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Review

# Seaweeds as a Source of Functional Proteins

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**Abstract:** Protein is one of the major macronutrients essential in human nutrition. Protein sources especially animal sourced proteins are expensive, thus much work has been carried out to explore alternative protein sources. Seaweeds, or macroalgae, are emerging as one of the alternative protein sources. They are rich in protein with an excellent amino acid profile comparable to the other conventional protein sources. Seaweed protein contains bioactive components, such as free amino acids, peptides, lectins, and phycobiliproteins, including phycoerythrin and phycocyanin, among others. Seaweed proteins have been proved for their antihypertensive, antidiabetic, antioxidant, anti-inflammatory, antitumoral, antiviral, antimicrobial, and many other beneficial functional properties. Therefore, seaweed proteins can be a natural alternative source for functional food development. This paper discusses the compositional and nutritional aspects of seaweed protein, protein extraction techniques, functional properties of various seaweed proteins, as well as their safety for new product development and functional food applications.

**Keywords:** seaweeds; seaweed proteins; protein quality; macroalgae; bio-active peptides



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## 1. Introduction

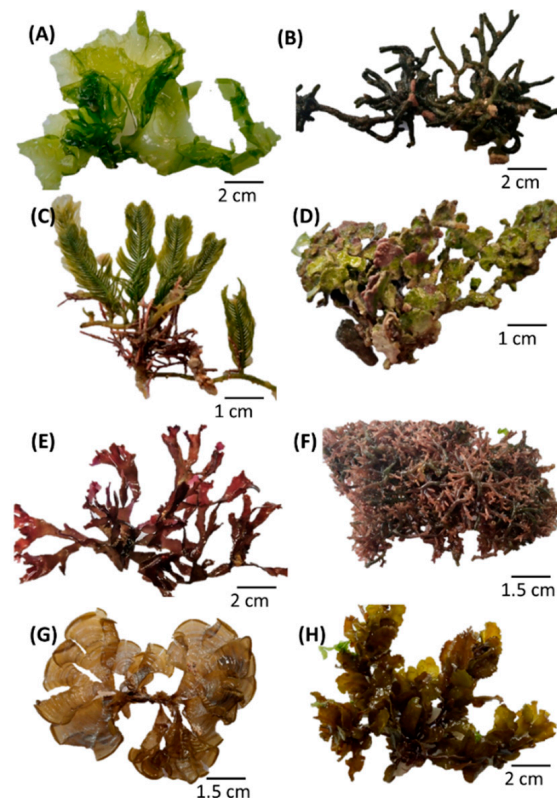
Traditional agriculture is no longer enough to meet the global food demand as the world population keeps rising, and as a result, protein is one of the main nutrients that will be in short supply in the near future. Therefore, alternative, unconventional protein sources and production methods are necessary to fulfil the global protein requirement and to improve the nutritional status of the global population [1,2].

Seaweeds are emerging as one of the alternative protein sources with several benefits over traditional high-protein crops in relation to nutritional value, productivity, protein yield per unit area, and the need for arable land, freshwater, and artificial fertilizer [3]. Algae are aquatic organisms categorized as microalgae and macroalgae based on their size. Multicellular macroalgae are referred to as seaweeds. Macroalgae are grown predominantly in the marine environment and classified into three main taxonomic groups based on color or pigments and their habitat: brown algae (Phaeophyta), red algae (Rhodophyta), and green algae (Chlorophyta) [4–6]. Seaweeds include more than 10,000 species, though only 145 species are harvested for human consumption for their flavor, texture, or culinary versatility, including *Enteromorpha*, *Monostroma*, *Caulerpa*, *Laminaria*, *Undaria*, *Hizikia*, *Palmaria*, and *Porphyra* [7]. More examples are listed below (Table 1 and Figure 1).

**Table 1.** Edible species of seaweeds.

Green Algae	Red Algae	Brown Algae
<i>Caulerpa</i> spp.	<i>Champia compressa</i>	<i>Alaria esculenta</i>
<i>Codium</i> spp.	<i>Chondrus crispus</i>	<i>Ascophyllum nodosum</i>
<i>Enteromorpha</i> spp.	<i>Eucheuma denticulatum</i> (formerly <i>Eucheuma spinosum</i> )	<i>Durvillaea antarctica</i>
<i>Monostroma</i> spp.	<i>Gelidiella acerosa</i>	<i>Eisenia bicyclis</i>
<i>Ulva</i> spp. (formerly <i>Enteromorpha</i> spp.)	<i>Gracilaria corticata</i>	<i>Fucus serratus</i>
<i>Ulva lactuca</i> (formerly <i>Ulva fasciata</i> ) (sea lettuce)	<i>Gracilaria edulis</i>	<i>Fucus vesiculosus</i>
<i>Ulva australis</i> (formerly <i>Ulva pertusa</i> )	<i>Gracilariopsis longissima</i> (formerly <i>Gracilaria verrucosa</i> )	<i>Himanthalia elongata</i>
	<i>Mastocarpus stellatus</i>	<i>Laminaria digitata</i>
	<i>Osmundea pinnatifida</i>	<i>Laminaria hyperborea</i>
	<i>Palmaria palmata</i> (dulse)	<i>Postelsia palmiformis</i>
	<i>Porphyra</i> spp. (nori)	<i>Saccharina japonica</i> (formerly <i>Laminaria japonica</i> )
	<i>Porphyra laciniata</i>	<i>Padina</i> spp.
	<i>Porphyra umbilicalis</i>	<i>Sargassum fusiforme</i>
	<i>Pyropia columbina</i> (formerly <i>Porphyra columbina</i> )	<i>Sargassum muticum</i>
	<i>Solieria robusta</i>	<i>Sargassum swartzii</i>
		<i>Sargassum vulgare</i>
		<i>Stoechospermum marginatum</i>
		<i>Undaria pinnatifida</i>
		<i>Undaria undarioides</i>

Source: Mahadevan, 2015 [8]; Pandey et al., 2020 [9]; Fleurence et al., 2018 [10]; Shannon and Abu-Ghannam [11].



**Figure 1.** Some edible algae species. (A) *Ulva lactuca*; (B) *Codium fragile*; (C) *Caulerpa sertularioides*; (D) *Halimeda* spp.; (E) *P. palmata*; (F) *Hypnea pannosa* (G) *Padina* spp.; (H) *Sargassum* spp. Photo courtesy by Piyumika Madhushani.

Edible seaweeds contain polysaccharides (starch, laminarin, floridoside, cellulose, hemicellulose, and hydrocolloids such as agar, alginate, and carrageenan), proteins, minerals (Na, Fe, Mg, Ca, I, K, Zn, F, and Se), vitamins (A, B<sub>1</sub>, B<sub>2</sub>, B<sub>9</sub> (folic acid), B<sub>12</sub>, C, D, E, and K), antioxidants (vitamin C and E, polyphenols, sulphated polysaccharides, carotenoids, sterols, phlorotannins, catechins and proteins), polyphenols (catechins, flavonols, and phlorotannins) and low amounts of fat, which are predominantly mono and polyunsaturated fatty acids with low caloric value [5,9,12–15].

Many countries produce seaweeds, and Chile, China, Korea, and Japan are the largest producers. Seaweeds are produced in two ways: (1) wild capture (from natural marine systems) and (2) aquaculture (controlled system). According to FAO statistics, 33.3 million MT of aquatic plants, primarily marine macroalgae, were produced globally in 2018, of which 0.95 million MT (2.9%) were produced by wild capture and 32.4 million MT (about 97.1%) from aquaculture [16]. The data also show that wild capture is declining, whereas aquaculture of seaweeds has steadily increased in the last ten years [16], due to increasing concern for the protection of a high biodiversity ecosystem as they play an essential role in water purification, coastal erosion protection, carbon fixation, and nursery habitats for several species [17,18].

Currently, several protein-rich macroalgae, such as *U. lactuca* (Chlorophyta), *U. pinatifida*, *F. serratus* (Phaeophyceae), *Neopyropia tenera* (formerly *Porphyra tenera*), *C. crispus*, and *P. palmata* (Rhodophyta) (17–44% of proteins), are approved by the European Food and Safety Authority for human consumption [19].

Seaweeds are widely used as human food, animal feed, dietary substitutes, gelling agents, stabilizers in food preparations, thickening agents (hydrocolloids such as agar, alginate, and carrageenan), and additives for functional foods. Some seaweeds have potential pharmaceutical and medicinal uses against cancer, allergies, diabetes, oxidative stress, inflammation, thrombosis, obesity, lipidemia, hypertension, iodine deficiency, and other degenerative ailments. Seaweeds have also been exploited as an ingredient in cosmetics (oil, peptides, amino acids, vitamins, amongst others) [20–22]. In addition, seaweeds can also be used in fertilizer and biofuel like biodiesel, bioethanol, biomethane, biogas, bio-oils, and hydrogen gas preparation [23,24].

Seaweeds have been used in human diet since ancient times and are traditionally consumed as raw, dried, baked, pickled form, or mixed with other food products (in soups, stews, bread, salads, and snacks) in East Asia, particularly in China and Japan [8,25,26].

Apart from satisfying hunger and providing energy and nutrition, the other functions of food are modulating physiological systems, preventing diseases, reducing health risks, and improving human well-being. In this context, the development of functional foods is becoming a primary focus of new product development [27].

Seaweeds are consumed for their functional benefits beyond their nutritional value and are highly marketed as “functional foods” or “nutraceuticals” [28,29]. Though these terms have no legal status in many countries, much of the literature defines them as “foods that contain bioactive compounds, or phytochemicals, that may benefit health beyond their nutritional value” [28].

