Technologies for Seaweed Polysaccharides Extraction

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Algal metabolites possess nutritional properties, but they also exhibit antioxidant, antimicrobial, and antiviral activities, which allow them to be involved in several pharmaceutical applications. Seaweeds have been incorporated since ancient times into diets as a whole food. With the isolation of particular seaweed compounds, it would be possible to develop new types of food with therapeutically properties. Polysaccharides make up the majority of seaweed biomass, which has triggered an increase in interest in using seaweed for commercial purposes, particularly in the production of agar, carrageenan, and alginate. The bio-properties of polysaccharides are strictly dependent to their chemical characteristics and structure, which varies depending on the species, their life cycles, and other biotic and abiotic factors.

Keywords: seaweed compounds ; nutraceutical ; functional food ; hydrocolloids extraction

1. Introduction

The use of seaweed (also called macroalgae) for medicinal purposes sees its roots in Asian countries, which, since ancient times, saw and explored the incredible benefits of seaweeds and algae, and introduced them into traditional medicine practices. Seaweeds are classified in phylum Ochrophyta (Phaeophyceae, brown algae), phylum Rhodophyta (red algae), and phylum Chlorophyta (green algae). Each group presents diverse bioactive compounds, with several properties and mechanism of actions. Seaweed metabolites, besides providing protective actions, possess a high nutritional content, and they assure several advantages for people’s health. Over the years, many researches, through pre-clinical and clinical studies, have confirmed the positive effects of seaweed extracts, exhibiting antibacterial [1], antiviral [2] anti-inflammatory, anticoagulant, antithrombotic [3], anticoagulant [4], and antitumoral effects [5].

The new challenge is to develop strategies to combine the benefits of seaweed with food products, to have in the market not only sustainable and natural products, but also products with therapeutical properties. Seaweed hydrocolloids such as agar, carrageenan (abundant in Rhodophyta), and alginates (abundant in Phaeophyceae), are abundantly extracted and employed in food (gelling agents), pharmaceutical products (dressings, coatings of medicaments, stabilizers), biotechnology (culture medium, the Petri dishes), and cosmetics (body lotions, soaps, shampoos, toothpaste) [6][7]. Therefore, by investigating their beneficial properties it might be possible to develop specific functional foods adaptable for diverse demands [8].

Every day, the global commercial seaweed market acquires value; in recent years, the inclusion of hydrocolloids in the food, pharmaceutical, and other industries, has increased. Since seaweed can grow in any sort of aquatic environment, and are simple to grow, many industries throughout the world are already investing in their production. These factors include sunlight, natural or artificial aeration, and nutrient-rich seawater. The consummation of natural products for health or ethical reason is increasing, therefore, seaweed in human food, animal feed, and pharmaceutical products, has largely expanded over the years (https://www.fortunebusinessinsights.com/industry-reports/commercial-seaweed-market-100077, accessed on 10 June 2022).

2. Therapeutic Properties of Seaweed Compounds

Seaweeds are ubiquitous, and to survive in harsh conditions they need to develop defense mechanisms; therefore, seaweeds have developed several metabolites that help their survival. Furthermore, seaweed bioactive compounds involved in the mechanisms of defense possess interesting properties that may ameliorate human health conditions.

Antioxidant activity, for example, is fundamental to prevent human cells and organs from the effects of oxidative stress, due to the presence of reactive oxygen species (ROS) and free radicals. Oxidative stresses caused by ROS may lead to harmful pathologies, such as cancer, diabetes, neurodegenerative and cardiovascular diseases. In seaweed, antioxidant activity is expressed by pigments as chlorophylls, xanthophylls (fucoxanthin), carotenoids, vitamins (vitamins B1, B3, C, and E), vitamin precursors, and phenolic compounds such as polyphenols, and flavonoids [9][10][11]. Moreover, the incorporation of antioxidant compounds in food will provide its spoilage.

