s[1] study on broiler chicken fed. As their results suggested, the diets with adding 5–10 g/kg seaweed blend consisting of an equal proportion of two brown, one green and two red seaweeds significantly improved the chicken growth performance and breast yield. A similar effect was also observed on hens. Nhlane et al.[137] proved that adding green seaweed (*Ulva* spp.) meal within the ranges of 2–3% to hens commercial grower diet will significantly promote the feed intake amount and overall body weight increase. In fact, this seaweed function can be enhanced after extraction. Ruiz et al.'s[138] study illustrated a proportion of 5 grams of seaweed extract per kilogram of pig feed not only boosted the slaughter weight from 90.97 kg to 92.38 kg with less fattening feed intake but also improved the gut health of nursery pigs by inhibiting the *E. coli* and promoting *Lactobacillus* sp. growth.

Intriguingly, liquid seaweed extracts (LSEs) can be used as bio-stimulants to enhance land crop growth, which can further assist with globally growing food demands. Compared to modern fertilizers, LSEs represent a sustainable tool for increasing crop production yield due to their non-toxic, biodegradable and environmental-friendly features.[139] According to Renaut et al.'s study,[140] the addition of 250 mL 286-fold diluted *Ascophyllum nodosum* extract in pure hen manure every two weeks significantly increased the fruit number of tomatoes and fruit fresh weight of peppers. Similar effects were also observed on grain crops. Rengasamy et al.[141] believed that the eckol extracted from *Ecklonia maxima* will play an indispensable role in enhancing agricultural productivity. This is because they found the culture solution containing eckol promoted mung bean (at 10^{-5} M) and maize (at 10^{-6} M) seedling growths regarding their root length, seminal root growth, and seedling weight. Another recent study can further support their findings. Rathinapriya et al.[142] illustrated that the foliar spray treatment of 20 + 20% (*v/v*) LSEs consisting of *Padina boergesenii* (Phaeophyceae) and *Gracilaria edulis* (Rhodophyta) extracts would synergistically stimulate plant growth, crop quality and yield of foxtail millet. In terms of oil crops, 400-fold diluted LSE prepared with *Sargassum* spp. powder increased leaf chlorophyll content, photosynthesis, dry matter accumulation, main stem height, and lateral branch length of peanut plants.[143] Meanwhile, Tursun[144] proved that applying LSE with a dose of 2 mL/L would significantly enhance the crop yield, protein content, essential oil components, and oil yield of coriander plants. Hence, there is a far-reaching significance in utilizing seaweed as an effective and sustainable fertilizer.

Health and well-beings

Seaweeds are rich in numerous essential nutrients and bioactive compounds which are beneficial for human health. Recently, Murakami et al.[145] found the diet supplemented with 6% *Sargassum horneri* ameliorated the high-fat diet-induced obesity by modulating the related metabolic disorders and suppressed the development of diabetes and hepatic steatosis by inhibiting the pancreatic lipase activity and lowering the intestinal lipid absorption in mice. Moreover, consuming seaweed has been proven to be a protective factor in preventing breast cancer. Teas et al.'s[146] study revealed the diet with 5 g day^{-1} of *Undaria* sp. resulted in a 50% reduction in urinary human urokinase-type plasminogen activator receptor concentrations, which is a critical point that could further explain the relatively lower post-menopausal breast cancer incidence in Japan than the rest of the world. Besides breast cancer, the biocompatible gold nanoparticles (AuNPs) biogenically synthesised from *Champia parvula* (Rhodophyta) has therapeutic effects on lung cancer. Viswanathan et al.[147] indicated that the AuNPs exhibited excellent free radical scavenging ability and high cytotoxic effects against lung cancer cells. Furthermore, a recent study has revealed the relationship between seaweed intake and the remission of depressive symptoms. Guo et al.'s[148] 3-year investigation pointed out that a higher intake (>2 g/1000 kcal day^{-1}) of edible seaweeds was highly associated with a significant decrease in depressive symptom incidences. Regarding animal health, the addition of seaweeds to animal feed can modulate the gut microflora of poultry and livestock and enhance their immune responses. Shimazu et al.[149] reported that the addition of 1% *Undaria pinnatifida* powder had positive immunomodulatory effects on pigs by boosting the percentage of natural killer (NK) cells ($CD3^-$, $CD4^-$ and $CD8^+$) in their peripheral blood. Instead of promoting the NK cell levels, the dietary supplementation of 2% brown and 2.5% red seaweed meals can boost the serum immunoglobulin (IgG and IgM) concentrations, thereby activating the immune responses of broiler chickens[150] and crossbred claves,[151] respectively. Besides directly contributing to human and animal health, applying LSEs can enhance the treated crops' nutritional profile and benefit crop consumers with improved nutrition. Taking the beans (*Phaseolus vulgaris* L.) as an example, Ozaktan and Doymaz[152] found that the LSE treatment with a 2500 mL/ha dosage had effectively improved the calcium and zinc contents and reduced the cooking time of beans.

Ecosystem services

Seaweeds have crucial ecosystem service functions. This is because, referring to Fig. 3, they can synthesise organic carbons throughout photosynthesis by using inorganic carbons, which will significantly increase the oceanic carbon sink capacity and mitigate worldwide climate change.[157] Statistically, the global seaweed communities were believed to be able to assimilate about 1.5 petagrams annually, which is roughly equal to 10% of global car emissions.[155] Besides, seaweeds work as an "ocean filter" and play an indispensable role in coastal water quality improvement. Taking China as an example, Zheng et al.'s[153] work estimated that aquaculture seaweeds had removed 9,592 t of phosphorus and 75,563 t of nitrogen (Fig. 3), sequestrated 539,555 t of carbon and absorbed 5809 t of iodine from coastal waters, which had significantly mitigated the severe eutrophication problems faced by China. Regarding UN SDG, seaweeds have been praised for their incredible contribution to Life Below Water by enriching biodiversity through new biotope formation and habitat support services.[156] Burkepile et al.'s[154] work further highlighted the role of marine algal in feeding the herbivorous fishes on coral reefs and accordingly improving the species richness on the biologic food chain and forming new biocenosis (Fig. 3). Furthermore, the harmful effects of methane emission from ruminant animals were first emphasized by Mathison et al. in 1998.[158] What they had been worried about was further confirmed by Tenzin et al.'s recent study.[159] They illustrated that the gas produced by ruminant enteric fermentation accounted for about 16% of the global methane emission. In fact, adding seaweeds to ruminant animal feed can substantially lessen the formation of this greenhouse gas.[156,160] Kinley et al.[161] found the *Asparagopsis taxiformis* (Rhodophyta) mixed in the high-grain total mixed ration at 0.2% resulted in a 98% decrease in enteric CH_4 emissions and a 1700% increase in H_2 production of sheep and cattle. More importantly, their study provided a sustainable option to produce carbon-neutral red meat without negatively impacting its eating quality.

