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REVIEW ARTICLE

Seaweeds: Bioactive components and properties, potential risk factors, uses, extraction and purification methods

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ABSTRACT

Seaweeds, also known as macroalgae, are abundant sources of various vital bioactive components with a wide range of biological functions. They are sold commercially and are primarily used in the food industry, pharmaceuticals, cosmeceuticals, and other related industries. The diverse biological activities linked with bioactive compounds obtained from seaweeds have the potential to expand their health benefit value in the food and pharmaceutical industries. Studies revealed that seaweeds have the potential to be used as complementary medicine due to its variety of biological properties that have been shown to be therapeutic for health and disease management, such as antibacterial, anticoagulant, anticancer, antidiabetic, antiestrogenic, antihypertensive, antihyperlipidemic, antifungal, anti-inflammatory, antioxidant, antiobesity, antiviral, immunomodulatory, neuroprotective, thyroid stimulant, tissue healing properties, and many more. Although seaweeds are generally beneficial to humans, they may still pose possible health risks due to high iodine concentration and exposure to heavy metals and arsenic concentrations. However, information on this topic is still limited. With the great importance of seaweeds, various green extraction methods such as Microwave-assisted Extraction (MAE), Supercritical Fluid Extraction (SFE), Pressurized Solvents Extraction (PSE) and Enzyme-ssisted Extraction (EAE) were used as an alternative to the conventional method to isolate bioactive components and further purified using chromatographic technique analysis to ensure the purity of the extract. This review covers the following topics: general structure and characteristics of seaweeds, seaweed production, bioactive components and properties of seaweed, possible risk factors of seaweeds, applications of seaweeds, extraction, and purification of seaweed extracts.

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Introduction

Since ancient times, natural products have played a significant role in diagnosing, treating, and preventing numerous ailments. The therapeutic characteristics of chemical compounds in natural products are optimized and augmented for human medical applications (Gnanavel et al., 2019). The plant-based and herbal medications generated from natural resources that are considered pure, healthy, and safe have grown in popularity over the years (Van Wyk & Prinsloo, 2020). As a result, several herbal-based pharmaceutical sources are now commercially accessible and offered as an alternative therapy and dietary supplement to treat various illnesses (Woo et al., 2012). In addition, the availability of novel metabolites with diverse uses such as cosmeceuticals, nutraceuticals, agrochemicals, medicals, and other relevant chemical industries has stimulated marine drug research in recent years (Rengasamy et al., 2020). It has been considered that the marine ecosystem is an excellent source of natural compounds with several functions (Hentati et al., 2020). Seaweeds are marine plant organisms capable of producing a wide range of active metabolites with a wide range of medical applications, which they also use to defend themselves against other invading species (Kolanjinathan et al., 2014). As results of these novel metabolites, seaweed has become one of the most important sources of natural components used in pharmaceuticals, accounting for 30% of the global market in 2018. It was expected to be greater than USD 10,486.8 billion (Rengasamy et al., 2020).

Seaweeds, or known as macroalgae, are marine photosynthetic, non-flowering plant-like organisms that are categorized into three major groups depending on their predominant pigment compositions, which are green (Chlorophyta), brown (Ochrophyta), and red (Rhodophyta) seaweeds (Baweja et al., 2016). They can be found all across the world's coastlines, from the warm tropics to the freezing and icy polar regions (Mahadevan, 2015). Seaweeds are commercially sold, with approximately 83% of its total global production is for direct human consumption (Mahadevan, 2015). They are commonly consumed in Asian countries as fresh, dried, or as ingredients in prepared foods (Kılınç et al., 2013). The remaining percentage is used as a source of phycocolloids extracted for the application in food (Fleurence., 2016), cosmetic (Morais et al., 2021), medical (Shelar et al., 2012) and other related industries (Hentati et al., 2020). There are 221 species of seaweeds are utilized in total, with 145 species used for food and 101 species used for phycocolloid synthesis (Fleurence et al., 2018). Seaweeds are also employed in aquaculture as probiotics (Vatsos & Rebours, 2015), animal feed additive (Makkar et al., 2016), fertilizer (Ruban & Govindasamy, 2018), and as water purifier (Arumugam et al., 2018). In this context, the goal of this article is to provide general information about seaweeds, including their biological features, potential therapeutic properties, potential risk factors, and some of the extraction methods used. Furthermore, due to their distinct metabolite contents, this study also investigates the relevance and applications of seaweeds as major marine bioresources in numerous industries.

Materials and Methods

This study reviewed the available articles regarding the information about seaweeds and their novel metabolites. The study searched the keywords: seaweeds, bioactive compounds, bioactive properties, extraction, and characterization methods in Google Scholar, Pubmed, Web of Science, Science Direct, Mendeley and Scopus databases from 2011 to 2021. Articles published after the date of this review were not considered. In addition, online thesis and conference proceedings were also taken into account.

General Structure and Characteristics of Seaweeds

Seaweeds are large and diverse group of macroscopic multicellular, benthic (some species), non-flowering, plant-like organisms found in the world's aquatic environments (Zamani et al., 2013; Kalasariya et al., 2021). They can be extremely small or very huge, reaching lengths of up to 60 meters (Yu et al., 2014). Although many seaweeds have plant-like features, they are still not classified as true plants because they lack a specialized vascular system (Yu et al., 2014; Kalasariya et al., 2021; Morais et al., 2021). This vascular system is an internal conducting system that connects all organs and distributes fluids, nutrients, and numerous signaling molecules throughout the plant body (Lucas et al., 2013). Seaweeds, on the other hand, receive nutrients straight from the seawater and hence do not require an internal conducting system (De San, 2012). Seaweeds are eukaryotic organisms (Charrier et al., 2017) , they are macroalgae and thalloids in nature, which means they have basic thallus structures but no real leaves, stems, or roots, unlike other terrestrial plants. They do, however, have roots-like structures known as holdfasts or rhizoids (Rao et al., 2019). Seaweeds, like terrestrial plants, serve vital roles in marine ecology as primary producers. They are photosynthetic organisms, which means they can transform sunlight energy into materials for growth (Sudhakar et al., 2018). Seaweeds include pigments such as chlorophyll, which aids in the absorption of sunlight for photosynthesis and is responsible for their green color (Chen et al., 2017). Other pigments found in seaweeds are responsible for their intriguing colors, such as red and brown seaweeds (Morais et al., 2021).