Seaweeds also possess antimicrobial activities. According to Rajauria et al. [12], the antibacterial activity is triggered by algal polyphenols such as tannins, quinones, flavones, flavonols, phlorotannins, and flavonoids. *Himanthalia elongata* methanolic extracts have shown antibacterial efficacy against pathogenic bacteria (*Listeria monocytogenes* and *Salmonella abony*), and food deterioration bacteria (*Enterococcus faecalis* and *Pseudomonas aeruginosa*) [12]. Gram-positive and gram-negative bacteria have both been demonstrated to be resistant in the antimicrobial effects of terpenes, phlorotannins isolated from *Ecklonia kurome*, *Ecklonia cava*, and *Fucus vesiculosus* [13]. Algal polysaccharides exhibit antimicrobial activity, in addition to polyphenols, by identifying and attaching to the glycoprotein receptors on bacterial surfaces, with the consequential disruption of the bacterial cell. Moreover, to survive several viral attacks in hostile environments, seaweeds have developed antiviral compounds that stop a virus from entering the host cell or stopping its reproduction cycle at a specific stage. Alginates, carrageenan, agarans, DL-hybrid galactans, laminarans, fucans, and fucoidans, are sulphated polysaccharides found in seaweeds that have been discovered to prevent the replication of a diversity of enveloped viruses [14].

Biological activities performed from carrageenan depend on molecule size, sulphation degree, and glycosides branching. Because of their physical qualities, such as thickness, gelling, and stabilizing capabilities, most carrageenans used in the manufacturing of functional food have a high molecular weight fraction (HMWF). However, because of their high viscosity, these qualities may cause problems in non-food applications. As a result, converting carrageenan's HMWF to a low molecular weight fraction (LMWF) could improve bioavailability, and enhance carrageenan's potential applications in the nutraceutical, pharmacological, and biological industries [15].

It has been already demonstrated that LMWF carrageenan showed interesting biological activities compared to HMWF, such as being antioxidant, antiproliferative, and antiviral. Common techniques used to depolymerize carrageenan are microwave, sonication, irradiation, and oxidation utilizing H_2O_2 [15]. In general, low molecular weight sulphated polysaccharides provides interesting biological activities. For instance, Chen et al. [16] revealed the action of seaweed LMWF sulphated polysaccharides that generates the immunostimulant activity against S180 tumors in mice. Another case study demonstrated that LMWF fucans from *Ascophyllum nodosum* showed a higher inhibition of cell growth action on fibroblast cell lines CCL39 [17]. Similarly, low molecular weight fucoidans from *Fucus vesiculosus* inhibited the proliferation of B16 melanoma cells, Lewis lung cancer, and Sarcoma 180 cell lines, showing greater anti-angiogenesis activity [18]. Sulphate content was high in both fucans and fucoidans, with increased antiproliferative activity, showing that sulphate content influenced anticancer action.

The therapeutic activities of seaweed bioactive compounds are multiple and depends on the characteristics of seaweeds and their compounds, but also depend on the extraction processes. The nutraceutical industry provides the development of therapeutical food made by the incorporation of seaweed compounds, which provide advantages to our health. Among seaweed polysaccharides, carrageenan, agar and alginate are the most involved in nutraceutical and the food industry.

3. Extraction Processes for Seaweed Hydrocolloids

In traditional extraction methods, maceration occurs in water at high temperatures. The extraction procedures differ by sources and application of polysaccharides. Cleaning the seaweed of epiphytes, debris, salts, pollutants, sand, and toxins, is necessary prior to extraction. Alkali pre-treatment of agar and carrageenan improves the gelling characteristics by reducing unstable sulphate molecules into 3,6-anhydro-L-galactopyranose (3,6-AG) [19]. In order to increase alginate yield and remove color pigments from seaweed tissue, alginate is pre-treated with formaldehyde. It is also pre-treated with hydrochloric acid (HCl) in order to “clarify” the phenolic compounds and formaldehyde residue, and to encourage the conversion of insoluble salts (calcium, magnesium, etc.) into soluble salts [20][21][22][23][24].

Hot water extraction is used for carrageenan and agar, followed by alkali extraction, to obtain molecules with the desired characteristics and functions by manipulating conditions such as time, pH, solvent concentration, and temperature, etc.