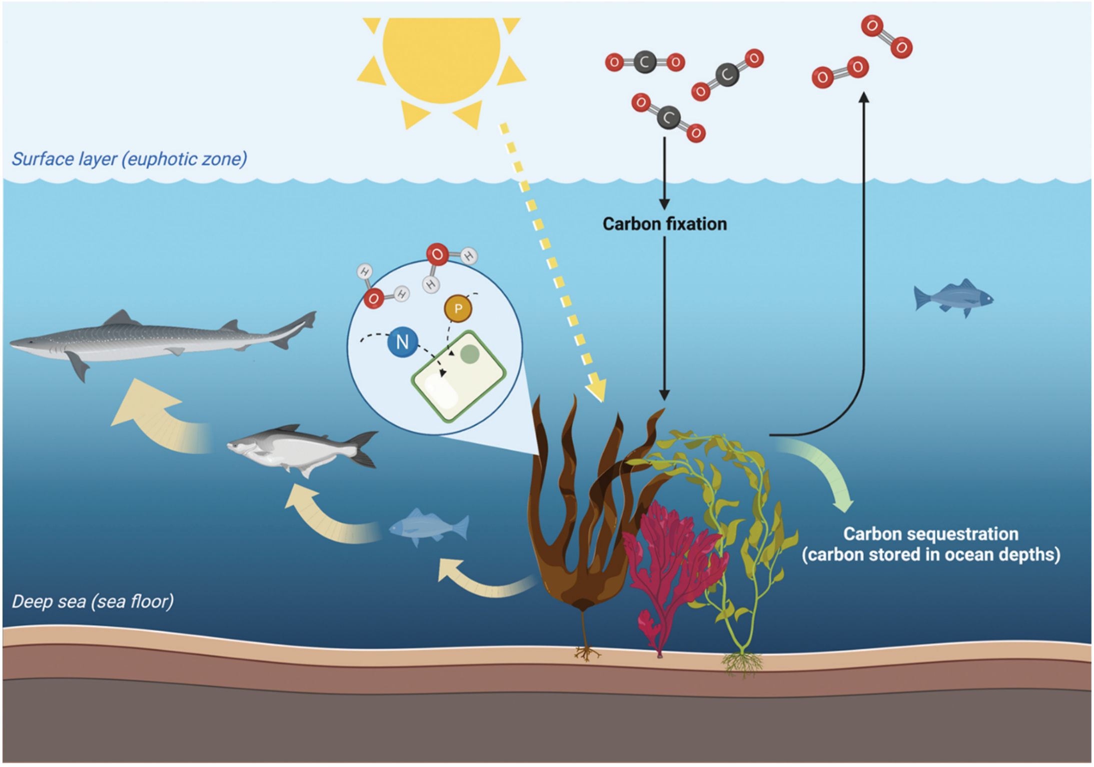

Figure 3. Ecosystem services of seaweeds.[153–156] drawn by BioRender.

Bioenergy

Seaweeds are promised to become a source of third-generation gaseous biofuels in the form of biomethane. People consider seaweeds a sustainable energy source since they neither occupy the agricultural land nor interfere with food production. Allen et al.[162] assessed the biomethane potential of ten seaweed species. They illustrated that the methane yields varied in species and ranged from 13.5–34.5 m^2 CH_4 t^{-1} on a wet weight basis, which predicted the gross energy yield generated by seaweeds might be up to 700 GJ ha^{-1} yr^{-1}. At the same time, the gross energy yields of *Ulva lactuca* (Chlorophyta) (186 GJ ha^{-1} yr^{-1}) and *Saccharina latissima* (Phaeophyceae) (365 GJ ha^{-1} yr^{-1})were highlighted due to their considerably higher yields than the first-generation liquid biofuels, such as palm oil biodiesel (120 GJ ha^{-1} yr^{-1}). However, their assumptions relied too heavily on the quantitative analysis of the energy yield and productivity but ignored commercial feasibility. Soleymani and Rosentrater argued that,[163] on the one hand, the optimized seaweed-derived bioethanol fuel price was estimated to be 0.93 USD L^{-1} which has almost doubled the commercially available ethanol price. On the other hand, meeting the 0.07 USD kWh^{-1} budget for seaweed-derived bioelectricity required 3.7 million tonnes (DW) of seaweeds, of which fresh weight is about half to one over a third of current global seaweed production. Therefore, they believed the economical production and commercialisation of seaweed-derived bioenergy was currently impossible. In fact, Lin et al.'s[164] recent study developed a feasible solution to Soleymani and Rosentrater's worries. They found the hydrothermal pretreatment (140°C) not only enhanced the CH_4 yield by around 23%, but also boosted the energy conversion efficiency to almost 73% and optimised the process energy efficiency to about 57%. This optimization of efficiency has primarily increased the feasibility of seaweed-derived bioenergy. Intriguingly, besides fuel energy, seaweeds can contribute to offshore wind energy production indirectly. This is because the seaweed farms can be co-located with the fish and offshore wind farms.[156] Consequently, this new concept of multiple-use of sea space by combining offshore wind turbines and seaweed farms will optimize the untapped space to capture carbon,[165] and increase societal licenses for offshore wind power station development.[166]

Challenges and limitations

Even though seaweeds have been praised for their bioaccessibilities of diverse nutritional elements and bioactive compounds, which are highly associated with an intense array of bioactivities and health benefits, the digestibility and bioavailability of these bioaccessible compounds contained in seaweeds have been vigorously challenged in recent years by many studies and become a debatable research topic. Taking seaweed protein as an example, Sun et al.[167] argued that the anti-nutritional substances contained in seaweeds, like tannins and phytic acid, could form a combination complex with seaweed proteins which would significantly reduce protein solubility, thereby inhibiting their digestion and absorption. The bioavailability of seaweed proteins could also be prevented by the insoluble fibre contents contained in seaweed and hampered by the entrapped nature of cellular matrix proteins. This view was consistent with Vasconcelos et al.'s[168] study discovering that the amount of undigested protein was positively associated with insoluble fibre content in samples. Meanwhile, they indicated that the strong cell structure composed of insoluble fibre would result in a low rate of gastric disintegration which would be directly associated with the low digestibility of proteins. Their explanation can be further supported by Demarco et al.'s findings.[169] As discovered, the protein digestibility of *Undaria pinnatifida* (Phaeophyceae) was 85%, whereas that of *Gracilariopsis longissima* (Rhodophyta) was only up to 30%. The main reason for this dramatic difference was whether there was a rigid cell wall. They illustrated that the wooden cell wall consisting of ceramides and silicates was the hurdle to disrupting cells and accessing the digestible proteins.

Although consuming seaweeds has been promised various health benefits, the triggered food safety issue has raised grave concerns for their consumers. Silva Junior et al.[170] presented that excessive heavy metal contents in commercial edible seaweeds could take a toll on human health. As assessed, the As and I contents in the kombu sample were 38,373 μg/kg and 1,461 mg/kg, and the Cd content in the nori sample was 1,590 μg/kg, which exceeded the As, I and Cd permitted values 85%, 4% and 39%, respectively. Even though washing and boiling have been provided as dietary strategies to reduce the poisoning risk, the potential heavy metal contamination of seaweeds should be paid more attention and reported to food safety authorities to ensure the edible seaweed quality, distribution and marketing. The same issue has been reported in the Italian market as well. As Panebianco et al.'s results suggested,[171] almost one over a fifth of edible seaweed samples from the market was out of the Cd limit proposed by the CEVA algae technology and innovation centre (France). This toxic heavy metal contamination has been found even worse in Oman Sea water and is believed to be caused by sewage outfall-induced pollution. Shahri et al. stated that,[172] to prevent human health from toxic heavy metals, seaweeds acquired from Oman Sea water should be prohibited for food purposes.