Basic Parts of Seaweed

Some seaweeds employ *holdfast*, a root-like structure used only for anchoring, to attach themselves to the ocean floor. Other seaweeds, such as floating seaweeds, may have floating or *air sacs* that maintain them above the water's surface and expose them to sunlight for photosynthesis. Another seaweed component is *stipe*, a stem-like structure that holds the blades to the water's surface. *Blades* are primary photosynthetic leaf-like flattened parts that absorb sunlight. Furthermore, *thallus* refers to the fundamental or advanced body-like structure of seaweeds that can conduct photosynthesis with all its parts (Figure 1) (Suryanarayana Murty & Banerjee, 2011; Baweja et al., 2016; Sudhakar et al., 2018).

Figure 1. Basic parts of seaweed (Ha et al., 2021)

Classification of seaweeds

Based on their photosynthetic pigments, seaweeds are classified into three categories: brown (Ochrophyta or Class Phaeophyta), green (Chlorophyta), and red (Rhodophyta). There are around 10,000 seaweed species, including about 2000 brown, 1500 green, and 6500 red seaweeds (Collins et al., 2016; Gutiérrez-Rodríguez et al., 2018). Furthermore, seaweeds are classified using molecular techniques based on evolutionary processes (Figure 2) (Ruggiero et al., 2015).

Distribution of Seaweeds

With an average depth of 5 km, the water surface covers more than 70% of the earth's surface (Baweja et al., 2016), to which seawater accounts for more than 90% of all water on the planet earth (Sudhakar et al., 2018). Moreover, oceans support floating forests with a broad range of marine animals and plants, where the marine vegetation is more primordial and diversified than the terrestrial vegetation (Baweja et al., 2016). Algae are photosynthetic plant-like creatures that are the sole primary producers in the oceans (Sudhakar et al., 2018), with a photosynthetic efficiency (PE) that is 6–8% greater than that of terrestrial plants (1.8–2.2%) (Ashraf et al., 2016; Gutiérrez-Rodrguez et al., 2018). Seaweeds, also known as marine macroalgae or edible macroalgae, are benthic marine algae that thrive in brackish or saltwater environments (George & Mathew, 2017) found in shallow and open water up to 180m deep (Khalid et al., 2018). They are the most numerous marine vegetation and one of the essential biomass producers in the ocean that gives food and shelter to aquatic life (Ghadiryanfar et al., 2018). However, the distribution of seaweeds in the marine environment is limited only to the littoral and sublittoral zones. (Premarathna et al., 2019a). They may be found to a depth where 0.01% photosynthetic light is accessible (George & Mathew, 2017).

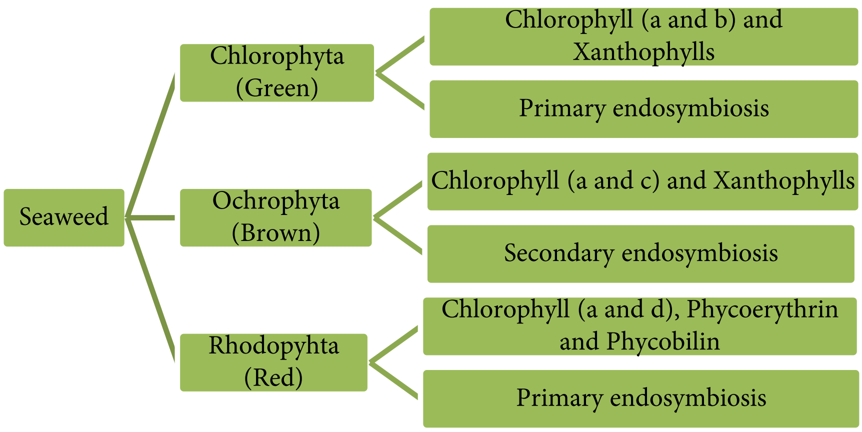

Figure 2. Classification of seaweeds

Table 1. Factors that affect the distribution of Seaweeds (adapted from Baweja et al., 2016)

Physical Parameters	Chemical Parameters	Biological Parameters
Substrate, temperature, light quality and quantity, dynamic tidal activity, winds, and storms.	Salinity, pH, nutrients, gases, and pollution level.	Herbivores, microbes, epiphytes, endophytes, symbionts, parasites, and diseases.

Table 2. Some pigment content of seaweeds (adapted from Yu et al., 2014)

Seaweeds	Pigments
Green seaweeds	α-, β-, and γ-carotene, chlorophylls a and b, lutein, siphonoxanthin, and siphonein
Brown seaweeds	Chlorophylls a, c1, and c2, β-carotene, and fucoxanthin
Red seaweeds	Chlorophyll a, r-phycocyanin, allophycocyanin, c-phycoerythrin, α- and β-carotene

Table 3. Chemical composition of seaweeds (% dry weight)