The choice between alkaline extraction, or water extraction for agar extraction, depends on the species. For example, alkali treatment is necessary for *Gracilaria* spp. in order to produce 3,6-anhydrogalactose, which is accountable for forming a strong agar gel, but it is not necessary for *Gelidium* spp. [25]. The alkaline treatment, however, can be used to increase the gel strength of carrageenan even though it is not necessary for carrageenan extraction [26].

The temperature at which hydrocolloids are extracted varies depending on the hydrocolloids of interest; for instance, agar extraction is performed at temperatures higher than 85 °C. Carrageenans can dissolve in either cold or hot water due to their chemical composition; however, pH should be maintained above the pKa value of alginate (between 3.4 and 4.4) because pH is the most crucial solubilizing parameter for alginate extraction [27].

Alginate extraction is performed only with alkali extraction. Later, all phycocolloids are then neutralized by eliminating chemicals and solvents in excess; residuals are then removed using precipitation and filtering, leaving just the pure compound; finally, grinding and drying are carried out to produce the finished products, which are dried, cleansed, and prepared for use in commerce (**Figure 1**) [19].

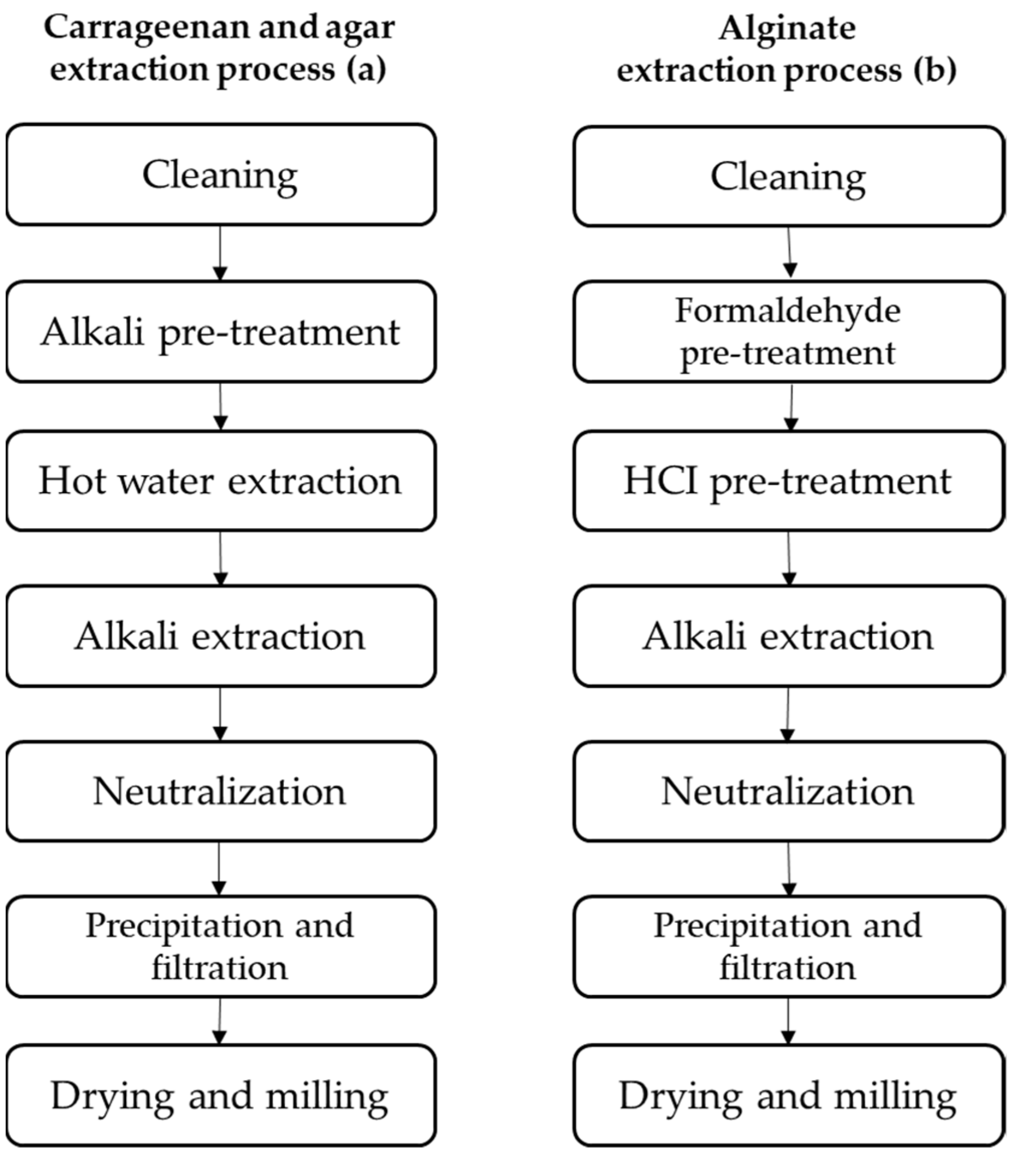

Figure 1. Extraction processes for commercial macroalgal hydrocolloids: (**a**) carrageenan and agar; and (**b**) alginate.

Traditional approaches for processing seaweed to generate hydrocolloids necessitate an intensive use of time and solvents. Innovative technologies for hydrocolloid extraction and production are currently being investigated at various stages of macroalgae processing, with the goal of improving the yields of valuable compounds, while improving the productivity of actual industrial procedures and minimizing, or avoiding, the use of organic solvents [28].

3.1. New Extraction Methods

Common hydrocolloid extraction has several drawbacks, including huge time, energy, and water consumption. Furthermore, many chemical solvents are employed to achieve an optimal yield, some of which are health concerns; due to poor regulation throughout the entire manufacturing process and discharge, the use of chemicals may pose a major threat to both human health and the environment [29][30]. A disadvantage of the old extraction method is the high price of solvents used during carrageenan precipitation to create refined carrageenans [29].