Seaweeds are rich in protein (up to 47%) and contain bioactive compounds such as peptides, glycoproteins, lectins, mycosporine-like amino acids, and phycobiliproteins [30]. At present, seaweed proteins or purified protein fractions are rarely used in functional food development. Therefore, this paper discusses the seaweed as a potential source of functional proteins with regards to protein composition and amino acid profile, nutritional aspects of seaweed protein, protein extraction techniques, functional properties of various seaweed proteins, applications, as well as their safety in the interest of new product development or functional food applications.

## 2. Protein Content of Seaweeds

Seaweeds contain up to 47% of protein on a dry weight basis, which is close to the protein content of traditional protein sources such as meat, egg, soybean, and milk [31].

Generally, the protein content is low in brown algae (4–24% of dry weight) and high in red (8–47% of dry weight) and green algae (9–33% of dry weight) and can be comparable to other protein sources such as soybean (38% of dry weight) [32,33]. Table 2 summarizes the protein content of some edible seaweed in three phyla (Table 2).

**Table 2.** The protein content of selected edible seaweeds on a dry weight basis.

Seaweed Species or Genus	Protein (% of Dry Mass)	Reference
<b>Phaeophyceae (Brown Algae)</b>		
<i>A. nodosum</i>	3–15	[10]
<i>A. esculenta</i>	9–20	[34]
<i>F. serratus</i>	3–11	[35]
<i>F. vesiculosus</i>	12.9	[36]
<i>Fucus</i> spp.	3–11	[37]
<i>H. elongata</i>	6–11	[38]
<i>L. digitata</i>	8–15	[10,35]
<i>S. japonica</i> (formerly <i>L. japonica</i> ) (kombu)	12	[39]
<i>U. pinnatifida</i> (wakame)	11–24	[10,40]
<b>Chlorophyta (Green Algae)</b>		
<i>Caulerpa lentillifera</i>	19.38	[41]
<i>Cladophora rupestris</i>	29.8	[35]
<i>Ulva intestinalis</i> (formerly <i>Enteromorpha intestinalis</i> )	10–18	[38]
<i>U. lactuca</i> (formerly <i>U. fasciata</i> ) (sea lettuce)	8.7–32.7	[10,35]
<i>U. australis</i> (formerly <i>U. pertusa</i> )	17.5–26.0	[10]
<i>Ulva rigida</i>	15–25	[38]
<i>Ulva rotundata</i> (formerly <i>Ulva pseudorotundata</i> )	10.0	[42]
<b>Rhodophyta (Red Algae)</b>		
<i>Agarophyton vermiculophyllum</i> (previously <i>Gracilaria vermiculophylla</i> )	17.0%	[43]
<i>C. crispus</i>	21–27	[10,44]
<i>Gracilaria</i> spp.	7–13	[45]
<i>G. corticata</i>	22.8	[46]
<i>G. edulis</i>	25.3	[46]
<i>Gracilaria salicornia</i>	9.58	[45]
<i>Gracilaria gracilis</i>	31–45	[42,47]
<i>O. pinnatifida</i>	20.6–27.3	[35,48]
<i>P. palmata</i> (dulse)	8–35	[10,49]
<i>Porphyra</i> spp. (nori or purple laver)	33–50	[35]
<i>P. columbina</i> (formerly <i>P. columbina</i> )	25	[50]
<i>N. tenera</i> (formerly <i>P. tenera</i> ) (nori)	33–47	[10]
<i>P. umbilicalis</i> (nori)	15–37	[38]

The content of protein, peptides, and amino acids varies with the species, season, maturity, and environmental factors [43,51–53]. Moreover, differently processed samples, protocols used for protein evaluation, and nitrogen-to-protein conversion factors affect the accuracy of protein quantification, such that it is difficult to compare the results from different studies [54,55]. The crude protein content of seaweeds is widely calculated from total nitrogen content ( $N \times 6.25$ ). Studies showed that the traditional nitrogen to protein conversion factor of 6.25 leads to an overestimation of the protein content of seaweed and the true nitrogen to protein conversion factor for each seaweed species is found in the range of 3–5 [54–57].

### 3. Quality of Protein in Seaweeds

The quality of a protein can be determined by amino acid composition, proportion or ratios, digestibility, and bioavailability [29,58]. Since different methods with various

standard patterns are used to assess protein quality, it is difficult to compare the published data [58].

### 3.1. Amino Acid Composition

The amino acid composition is essential to determine the protein quality of seaweeds and to ensure the adequate intake of essential amino acids [59]. Seaweeds contain all the amino acids required for human nutrition, especially glycine, alanine, arginine, proline, glutamic, aspartic acids, and almost all essential amino acids [60]. Table 3 shows the essential amino acid (EAA) composition of selected species of seaweeds.

**Table 3.** Comparison of EAA composition (mg/g protein) of selected edible seaweeds with FAO/WHO/UNU, 2007.

	Protein (% dw)	His	Ile	Leu	Lys	Met + Cys <sup>2</sup>	Met	Cys	Phe + Tyr <sup>3</sup>	Phe	Tyr	Thr	Trp	Val	EAA/NEAA	EAA%
<b>FAO/WHO/UNU, 2007 AA Scoring Pattern<sup>1</sup> [61]</b>		15	30	59	45	22	16	6	38			23	6	39		
<b>Brown Seaweeds</b>																
<i>U. Pinnatifida</i> [53]	13.1	68.2	50.8	78.5	69.6	NR	30.9	NR	93.2	47.1	46.1	42.7	NR	35	NR	NR
<i>U. pinnatifida</i> [62]	12.5	21.6	47.3	89	58	73.1	7.3	65.8	110.4	49.4	61	53.6	NR	31.1	NR	48.4
<i>H. elongata</i> [62]	5	20.2	43.6	79.3	60.9	68.8	4.3	64.5	113.7	55.9	57.8	54.8	NR	28.2	NR	47
<i>A. nodosum</i> [63] <sup>a</sup>	7.6	49.8	48	58.8	14.3	11.2	NR	NR	46.6	30.7	15.9	62.4	5.8	54	1	37.7
<b>Green Seaweeds</b>																
<i>U. australis</i> (formerly <i>U. pertusa</i> ) [64]	15.4	8.6	25.9	52	30.1	NR	NR	NR	59.6	36.7	22.9	34.8	NR	39.1	0.72	42
<i>U. intestinalis</i> (formerly <i>E. intestinalis</i> ) [64]	17.9	7.4	25.3	49.7	19.6	NR	NR	NR	52.1	35.9	16.2	41.7	NR	40.5	0.67	40
<i>U. rigida</i> [29]	10.2	30.7	46.1	82	49.4	19.9	NR	NR	93.9	NR	NR	50.8	8.8	60.1	0.69	40.8
<i>U. lactuca</i> (formerly <i>U. fasciata</i> ) [65]	7.1	13.1	40	72.6	46.4	6.1	6.1	0	93.4	57.1	36.3	62	NR	70.1	NR	NR
<b>Red Seaweeds</b>																
<i>P. umbilicalis</i> [62]	39	15.7	36.5	76.8	56.1	75.9	8.7	67.2	93	46.8	46.2	57.8	NR	12.3	NR	42.4
<i>P. palmata</i> [31]	15.2	18.5	65	81	107.8	34.7	28	6.7	93.3	NR	NR	47.4	NR	143.6	0.89	47
<i>P. columbina</i> (formerly <i>P. columbina</i> ) [50] <sup>a</sup>	24.6	12.6	27.1	73.8	60.1	35.7	16.8	18.9	62.5	37	25.5	59.1	6.3	58.5	0.65	NR
<i>Gracilaria changii</i> [66]	12.6	NR	42.3	53.4	48.7	16.1	NR	NR	63.5	NR	NR	49.3	NR	39.1	1.61	NR
<i>A. vermiculophyllum</i> (formerly <i>G. vermiculophylla</i> ) [29]	13.4	10.7	54.9	84.5	54.4	12.9	NR	NR	90.8	NR	NR	58.2	4.0	64.1	0.67	40.1

<sup>1</sup> FAO/WHO/UNU, 2007 amino acid scoring pattern for adults in mg/g protein. <sup>2</sup> Sulfur amino acids (methionine + cysteine). <sup>3</sup> Aromatic amino acids (phenylalanine + tyrosine). NEAA, non-essential amino acids. Amino acids are represented using the three-letter abbreviation code: His, histidine; Ile, isoleucine; Leu, leucine; Met, methionine; Cys, cysteine; Phe, phenylalanine; Tyr, Tyrosine; Thr, threonine; Trp, tryptophan; Val, valine. NR, Not Reported. <sup>a</sup> The data was originally expressed as g/100 g protein.

The most abundant essential amino acids in seaweeds are leucine, valine, threonine, and the aromatic amino acid phenylalanine, of which leucine makes up the highest amount in most seaweeds (Table 3). The most abundant EAA in brown seaweed, *H. elongata* (sea spaghetti), *A. esculenta* (Irish wakame), and red seaweed, *P. umbilicalis* (nori), is leucine [67]. De Bhowmick and Hayes found that leucine is the most predominant amino acid in *A. esculenta* and *F. serratus*, and valine, followed by leucine in *U. lactuca* (formerly *U. fasciata*) and *P. palmata* [68].

Aspartic acid and glutamic acid together constitute a large proportion of total amino acids in many seaweeds [69,70], notably in *A. nodosum* (38.22% of total amino acids) [71], *P. palmata* (25.42%), *C. crispus* (38.62%) [52], *Ulva* spp. (formerly *Enteromorpha* spp.) (28.11%), *Gracilaria* spp. (25.82%) [72], *Fucus* spp. (22–44%), *U. rotundata* (32%), and *U. rigida* (26%) [37]. The abundance of these amino acids is responsible for the special flavors and tastes of seaweed, and glutamic acid is the main component in the taste sensation of “umami” [5,64].