Chemistry of seaweed-derived polysaccharides

Polysaccharides are long-chain polymeric carbohydrates comprised of monosaccharides units that are connected by glycosidic linkages. As discovered, the considerably high carbohydrate contents in seaweeds are mainly contributed by their high content of polysaccharides which are promised with an intense array of bioactivities.[16] In fact, the functional properties of seaweed polysaccharides are mainly contributed by their complex structural features, such as glycosidic linkages, chain conformation, and molecular weight. As an illustration, Saravana et al.[173] found the subcritical water treatment could depolymerize the fucoidan extracted from *Undaria* *pinnatifida* and form low-molecular-weight fucoidan. What is noteworthy is that the fucoidan with a decrease in molecular weight showed an increase in antidiabetic, antioxidant, anticoagulant, and antimicrobial activities. Therefore, it is essential and necessary to understand the chemistry of polysaccharides to further understand and investigate the linkage between their structural features and relevant bioactivities.

Brown seaweed polysaccharides

Brown seaweeds are the second largest group of marine macroalgae after red seaweeds. What is distinct is brown seaweeds are rich in photosynthetic pigments, particularly chlorophyll c and fucoxanthin, which is also the reason for their derived green-brown colour.[174] The significant polysaccharides in brown algae cell walls are alginates, fucoidans, and laminarins.[175]

Alginates

Alginates are the main polysaccharide component in brown seaweed intercellular matrix and cell walls.[175] Generally, the alginate contents of brown seaweeds range from 17 to 47%, with the highest content recorded in July from young blades.[176] In brief, alginates are linear polysaccharides consisting of (1→4)-linked α-L-guluronic acid (G) and β-D-mannuronic acid (M) units with an anionic polymeric structure.[177] These two conformational isomer residues are connected through (1→4)-glycosidic linkages.[113] Therefore, in terms of the structural blocks, alginic acids may compose of three patterns, including homo-polymeric sections of consecutive G blocks, homo-polymeric sections of consecutive M blocks, or hetero-polymeric sections of randomly connected G and M residues usually with a 1:1 (Gs:Ms) ratio.[113] The M/G ratio can be affected by various factors, such as species, harvest time, growth condition, harvest location, and extraction processes of the algae.[178] For instance, the M/G ratio of alginates extracted from the old stipes of *Laminaria hyperborea* was around 0.4, whereas the M/G ratio of alginates isolated from *Saccharina japonica* ranged from 0.77 and up to 2.76.[179]

Different tissues of the kelps show diverse levels of flexibility and rigidity due to the variances of block compositions and M/G ratio.[177] This is because β-D-mannuronic acid units are present in a $^4C_1$ chair conformation in the M blocks, whereas α-L-guluronic acid units are present in the $^1C_4$ conformation in the G blocks.[179] Therefore, stronger hydrogen bonds and a more rigid structure are formed in the G blocks.[175] As a result, alginates rich in α-L-guluronic acid units have a higher water solubility than those rich in β-D-mannuronic acid units. Besides, since the α-L-guluronic acid residues can interact with Ca^{2+} and form an "egg-box" junction expressing a hydrogel texture.[175,179] Consequently, the gel rigidity shows a decreasing order: gel formed by homo-polymeric G blocks > gel formed by homo-polymeric M blocks > gel formed by hetero-polymeric MG blocks.[179] Together, alginates with a lower M/G ratio show higher gel strength, while alginates with a higher M/G ratio display greater flexibility.[180] At the same time, this finding suggests that the M/G ratio can decide the properties of alginate and further direct the application of alginate. Different external factors can affect the M/G ratio of alginate. The formations of C-5 monomers, including D-mannuronic and L-guluronic acids, are highly related to the alginate biosynthesis pathway, which is controlled by the enzyme mannuronan C-5 epimerase (MC5E).[177] Referring to Fig. 4, the MC5E identified in the cell protoplasts of *Laminaria digitata* could convert the D-mannuronic acid residues into L-guluronic acid residues and assist with the formation of algae cell walls.[181,182]

Fucoidans

Fucoidans are a type of fucose-containing sulphated polysaccharides which have been identified in many brown seaweed species.[183] Basically, fucoidans consist of fucose and sulphate ester groups, along with additional sugar constituents, such as glucose, mannose, galactose, xylose, acetyl groups and uronic acids.[184] As one of the anionic polysaccharides, fucoidans are one of brown seaweeds' primary cell wall components and are not found in terrestrial plants.[177] It was illustrated that fucoidans could assist with seaweeds staying moist in low-tide conditions and increase their

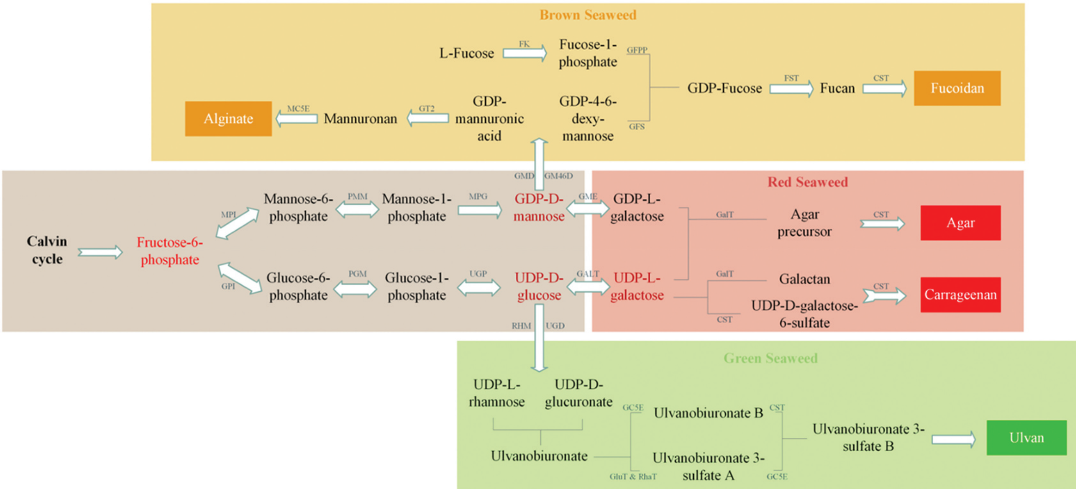

Figure 4. Proposed biosynthesis pathways of seaweed polysaccharides.[177] MPI, mannose-6-phosphate isomerase; GPI, glucose-6-phosphate isomerase; PMM, phosphomannomutase; PGM, phosphoglucomutase; MPG, mannose-1-phosphate guanylyltransferase; UGP, UTP-glucose-1-phosphate uridylyltransferase; GME, GDP-mannose-3′,5′-epimerase; GALT, galactose-1-phosphate uridylyltransferase; GalT, galactosyltransferase; CST, carbohydrate sulfotransferase; GC5E, glucuronyl C5-epimerase; GluT, glucuronyltransferase; RhaT, α-1,4-rhamnosyltransferase; MC5E, mannuronate C5-epimerase; GT, glycosyltransferase; GFS, GDP-fucose synthetase; GFPP, GDP-fucose pyrophosphorylase; FK, fucokinase; FST, fucosyltransferase; GMD, GDP-mannose dehydrogenase; RHM, rhamnose synthase; UGD, UDP-D-glucose dehydrogenase; GM46D, GDP-mannose 4,6-dehydrogenase.

desiccation tolerance.[113] The concentrations of fucoidans vary among reproduction periods, seasons, algal species, tissue positions and environmental factors. Still, they are not highly correlated with seawater salinity, temperature, oxygen level, and biogenic elements.[177] The fucoidan contents of brown seaweeds usually range from 10 to 20%, and the highest concentration reported so far was 46.6% in *Laminaria digitata*.[113,185]