Species	Chemical composition of seaweed			
	Protein[a]	***Lipids***[b]	***Ash***[d]	***References***
Green seaweeds: *Caulerpa sertularioides, C. lentillifera, C. patentiramea, D. tenuissima, Ulva* sp., *Caulerpa* sp., *C. glomerata, Codium* sp., *Enteromorpha* sp., *Halimeda* sp., *M. oxyspermum, U. clathrata, U. lactuca*	32.7-3.3	13.04-1.57	27.5-19.59	Černá, 2011[a]; Mišurcová et al., 2011[b]; Gosch et al., 2012[b]; Fleurence et al., 2018[a]; Susanto et al., 2019[b]; Peñalver et al., 2020[d]
Brown seaweeds: *Costaria costata, D. bartayresii, D. dichotoma, H. fuziformis, Laminaria* sp., *S. japonica, Sargassum* sp., *S. macrodontum, A. nodusum, Dictyota* sp., *D. antartica, U. pinnatifida, Padina* sp., *Sargassum* sp., *B. bifurcata, F. vesiculosus, S. latissima, S. fusiforme, U.pinnatifida*	25.70-5.4	11.91-0.38	39.3-20.71	Černá, 2011[a]; Gosch et al., 2012[b]; Fleurence et al., 2018[a]; Susanto et al., 2019[b]; Peñalver et al., 2020[d]
Red seaweeds: *Laurencia papillosa, C. crassicaulis, C. yendoi, G. longissima, M. japonica, Palmaria* sp., *A. concinna, A. multifida, A. taxiformis, Bryothamnion* sp., *C. officinali, D. simplex, E. duperreyi, Eucheuma* sp., *G. acerosa, Gracilaria* sp., *G. turuturu, H. formousa, Hypnea* sp., *Chondrus* sp., *Laurencia* sp., *O. secundiramea, P. palmata, P. brasiliense, Porphyra* sp., *S. filiformi, V. obtusiloba, P. capillacea, J. rubens*	47.0-2.3	5.0-0.64	44.03-17.50	Černá, 2011[a]; Mišurcová et al., 2011[b]; Fleurence et al., 2018[a]; Susanto et al., 2019[b]; Peñalver et al., 2020[d]

In addition, their vertical and horizontal distribution differences demonstrate their adaptation to their surroundings. As a result, several species are confined to sheltered coves and bays, while others may be restricted to exposed cliffs along the coast or at the reef's margins. Different species of seaweeds may exist in a variety of transitional habitats; hence, the combined effects of various physical, chemical, and biological parameters on the distribution of seaweeds may determine the existence or absence of a species in a habitat (Table 1) (Baleta & Nalleb, 2016).

Production of Seaweeds

The Food and Agriculture Organization of the United Nations' recently published World State of Fisheries and Aquaculture Reports held biennially until 2018 (FAO, 2020). In the output of FAO, the total world fisheries and aquaculture production, roughly 54.1%, is represented by aquaculture, and in terms of overall world aquaculture production, coastal and marine aquaculture production accounted for around 55.2%. In the total coastal and marine aquaculture production, approximately 51.3% of it is represented by seaweeds with 32.4 million tons of total production, followed by mollusks with 17.3 million tons, approx. 27.4%, finfish with 7.3 million tons, approx. 11.6%, crustaceans with 5.7 million tons, approx. 9.1%, and other aquatic resources with 0.4 million tons, approx. 0.6% (Chopin & Tacon, 2021). In June 2021, FAO published a factsheet for the Global seaweeds and microalgae production from 1950-2019. According to the report, the global algal production, including cultivation and wild harvest, has increased more than 60 times since 1950, from 0.56 million tons of wet to 35.82 million tons in 2019. The increased in seaweed production is largely due to cultivation, which accounts for 34.74 million tons, or nearly 97% of total production, whereas natural harvesting produced only 1.08 million tons of wet (FAO, 2021a).

In 2019, around 97% of total world seaweed production (cultivated and wild) is centered in Asia, where China (20,351,442 tons, approx. 56.82%) is the top producer, followed by Indonesia (9,962,900 tons, approx. 27.81%), the Republic of Korea (1,821,475 tons, approx. 5.09%), the Philippines (1,500,326 tons, approx. 4.19%), the Democratic People's Republic of Korea (603,000 tons, approx. 1.68%), Japan (412,300 tons, approx. 1.15%), Malaysia (188,100 tons, approx. 0.53%). Other countries such as in Americas, Europe, Africa, and Oceania contributes only 1.36%, 0.08%, 0.41%, and 0.05% of the total world seaweeds production (cultivated and wild), respectively (FAO, 2021a). Species group of seaweeds such as brown seaweeds: *Laminaria/Saccharina* sp. (12,411,987 tons, approx. 34.65%), *Undaria* sp. (2,566,316 tons, approx. 7.16%), red seaweeds: *Kappaphycus/Eucheuma* sp. (11,685,174 tons, approx. 32.62%), *Gracilaria* sp. (3,695,231 tons, approx. 10.32%), and *Porphyra* sp. (2,984,573 tons, approx. 8.33%) are the top 5 species of seaweeds that contribute to the 99.84% of the world production of seaweeds both in wild and cultivation (FAO, 2021a). Furthermore, the value of the seaweed farming business might be far higher, particularly if monetary value is assigned to the ecological services supplied by seaweeds (Chopin & Tacon, 2021).

Bioactive components and biological properties of seaweeds

Seaweeds are renowned for their ability to produce a diverse range of biologically active macromolecules. Significant components of seaweeds are pigments, phenolic compounds, lipids, proteins, vitamins, minerals, and carbohydrates (polysaccharides) (Bedoux et al., 2014). Many studies have revealed that algae are the most abundant source of these bioactive chemicals, particularly polysaccharides that can be sulfated and non-sulfated (Jiménez-Escrig et al., 2011; Jesumani et al., 2019; Venugopal, 2019; Hentati et al., 2020; Rengasamy et al., 2020). Sulfated polysaccharides are represented by agars, carrageenans, fucoidans, and galactans, while non-sulfated polysaccharides are represented by alginates and laminaran (Rupérez et al., 2013; Hentati et al., 2020).

Table 4. Vitamin content (mg/100g dw) of seaweed (adapted from Škrovánková (2011) and Martínez–Hernández et al. (2018)).