Various factors, such as species, preservation method, extraction method, seasonal variation, and the environment in which they grow, influence the amino acid composition of seaweeds [29,53,73,74].

### 3.2. Amino Acid Ratio

Proportion or ratios of amino acids, such as the ratio of EAA to non-essential amino acids or total amino acids (EAA/NEAA or EAA/total AA), essential amino acid index (EAAI), and amino acid score (AAS), have been used to assess the protein quality of seaweeds in various studies [29].

Based on Table 3, seaweeds consist of 37.7–48.4% of EAA, and the ratio of EAA to NEAA is in the range of 0.65–1.61. Though red seaweed generally contains a higher amount of protein (Table 2), the concentration of EAAs per gram of protein or the ratio of EAA/NEAA is lower in red seaweed (Table 3) [62].

Almost half of the total amino acids (about 40–50%) in seaweeds consists of EAA [42], which is close to the value of soya (39%) and egg protein (47%) [31]. Furthermore, the ratio of EAA/NEAA is used to evaluate the distribution of amino acids in seaweed proteins [29]. The EAA/total AA ratio or EAA percentage for three brown seaweeds, *A. nodosum*, *F. vesiculosus*, and *Bifurcaria bifurcata*, were reported as 38.87, 40.99, and 39.99%, respectively [36]. The under-exploited edible seaweeds in India, such as *Acanthophora spicifera*, *G. edulis* (Rhodophyta), *Padina gymnospora* (Phaeophyceae), *U. lactuca* (formerly *U. fasciata*), and *Ulva flexuosa* (formerly *Enteromorpha flexuosa*) (Chlorophyta) were reported to contain 41–50% (0.41–0.50) of EAA in total AA with an EAA/NEAA score of 0.72–1.02 [75]. Similar results also have been recorded for *Hypnea japonica*, *Hypnea charoides* (Rhodophyta), *U. lactuca* (formerly *U. fasciata*) (Chlorophyta) (36.2–40.2%) [76], and *P. palmata* (Rhodophyta) (40.9–42.1%) [55]. Norziah and Ching also stated that the ratio of EAA to total AA is 0.4 in *Gracilaria changgi* [77]. The EAA/total AA and EAA/NEAA ratios for brown seaweed *Sargassum polycystum* were reported as 0.5 and 1.0, respectively [78]. Rosemary et al. reported that red seaweeds, *G. corticata* and *G. edulis*, have a good EAA/NEAA ratio (0.62 and 1.19, respectively) and EAA/total AA ratio (0.29 and 0.54, respectively) [46].

### 3.3. Amino Acid Score

Amino acid score (AAS) or chemical score is calculated using the following equation:

$$\text{AAS (\%)} = \frac{\text{mg AA in 1 g of the seaweed protein tested}}{\text{mg AA in 1 g reference protein}} \times 100 \quad (1)$$

The amino acid composition in the tested sample is compared with a reference protein, the amino acid requirement pattern defined by the FAO/WHO/UNU for children (3–10 years of age) or adults [61], or the respective amino acid content for eggs or leguminous plants (soybean) [42,57,77]. The AAS evaluates the actual abundance of individual EAA in food material and relates it to dietary requirements or a reference protein, and thereby, it is also possible to determine the limiting amino acid. The lowest score (<0.100) obtained for the essential amino acids in a tested protein is the “most limiting amino acid”, which means the concentration of the corresponding amino acid is lower than the reference standard [40,79].

The sulfur amino acids (methionine and cysteine), lysine, and tryptophan are often limiting amino acids in seaweed protein [80]. This composition pattern varies with the species. In comparison, leucine and isoleucine in red algae, and methionine, cysteine, and lysine in brown algae, are often deficient amino acids [40,52].

Limiting amino acids in *H. japonica*, *H. charoides*, and *U. lactuca* (formerly *U. fasciata*) are methionine (0.24–0.79 AAS) and lysine (0.68–0.80 AAS) [65]. Machado et al. identified methionine (58.4–93.4% AAS) as limited EAA in *Porphyra dioica*, *P. umbilicalis*, *A. vermiculophyllum* (previously *G. vermiculophylla*) (Rhodophyta), and *U. rigida* (Chlorophyta) [29]. The most limiting amino acid in *U. australis* (formerly *U. pertusa*) and *U. intestinalis* (formerly *E.*

*intestinalis*) was lysine, followed by leucine, despite the fact that leucine was present at a higher amount in both species (49.7–52.0 mg/g protein) [64].

When egg protein is used as a reference protein, seaweeds have better sources for isoleucine, threonine, and valine (>1.00 or 100% EAA score), and are deficient in methionine (0.5 or 50%), whatever the phylum considered [42]. In another study, lysine was identified as a limiting amino acid in *G. changgi* [77].

Seaweeds can be a good source of high-quality protein as it consists of a high concentration of EAA (40–50% of total amino acids) with an excellent EAA profile close to that of egg protein and a higher AAS than other plant-based protein, except soy, which has an AAS of 1.00 [11]. Therefore, seaweeds can be an alternative source of traditional protein in human food and animal feeds.

### 3.4. Digestibility and Bioavailability

Protein quality does not solely depend on the amino acid profile. Even with an excellent amino acid profile, the protein may have lower nutritional value if the digestibility is low due to poor bioavailability [81]. Therefore, the bioavailability of proteins is an essential factor in determining protein quality, and can be described as the degree to which amino acids or small peptides from a test protein consumed by a living organism are finally transported across the intestinal membrane and into the body [82]. As bioavailability includes digestibility and absorption mechanisms [82], studies examining the bioavailability of protein are required to incorporate in vivo experiments.

Using animal assay, in vivo protein digestibility can be determined by measuring the amount of nitrogen absorbed (the difference between the nitrogen intake and nitrogen recovered from the feces) relative to the nitrogen intake [83]. However, compared to the in vivo method, the digestibility of seaweeds has been widely studied based on rapid and cost-effective in vitro methods [65,84,85], which also give information about the bioavailability of food proteins [82]. In vitro digestibility relies on several proteolytic enzymes such as pepsin, pancreatin, trypsin, chymotrypsin, or a mixture of these enzymes [50,65,86,87]. This enzymatic approach is based on in vitro simulations of human digestion, and most methods use mammalian gastric and/or pancreatic and intestinal enzymes in the assay [83,86,87].

Red seaweed has the highest digestibility among the three phyla [65,85], whose values are comparable with some plant sources, including grains (69–84%), legumes (72–92%), fruits (72–92%), and vegetables (68–80%), and slightly lower than animal protein sources (casein and whey) [1,85]. Table 4 shows the relative in vitro digestibility of selected seaweeds using a multi-enzyme assay (porcine pancreatic trypsin, bovine pancreatic chymotrypsin, and porcine intestinal peptidase) at pH 8.0 and 37 °C.

However, the values reported for in vitro digestibility of seaweeds are highly variable depending on the particular assay used [37,85,86]. Further, the in vitro digestibility of seaweed proteins can differ according to the species and seasonal variations in glycoprotein and antinutritional factors such as phenolic molecules or polysaccharides [37,65]. This lack of consistency makes the resulting data challenging to compare.

In vitro digestibility (using multi-enzyme assay; pepsin, trypsin, and chymotrypsin at neutral pH) of *A. esculenta*, *F. serratus*, *F. vesiculosus* (Phaeophyceae), *U. lactuca* (formerly *U. fasciata*) (Chlorophyta), *P. palmata*, and *Asparagopsis taxiformis* (Rhodophyta) were quite similar (0.77–0.82) [68]. The digestibility of *U. pinnatifida* (brown) was recorded as 17% and 66.6% when using pepsin (acidic pH, 37 °C) and pancreatin (pH 7.6, 37 °C), respectively [37,88]. When using the combination of pepsin and pancreatin, the digestibility of *P. columbina* (formerly *P. columbina*) was reported as 74.3% [50]. Table 5 shows the digestibility of selected seaweeds using various assays.



**Table 4.** Relative digestibility of selected seaweeds.

Seaweeds	Digestibility (%) <sup>1</sup>
<b>Red Seaweed</b>	
<i>H. charoides</i> [65]	88.7
<i>H. japonica</i> [65]	88.9
<i>P. palmata</i> [85]	85.8
<i>C. crispus</i> [85]	84.2
<i>Sarcodiotheca gaudichaudii</i> [85]	86.7
<b>Green Seaweed</b>	
<i>U. lactuca</i> (formerly <i>U. fasciata</i> ) [65] (green seaweed)	85.7
<b>Brown Seaweed</b>	
<i>A. nodosum</i> [85]	78.7
<i>F. vesiculosus</i> [85]	78.8
<i>A. esculenta</i> [85]	79.2

<sup>1</sup> Relative digestibility is expressed as a percentage compared with casein digestibility (100%). The in vitro digestibility was determined by multi-enzyme hydrolysis using porcine pancreatic trypsin, bovine pancreatic chymotrypsin, and porcine intestinal peptidase at pH 8 and 37 °C.