Even though more than a century has passed since the first discovery of fucoidan, its chemical structure still has not been ultimately determined. This is reasonable since brown seaweed synthesises highly branched polysaccharides, which proportions and forms differ in dependence on the classified taxonomic position.[177,184] For example, it has been illustrated that the backbone structure of fucoidan presented in *Chorda filum* differed from that shown in *Fucus vesiculosus*.[186,187] However, in terms of the positions of inter-glycosidic linkages, there is still a certain similarity in the backbone structures of fucoidan molecules. Generally, fucoidans compose of α-L-fucopyranose.[184] The α-L-fucose residues are usually sulphated at C-2 and C-4 positions, also at the C-3 position, but rarely.[184,187] Therefore, the backbone structures of fucoidans can be summarized as two main structures, including a linear backbone consisting of α-(1→3)-L-fucose residues and a backbone consisting of alternating (1→3)-linked and (1→4)-linked α-L-fucose residues. For instance, the fucoidan extracted from *Chorda filum* was investigated to have consisted of linear chains built up by α-(1→3)-L-fucose residues, whereas the backbone structure of fucoidan extracted from *Hormophysa cuneiformis* was composed of alternating (1→3)-linked and (1→4)-linked fucose residues.[184,188] The fucoidan biosynthesis pathway was first reported in *Ectocarpus siliculosus*.[189] Referring to Fig. 4, it involves a *de novo* pathway catalysed by GDP-fucose synthetase (GFS) and GDP-mannose 4,6-dehydratase (GM46D) and a salvage pathway with the assistance of GDP-fucose pyrophosphorylase (GFPP) and fucokinase (FK).[177,189]

Laminarins

Laminarins are one of the significant storage carbohydrates of brown algae with low molecular weight.[175] Although the laminarin content is associated with numerous factors, such as species, harvest time and habitat of seaweeds, the highest level is up to 35% of DW.[190] In general, laminarin can be commonly found in *Saccharina* spp. and *Laminaria* spp., whereas it represents a minor content level in *Fucus* spp., *Undaria* spp. and *Ascophyllum* spp.[175] It is worth mentioning that the molecular weight (MW) of laminarin is around five kDa which is much lower than most of the other seaweed polysaccharides.[190] In fact, the molecular weight highly depends on the degree of polymerization.[191] This is because, regarding the polymeric structure, laminarin consists of a main polysaccharide chain formed by (1→3)-linked β-D-glucopyranose residues with variable degrees of β-(1→6)-intrachain links and 6-*O*-branching.[192] There are two main types of polymeric chains, G-chain and M-chain. In detail, the M-chain structure has D-mannitol at the reducing end of the chain, while no D-mannitol is presented at the reducing end of a G-chain.[175] For instance, it was reported that the MW of laminarin extracted from *Laminaria hyperborea* was around 5.7 ~ 6.2 kDa, which is higher than the normal MW range.[192] This might be because of its higher level of polymerization. Besides, it was found that the solubility of laminarin was related to its level of ramification, and highly branded laminarin can dissolve in cold water.[193]

Red seaweed polysaccharides

Among all the eukaryotic algae, red seaweeds are believed to be the phylogenetically oldest division.[113] Thus far, approximately 6500 red algal species have been identified, making them the most diversified taxonomical group.[118] As a common characteristic, red seaweeds contain galactan as the main structural building block of their intercellular matrix and cell walls.[194,195] Nowadays, a diversity of polysaccharides has been identified in red algae, such as carrageenans, agars, porphyrins, xylans, and floridean starch.[113,196] Among these identified polysaccharides, carrageenan, sulphated galactans and agars have been considered the significant and unique polysaccharides that can be derived from red algae.[197]

Carrageenans

Carrageenans are marine hydrocolloids and red algae's main structural building component.[198] Commercially, carrageenans are usually extracted from *Eucheuma denticulatum* and *Kappaphycus alvarezii*.[177] The linear chains of carrageenans are composed of repeating di-saccharide units of 3,6-anhydro-galactose and D-galactose, linked by alternating 4-α-D-galactose and 3-β-D-galactose, and modified by substitution with methyl, ester sulphate, or pyruvate, which contains 15–40% sulphate ester groups depending on carrageenan types.[196,198] Based on the structural composition and sulphate content, carrageenans can be divided into three families: the beta (β) family, including beta (β), gamma (γ), omega (ω) and psi (ψ) carrageenans; the kappa (κ) family, including kappa (κ), mu (μ), iota (ι) and nu (ν) carrageenans; and the lambda (λ) family, including lambda (λ), alpha (α), delta (δ), theta (θ) and xi (ξ) carrageenans.[113,196] The κ-carrageenans mainly from *Kappaphycus alvarezii* and ι-carrageenans mainly from *Eucheuma denticulatum* are two major commercial carrageenans with distinct gelatinization properties.[199] The ι-carrageenans form soft gels, whereas the κ-carrageenans produce brittle gels.[200] When fully transformed, the gametophyte generation of these two commercial species contains only one primary carrageenan type (>75%), either ι-carrageenans or κ-carrageenans.[199] Whereas in some other species, such as *Mastocarpus stellatus*[201] and *Chondrus crispus*,[202] carrageenans are generally presented as hybrid structures instead of pure forms.[113] For instance, many seaweed species contain carrageenans with intermediate rheological properties due to different ratios of ι-carrageenans and κ-carrageenans.[199] These types of carrageenans are called κ/ι-hybrid carrageenans. Except for κ/ι-hybrid polymers, natural carrageenans appear as ν/ι-hybrid polymers, μ/κ-hybrid polymers and so on.[196] Therefore, the structural sequences of transformed (κ, ι) gelling and precursor (μ, ν) nongelling units in the carrageenan polymer chain can essentially decide the bioactivities and physicochemical properties of the carrageenan chain.[199] In fact, the relative amount of gelling and nongelling units contained in the hybrid polymer sequence can be affected by the carrageenan extraction procedure. Azevedo et al.'s[203] previous study indicated that the high-temperature alkaline pre-treatment on seaweeds can convert the comprised μ- and ν-carrageenans to κ-and ι-carrageenans, respectively. However, research on carrageenan biosynthesis is minimal. As Fig. 4 illustrates, galactose sulphurylases are the only identified enzymes on the carrageenan synthesis pathway.[204] Moreover, the genes encoding carrageenan-synthesis-relevant enzymes, including carbohydrate sulphotransferase (CST), glycoside hydrolase (GH16), glycosyltransferase (GT), and galactose-6-sulphurylase were previously identified in the genome dataset of *Chondrus crispus*.[205]