Seaweeds	Vitamin content						
	E	***C***	***B12***	***B3***	***B2***	***B1***	***A***
Green seaweeds: *Caulerpa lentillifera, C. fragile, U. lactuca, U. pertusa, U.rigida, E. flexousa*	19.70-2	746.4-<0.223	142[a]	1.09-<0.5	0.559-0.02	4-< 0.02	9581-0.01
Brown seaweeds: *Alaria esculenta, F. vesiculosus, H. elongata, L. digitata, L. ochroleuca, S. japonica, S. latissima, U. pinnatifida, S. hemiphylum,*	3.43-1.4	785.1-153.8	99.1-4.4[a]	61.2-1.58	11.7-0.02	5-0.02	0.481-0.04
Red seaweeds: *Chandrus crispus, Gracilaria sp., G. changii, P. palmata, P. umbilicalis, P. yezoensis, K. alvarezii, Porphyra* sp.	13.9-0.267	711.9-107.1	760-122.4[a]	11.0-1.89	1.91-0.36	1.56-0.073	4.8-1.59

Note: [a] µg/kg

Pigments

Seaweeds include three forms of pigments: chlorophyll, carotenoid, and phycobiliproteins, all of which have great potential as ingredients for nutraceutical, as physiologically active agents due to their antiangiogenic, anticancer, antidiabetic, anti-inflammatory, antioxidant, and immunomodulatory characteristics, as well as used as food dyes. Chlorophylls are greenish pigments that are soluble in lipids and are essential for photosynthesis in seaweeds. The most common algal carotenoids include astaxanthin, carotenes, fucoxanthin, lutein, lycopene, neoxanthin, violaxanthin, and zeaxanthin. Carotenoids are tetrapenoid molecules that aid in seaweed photosynthesis. However, among these carotenoids, fucoxanthin, derived from brown seaweed, is the most prevalent, having potential applications in the food business. Finally, phycobiliproteins are pigments soluble in water and occur as proteins. Phycobiliproteins are composed of three different pigments: phycoerythrin is the most prevalent red pigment, allophycocyanin is the light-blue pigment, and phycocyanin is the blue pigment. These three pigments show different forms of protein, different bilin contents, and spectral properties (Table 2) (Aryee et al., 2018; Cherry et al., 2019).

Phenolic Compounds

Seaweed contains catechins, flavonoids, phenolic acids, phlorotannins, tannins, and other phenolic chemicals. Thus, seaweed species have a considerable effect on the kind and quantity of phenolic chemical extraction. Bromophenols, flavonoids, and phenolic acids are abundant in green and red seaweeds. Brown seaweeds have complex polymers mostly of phlorotannins and phloroglucinol oligomers (1,3,5-trihydroxy benzene). Seaweed polyphenols have been linked to many biological activities, including antibacterial, anticancer, antidiabetic, anti-inflammatory, antiobesity, antioxidant, antiproliferative, antitumor, and antiviral effects (Montero et al., 2017; Gómez-Guzmán et al., 2018; Cotas et al., 2021).

Lipids

The majority of seaweeds have low lipid concentrations of up to 5% by weight of the dry weight (DW) sample (Table 3) (Mišurcová et al., 2011). However, there are a number of species with total lipid content greater than 10% dw (Table 3), making them viable candidates for oil-based goods (Gosch et al., 2012). The total lipid content varies according to geographical location, interactions, light intensity, salinity, seasonal change, species, and temperature (Susanto et al., 2019). Seaweed lipids, on the other hand, include large quantities of Polyunsaturated Fatty Acids (PUFAs) such as Linolenic acid, Stearidonic acid, Eicosapentaenoic acid (as n-3 PUFAs), and Arachidonic acid (as n-6 PUFAs). In addition, various bioactive chemicals, including sterols, are found in lipids (Luo et al., 2015; Pérez et al., 2016; Susanto et al., 2019). These sterols, which are mostly represented by cholesterol and clionasterol, are important bioactive substances with fundamental nutritional and biological qualities such as anticancer, antiobesity, antioxidant, antitumor, antiviral, and are effective in the prevention of cardiovascular disorders, The main nutritional components discovered in seaweeds are fucosterol and isofucosterol (Kendel et al., 2015).

Proteins

The concentration of protein in seaweed varies according to species, seasonal cycle, and seasonal fluctuation factors. It is generally higher for red seaweeds (up to 47% of the dry weight), medium for green seaweeds (35% of the dry weight), and lower for brown seaweeds (24% of the dry weight) (Table 3) (Černá, 2011; Fleurence et al., 2018). Because seaweeds include non-protein nitrogen, their protein content has been overstated, and nitrogen-to-protein conversion ratios smaller than 6.25, often employed for feed components, have been recommended (Makkar et al., 2016). Furthermore, seaweeds include essential amino acids, including glycine, alanine, proline, arginine, glutamic acid, and aspartic acid (Gullón et al., 2020). Phycobiliproteins are of particular interest among algal proteins because, by enzymatic breakdown, peptides with established hypertensive action may be produced by blocking the angiotensin I converting Enzyme (Furuta et al., 2016).

Vitamins

Seaweeds are high in fat-soluble vitamins, including vitamin A, vitamin D, vitamin E, and provitamin A, as well as water-soluble vitamins, including vitamin C, folic acid, pantothenic acid, niacin, riboflavin and vitamin B such as vitamin B12, vitamin B6, vitamin B3, vitamin B2, and vitamin B1 (Hentati et al., 2020). However, some of them only in relatively low content (Škrovánková, 2011) because the vitamin content of seaweeds varies depending on the species. Green seaweeds, for example, had vitamin E concentrations ranging from 8.8-12.0 mg/kg, red seaweeds ranging from 10-26 mg/kg, and brown seaweeds ranging from 1.6-122 mg/kg dried weight (Biancarosa et al., 2018). For vitamin C concentrations, green seaweeds have 0.0347-1.25g/100g, red seaweeds have 0.0353-1.61g/100g, and brown seaweeds 0.0345-1.85g/100g dried weight, and as for essential vitamin B3, green seaweeds range from 0.005–1.0g/100g, red seaweeds range from 0.0951-0.10g/100g and brown seaweeds range from 0.612–0.90g/100g dried weight (Hentati et al., 2018). In addition, the contents of Vitamin B12 in seaweeds also vary. For example, green seaweeds are between 0.06 and 0.786 g/100 g; red seaweeds are between 0.0961 and 1.34g/100g, and brown seaweeds range between 0.0164 and 0.0431g/100g dried weight (Table 4) (Hentati et al., 2018; Cherry et al., 2019).

Minerals

Seaweeds also have a significant concentration of minerals (8-40%), including Na, K, Mg, Fe, and others (Table 5) (Cofrades et al., 2017; Lorenzo et al., 2017). Calcium is the most visible mineral, and it is found in the highest concentration in plant sources. They also contain a lower Na/K ratio than other foods often found in Western diets, which is advantageous for maintaining a healthy cardiovascular system (Circuncisão et al., 2018). In addition, seaweeds contain substantial quantities of iodine, and their consumption can aid in treating iodine deficiency (Zava & Zava, 2011).