**Table 5.** Relative digestibility of selected seaweeds using various assays.

Seaweeds	Digestibility (%) <sup>1</sup>				Reference
	Pepsin	Pancreatin	Pepsin+Pancreatin	Pronase	
<i>U. australis</i> (formerly <i>U. pertusa</i> ) (green)	17.0	66.6	-	94.8	[37,88] <sup>a</sup>
<i>U. pinnatifida</i> (brown)	23.9	48.1	-	87.2	
<i>N. tenera</i> (formerly <i>P. tenera</i> ) (red)	56.7	56.1	-	78.4	
<i>S. japonica</i> (formerly <i>L. japonica</i> ) (brown)	39.0	54.0	-	83.9	
<i>P. palmata</i> (red)	-	56.0	-	-	
<i>P. columbina</i> (formerly <i>P. columbina</i> ) (red)	-	-	74.3	-	[50] <sup>b</sup>
<i>P. palmata</i> (red)	87.4	84.9	87.3	-	[86] <sup>c</sup>
<i>N. tenera</i> (formerly <i>P. tenera</i> ) (red)	73.2	65.9	70.2	-	
<i>E. bicyclis</i> (brown)	57.6	73.2	57.1	-	
<i>Sargassum fusiforme</i> (formerly <i>Hizikia fusiformis</i> ) (brown)	51.8	65.8	51.8	-	
<i>S. japonica</i> (formerly <i>L. japonica</i> ) (brown)	70.2	76.1	72.1	-	
<i>U. pinnatifida</i> (brown)	69.1	87.5	68.6	-	

<sup>1</sup> Relative digestibility is expressed as a percentage compared with casein digestibility (100%). The in vitro digestibility was determined by various assays using, <sup>a</sup> pepsin in acidic pH, pancreatin in pH 7.6, and pronase in pH 8.6 at 37 °C; <sup>b</sup> not reported; <sup>c</sup> pepsin at pH below 1.7 and 40 °C followed by pancreatin at pH 7.5 and 40 °C for 24 h.

Though the seaweeds contain a higher amount of protein, the inhibitory effect of macroalgal compounds like glycoprotein and other antinutritional factors (phenolic compounds or polysaccharides) reduces the digestibility [1,37].

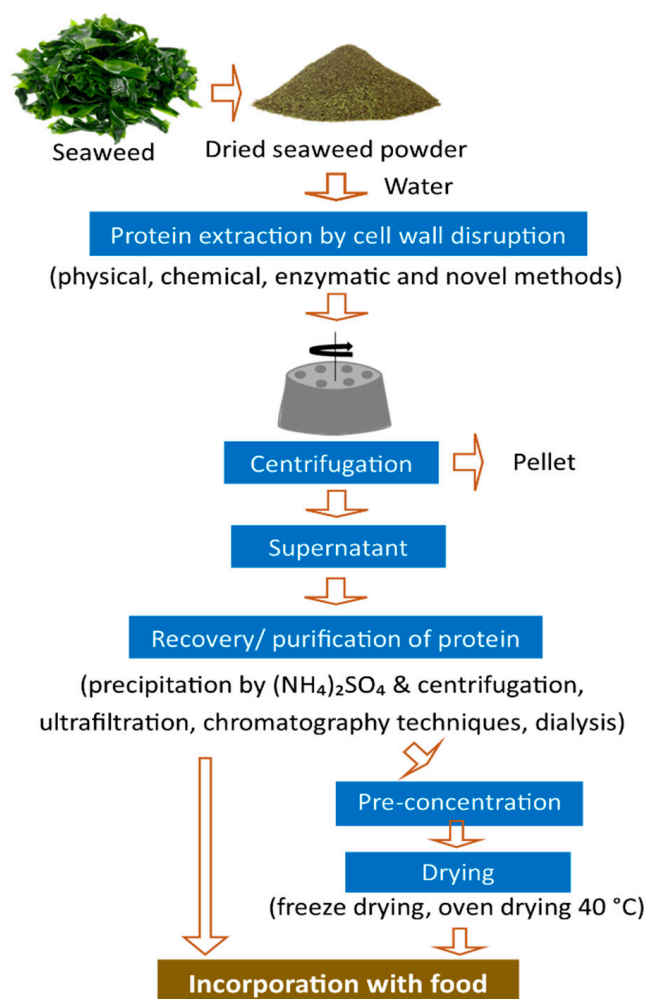
Polysaccharides, notably soluble fibers (xylan and carrageenan) and their interaction with proteins or proteolytic enzymes, reduce protein hydrolysis in seaweed [84,85]. Fleurence also suggested that the glycosylation level of the protein fraction or glycoprotein content may decrease the rate of hydrolysis by enzymes such as trypsin and chymotrypsin and influence the digestibility of *Ulva armoricana* protein [37]. Further, Marrion et al. reported that the presence of higher soluble fiber reduced the digestibility of *P. palmata* and *G. longissima* (formerly *G. verrucosa*) [84].

Oxidized phenolic compounds may react with amino acids and proteins, thereby inhibiting the activity of proteolytic enzymes. A strong negative correlation between total phenolic content and in vitro digestibility of seaweed protein has been reported in various studies [65,85]. Typically, brown seaweed contains a higher amount of phenolic compounds, including catechins, flavanols, and phlorotannins, which greatly influence protein digestibility [1].

However, these *in vitro* studies only give an approximation of the true protein digestibility. Therefore, biological evaluation using human and animal feeding studies (*in vivo* protein digestibility) is required for an accurate prediction of the nutritional value of seaweed protein.

#### 4. Protein Extraction Methods

Seaweed has poor protein digestibility in its raw, unprocessed form because of its complex cell wall, which poses a physical barrier in the absence of digestive enzymes in the gastrointestinal tract, and greatly emphasizes the need for protein extraction techniques to improve their digestibility [52]. Protein can be extracted from dried seaweed powders using conventional or classical methods, including physical, chemical, enzymatic methods, and other novel methods [42,71], then the protein can be collected by centrifugation or filtration. The dissolved protein can be obtained by various recovery and purification techniques, such as ultrafiltration, chromatography techniques, dialysis, and/or precipitation using ammonium sulphate followed by centrifugation [89–91]. High-purity proteins are not required to produce regular food and feed but are essential for functional food development. Chromatography is the main purification technique that uses molecular exclusion, ion exchange, affinity, and hydrophobic interactions [92]. The extracted protein can be preserved by preconcentration and drying techniques (freeze-drying and oven drying at 40 °C) [89–91]. Figure 2 illustrates the basic steps involved in protein extraction from seaweed.



**Figure 2.** Simplified diagram for protein extraction from seaweeds.

Physical cell disruption methods include grinding followed by aqueous treatment, osmotic shock, or high shear force, and the extraction is carried out based on the hydrophilic property of most proteins. Chemical methods include acidic (HCl) and alkaline (NaOH) treatment, which significantly improves the solubility and extraction of highly water-insoluble proteins from seaweeds. However, these two methods are relatively time-consuming, and the efficiency of extraction (29–59% of protein content) is limited [1,93]. Proteins in seaweed species are bound to non-protein components such as polysaccharides and polyphenols [79]. Therefore, cell disruption techniques are required to enhance the efficiency, extraction rate, and yield. Enzymes such as polysaccharidases (cellulase, hemicellulose, xylanase, k-carrageenase,  $\beta$ -agarase,  $\beta$ -glucanase, amylases, arabinase) or proteases can be applied before protein extraction in order to degrade polysaccharides, such as carrageenans, alginates, ulvans, xylans, galactans, cellulose, fucoidan and laminarin, and improve the protein yield by up to 67% [1,71,94].

Many non-conventional novel protein extraction techniques have been used for protein extraction: microwave-assisted extraction, supercritical fluid extraction, ultra-high-pressure extraction, pressurized liquid extraction, pulsed electric field, and ultrasound-assisted extraction [1,71,95].

The amount of protein that can be extracted from seaweeds depends on various factors, such as the species, seasonal variation, pre-treatment, the combination of extraction methods, preservation method, extraction method, and its processing parameters, such as extraction temperature, time, and pH [3,71,96]. The most influencing factor in seaweed protein extraction is the complex rigid cell wall, and its composition varies with species. In addition, seaweed proteins are bound to non-protein components such as polysaccharides (alginates, agar, carrageenan) and polyphenols that influence protein extraction efficiency [91,97]. Seaweeds are seasonal, and fresh seaweeds can deteriorate quickly after harvest. Therefore, seaweeds are preserved by freezing or freeze-, sun-, vacuum-, or air-drying at different temperatures to ensure year-round availability [3]. The methods used for protein extraction and the processing parameters also have an effect on the amino acid profile [74,98].

Compared to the physical method (sonication), the pH-shift method (using NaOH and HCl) recovered more protein from *P. umbilicalis* and *Saccharina latissima*, and a higher EAA percentage (42.2–42.6%) from *P. umbilicalis*, *S. latissima*, and *U. lactuca* (formerly *U. fasciata*) [99]. When compared to the high-pressure processing and autoclave method, the classical method (cell lysis induced by osmotic shock and sonication) produced a higher protein yield for *C. crispus* (35.2%), *Fucus vesiculosus* (35.1%), and *A. esculenta* (18.2%) with a good EAA profile [52]. The brown seaweed *Macrocystis pyrifera* (74.6%) yielded significantly more protein than the red seaweed *Chondracanthus chamissoi* (36.1%) when using enzyme-assisted extraction with cellulase [91]. A combination of various protein extraction methods has been used to obtain higher protein yields. Sequential extraction using acid treatment followed by alkaline treatment has also increased protein extraction (59.76%) [71]. For *P. palmata*, up to 90% of the protein was extracted using a combination of enzymes followed by the N-acetyl-L-cysteine-assisted alkaline extraction method [31].