Agars

Agars have been commonly exploited due to their excellent hydrocolloid properties. Globally, the industry use agar is usually extracted from *Gelidium* spp., *Gracilaria* spp., and *Pterocladiella capillacea*.[206] Agars are hydrocolloids mainly consisting of agarose and agaropectin. In terms of their chemical structure, agars are linear seaweed polysaccharides built up of alternating α-(1→3)-$_D$-galactopyranose and β-(1→4)-linked 3,6-anhydro-$_L$-galactopyranose residues with intermittent sulphate groups at the C-6 position.[196,206] The hydrocolloid properties of agars are highly associated with their polymeric structures. For instance, α-(1→4)-linked 3,6-anhydro-$_D$-galactopyranose residues may also appear on the polymer chain, enhancing the hydrocolloid properties of agars.[196] Based on the backbone structure of agars, together with carrageenans, they are classified as sulphated galactans. Furthermore, the anionic charges of agar polymers will be altered depending on their sulphation degree.[207] As a result, it can form more neutral agarose, or agaropectin with a higher sulphation degree.[196] Due to the presence of α-(1→4)-linked 3,6-anhydro-$_D$-galactopyranose residues, agarose gel shows a higher viscosity.[206,207] Whereas agaropectin has been characterized by the presence of more elevated pyruvate and acetate substitutions, resulting in lower water solubility.[196,207] Similar to carrageenans, research on the biosynthesis pathway of agars is still limited. As Fig. 4 suggested, the biosynthetic pathway proposed by previous studies started from fructose-6-phosphates (F6Ps), then they were catalysed to either GDP-$_L$-galactose by GDP-mannose-3,5-epimerase (GME) or UDP-$_D$-galactose by galactose-1-phosphate uridylyltransferase (GALT) to form agar precursor units.[208,209]

Green seaweed polysaccharides

As previously discussed, green seaweeds contain high levels of fibres, proteins, and bioactive compounds. It is true that the polysaccharide contents in green seaweeds are relatively lower than the other seaweeds.[196] For example, Farias et al.[210] indicated that the total polysaccharide content accounted for about 5% DW of *Codium isthmocladum*. Notably, ulvans are the distinct sulphated polysaccharides that are exclusively contained in green seaweed *Ulva* genus[114] and exhibit prominent antioxidant activities.[211]

Ulvans

The soluble dietary fibres in *Ulva* species account for up to 40% DW of their biomass, with a majority of ulvans and minor compositions of xylo-glycans and glucuronans.[212] The pioneering works indicated that ulvans had a distinct heterogeneous composition with repeated disaccharide sequences such as xylose, sulphated rhamnose, and uronic acids (iduronic or glucuronic acids).[213] The most frequently repeated disaccharides in the ulvans were characterized to comprise two different types of aldobiorunic acids, which are designated as type A (A_{3s}) and type B (B_{3s}).[212] The A_{3s} repeats [→4)-β-$_D$-glucuronic acid-(1→4)-α-$_L$-rhamnose-3-sulfate-(1→], whereas B_{3s} repeats [→4)-β-$_L$-iduronic acid-(1→4)-α-$_L$-rhamnose-3-sulfate-(1→].[184,212] The sulphated rhamnose residues mainly occupy the C-3 position or both C-1 and C-3 positions; however, sulphated xylose residues might be present in the place of uronic acids.[184,196,212] Therefore, the repeating disaccharide sequences of ulvans are called type A U_{3s} and type B $U_{2,3s}$.[212,213]

Bioactivities of seaweed-derived polysaccharides and their derivatives

Polysaccharides are versatile biopolymers that can be derived from many natural resources, especially seaweeds. Most notably, sulphated polysaccharides are the main bioactive polymers abundantly distributed in various seaweed species.[214] Due to their complex chemical structures and diversity of functional groups, seaweed sulphated polysaccharides (SSPs) can interact with multiple textures, chemical compounds, lipids, cellular proteins, and microbiota.[215–217] Benefitting from these interactive effects, SSPs have possessed an extensive array of bioactivities, such as antioxidant, antimicrobial, anticarcinogenic, immune-enhancing, and anti-inflammatory activities.[218–222]

Antioxidant activities

Many previous studies have demonstrated that algal polysaccharides are vital antioxidants and *in-vitro* free radical scavengers to prevent living organisms from oxidative damage.[223,224] In general, the antioxidant activities of polysaccharides are investigated regarding the steps taking place in a radical substitution reaction, including blockage of the initiation, such as total antioxidant capacity (TAC), reducing power activity (RPA), and DPPH/ABTS free radical scavenging ability; branching and propagation, such as iron/copper chelation ability; and termination, such as superoxide/hydroxyl radical scavenging capacity.[225] The TAC, RPA, DPPH and ABTS assays are mainly used to determine the ability to neutralize the free radicals by donating the hydrogen or electrons to reactive oxygen species (ROS), thereby interrupting the initiation phase of the free-radical chain reaction (Fig. 5).[230] As an example, Rodrigues-Souza et al.[225] indicated that the TAC of fucan and galactan extracted from *Codium isthmocladum* was 26.2 mg/g ascorbic acid and 11.01 mg/g ascorbic acid, respectively. Even though the TAC and RPA assays had a similar antioxidant mechanism, unlike the TAC, their reducing power was hard to detect. A relatively lower RPA had also been found Arunkumar et al.'s study.[226] As they discovered, the highest RPA of sulphated polysaccharides among five edible seaweed species was 0.4 mg/mL for the *Padina pavonica*, which was much lower than that of the ascorbic acid standard. As an optimization, the ferric-reducing power of polysaccharides could be largely improved by fermentation. As Lee et al. illustrated,[231] after fermentation with alginate and laminarin, the RPA of the culture medium was around four and two times higher than the control group, respectively. Besides, according to Tian et al.,[227] the polysaccharide fraction extracted from *Sargassum carpophyllum* with an average of 125 kDa average MW showed excellent concentration-dependent DPPH and ABTS radicals

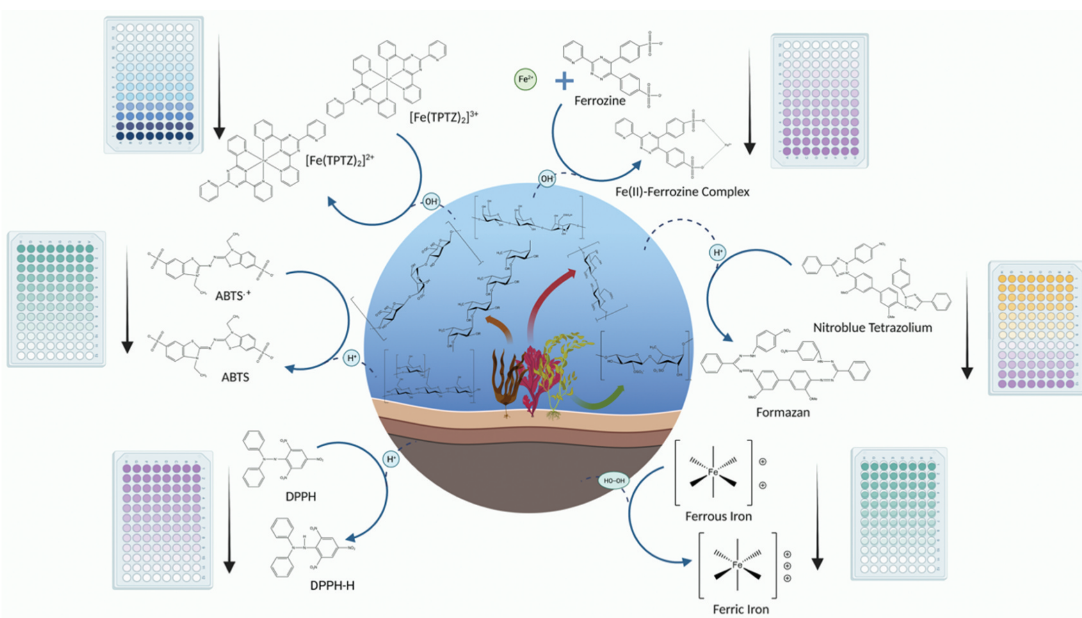

Figure 5. Proposed antioxidant mechanisms of seaweed-derived polysaccharides.[192,218,226–229] drawn by BioRender.