Polysaccharides (Hydrocolloids)

Phycocolloids, are hydrocolloids (substances that form a viscous solution when mixed with water) derived from seaweeds. In 2019, the total global import and export of seaweeds and seaweed-based hydrocolloids ($1.74 billion) are estimated at $2.9 billion and $2.65 billion, respectively (FAO, 2021b). Numerous polysaccharides are derived from phycocolloids, including major seaweed polysaccharides like alginate, agar, and carrageenan, which are economically valuable for the pharmaceutical and nutraceutical sectors (Gnanavel et al., 2019). Depending on the species, seaweed polysaccharides range from 4% to 76% by dry weight. Brown seaweeds contain alginates, fucoidans, and laminarin; red seaweeds have carrageenans and agarans; green seaweeds include ulvans. These seaweeds polysaccharides are primarily sulfated (such as agars, carrageenans, fucoidans, and galactans) and non-sulfated (such as alginates and laminaran) polysaccharides that are high in dietary fiber. In addition, they may have prebiotic properties that have been related to the antibacterial, anticancer, anticoagulant, antihyperlipidemic, anti-inflammatory, antiobesity, antioxidant, antiviral, gastroprotective, and immunomodulatory effects (Seong et al., 2019; Gullón et al., 2020; Hentati et al., 2020). Important hydrocolloids, such as agar, carrageenan, and alginates, are also called phytochemicals. They are primarily utilized in human and animal foods, dairy products, confectionery, textiles, paper industries, and in certain other countries, as manure. (Pal et al., 2014).

Red seaweeds (Rhodophyta) such as *Gelidiella* or *Pterocladia, Gelidium,* and *Gracilaria* are sources of agar which composed of two polysaccharides, such as agarose (for gelling) and agaropectin (for thickening). However, agarose is accounting for around 70% of the total in the mixture. Agar also contains hydrophilic galactans consist of α(1-4)-3,6-anhydro-L-galactose, and β9(1-3)-D-galactose (Lee et al., 2017) and it is the first hydrocolloid with the European registration number E406. The Food and Drug Administration (FDA) has designated agar as Generally Recognized as Safe (GRAS) for use as a food additive which approximately 80% of are produced globally. The remaining 10–20% were employed in the pharmaceutical and other biotechnology sectors. Agar may be used in a variety of ways depending on its quality. Low-grade agar is used in foods and industrial applications such as adhesives, casting, impression, paper coating, textile printing dyeing, and other applications. In the medical and pharmaceutical fields, medium grade agar is employed as a gel substrate in biological culture media, anticoagulant agents, bulking agents, capsules, laxatives, and tablets. Finally, highly purified agar, a high-grade agar, is utilized in intermolecular biology separation procedures like electrophoresis, gel chromatography, and immunodiffusion (Pal et al., 2014; Abdul Khalil et al., 2018). On the other hand, carrageenan with European registration name E407 is similar to agar that are derived from red seaweeds but mostly from the species of *Kappaphycus alvarezii, E. denticulata, E. spinosum, B. gelatinae, C. crispus, Gigartina* sp.*, and Hypnea* sp., making up as much as half of the dry weight (Abdul Khalil et al., 2018). It is the general name for a group of naturally occurring water-soluble sulfated galactans with alternate backbones of α(1-4)-3,6-anhydro-D-galactose, and β(1-3)-D-galactose (Subaryono, 2018). There are three basic types of Carrageenan that are commercially classified, these includes iota (ι)-carrageenan, kappa (κ)-carrageenan, lambda (λ)-carrageenan, although other types of carrageenan are also reported such as μ-carrageenan, ν-carrageenan (Rhein-Knudsen et al., 2017). Carrageenan is mainly used in different foods as emulsifiers, thickeners, stabilizers, and protective coating on fresh-cut packaged food. However, since red seaweeds have a variety of species and compositions, this makes the carrageenan as one of the most challenging phycocolloids to characterized. (Abdul Khalil et al., 2018).

Table 5. Mineral content of seaweed (adapted from Circuncisão et al. (2018), Martínez–Hernández et al. (2018), Olsson et al. (2020))

Species	Mineral contents										
	Na	*Cl*	*K*	*S*	*Mg*	*Ca*	*P*	*Br*	*Sr*	*I*	*Cr*	*Pb*
Green seaweeds: *Ulva* sp.	10.8[a]	28.5[a]	19.5[a]	50.7[a]	33[a]	9.1[a]	1.1[a]	451.4[a]	101.9[a]	69[a]	-	-
Brown seaweeds: *Laminariia ochroleuca, U. pinnatifida, H. elongata*	40.2-113[a]	91.6-84.3[a]	84.3-3.7[a]	12.6-9.1[a]	7.6-4.1[a]	11.2-10.6[a]	5.4-1.2[a]	847-364[a]	789.1-629.7[a]	5552-96[a]	-	-
Red seaweeds: *Palmaria palmata, C. crispus, Porphyra* sp.	77.5-22.2[a]	91.9-23.7[a]	76.2-31.9[a]	53-5.6[a]	7.5-2.3[a]	22.3-4.3[a]	3.2-1.6[a]	1191-359.3[a]	167.5-43.8[a]	472-76[a]	-	-
Green seaweeds: *Cladophora rupestris, Cladophora* sp., *U. intestinalis, U. lactuca*	73-31[b]	-	85-17[b]	-	26.6-4.4[b]	10.4-5.4[b]	171-0.97[b]	-	-	-	19.4-0.5[a]	4.32-0.11[a]
Brown seaweeds: *Ascophyllum nodosum, C. filum, D. aculeate, F. serratus, F. vesiculosus, H. siliquosa, L. digitata, S. latissima, S. cirrosa*	51-25[b]	-	84-15[b]	-	8.9-4.6[b]	47.9-9.5[b]	2.16-0.67[b]	-	-	-	2.8-0.2[a]	10.0-0.05[a]
Red seaweeds: *Ahnfeltia. plicata, B. byssoides, Ceramium sp., C. crispus, C. purpureum, D. sanguinea, D. carnosa, F. lumbricalis, R. confervoides*	52-25[b]	-	58-22[b]	-	15.1-5.1[b]	82.2-3.2[b]	2.42-1.03[b]	-	-	-	4.0-0.3[a]	7.24-0.08[a]
Green seaweeds: *Ulva* sp.	24.0-11[b]	-	26.0-12[b]	-	38-15[b]	20-3.7[b]	0.5-7[b]	-	-	130-8[a]	-	-
Brown seaweeds: *Ascophyllum nodosum, A. esculenta, F. spiralis, F. vesiculosus, H. elongata, Laminaria* sp., *S. latissima, U. pinnatifida*	71-6[b]	-	120-8[b]	-	12.0-2[b]	31.0-1[b]	4-0.5[b]	-	-	9014-17[a]	-	-
Red seaweeds: *Chondrus crispus, Gracilaria sp., P. calcareum, P. palmata, Porphyra sp.*	44-3[b]	-	96-1[b]	-	9.0-1[b]	303-0.4[b]	6-0.6[b]	-	-	260-34[a]	-	-