## 5. Functional Properties of Seaweed Proteins and Their Role in Health

Functional foods can be defined as foods and food components that provide a health-promoting benefit beyond basic nutrition and energy [28]. “Let food be your medicine and medicine be your food” is a popular quote by the father of medicine, Hippocrates. Many studies have confirmed a direct relationship between diet and health, and the regular inclusion of functional ingredients in has an impact on the quality of life [100]. Seaweeds contain several bioactive compounds, including polysaccharides, polyphenols, lipids, polyunsaturated fatty acids (PUFAs), sterols, proteins, dietary fiber, pigments, and vitamins [101,102]. Several studies have revealed that the seaweeds are an excellent source of various proteins (amino acids, peptides, phycobiliproteins, and lectins) with interesting biological properties, such as antihypertensive, antioxidant, antidiabetic, anti-inflammatory,

antitumoral, antiviral, and antimicrobial [20,32,103]. Table 6 summarizes the bioactive compounds and their functional properties for selected seaweeds.

**Table 6.** Seaweed protein exhibits potential bioactivities.

Seaweed	Bioactive Compounds	Properties	References
<i>Bryopsis</i> spp. (green)	Cyclic depsipeptide	Antimicrobial activity against <i>Mycobacterium tuberculosis</i>	[104]
<i>Gracilariopsis lemaneiformis</i> (red)	TGAPCR, FQIN [M(O)] CILR	Angiotensin-I-converting enzyme (ACE) inhibitory activity	[105]
<i>Mazzaella japonica</i> (red)	YRD, VSEGLD, TIMPHPR, GGPAT, SSNDYPI, SRIYNVKSNG, VDAHY, CPYDWV, YGDPDHY, NLGN, DFGVPGHEP	ACE inhibitory activity	[106]
<i>Neopyropia yezoensis</i> (formerly <i>Porphyra yezoensis</i> ) (red)	YRD, LDY, LRY, VY, LF, FY	ACE inhibitory activity	[107]
	Di- and tripeptides	ACE inhibition/antihypertensive activity	[108]
	TPDSEAL	Antimicrobial activity against <i>Staphylococcus aureus</i>	[109]
	Peptides derived from phycobiliproteins: YRD, AGGEY, VYRT, VDHY, IKGHY, LKNPG, LDY, LRY, FEQDWAS	ACE inhibition, antioxidant,	[110]
<i>P. palmata</i> (dulse) (red)	Alcalase, bromelain, and Promod-derived hydrolysates	dipeptidyl peptidase IV (DPP-IV) inhibitory activities,	[111]
	Alcalase/Flavourzyme hydrolysates	Antihyperglycemic/antidiabetic potential	[112]
	Peptides: ILAP, LLAP, MAGVDHI	DPP-IV inhibitory activities	[113]
	Papain hydrolysates: NIGK	Platelet-activating factor acetyl-hydrolase (PAF-AH) inhibitory peptides	[114]
	IRLIIVLMPILMA	Renin inhibitory activity	[115]
	SDITRPGGQM	Antioxidant	[116]
<i>P. dioica</i> (red)	Peptides	Antioxidant, ACE inhibition, DPP-IV inhibitory activities	[117]
<i>P. columbina</i> (formerly <i>P. columbina</i> ) (red)	DYYKR, YLVA	ACE inhibitory, immunosuppressive, antioxidant properties	[118]
	Peptides		
<i>Saccharina longicuris</i> (formerly <i>Laminaria longicuris</i> ) (brown)	TITLDVEPSDTIDGVK, ISGLIYEETR, MALSSLPR, ILVLQSNQIR, ISAILPSR, IGNGGELPR, LPDAALNR, EAESSTGGNGCAK, QVHPDTGISK	Antibacterial activities	[119]
<i>Sargassum pallidum</i> (brown)	Dipeptides (aurantiamide, aurantiamideacetate, dia-aurantiamide)	Antibiotic activity in vitro against <i>S. aureus</i> , <i>Staphylococcus epidermidis</i> , and <i>Pseudomonas aeruginosa</i>	[120]
<i>Sargassum thunbergia</i> (brown)	Iodo-amino acids	Possibly helps in human thyroid metabolism	[79]
<i>U. rigida</i> (green)	Peptides	ACE inhibition	[121]
<i>U. pinnatifida</i> (brown)	Di-, tri-, and tetrapeptides	ACE inhibition/ antihypertensive activity, antioxidant	[122,123]
	VYIY, AWFY, VW, IW, LW, YNKLKFGY, YKYY		
<i>Boodlea coacta</i> (green), <i>Griffithsia</i> spp. (red)	Lectins	Antiviral effects against human immunodeficiency virus (HIV), Hepatitis C virus and SARS-CoV/ e	[124,125]
	griffithsin	SARS-CoV-2 by preventing the entry into the host cells	
<i>Caulerpa cupressoides</i> (green)	Lectins	Antinociceptive and anti-inflammatory activities	[126]

Table 6. Cont.

Seaweed	Bioactive Compounds	Properties	References
<i>C. fragile</i> (green), <i>Eucheuma serra</i> (red)	Lectins	Mitogenic activities, lipogenic activity	[127]
<i>Mimica amakusaensis</i> (formerly <i>Eucheuma amakusaense</i> ) (red), <i>Ulva</i> spp. (formerly <i>Enteromorpha</i> spp.) (green)	Lectins	Induce apoptosis, metastasis, and cell differentiation in cancer cells, antibiotic, anti-inflammatory, anti-HIV activity, and human platelet aggregation inhibition	[128]
<i>N. yezoensis</i> (formerly <i>P. yezoensis</i> ) (red)	Taurine	Antioxidant	[129,130]
<i>Saccharina angustata</i> (formerly <i>Laminaria angustata</i> ) (brown), <i>Chondria armata</i> (red)	Laminine	Hypertensive effect, depress contraction of smooth muscles	[131]
<i>C. crispus</i> , <i>Gelidium pusillum</i> , <i>Dasysiphonia japonica</i> (formerly <i>Heterosiphonia japonica</i> ), <i>P. palmata</i> (red)	Phycobiliproteins	Antioxidant, antidiabetic, antitumor, anti-inflammatory, neuro-protective, and hepato-protective properties	[132]
<i>Gracilaria tikvahiae</i> , <i>P. palmata</i> (red)	Phycobilliproteins (phycocyanins and allphycocyanins)	Anti-inflammatory, liver-protecting, antiviral, antitumor, antiatherosclerosis, lipase activity inhibitor, serum lipid reducing agent, and antioxidant	[128]

Abbreviation of amino acids as per Jones, 1999 [133]: A, Ala; R, Arg; N, Asn; D, Asp; C, Cys; Q, Gln; E, Glu; G, Gly; H, His; I, Ile; L, Leu; K, Lys; M, Met; F, Phe; P, Pro; S, Ser; T, Thr; W, Trp; Y, Tyr; V, Val.

### 5.1. Amino Acids

Amino acids are building blocks of polypeptides and proteins, and the amino acid composition varies with seaweed species. Amino acids serve as essential precursors for the synthesis of low molecular-weight substances (e.g., NO, polyamines, glutathione, creatine, carnitine, carnosine, thyroid hormones, serotonin, melanin, melatonin, and heme) with enormous physiological roles, including regulating nutrient transport and metabolism, cell-to-cell communication, gene expression, protein phosphorylation, antioxidative defense, immune function, reproduction, lactation, fetal and postnatal growth and development, tissue regeneration, neurotransmission, acid-base balance, homeostasis, intestinal microbial growth, and metabolism, among many others [134].

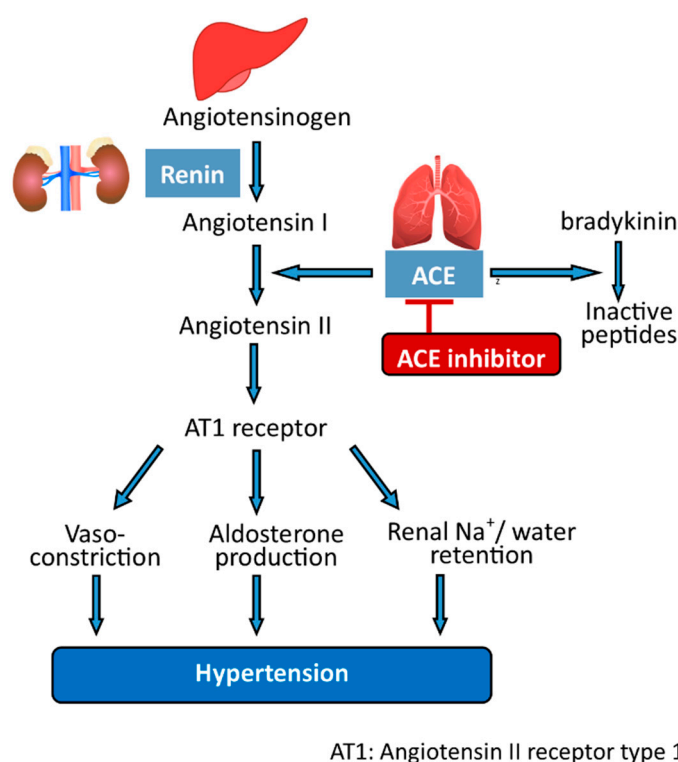
In general, glycine, alanine, arginine, proline, aspartic acid, and glutamic acid make up a larger portion, and cysteine, methionine, and tyrosine are found in lower concentrations in seaweeds [58]. Supplementation with amino acids has a beneficial effect on disease management, e.g., methionine for patients with multiple sclerosis; arginine has a neuroprotective effect after brain ischemia injury and in infertility; histidine improves insulin sensitivity in hyper-insulinemia; glycine alleviates liver and lung injury; tryptophan improves sleep disorders and depression [29,134]. Glutamic acid plays an important role in key physiological functions, including maintaining brain function and mental activity. Aspartic acid helps to initiate important metabolic pathways like the Krebs and urea cycles [58]. However, elevated amino acid levels and their products, such as ammonia, homocysteine, and asymmetric dimethylarginine, are pathogenic factors for neurological disorders, oxidative stress, and cardiovascular disease. Therefore, it is vital to maintain an optimal amino acid balance in the diet and circulation for whole-body homeostasis [134].