scavenging abilities, which were about 65% and 91% at 10 mg/mL concentration, respectively. Furthermore, seaweed-derived polysaccharides have also been identified with great antioxidant activities at the propagation and branching phase of the radical substitution reaction. As Fig. 5 indicates, the ferrous ion chelating ability determines the ability of the compounds donating an electron to reduce the TPTZ – Fe (III) complex to the TPTZ – Fe (II).[192] For instance, the polysaccharide fraction extracted from *Gracilaria caudata* showed an outstanding metal chelating activity at 4 mg/mL (69.8%).[228] Regarding the termination step of the radical substitution reaction, fucoidan (1 mg/mL) extracted from *Sargassum fusiforme* (formerly *Hizikia fusiformis*) (Phaeophyceae) and polysaccharides (20 mg/mL) from *Sargassum carpophyllum* with an average 125 kDa average MW scavenged 32.98%[229] and 73.80%[227] hydroxyl radicals, respectively. Besides ROS, lipid peroxidation (LPO) is another type of oxidative stress in human and animal cells, which is believed to be highly associated with the causes of many malignant diseases, such as lung cancer.[232] In fact, superoxide free radicals are the primary oxidative stress in the human body, which can damage the cells through LPO.[227] Notably, SSPs refined from *Sargassum fusiforme* (100 μg/mL) and *Sargassum carpophyllum* (12 mg/mL) displayed remarkable dose-dependent superoxide radical scavenging activities by 73.56%[229] and 71.30%,[227] respectively. In summary, seaweed-derived polysaccharides have excellent antioxidant capacities that could protect cells against damage caused by a wide range of free radicals. Meanwhile, the presentence of these antioxidant activities could further contribute to the expression of other bioactivities of seaweed-derived polysaccharides, such as anti-inflammation and anticancer.

Antimicrobial activities

In recent years, many studies have demonstrated the excellent antimicrobial activities of seaweed polysaccharides against plentiful human bacterial pathogens,[233] foodborne fungi,[234] and a broad spectrum of viruses.[235] Jun et al.[233] indicated that the fucoidans extracted from *Fucus vesiculosus* had inhibited not only the growth of two Gram-positive bacterial strains but also suppressed their biofilm formation. As discovered, the extracted fucoidans inhibited the growth of *Staphylococcus aureus* and *Listeria monocytogenes* at 500 μg/mL and 250 μg/mL concentration, respectively. Although they had even suppressed the biofilm formation of *Enterococcus faecalis* over 90% at a 1000 μg/mL concentration in contrast to the control group, the fucoidans extracted from *Fucus vesiculosus* did not express any inhibitory activities to the Gram-negative bacteria. Whereas alginates had been observed to have solid inhibitory activities against Gram-negative bacteria. Arafa et al.[236] found the hydrogel formed by alginates possessed a 69.85% inhabitation rate against *Agrobacterium tumefaciens* at a 3.90 μg/mL concentration. Meanwhile, its inhibitory activity against *Bacillus cereus* (Gram-positive) was even higher, reaching 100% at a 1.95 μg/mL concentration. Besides, seaweed-derived polysaccharides showed notable antifungal activities. Fayoumy et al.[234] had previously examined the antifungal activities of ulvans against three foodborne fungicidal strains. As their results suggested, the 10 mM and 15 mM of ulvans extracted from *Ulva lactuca* had significantly restrained the growth of *Aspergillus flavus* by 91% and *Rhizopus stolonifera* by 89%, accordingly. The carrageenan nanoparticle encapsulations also enhanced the phytopathogenic and buccal fungi inhibitory activities of commercial fungicides. Kumar et al.[237] showed the fungicide-loaded chitosan-carrageenan nanoparticles at 1 mg/mL concentration not only exhibited the same fungi radial growth inhibition (100%) against *Septoria lycopersici* and *Sclerotinia sclerotiorum* as the commercial fungicide mancozeb, but also displayed less toxic and better cell viability than the mancozeb. Their finding was consistent with Özkahraman et al.' study.[238] As indicated, the triamcinolone acetonide loaded κ-carrageenans/pectin patches performed more vigorous antifungal activities against *Aspergillus flavus* and *Aspergillus fumigatus* with no cell cytotoxicity. Furthermore, many previous studies have examined the antiviral activities of seaweed-derived polysaccharides. The international pandemic, coronavirus disease (COVID-19), has caused a worldwide health threat due to its rapid spread. Fucoidan treatment has been found out as an effective potential therapy or complementary treatment to the medical prescription for COVID-19-recovered patients suffering long-term sequelae. As Díaz-Resendiz et al. investigated,[239] the fucoidan

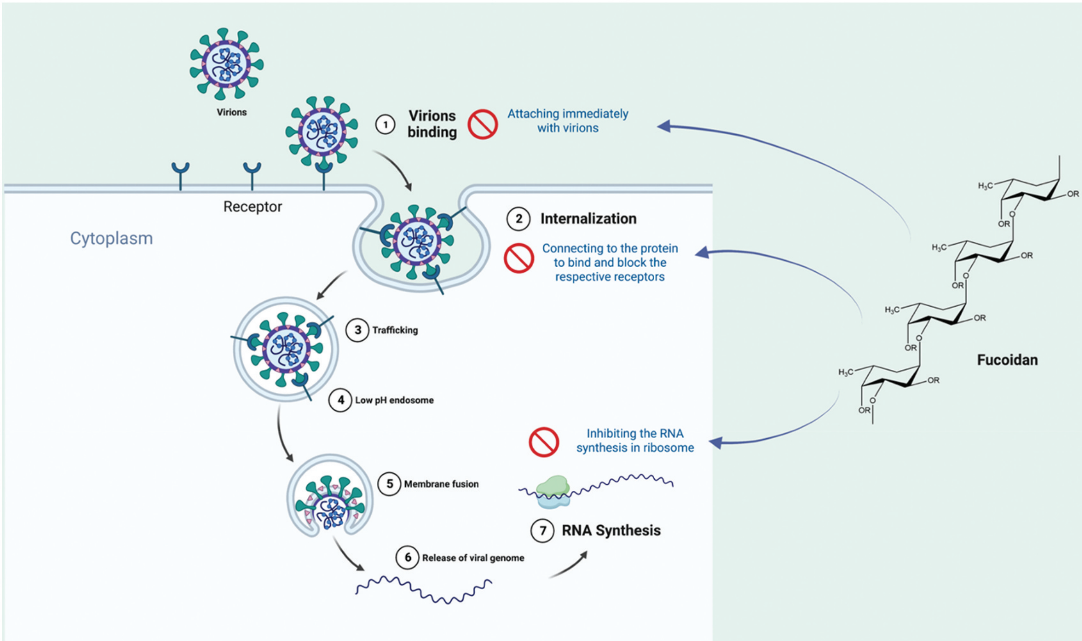

Figure 6. Proposed antiviral mechanisms of fucoidans.[239,240,243–245] drawn by BioRender.