Traditional extractions processing can result in enormous amounts of hazardous waste. Furthermore, if the solvent being used is noxious, additional processing steps are required to meet alimentary and pharmaceutical sector rules to use extracted compounds incorporated in safe products [31]. With this concern, sustainable extract technologies are currently a primary issue in natural product recovery research and development [19][31]. The use of eco-friendly solvents, such as ionic liquids, eutectic solvents, surfactants, or solvents from biological origin, is an alternative way to minimize the adverse effects of hazardous chemicals used in the extraction process. For example, deep eutectic solvents are available from natural chemicals. Smith et al. [32] divided deep eutectic natural solvents into four categories: (a) mixtures of organic salts and metal salts; (b) mixtures of organic salts and metal hydrates; (c) mixtures of organic salts and hydrogen bond donors; and (d) mixtures of metal chlorides and hydrogen bond donors. When extracting seaweed polysaccharides, deep eutectic natural solvents are a more environmentally friendly choice than organic solvents because of their lower price, biopolymer dissolving capabilities, biodegradability, non-toxicity, polarity, and recyclability [33]. Natural deep eutectic solvents based on choline chloride, lactic acid, betaine, and glucose, have been already used to extract phlorotannins from brown algae *Fucus vesiculosus* and *Ascophyllum nodosum*. Extraction yields of phlorotannins achieved was around 60–72%. Nie et al. [34] proposed the extraction of polysaccharides from *Sargassum horneri* using ultrasonic extraction and deep eutectic solvents composed of choline chloride, 1,2-propanediol, and water. The results indicated that deep eutectic solvents had stronger protein and $CaCO_3$ removal ability than that of a conventional hot water extraction method, suggesting these solvents were good alternatives [34]. A solid-phase extraction (SPE) of fucoidan and laminarin was performed on kelps. The deep eutectic solvent prepared by choline chloride and urea had the best extraction efficiencies for fucoidan and laminarin (95.5% and 87.6%, respectively) [35].

Three different deep eutectic solvents prepared by the complexation of choline chloride with urea, ethylene glycol, and glycerol, as well as their hydrated counterparts, were used for the selective extraction of κ-carrageenan from *Kappaphycus alvarezii,* and the obtained yield was compared with κ-carrageenan extracted using a conventional method. It was inferred from the studies that the physicochemical as well as rheological properties of the polysaccharide, obtained using eutectic solvents, were superior in comparison to the κ-carrageenan obtained using water as solvent [36].