### 5.2. Peptides

Peptides that are 2–20 amino acids in length can be linear, cyclic, depsipeptides, dipeptides (carnosine, almozole D), tripeptides (glutathione), pentapeptides (galaximide), hexapeptides, oligopeptides, and phycobiliproteins [32,79]. These isolated bioactive peptides have hormone-like properties that are inactive within the parental proteins, but

become activated upon release during fermentation or hydrolysis [1,128]. Based on their structural properties, amino acid composition, and sequences, they can display a wide range of biological functions, including antihypertensive (ACE inhibitory), antioxidant, antidiabetic (DPP-IV inhibitory,  $\alpha$ -amylase inhibitory), appetite suppression, antitumoral, antimicrobial, antiviral, opioid agonistic, immunomodulatory, prebiotic, opioid, mineral binding, tyrosinase inhibitory, anticoagulatory, anti-thrombotic and hypocholesterolemic effects [1,27,32,135,136].

Hypertension is one of the major risk factors for cardiovascular disease (CVD) [27,137]. Renin and ACE are the two key enzymes in the renin-angiotensin system (RAS), which regulates peripheral blood pressure. ACE catalyzes the conversion of angiotensin-I to a potent vasoconstrictor, angiotensin-II, and degrades the vasodilator peptides bradykinin [121,138]. Thus, inhibition of ACE is one of the key therapeutic approaches in the management of hypertension (Figure 3) [27].



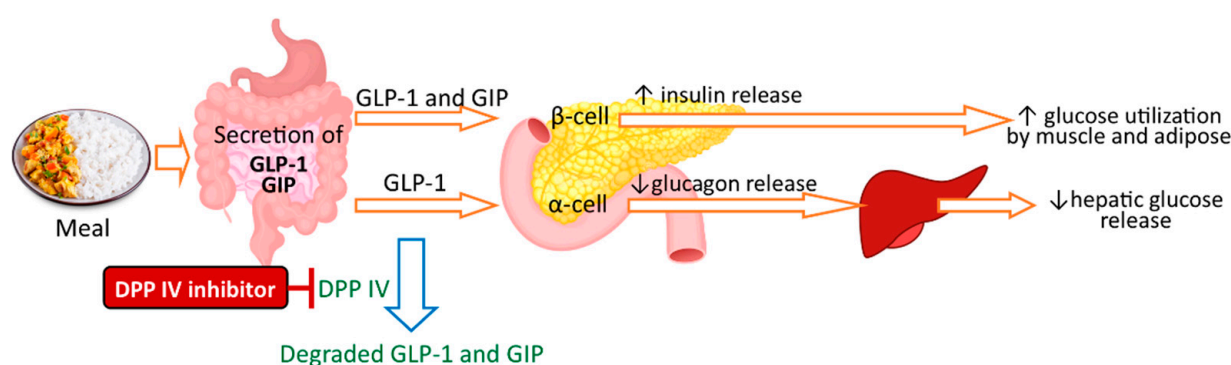
**Figure 3.** Mechanism of ACE inhibition and antihypertension.

To date, a number of ACE inhibitory or antihypertensive macroalgal peptide hydrolysates have been identified [137]. Paiva et al. revealed that ACE inhibitory peptides from *U. rigida* have potential therapeutic benefits for the prevention and/or treatment of hypertension and its related diseases [121]. ACE inhibitory peptides have also been reported in *P. columbina* (formerly *P. columbina*), *P. palmata*, *N. tenera* (formerly *P. tenera*), *N. yezoensis* (formerly *P. yezoensis*), *S. chordalis*, *M. japonica* (Rhodophyta), *S. fusiforme* (formerly *H. fusiformis*), *U. pinnatifida* (Phaeophyceae), *Ulva prolifera* (formerly *Enteromorpha prolifera*), and *U. intestinalis* (formerly *E. intestinalis*) (Chlorophyta) [27,107,118,119,122,137,139].

Furthermore, the recent outbreak of SARS-CoV-2 (or 2019-nCoV) responsible for the COVID-19 pandemic, enters host cells through an interaction between the spike viral protein and angiotensin-converting enzyme 2 (ACE 2) [140]. ACE inhibitory peptides with antiviral activity in edible seaweeds (*U. pinnatifida*, *S. fusiforme*, *Porphyra* spp.) could exert a protective effect against COVID-19 by reducing the dominance of the ACE/Ang II/ATR1 axis [141].

A few studies have reported the antidiabetic potential of seaweed protein/peptides that inhibit the  $\alpha$ -amylase,  $\alpha$ -glucosidase, and DPP-IV [112,113]. One therapeutic approach

for type 2 diabetes mellitus (T2DM) management is to lower blood glucose levels by inhibiting the key enzymes involved in intestinal carbohydrate digestion ( $\alpha$ -amylase and  $\alpha$ -glucosidase). Two  $\alpha$ -amylase inhibitory peptides have been identified in proteolytic enzyme hydrolysates of seaweed laver (*Porphyra* spp.) that can prevent postprandial hyperglycemia [142]. Another, newer, therapeutic approach for T2DM is to inhibit DPP IV as an insulin regulatory strategy. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) are the two incretin hormones that stimulate glucose-induced insulin secretion, inhibit postprandial glucagon release, and delay gastric emptying, which results in lower blood glucose level. DPP-IV inactivates GLP-1 and GIP, resulting in the loss of their insulintropic potential in vivo. Hence, DPP-IV inhibitors prevent the degradation of GLP-1 and GIP and enhance its insulintropic effects, and thus, can be used in the management of T2DM [113,143]. Figure 4 illustrates the simplified mechanism of DPP-IV inhibitors and antidiabetic activity.



**Figure 4.** Antidiabetic activity of DPP-IV inhibitors.

Seaweeds can be a natural source of DPP-IV inhibitors. Studies have reported that protein hydrolysates of *P. palmata* have DPP-IV inhibitory activities that are useful for the management of T2DM [111,144] and obesity [111]. Oral administration of *P. palmata* protein hydrolysate derived from Alcalase and Flavourzyme reduced food intake by streptozotocin-induced diabetic mice and showed antihyperglycemic effects [112].

Reactive oxygen species (ROS) contribute to the development of chronic diseases, including cardiovascular diseases, cancer, diabetes mellitus, cataracts, and neurodegenerative disorders [116]. ROS includes free radical species, such as superoxide anions, hydroxyl radicals, and singlet oxygen, and non-radical species, such as hydrogen peroxide ( $H_2O_2$ ), generated during the metabolic process [145]. The antioxidant activity of bioactive peptides is attributed to the hydrophobicity of valine, leucine, isoleucine, glycine, methionine, proline, and alanine and some aromatic amino acids (tyrosine, histidine, tryptophan, and phenylalanine) [116]. They exert a protective effect on the body by binding free radicals and other reactive oxygen compounds. Furthermore, the regulation of oxidative stress is an essential factor in tumor development and anticancer therapies [146]. Protein hydrolysates or peptides and amino acids exhibit multiple antioxidant properties. Two antioxidant peptides, such as carnosine and glutathione, generally present in high concentrations in animal muscle, have been found in seaweed [116]. Antioxidant peptides have been isolated from several species of macroalgae, including *Scytosiphon lomentaria* [147], *Ecklonia cava*, *Sargassum coreanum* (Phaeophyceae) [148], *P. palmata* [49], and *P. columbina* (formerly *P. columbina*) (Rhodophyta) [118]. Antioxidant and anticancer bioactivity have also been reported in Sri Lankan seaweed, and the highest value was reported for *Caulerpa racemose* [149]. *N. yezoensis* (formerly *P. yezoensis*), *G. pusillum*, and many other seaweed species have been studied for their antioxidant properties [130].

Antimicrobial peptides have been identified in *S. longicuris* (formerly *L. longicuris*) against *S. aureus*, and cyclic depsipeptide from *Bryopsis* spp. demonstrated activity against *M. tuberculosis* [104,119]. Protein hydrolysates from *P. columbina* (formerly *P. columbina*) also have immunosuppressive, antihypertensive, and antioxidant capacities [50].

Furthermore, inhibition of platelet-activating factor acetyl-hydrolase (PAF-AH) has been reported for peptides derived from *P. palmata* that could prevent high blood pressure and atherosclerosis [114]. PAF-AH plays an active role in atherosclerotic development and progression [114]. PAF-AH is thought to be involved in the generation of pro-inflammatory mediators, such as lysophosphatidylcholine (LPC) and oxidized non-esterified fatty acids (NEFA) [144,146]. In addition, macroalgae peptides from different species display many other biological activities (Table 6).

### 5.3. Lectins

Lectins and phycobiliproteins are two groups of functionally active proteins in seaweeds [150]. Lectins are proteins, glycoproteins, or hemagglutinin proteins that reversibly bind specific mono- or oligo-saccharides [126,128]. Lectins have been found in red and green algae, such as *Eucheuma* spp., *Solieria filiformis*, *Enantiocladia duperreyi*, *Pterocladia capillacea*, *Gracilaria cornea*, *Gracilaria ornata*, *Bryothamnion* spp., *M. amakusaensis* (formerly *E. amakusaense*) (Rhodophyta), *Ulva* spp. (formerly *Enteromorpha* spp.), and *C. fragile* (Chlorophyta) [32,60,128]. Lectins are involved in numerous biological processes, such as host-pathogen interactions, intercellular communication, recognizing and binding carbohydrates, induction of apoptosis, metastasis, and cell differentiation in cancer cells [128,131]. These proteins also have other bioactive properties, including antibiotic, antibacterial, antifungal, anti-inflammatory, mitogenic, cytotoxic, antinociceptive, anticancer, fibroblast, human platelet aggregation inhibition, antiviral, and anti-human immunodeficiency virus (anti-HIV) activities [30,38,60,128,151].