Table 5 continued

Species	Mineral contents										
	Si	*Fe*	*Al*	*Mn*	*Zr*	*Ti*	*Cu*	*Zn*	*Ni*	*As*	*Cd*	*Co*
Green seaweeds: *Ulva* sp.	1390[a]	273.5[a]	407[a]	17[a]	57.5[a]	18[a]	10[a]	60.2[a]	-	-	-	-
Brown seaweeds: *Laminariia ochroleuca, U. pinnatifida, H. elongata*	930.5-180[a]	229-87[a]	375-59[a]	73-20[a]	36-32[a]	228-24[a]	18.5-10.5[a]	243-42.4[a]	-	-	-	-
Red seaweeds: *Palmaria palmata, C. crispus, Porphyra* sp.	1120-546.5[a]	205.5-123.5[a]	360-178.5[a]	33.5-26[a]	45.5-40[a]	29.5[a]	15.5-14[a]	53.9-22.6[a]	-	-	-	-
Green seaweeds: *Cladophora rupestris, Cladophora* sp., *U. intestinalis, U. lactuca*	1.93-0.31[a]	452-89[a]	499-64[a]	418-19[a]	-	-	97-4.6[a]	22.0-6.0[a]	7.0-1.5[a]	117-3.7[a]	0.73-0.06[a]	1.44-0.09[a]
Brown seaweeds: *Ascophyllum nodosum, C. filum, D. aculeate, F. serratus, F. vesiculosus, H. siliquosa, L. digitata, S. latissima, S. cirrosa*	4.42-<0.1[a]	910-24[a]	1130-4[a]	237-3[a]	-	-	16.4-1.1[a]	68-14[a]	18.3-0.5[a]	58.9-19.6[a]	1.46-0.06[a]	1.63-0.08[a]
Red seaweeds: *Ahnfeltia. plicata, B. byssoides, Ceramium sp., C. crispus, C. purpureum, D. sanguinea, D. carnosa, F. lumbricalis, R. confervoides*	5.77-<0.1[a]	1710-59.3[a]	2060-10[a]	1820-18[a]	-	-	13.4-3.0[a]	254-20[a]	11-3.2[a]	35.8-6.2[a]	7.76-0.12[a]	4.91-0.20[a]
Green seaweeds: *Ulva* sp.	-	6000-139[a]	-	637-13[a]	-	-	33-2[a]	64-4[a]	-	-	-	1.4-0.2[a]
Brown seaweeds: *Ascophyllum nodosum A. esculenta, F. spiralis, F. vesiculosus, H. elongata, Laminaria* sp., *S. latissima, U. pinnatifida*	-	1854-4[a]	-	547-1[a]	-	-	80-0.3[a]	740-2[a]	-	-	-	5-0.01[a]
Red seaweeds: *Chondrus crispus, Gracilaria sp., P. calcareum, P. palmata, Porphyra sp.*	-	2110-35[a]	-	653-2[a]	-	-	35-1[a]	95-5[a]	-	-	-	7-0.03[a]