Alternative extraction and processing methods include microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), high-pressure technique, and enzyme-assisted extraction (EAE). Some of these techniques have already been applied to the extraction of bioactive chemicals from plants [37][38]. Nevertheless, all of these processes have advantages and disadvantages in terms of time, expenses, and production output [19].

3.2. Traditional Extraction Techniques vs. Alternative Extraction Techniques

Traditional extraction techniques involve increased temperatures and are time-consuming, which could harm the molecules and their functions, having negative effects. The use of novel techniques has proved abundantly significant benefits, such us extraction time and temperature savings. These energy reductions (0.2 kW/h) and environmental benefits (200 g CO_2/100 g extracted solid material) were noted for UAE, in comparison to maceration (6 kW/h and 3600 g CO_2/100 g extracted solid material) [39]. Therefore, these techniques are consistent with extraction principles that are environmentally friendly [40]. Moreover, characteristics of the extracted compounds are also optimal. However, investigations have revealed some drawbacks related to the new extraction processes, due to safety (high noise/pressure levels), and the likely degradation of molecules under strong conditions (high ultrasound can depolymerize of hydrocolloids) [39]. To solve extraction limitations, a mix of extraction approaches has been suggested [40]. Most of these techniques can be scaled up to industrial scales or are currently being used successfully at industrial or semi-industrial scales. These techniques include advantages such as the ability to use water to produce larger yields of molecules. Nevertheless, despite the fact that the majority of novel technologies are frequently described as low-energy approaches, these findings should be confirmed using appropriate life cycle assessment methodologies, which assess these techniques' efficacy for particular applications based on compound yields and energy and resource consumption [41]. Furthermore, depending on treatment conditions, unique extraction processes can cause a change in the conformation and structure of molecules, potentially altering them. Nevertheless, the adoption of emerging techniques, including their combined use, has shown promising results in terms of enhancing extraction yields and efficiency, and in the meantime, in reducing the processing time (**Table 1**). Future challenges include the need to scale up methods that are now being developed at the laboratory stage, so that they may be adapted to commercial needs.

Table 1. Advantages and disadvantages of different extraction methods.

Extraction Method	Advantages	Disadvantages
Hot water/alkali extraction	Optimal rheological properties and purity of the extracted hydrocolloids	Involves high temperatures and very long extraction time Long extraction time and high temperature may affect extracted compounds' functionalities Use of hazardous chemical solvents High cost of chemical solvents
Microwave-assisted extraction (MAE)	Use of water instead of chemical solvents It provides locally heat raw materials, enhanced biomass digestion, reduced process time, solvent consumption, and costs Extracted compounds possess good quality It utilizes directly on fresh biomass from seaweed	High temperature can deteriorate thermolabile compounds
Ultrasound-assisted extraction (UAE)	Ability to achieve larger yield of extracts utilizing water It increases extraction yield with lower extraction time Efficient, environmentally friendly, and low extraction processes. Low equipment expenses and maintenance, possibility to scale-up to industrial production, reduced number of process steps Extraction techniques used in food industry	High noise levels involved (safety issues) Ultrasound might bring to depolymerization of compounds Due to the high cost of energy and equipment, UAE needs a large amount of capital to get started on an industrial scale UEA applications are still limited
	Ability to obtain larger yield of extracts utilizing aqueous-based solvent	High-pressure involved (safety issue)

Extraction Method	Advantages	Disadvantages
Pressurized solvent extraction (PSE)	It has high extraction performance, less solvent usage, quick extraction time, and does not imply the use of hazardous solvents	High-pressure power can bring depolymerization of compounds These processes might degrade labile compounds due to high temperature and pressure Scarcity of application on seaweed extractions
Enzyme-assisted extraction (EAE)	Ability to achieve larger yield of compounds utilizing water It is inexpensive, highly efficient, possibility to scale up, avoid the use of any harmful chemicals or organic solvents and it has shorter extraction time It preserves the structural integrity of the target compounds extracted that exert important bioactivities suitable for cosmetic, nutraceutical and pharmaceutical industries	Scarcity of application on seaweed extractions