Lectins from red algae *Alsidium triquetrum* (formerly *Bryothamnion triquetrum*), *P. capillacea*, *Hypnea cervicornis*, *S. filiformis*, and green seaweed *C. cupressoides* have demonstrated anti-inflammatory activities in different studies [152]. Lectin is the only seaweed protein reported as an antibacterial in the literature [119,150]. The lectins found in *Alsidium seaforthii* (formerly *Bryothamnion seaforthii*) and *Hypnea musciformis* show bactericidal activity, especially inhibiting the growth of *S. aureus* and *P. aeruginosa* [153]. Lectin extracted from red seaweed showed antibacterial activity against six pathogenic Gram-negative species, including *Serratia marcescens*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus* spp., and *P. aeruginosa* [60]. The lectin isolated from *B. seaforthii* has a pro-healing property responsible for accelerating the healing of skin wounds [154]. Because of these antimicrobial properties, lectins are used to treat many pathologies such as cancer and chronic bacterial diseases, chronic otitis, tonsillitis, cystic fibrosis, periodontal diseases, and urinary tract infections [153].

Lectins have the ability to precipitate glycoprotein and agglutinate red blood cells [30,60]. Further, lectins have displayed antiviral effects against human immunodeficiency, hepatitis C, and SARS-CoV viruses, mainly by preventing entry of the virus into host cells, and thereby, their propagation [125]. Griffithsin, a highly potent broad-spectrum antiviral lectin from *Griffithsia* spp. has an antiviral effect against HIV [155], SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) [156]. Lectins have also been widely studied for their antiviral activity against SARS-CoV-2 (or 2019-nCoV) since they can inhibit coronavirus infectivity by specifically binding to the spike glycoprotein. Glycoproteins, especially the spike protein of SARS-CoV-2, are involved in cell adhesion and invasion, morphogenesis, and modulation of immune response processes. This spike protein mediates viral adhesion through human ACE 2. Lectins that bind SARS-CoV-2 spike protein via their ability to recognize glycans can inhibit the adhesion of coronavirus and impair the initial steps of viral pathogenesis [157]. Many studies have highlighted lectins from seaweeds and their potential antiviral therapeutic activity against SARS-CoV and SARS-CoV-2 (COVID 19) [124,158]. Thus, seaweed lectins should be considered when developing new antiviral approaches because of their antiviral properties.



#### 5.4. Phycobilliproteins

Phycobiliproteins are the only water-soluble algal pigments in red seaweeds [32]. Phycobiliproteins are the most abundant proteins in red seaweeds, representing nearly 50% of the total protein content [159]. Phycobiliproteins are grouped into the following four groups: phycoerythrin (purple), phycocyanin (blue), phycoerythrocyanins (purple), and allophycocyanin (bluish-green), whereas phycoerythrin is the main pigment [30,160]. Phycobiliproteins have been reported in many species, including *Porphyra* spp. [160], *Gracilaria canaliculate* (formerly *Gracilaria crassa*) [161], *P. palmata* [162], and *G. tikvahiae* [131]. Phycoerythrin has been reported in *G. gracilis* [163], *Grateloupia turuturu* [164], *G. pusillum*, and *Rhododymenia pseudopalmata* [30]. Furthermore, extraction of phycocyanin has been reported for *C. crispus*, *G. gracilis*, and *Gelidium amansii* with many bioactivities, including anticancer activity, anti-inflammatory effect, antioxidative, and anti-irradiative effects [165].

Phycobiliprotein has become popular for its biological activities, including antioxidant, ACE inhibitory, antitumoral, antidiabetic, immunomodulating, anti-inflammatory, liver-protecting, antiviral, anticancer, antiatherosclerosis, antihyperlipidemic activities, lipase activity inhibitor, serum lipid reducing agent, and obstructing absorption of environmental pollutants into the body [110,128,164,166]. Other than these, it is also beneficial for preventing or treating gastric ulcers and neurodegenerative diseases caused by oxidative stress (Alzheimer's and Parkinson's) due to their antioxidant effects [20,32].

Phycocyanin improves the immune system and has several other bioactivities, including in vitro anticancer activity, chemotherapy sensitiveness, photosensitized tumor suppressor activity, anti-inflammatory effects, antioxidative, anti-irradiative, and neuroprotective effects [165].

#### 5.5. Free Amino Acids

The free amino acid fraction in seaweeds mainly consists of taurine, alanine, ornithine, citrulline, hydroxyproline, and aminobutyric acid [131]. Taurine content varies with the species. Red algae contains taurine in high concentrations, however it is rarely found in green and brown algae [40,167]. Seaweeds such as *N. yezoensis* (formerly *P. yezoensis*), *N. tenera* (formerly *P. tenera*), *Gloiopeltis tenax*, *Gloiopeltis furcate*, *Gracilaria textorii*, *A. vermiculophyllum* (formerly *G. vermiculophylla*) (Rhodophyta), *U. pinnatifida*, *S. japonica* (formerly *L. japonica*), and *Sargassum confusum* (Phaeophyceae) contain a high amount of taurine [10,129,167,168] and can be used in functional foods that contain naturally occurring taurine [40,167,169]. Taurine plays an important role in physiological functions such as bile-acid conjugation, retinal and neurological development, osmoregulation, antioxidant, a modulator of intracellular calcium level, and immune function [169]. In addition, taurine acts as an antioxidant and protects against the toxicity of various heavy metals, including lead and cadmium, by preventing their absorption in the stomach [128]. Taurine also has antihypertensive and hypocholesterolemic activities by reducing the secretion of serum lipids and apolipoprotein (very low-density lipoprotein, VLDL, and intermediate-density lipoproteins, IDL) [38,170].

In addition to taurine, macroalgae contain unusual amino acids, such as laminine, kanoids (kainic and domoic acid), and mycosporine-like amino acids with bioactivity [38,131]. Many macroalgae species, including *Digenea simplex*, *C. armata*, *P. palmata*, among others, contain kanoid amino acids (kainic and domoic acids), and extraction from *D. simplex* has been commercialized [127,131]. Kanoid amino acids are reported to have insecticidal, neuroexcitatory and anthelmintic properties [131]. In Japan, *D. simplex* and *C. armata* extracts contain kanoids and have been used for centuries as anthelmintic agents to treat ascariasis (a disease in humans caused by the parasitic roundworm). They also act as central nervous system stimulants and assist in neurophysiological disorders such as Alzheimer's disease, Parkinson's disease, and epilepsy. However, they become neurotoxins when safe levels are exceeded [38]. Laminine, a choline-like basic amino acid, has been isolated from *S. angustata* (formerly *L. angustata*) and *C. armata*, and can depress the contraction of excited smooth muscles and exert a transitory hypotensive effect [131].

## 6. Applications

Nowadays, consumers are more health-conscious, and as a result, they seek more and more natural sources to treat or prevent health issues. The functional food market has been growing over the years and can be categorized as fortified, enriched, altered, or enhanced commodities (naturally enhancing one of the components) [171–173]. In this context, the food industry has emerged to develop and market a diverse group of functional food products using natural ingredients [128].

Over the last few decades, seaweeds have been widely studied for their bioactive compounds. Hydrocolloids like agar, alginates and carrageenan, and alkaloids, carotenoids, polyphenols, terpenes, tocopherols, laminarin, and fucoidan, among many others, have all been used as functional ingredients in bakery, dairy, fish, meat, and vegetable-based products [11,32]. Seaweed contains a considerable amount of protein that can be used to fulfil nutritional requirements or to treat malnutrition [9]. *N. tenera* (formerly *P. tenera*), *N. yezoensis* (formerly *P. yezoensis*), *P. columbina* (formerly *P. columbina*), and *P. umbilicalis*, *Gracilaria* spp., *Sargassum wightii*, *Eucheuma* spp., and many other species have been used in different varieties of seaweed-based foods and beverages such as wine, instant soup, noodles, jam, jelly, tea, porridge, soft cheese, sausages, among others, to enhance their nutritional value [32,174].

Wheat flour used for making pasta and noodles has relatively low protein content (10% to 15%) and lacks some EAA, such as lysine, threonine, and methionine [175]. In such cases, seaweed or macroalgal supplementation can improve the protein quality of the bakery foods, pasta, and cereals due to their essential amino acid content. Bakery, pasta, and cereal products are widely consumed food products, which can be used as food vehicles for the delivery of bioactive compounds. In Wales, United Kingdom, *Porphyra* species are traditionally used to make a dish known as laverbread. Wakame (*U. pinnatifida*)-incorporated pasta was reported to have improved bio-functional properties and enhanced interactions between starch granules and the protein matrix [176]. Seaweeds such as *Caulerpa racemosa*, *U. lactuca* (formerly *U. fasciata*), *Chnoospora minima*, *P. gymnospora*, and *A. spicifera* have an excellent amino acid profile rich in lysine and methionine. Hence, they are utilized in highly nutritive food formulations with cereals and legumes (seaweed-based bread, biscuits, and idly) to balance the amino acid profile and provide a balanced diet to the individual [174]. However, consumer acceptance of seaweed-containing foods in the Western world is limited due to undesirable sensory characteristics. Whole-wheat bread containing *C. crispus* and *A. nodosum* was acceptable at lower concentrations (2% and 4%, respectively) with no significant changes in protein content [12].