treatment (20 μg/mL) had significantly restored and increased the mitochondrial membrane potential ($\Delta\psi_m$) by an average of 10% in peripheral blood mononuclear cells (PBMCs) from SARS-CoV-2 recovered female patients in contrast to the control group. Meanwhile, their follow-up study suggested that the fucoidan treatment had no toxicity to human PBMCs, which further supported the feasibility of this seaweed-polysaccharide treatment.[240] Except for the SARS-CoV-2 virus, sulphated polysaccharides extracted from seaweeds, such as fucoidan and carrageenan, also showed antiviral activity against HIV infections. As Harb & Chow discovered,[241] the practical anti-HIV activities of seaweed-derived polysaccharides were shown as their IC_{50} values of inhibiting the HIV infection process were relatively low. The HIV inhibition mechanism of these polymers has been further investigated by Sanniyasi et al.[242] They found the maximum inhibitory activities of fucoidans extracted from *Turbinaria decurrens* and *Dictyota bartayresiana* (Phaeophyceae) were 92% (IC_{50} = 131.7 ng/mL) and 89% (IC_{50} = 57.6 ng/mL), respectively. Specifically, as Fig. 6 illustrates, fucoidans could bind with the HIV particle and hamper the viral infection at an early stage. The exact inhibition mechanism had been identified in the antiviral activities of other SSPs. Fucoidans extracted from *Monostroma nitidum* (Chlorophyta) and *Nizamuddinia zanardinii* (Phaeophyceae) had proven to be able to restrain the infection of IFN-γ–inducible enterovirus[246] and herpes simplex virus[247] by binding virus particles and entering into Vero cells. Altogether, the remarkable antimicrobial activities of seaweed-derived polysaccharides have been confirmed by a series of research studies and bioactivity assays. These constructive findings further supported the rationality and feasibility of food and medicine applications of seaweed-derived polysaccharides.

Anticarcinogenic and immune modulation activities

Seaweed-derived polysaccharides have attracted significant research interest due to their therapeutic effects on cancers.[248] Specifically, many previously conducted *in vitro* studies have found they showed the tumour cells' inhibitory activities by enhancing the immune function of cancer patients or suppressing tumour cell metastasis.[249] Benefiting from their sulphated functional groups, SSPs like fucoidans can prevent tumour cell growth by inhibiting free radical generation and reducing tumour chemotherapy drug resistance.[250] Referring to the anticancer assays conducted by Alboofetileh et al.,[251] fucoidans extracted from *Nizamuddinia zanardinii* with 400 μg/mL concentration inhibited the 67.46% and 55.94% growth of HeLa (cervical cancer) and Hep-G_2 (hepatocellular carcinoma) cell lines. Meanwhile, their study proposed the potential anticancer mechanism by further investigating the effects of fucoidans on RAW264.7 cell proliferation and nitric oxide production. As discovered, fucoidans extracted by enzymatic-assisted method had significantly activated the mitogen-activated protein kinases (MAPKs), thereby stimulating the RAW264.7 murine macrophage cells which are mainly responsible for the innate immune response to malignant tumour cells. The observed significant increase in NO assisted to confirm this immunostimulatory process. Inhibitory activities of Hep-G_2 and HeLa cell growth had also been reported on other SSPs. In detail, Chen et al.'s[252] investigation showed that 250 μg/mL SSPs from the green microalga *Tribonema* sp. inhibited up to 66.8% growth of Hep-G_2 cells by upregulating tumour necrosis factor α (TNF-α), interleukin 6 (IL-6) and interleukin 10 (IL-10). Whereas Digala et al.'s[253] study found the SSPs (800 μg/mL) from *Sargassum polycystum* had significantly induced the apoptosis of HeLa cells and decreased almost 80% of the HeLa cell viability. Except for cervical cancer and hepatocellular carcinoma cells, SSPs were also cytotoxic to prostate cancer cells. Pham et al.[254] illustrated that the sulphated galactans extracted from *Neopyropia yezoensis* (formerly *Pyropia yezoensis*) (Rhodophyta) could induce the modulation of the intracellular reactive oxygen species production to regulate the PI3K/AKT/mTOR signalling pathway, thereby inhibiting up to 73% and 80% of PC-3 and DU145 cell growths at same 750 μg/mL concentration. Besides, seaweed-derived polysaccharides could protect patients from radiotherapy-induced immune cell and blood cell damage. Referring to the *in-vivo* study based on a rat model conducted by Rhee and Lee,[255] the fucoidan-treated rats (100 mg/kg) showed not only strong resistance to the thrombocytes and leucocytes damage induced by irradiation but also significantly less hypoplasia of bone marrows in contrast to the control group. Their groundbreaking findings could further support that SSPs could be considered a promising therapy or complementary treatment for patients having hematopoietic dysfunction induced by long-term chemotherapy or radiotherapy. Notably, the anticarcinogenic activities of seaweed-derived polysaccharides are highly associated with their immune activation capacities. Besides macrophage cells, SSPs can also modulate the immune system by stimulating T cells, B cells, and natural killer (NK) cells. Zhu et al.[256] investigated the NK cells' stimulative capacities of laminarins from *Saccharina japonica* (formerly *Laminaria japonica*) (Phaeophyceae) in the immunosuppressed mouse. As a result, the extracted laminarin (1000 mg/mL) significantly enhanced the IL-12, TNF-α and NK cell levels in the serum, thereby potentiating the damaged immune system. Their findings were consistent with another recent study. As An et al. discovered,[257] treatment (100 mg/kg) with fucoidans extracted from *Saccharina japonica* not only elicited T cells, IFN-γ, and NK cell cytotoxic mediator production, but also stimulated the anticarcinogenic efficacy of anti-programmed Death-Ligand 1 antibody against lung carcinoma. In summary, on the one hand, seaweed-derived polysaccharides can directly suppress cancer cell metastasis. On the other hand, they can also work as immune stimulatory compounds to promote the production or anticancer efficacies of immune checkpoint inhibitors.

Anti-inflammatory activities

Many recent studies have demonstrated the significant effects made by seaweed-derived polysaccharides in different inflammatory pathology models, showing such as the reduction of pro-inflammatory cytokines, cell migration, oxidative stress, and criteria of tissue injury.[258] As an illustration, according to Cui et al.,[259] sulphated polysaccharides derived from *Gelidium pacificum* (Rhodophyta) had markedly inhibited the mRNA and protein expression levels of tumour necrosis factor receptor-associated factor 6 (TRAF6), myeloid differentiation factor 88 (MyD88) and Toll-like receptor 4 (TLR4) in lipopolysaccharide (LPS)-stimulated cells. Specifically, the overexpression of TRAF6 not only enhanced the inflammatory responses by triggering T and B cell activation,[260] but also exacerbated the tumour invasion and metastasis.[261] Whereas MyD88 and TLR44 were responsible for releasing pro-inflammatory factors induced by immune danger signals,[262] and inflammatory cytokines production via the NF-κB signalling pathway,[263] respectively. The anti-inflammatory effects of SSPs had been further supported by an *in-vivo* zebrafish model conducted by Wang et al. As they investigated,[217] the survival rate of the zebrafish embryo treated with 100 μg/mL SSPs from *Codium fragile* (Chlorophyta) had significantly increased to 73.33% in contrast to the non-treatment group (56.67%). Meanwhile, this SSPs treatment also dramatically decreased the ROS levels from 295.22% to 185.58% and the NO production from 220.45% to 133.51% in LPS-induced zebrafish compared to the control group (100%). Additionally, protein denaturation[264] and free radicles[265] had been highly correlated with the occurrences of inflammatory responses, which could potentially trigger a diversity of inflammatory diseases, such as arthritis. Obluchinskaya et al.'s[266] recent study found the fucoidan fraction extracted from *Fucus vesiculosus* showed prominent free radical scavenging activity (IC_{50} = 0.05 mg/mL) and against protein denaturation ability (IC_{50} = 0.20 mg/mL). In general, many polysaccharides derived from marine macroalgae, especially SSPs, had possessed excellent anti-inflammatory activities in recently conducted studies, which could further instruct the application direction of seaweed-derived polysaccharides as promising anti-inflammatory agents.