Note: [a] μg/kg, [b] g/kg

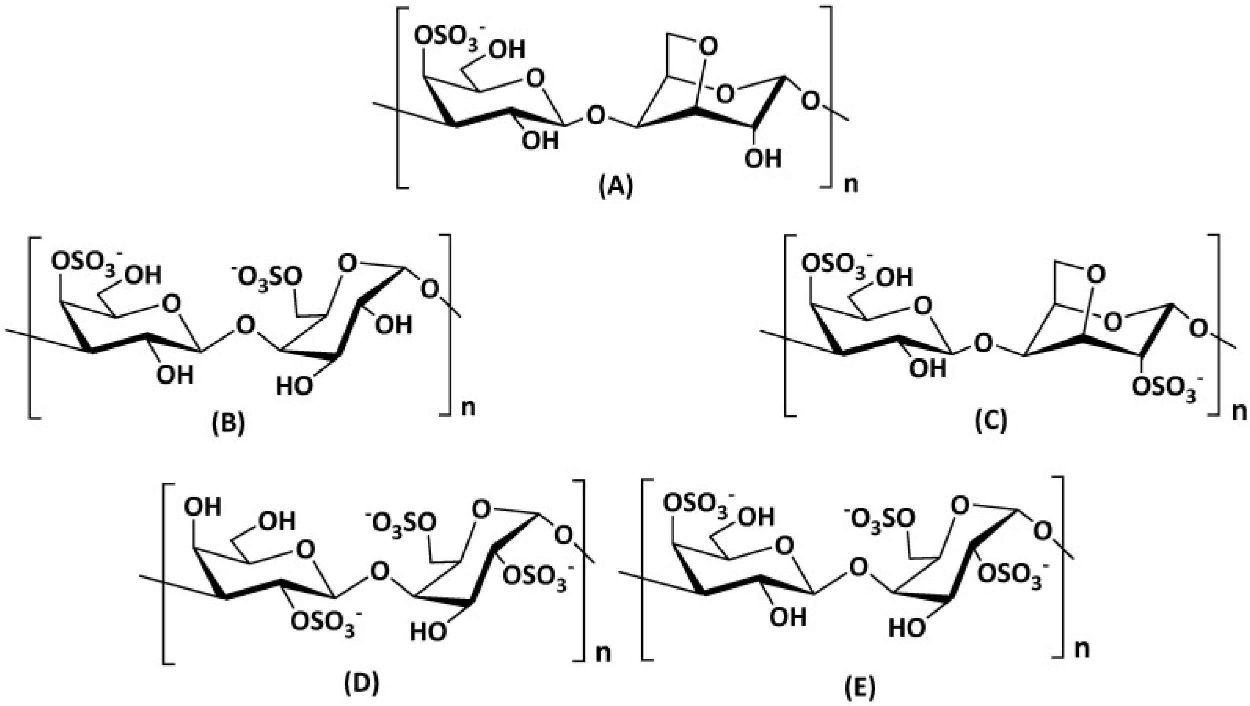

Figure 3. Structure of different types of carrageenans. (A) κ-carrageenan, (B) μ-carrageenan, (C) ι-carrageenan, (D) λ-carrageenan and (E) ν-carrageenan (adapted from Nešić et al., 2019)

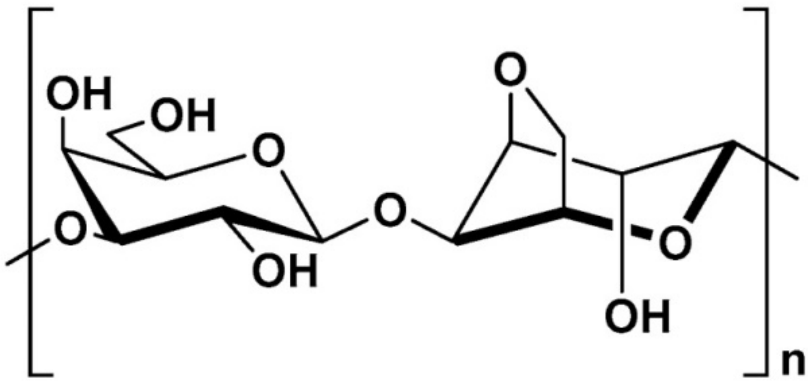

Figure 4. Structure of agar (adapted from Nešić et al., 2019)

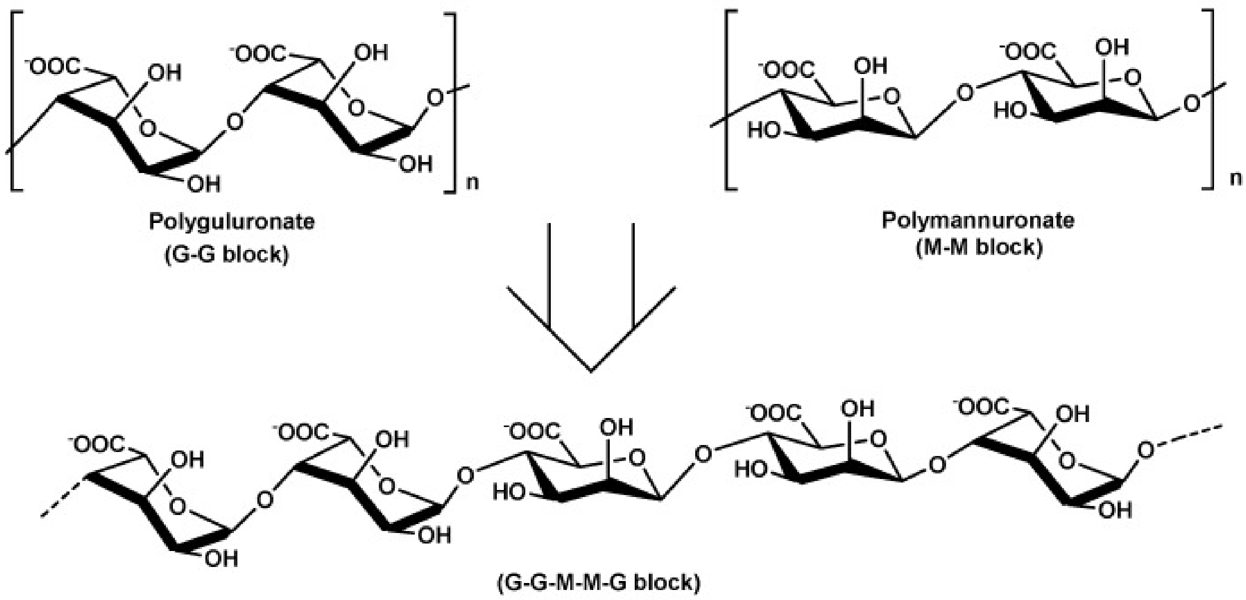

Figure 5. Structure of alginate (glycosidic bond conformations of β-d-mannuronic acid and α-l-guluronic acid) (adapted from Nešić et al., 2019)

Alginates, with a European registration number of E401 to E405 are derived from brown seaweeds such as A*scophyllum nodosum, E. maxima, L. digitata, L. hyperborean, L. japonica, L. nigrescens, M. pyrifera, Sargassum* sp. and other brown seaweeds. Alginates are copolymers of α(1–4) linked α-L-galactouronic and β-D-mannouronic acids (Ramnani et al., 2012; Abdul Khalil et al., 2018). It is mainly utilized in the food and pharmaceutical industries due to binding metal ions and generating viscous solutions. It is used as gelling agents and also as sizing agent for cotton yarn in the textile sectors. Alginate comes in two types: acid and salt. The asalginic acid is the acid type, it is a linear polyuronic acid, whereas the salt type is an important component in the cell wall of brown seaweeds, accounting from 40 to 47% of the algal biomass by dry weight (Pal et al., 2014; Abdul Khalil et al., 2018).