Few studies mention the application of seaweed protein in the development of functional food. Proteins, peptides, and amino acids derived from seaweeds are used as nutraceuticals but are best utilized during the dietary consumption of seaweeds [177]. Food applications of seaweed-derived proteins, peptides, and amino acids have become popular in the last few decades since most of these components have anti-inflammatory, antioxidant, antitumor, anti-aging, and protective activity [60], although at present, macroalgal proteins or purified protein fractions are rarely used as ingredients in the food industry [10].

*S. japonica* (formerly *L. japonica*) has been used as a flavor enhancer in Japanese cooking for many years [40]. The high content of free amino acids such as glutamic acid, aspartic acid, alanine, and glycine has been described as responsible for the unique flavor of seaweeds [29]. Free glutamic acid and aspartic acid (to some extent) are the main components in the taste sensation of ‘umami’ [178], whereas glycine and alanine give a sweet flavor [77]. The enzymatic (bromelain) hydrolysis of protein from *Gracilaria fisheri* yields a roasted seafood-like flavor that can be used as a flavoring agent in the food industry [179].

Mainly in Japan, several seaweed-derived peptides containing functional foods are currently commercialized and approved as Foods for Specified Health Uses (FOSHU). Foods containing peptides from nori and wakame are approved for antihypertensive claims [146]. Peptides derived from *P. palmata* protein can be incorporated into bread to

enrich its renin-inhibitory capacity without affecting the texture or sensory properties of the bread to a large degree [180].

Currently, considerable interest has been mounting for finding alternative sources of synthetic antioxidants for application in food [148]. Synthetic antioxidants/preservatives and other bioactive additives are highly used in processed food. These can oxidize functional components in the food, resulting in increased oxidative stress that can lead to hypertension and cardiovascular diseases. Natural bioactive compounds extracted from natural commodities like seaweeds can be used to replace these synthetic additives [174]. *P. palmata*-derived peptides have potential applications as health-promoting ingredients and food preservatives because of their antioxidant activity [116].

Various polysaccharides are present on cell surfaces, and as a result, many cells, including microbes, lymphocytes, tumor cells, and erythrocytes, are selectively agglutinated by lectins. Lectins have been used as specific probes in immunological, cell biology, membrane structure, biomarker, drug delivery/targeting, mitogenic, antitumor, and cancer studies. Lectins specifically agglutinate human blood groups, which has led to their use in assays for blood typing [127,151].

The phycobiliproteins are an interesting group of high-value (approximately \$5000/g) macroalgal products [181]. Despite their lower stability in heat and light, phycobiliproteins are used as natural colorants for food (phycocyanin) and cosmetics (phycocyanin and phycoerythrin) [60,182]. Phycobiliproteins are used as colorants in many food products, including fermented milk, ice creams, desserts, milkshakes, jelly gum, and coated soft candies [60,183].

R-phycoerythrin is currently derived from a species of *Porphyra* [181] and can be used as a food colorant [159]. Phycobiliproteins from *G. longissima* (formerly *G. verrucosa*), *U. lactuca* (formerly *U. fasciata*), and *S. wightii* can be used as natural food colorants for jelly without a change in color for more than three months [184]. Phycoerythrin, the most abundant phycobiliprotein in *G. turuturu*, has many applications, such as natural colorant, fluorescent probe, antioxidant, antitumoral, and antidiabetic compounds [164]. In general, phycobiliproteins are used as labels or markers in immunolabeling experiments, fluorescence microscopy, and diagnostics. R-phycoerythrin is a powerful and highly sensitive fluorescent reagent used as labels or markers for antibodies, receptors, and other biological molecules in a fluorescence-activated cell sorter [60,183,185].

Only a few studies mention the applications of protein derived from seaweeds in functional food products, due in part to the fact that acceptability, toxicity, allergenicity, and microbial studies are required before they can be safely utilized.

## 7. Safety

Although seaweeds have gained much interest in food industrial applications based on their nutritive values, several factors limit their widespread usage, including the accumulation of toxic heavy metals, allergenicity (phycobiliprotein and phycolectins in red seaweeds), contamination with pathogens, and toxic synthetic compounds such as cyanotoxins (neurotoxin and hepatotoxin), amino acids (kainic acid), and radioisotopes [28]. Therefore, it is essential to determine their toxicological profile for the safety of the consumers.

Heavy metals such as arsenic, cadmium, and mercury, and microorganisms such as *Salmonella* have been identified as major hazards associated with seaweeds [169,186]. Seaweed absorbs heavy metals from seawater depending on various factors, such as species, location, season, wave exposure, temperature, salinity, light intensity, pH, nitrogen availability, and the age of the plant [187]. Chen et al. identified ten metals and metalloids—Al, Mn, As, Cu, Cr, Ni, Cd, Se, Pb, and Hg—in 295 dried brown and red seaweeds [188]. Generally, heavy metal concentrations in seaweeds are found below the toxic level. However, bioaccumulation of arsenic, lead, and cadmium beyond a hazardous level is the main risk for seaweed harvested from the wild and can result in allergies, hyperpigmentation, and cancer. Arsenic is a known carcinogen, and commonly consumed seaweeds were reported to contain high levels of arsenic, primarily in organic forms [189]. Iodine, a

component of thyroid hormones, plays a role in metabolism, and iodine deficiency causes goiter and hypothyroidism. Seaweeds such as *L. digitata* and *S. japonica* (formerly *L. japonica*) are a good source of iodine and can be used to prevent goiter. However, iodine-rich products such as dried seaweed can cause excessive iodine intake and induce hyper- or hypothyroidism [186,189].

Microplastics have become an emerging environmental pollutant because of their persistence, ubiquity, toxic potential, and distribution in various environments, including soil, lakes, rivers, sea surface water, and marine sediments. Microplastics have been reported to attach to marine macroalgae, which can be transferred and accumulated between organisms of different trophic levels in the marine food web, and consequently, affect human health [190,191].

Apart from the bioactive properties of lectins, the hemagglutinating mechanism is a reason for toxicity. The hemagglutination by lectins leads to growth retardation in animals, probably because of their ability to bind with specific receptor sites on the surface of the intestinal epithelial cells, resulting in impairment of nutrient absorption [192].

Though seaweed peptides are predicted as non-toxic, several sequences have been reported as allergenic [193]. Gammaridean amphipods and caprellid amphipods inhabit *Porphyra* spp. (nori) and can mix with nori sheets during harvesting and are consequently found in dried nori sheets, resembling small stones. Hence, dried *Porphyra* spp. (nori) products may contain amphipod allergens that can cause severe allergic reactions, particularly in crustacean-allergic people [169,194]. Amino acids such as kainic acid in dulce (*P. palmata*) and some other red algae (*D. simplex*) are structurally similar to glutamate (a neurotransmitter in the brain) and become neurotoxins at excessive levels. Food allergy is one of the main concerns for food safety; however, the potential allergenicity of proteins from macroalgae has not yet been fully explored [186,195].

## 8. Future Perspectives

Currently, exploitation of seaweed protein for human consumption is rare. Many studies have stated that seaweed has many biological properties such as antioxidant, anti-hypertensive, antioxidant, antidiabetic, antiviral, antimicrobial, among others. Although several publications are available on the quality of seaweed protein and its potential functional properties, only a few clinical studies have reached logical conclusions about actual functional food products [100].

Applications of new technologies need to be focused on identifying useful health-promoting compounds and eliminating chemical/microbiological risks and other current issues [196].

Since conventional protein extraction methods may require the use of non-negligible amounts of solvents, other environmentally friendly reagents or nonthermal techniques (membrane technologies such as ultrafiltration or nanofiltration) and economically viable processes should be investigated to produce, extract, and purify algal protein [1,95].

In addition, about half of all oxygen production on the planet comes from algae, which is another reason for saying “our lives depend on algae” [197]. Therefore, sustainable seaweed production should be carried out. Policies supporting seaweed production in aquaculture as a replacement for wild harvest and repopulation of natural sites are required to avoid an environmental crisis caused by the overexploitation of wild seaweed [18].

## 9. Conclusions

Seaweeds, also known as macroalgae or marine algae, are rich in protein, containing up to 40% protein with an excellent AA profile and high digestibility that is comparable, or even superior, to animal protein sources. More than 50% of the total amino acids are EAA in most seaweeds. Seaweed protein contains a number of bioactive components, including amino acids, free amino acids (especially taurine, laminine, kainic and domoic acids), peptides, phycobiliproteins (phycoerythrin and phycocyanin), and lectins. These bioactive compounds have many health benefits, including antihypertensive, antioxidant,

antidiabetic, antiatherosclerosis, anti-inflammatory, antitumoral, antimicrobial, antiviral, and neuroprotective effects, among others. More than ever, people are concerned about their diet and health, resulting in a huge demand for high value functional foods that have been developed using natural sources instead of synthetic compounds. Developing functional foods using proteins derived from seaweeds has become more popular in the last decade. Seaweeds are a source of natural food additives include colorants, flavoring agents, antioxidants or preservatives, and many other compounds with health claims. Currently, protein derived from seaweed is rarely used as ingredients in the food industry, and acceptability, toxicity, allergenicity, and microbial studies have yet to be conducted for seaweed.

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## Abbreviations

AA	Amino acid(s)
ACE	Angiotensin-I-converting enzyme
Ang II	Angiotensin II
DPP-IV	Dipeptidyl peptidase IV
EAA	Essential amino acid(s)
FAO	Food and Agriculture Organization of the United Nations
GIP	Glucose-dependent insulinotropic poly-peptide
GLP-1	Glucagon-like peptide-1
MERS-CoV	Middle East respiratory syndrome coronavirus
NEAA	Non-essential amino acid(s)
PAF-AH	Platelet-activating factor acetylhydrolase
SARS-CoV	Severe acute respiratory syndrome coronavirus
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization

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