4. Potential Use of Seaweed for Nutraceutical Applications

The most ancient information regarding the use of seaweed as food for therapeutical purposes goes back to ancient times in Japan. Even though many of the transcripts have been destroyed or lost, the properties of *Sargassum* sp. were investigated and compiled in Chinese medical literature "*Compendium of Materia Medica*", written by Shizhen Li in 1578. While the *Compendium* also states that *Sargassum* sp. can soften hard lumps, dispel nodes, eliminate phlegm, induce urination in humans [42], treat fever, infections, laryngitis, and other diseases [43], the most ancient information on *Sargassum* focuses on its ability to treat thyroid-related diseases, such as goitre, and iodine deficiency disorders [44]. Vietnamese medicine frequently employs species from the *Eucheuma* and *Kappaphycus* (Rhodophyta) genera to reduce the incidence of tumors, ulcers, and headaches.

Although recent researchers see *Sargassum* sp. as a suitable immunomodulator, due to its bioactive metabolites, which may improve immune function and inhibit thyroid growth caused by excessive iodine absorption, important information related to the treatment of thyroid-related conditions, such as goiter, as claimed for *Sargassum* sp. in traditional Chinese medicine, has not yet received enough research [45]. Asian cultures still consume seaweed for therapeutical applications, and this practice is widely spreading across the world as the beneficial properties of seaweed have been abundantly confirmed by scientists.

Currently, preclinical and clinical tests have demonstrated the efficacy of several biological activities of seaweed bioactive compounds.

Meinita et al. [46] collected case studies conducted on seaweed and the treatment of chronic disease [47]. The research records a higher percentage of experiments conducted with brown seaweed (68%), followed by red seaweed (18%), and green seaweed (14%). The most extensively investigated species of brown seaweed were *Ecklonia*, *Sargassum*, and *Fucus* (they represent 21.3%, 20.2%, and 9%, of the total of the studies collected, respectively). The two species of red seaweed that have been examined the most for potential application in the treatment of chronic illnesses are *Gracilaria*, (20.8%) and *Gelidium* (16.7%). While, *Ulva* (47.4%), *Codium* (26.3%), and *Caulerpa* (47.4%, 26.3%, and 15.8%, respectively) the three species of green seaweed explored the most. Brown seaweeds have been the most researched in relation to cancer, diabetes, arthritis, neurodegenerative illnesses, obesity, osteoporosis, liver disease, and cardiovascular disease. Not many clinical trials have been performed, however, one was carried out to evaluate a seaweed extract formulation from *Fucus vesiculosis*, *Macrocystis pyrifera*, and *Laminaria japonica,* on osteoarthritis patients. According to the study, the formulation would ameliorate osteoarthritis symptoms in a dose-dependent way [48].

Manufacturers and consumers have shown a growing interest in incorporating functional components into daily diets in recent years. Moreover, the antioxidant and antimicrobial activities exhibited by seaweed compounds will ensure safety and delete the spoilage of food. The presence of flavonoids in the green algae *Ulva reticulata* and *Ulva* sp. (Chlorophyta) showed potential free-radical-scavenging ability [49][50]. Strong DPPH-radical scavenging activity has been measured in brown algae including *Eisenia bicyclis*, *Ecklonia cava*, and *Ecklonia kurome* [51], as well as for red algae *Callophyllis japonica* and *Gracilaria tenuistipitata* ethanolic extracts [52][53]. Seaweed polar lipids are now well recognized as essential phytochemicals that contribute and add usefulness and potential advantages for our health. Lopes et al. [54] set out to reveal the lipid profile of *Palmaria palmata* raised in an integrated multitrophic aquaculture (IMTA) to test its antioxidant properties. A total of 143 lipids were discovered, spanning numerous polar lipid groups such as phospholipids, glycolipids, and betaine lipids. It is important to note that eicosapentaenoic acid (EPA) accounts for more than half of the lipid content. One of the primary determinants of the antioxidant effectiveness of *Palmaria palmata* may be its level of EPA. Therefore, this finding suggests that this red macroalga could be used in the future as a source of EPA-rich lipids and antioxidant activity for functional foods [54].