Effects of chemical compositions and structural features of seaweed-derived polysaccharides on the presentence of their triggered bioactivities

As previously discussed, seaweed-derived polysaccharides have exhibited a diversity of biological activities. In fact, these shown bioactivities could be seriously affected by their chemical compositions and polymeric structure features, such as MW, sulphation degree, variances in glycosidic branching, and types of sugar compositions.[113,223] The significant effects on the expression of bioactivities triggered by the differences in MW have attracted today's researchers' attention. For instance, Tian et al.[227] found the scavenging ratio of SSPs with 151 kDa and 125 kDa MW on DPPH, OH, O^{2-} radicals was 46.7%, 46.7%, 62.8%, 87.3% and 66.6%, 73.8%, 71.3%, 91.1%, respectively. Obviously, SSPs with lower MW showed more potent radicle scavenging abilities. Besides, MW differences could also affect the reducing power of seaweed-derived polysaccharides. As Saravana et al. investigated,[173] there was a significant increase in the ferric-reducing power of low-MW fucoidans induced by subcritical water treatment. Rodrigues-Souza et al. stated that,[225] the reducing power of compounds was mainly contributed by the number of reducing ends. Meanwhile, Qi et al.[267] illustrated the reducing end number of polysaccharides was negatively correlated with their MW by showing low-MW ulvans from *Ulva australis* (formerly *Ulva pertusa*) (Chlorophyta) degraded from 151.7 kDa to 28.2 kDa had more reducing ends and more substantial reducing power. Besides antioxidant activities, the MW change of polysaccharides resulted by the heat treatment could also dramatically affect their antimicrobial activities. According to Jun et al.,[233] the MW of fucoidans from *Fucus vesiculosus* after heat treatment (121°C, 15 min) dropped from 62.08 kDa to 13.88 kDa, but the resulted low-MW fucoidans (125 μg/mL) significantly restrained both the biofilm formation and planktonic cell growth. However, the low MW seems to be a disaster for the immunomodulatory activities of polysaccharides. Qi and Kim[268] demonstrated that the polysaccharides derived from *Chloroidium ellipsoideum* (formerly *Chlorella ellipsoidea*) (Chlorophyta) with higher MW induced higher nitric oxide production from murine macrophage J774A.1 cells and showed more vital immunomodulatory activities. Based on these results, it is apparent that thermal condition is one of the critical factors affecting the MW of extracted polysaccharides, thereby influencing the strength of seaweed polysaccharide-triggered bioactivities. As investigated, the thermal treatment involved in heat-assisted extraction (HAE)[269,270] and temperature increase induced by microwave-assisted extraction (MAE)[271] could be highly possible to cause the degradation of the seaweed-derived polysaccharides in the extraction process.

Besides MW, the sulphation degree of SSPs was another determining factor that had been shown to be highly related to the expression of bioactivities. For example, Makoto et al.[272] found that the removal of sulphate residues eliminated the bacteriostatic effect of ι-carrageenan, which suggested the antimicrobial impact of polysaccharides was highly associated with the sulphate residues. Regarding the antioxidant activities, Bhadja et al.[273] illustrated that the polysaccharide fraction extracted from *Bryopsis plumosa* (Chlorophyta) with the highest sulphate content (11.4%) showed the strongest DPPH and O^{2-} radical scavenging abilities (IC_{50} = 1.7 mg/mL, IC_{50} = 9.2 mg/mL, respectively). This result suggested that the antioxidant capabilities of seaweed-derived polysaccharides were positively correlated with the sulphate contents. Meanwhile, their study also indicated the SSPs with higher sulphate contents had a higher capacity to repair oxalate-induced damaged human kidney proximal tubular epithelial cells by showing SSPs with 5.5% and 21.7% sulphate contents accordingly increased the cell viabilities of damaged cells to 87.9% and 94.3% in contrast to the control group (62.3%). Moreover, the *in vitro* assay performed on LPS-stimulated inflammation in RAW264.7 macrophages conducted by Cui et al. further confirmed the vital role played by the sulphation degree of SSPs in anti-inflammatory activities. As they discovered, compared to non-sulphated polysaccharides, SSPs extracted from *Gelidium pacificum* had higher sulphation degrees and markedly suppressed the TNF-α production and IL-6 secretion, thereby regulating the inflammatory responses.[259,274] Based on recent studies, ultrasound-assisted extraction (UAE) and MAE methods could essentially retain the sulphate contents of SSPs. For instance, the sulphate content of SSP extracted from *Saccharina japonica* was up to 13.26% by using the UAE method[275] and that obtained from *Nizamuddinia zanardinii* was up to 27.50% via the MAE method.[247]

Besides sulphate contents, the other polymeric constitutions of seaweed-derived polysaccharides could also severely affect the expression of bioactivities. Taking alginate as an example, Hu et al.[276] found the alginate consisting of guluronic acids displayed less potent antibacterial activity against *Escherichia coli*, *Salmonella paratyphi* B, *Bacillus subtilis* and *Staphylococcus aureus* than that composed of mannuronic acids. Meanwhile, Ale et al.'s investigation could also prove the effects of monosaccharide constituents and their linkage pattern on the bioactivities. As they discovered,[277] the fucoidans extracted from *Sargassum* sp. had significantly inhibited the proliferation of melanoma B16 cells in contrast to that acquired from *Fucus vesiculosus*. The difference in cancer cell inhibitory activities could be explained by their monosaccharide constituent differences. This is because, although both extracted fucoidans had similar sulphate contents, the *Sargassum* sp. fucoidans mainly consisted of glucuronic acids, whereas *Fucus vesiculosus* fucoidans contained more fucoses. In fact, the influences of the polymeric constitution would be amplified among different polysaccharides due to their significantly different monosaccharide constituents and linkage patterns. As an illustration, it was found that alginate-derived oligosaccharides displayed intense hydroxyl radical scavenging activity but performed low activities in assays of scavenge superoxide radicals and hardly any iron chelating activity.[223,226,278] Whereas fucoidan-derived oligosaccharides showed excellent iron chelating activity but hardly scavenged superoxide radicals.[223,278]

Conclusion

Benefiting from a diversity of macro- and micro-nutrients and their triggered bioactivities, seaweeds have a vast potential to become part of human health diets. From a sustainable perspective, seaweeds can directly profit the achievement of UN SDGs in terms of food security, health and well-being, ecosystem protection and bioenergy development. Even though the consumption of seaweed has been promised a variety of health benefits, the triggered food safety issue has raised a grave concern for today's consumers. Meanwhile, future research can also focus on seaweed fermentation, capsulation and processing methods to improve the biodigestibility and bioavailability of the containing nutrients. Besides, this review has demonstrated the remarkable bioactivities of seaweed-derived polysaccharides, such as antimicrobial, antitumour, anti-inflammatory and immune-enhancing activities, which can be attributed to the polymeric structure features and chemical compositions like MW, degree of sulphation and monosaccharide compositions. Due to these physiochemical attributes can be remarkedly affected by extraction methods and conditions, in future studies, the structure-bioactivity relationship can be further investigated to modify these bioactive polymers and improve their bioactivities and application potential.

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Disclosure statement

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