The inclusion of seaweed molecules in food can contribute to ameliorate the lifestyle of people with certain medical conditions, as they possess interesting biological properties that guarantee health benefits. Seaweed, as a nutritional source, inhibits the growth of cancer cells, most likely due to its antioxidant characteristics. Antioxidants are clearly important in the later phases of cancer formation, as evidenced by the mechanisms of carcinogenesis promoted by oxidation activity. As a result, antioxidants are regarded as a viable method for regressing premalignant lesions and preventing cancer development [55]. Sulphated polysaccharide, derived from *Gracilaria lemaneiformis,* showed exceptional anti-cancer and immunomodulatory activity against transplanted H22 hepatoma cells in mice. Tumor growth was significantly slowed, splenocyte proliferation was boosted, macrophage phagocytosis was increased, and the number of IL-2 and CD8+ T cells in the blood increased [56]. The antiproliferative effect of κ-and λ-carrageenan extract from the red seaweed *Laurencia papillosa* has been demonstrated in vitro with human breast cancer cell line MCF-7 [57]. κ-carrageenan from *Kappaphycus alvarezii*, an edible seaweed, have been investigated for their antiproliferative activity. Results from the incubation of two LMWF of carrageenan with human colon cancer cells HCT116 revealed that these fractions may induce apoptosis via the ROS-mediated mitochondrial pathway by upregulating the latter, along with upregulating Bcl-2 and Bcl-xL, caspase3, and downregulating XIAP, an inhibitor of apoptosis. The investigated fractions could be incorporated in food to prevent colon carcinogenesis. Dietary behaviors influence the development of colorectal cancer; therefore, identifying dietary components that can help to prevent cancer could help people acquire healthier eating habits. LMWF soluble dietary fibers could be a potential additive in nutraceutical food, contributing to the efficacy of several health-promoting advantages as cancer treatment coadjutants. Exploring their health advantages would offer up new avenues for research in the nutraceutical field [58].

Antimicrobial and antioxidant properties of *Kappaphycus alvarezii* extracts were tested in both hot water and ethanolic extracts by Bhuyar et al. [59]. *Escherichia coli* and *Bacillus cereus* were used as pathogenic bacteria in the investigation of antibiotic activity. Both extracts' antibacterial activity was more potent against *Bacillus cereus* than against *Escherichia coli*, suggesting that they might be able to maintain a healthy level of reactive oxygen species. Levoglucosenone, which has a highly functionalized chiral structure and can be used as a crucial intermediate in the development of biologically active compounds, and pyridinemethanol, a functional pyridine that is used as an intermediate in the pharmaceutical industry, were among the fatty acids found in both extracts; 1,2,5- Thiadiazole-3-carboxamide, which can be utilized as an antibacterial; and hexamethylcyclotrisiloxane, which is widely employed in medical, military aircraft, and other petrochemical sectors. Furthermore, GC-MS analysis revealed that considerable levels of levoglucosenone (48.9%) and 4-pyridinemethanol (28.21%) were found in hot water extract, suggesting that it may have antitumor potential [59].

Among Asian seaweeds, the popular red edible seaweed *Gelidium amansii* is frequently utilized in Korea, Taiwan, China, and Japan, as a cuisine ingredient. Particularly appreciated in Taiwan and Japan, agar jelly is prepared from hot-water extracts of *Gelidum amansii* [60]. Galactose (23%) and glucose (20%) are particularly abundant in this red seaweed's carbohydrate content [61]. Due to its easy and low-cost cultivation, *Gelidium amansii* is commonly involved in the manufacturing of agar [62]. Moreover, extracts of this alga showed that diabetic rats' liver and plasma lipid levels could be lowered by supplementing high-cholesterol and high-fat diets [60]. Due to its numerous health benefits, *Gracilariopsis chorda* (Rhodophyta) is another popular seaweed in Korea, and it is also used as a food component [63]. In addition to Korea, France, Indonesia, Mexico, Morocco, Portugal, and Spain, also use *Gracilariopsis chorda* as a raw material to extract agar [64].

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