Potential risk factors of seaweeds

Seaweeds, well-known for their health advantages and high concentrations of essential components, might represent a health danger by absorbing high quantities of heavy metals and Iodine from the environment (Filippini et al., 2021).

Exposure to Heavy metals

There are approximately 145 species of seaweeds that are consumed globally in amounts as high as 97,000 tons annually in some countries such as Japan (Cheney, 2016). *Porphyra* sp. is one of the famous edible seaweed in Southeast Asia and around the world. In Japan, it is known as “nori” and is eaten as nori sheets with the Japanese delicacy “sushi.” It is also known as “kim” in Korea, “zicai” in China, “purple laver” in the Britain and Ireland, “karengo” in New Zealand, and “Laver” in the United States, United Kingdom, and Canada (Baweja et al., 2016). According to Rubio et al. (2017), red seaweeds, particularly the *Porphyra* species, have more trace and dangerous elements. As a result, the average cadmium (Cd) level in conventional farming is two points higher (0.28 mg/kg) than in organic cultivation (0.13 mg/kg). Furthermore, 4g per day of seaweeds intake helps increase the dietary intake of metals like magnesium (Mg) and chromium (Cr). In addition, the average aluminum (Al), cadmium (Cd) and lead (Pb) daily intakes were 0.064, 0.001, and 0.0003 mg/day, respectively. According to the research, exposure to these toxic metals (Al, Cd, and Pb) did not pose serious health risks. But, other hazardous metals should also be monitored as per recommendation of the author (Rubio et al., 2017).

Exposure to Arsenic

Another critical health concern connected with seaweed is arsenic. Arsenic species can be harmful (inorganic arsenic, a carcinogen of class I), innocuous (arsenobetaine), or potentially dangerous (fat-soluble arsenic, arsenosugars, and other organoarsenic). The International Agency for Research on Cancer has identified inorganic arsenic as a human carcinogen capable of causing bladder, skin, and lung cancer. Arsenic use has also been related to an increased risk of heart diseases and diabetes (Murai et al., 2021). Arsenic is naturally accumulated in seaweeds, particularly Hijiki, an edible brown seaweed (Flora, 2015) that is harvested and consumed in Japan. It is sun dried, boiled, then dried again until it is completely black. It is frequently used as a topping for cooked rice or as a breakfast condiment. However, because of the high levels of arsenic, people were warned not to consumed too much of it (Mouritsen et al., 2018). This wet Hijiki has 0.22 mg of inorganic arsenic per serving (20g), accounting for 80% of the arsenic content (Yokoi & Konomi, 2012) that exceeds the World Health Organization’s recommended daily intake standards. However, there are no evidence of the health consequences of arsenic poisoning induced by the inorganic arsenic from Hijiki has been shown. It has been claimed that adverse effects on people’s health are rare unless they consume vast amounts of Hijiki (Murai et al., 2021).

High Iodine Concentrations

Excessive iodine content is another potential concern of seaweeds (Bouga & Combet, 2015). Seaweed absorbs iodine from seawater and is hence an excellent source of iodine in the diet. Eating enough seaweeds may help to eliminate iodine deficiency. Too much iodine, on the other hand, is hazardous to one’s health (Yeh et al., 2014). Kombu (*S. japonica*), wakame (*U. pinnatifida*), and nori (*Porphyra* sp.) are edible seaweeds that are commonly consumed in Asia and have a high concentration of iodine. According to Yeh et al. (2014), the highest average iodine content is found in kelp (*S. japonica*), commonly known as Kombu in Japan, with 2523.5 mg/kg, followed by wakame (139.7 mg/kg) and nori (36.9 mg/kg). Kombu is a popular food and dietary supplement, notably in Japan. However, research suggests that kombu contains a high iodine concentration, implying that consuming too much kelp/kombu supplements on a daily basis for an extended period of time may represent a risk to consumers, such as thyroid dysfunction or hyperthyroidism (Dasgupta & Wahed, 2014). Iodine levels in seaweed can be extremely high and even hazardous. Surprisingly, Japanese people's high iodine consumption is regarded as one of the reasons they are among the healthiest people on the planet. In Japan, however, the average daily consumption of Iodine is estimated to be 1,000–3,000 μg (667–2,000% of the RDI). This poses a concern to people who consume seaweed daily, as the tolerable upper limit (TUL) for adults is 600 g/d (EFSA) and 1100 g/d (World Health Organization) (Zava & Zava, 2011; Cherry et al., 2019).

Furthermore, several studies have found a link between excessive iodine intake and illnesses such as hypo- and hyperthyroidism, goiter, and thyroiditis, whereas, iodine deficiency causes hypothyroidism (Combet et al., 2014; Desideri et al., 2016; Aakre et al., 2020). Many of the symptoms of hyperthyroidism may differ from different individual person. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), common hyperthyroidism symptoms include fatigue or muscle weakness, diarrhea, hand tremors, heat intolerance, mood swings, nervousness or irritability, rapid and irregular heartbeat, sleeping difficulties, weight loss, and goiter (an enlarged thyroid that causes the neck to appear bloated and can obstruct regular breathing and swallowing) (NIDDK, 2016). However, the epidemiological research describing the risks and benefits of consuming iodine from seaweeds is inconclusive (Cherry et al., 2019).

Uses of Seaweeds

As previously indicated, seaweeds have a high concentration of bioactive compounds. Previously, seaweed was mainly used as a vegetable and consumed as raw. It is also an excellent source of gelling and thickening ingredients in food for humans and animals (Hentati et al., 2020). A new study has shown its potential for alternative medicine in recent years. Antibacterial (Moubayed et al., 2017), anticancer (Haq et al., 2019), anticoagulant (Liu et al., 2018), antidiabetic (Gunathilaka et al., 2020), antiestrogenic (Teas et al., 2013), antifungal (De Corato et al., 2017), antihyperlipidemic (Yim et al., 2019), antimycotic (Saito & Lal, 2019), antihypertensive (Seca & Pinto, 2018), anti-inflammatory (Saraswati et al., 2019), antiobesity (Sun et al., 2018), antioxidant (Hermund, 2018), antiviral (Gheda et al., 2016), immunomodulatory (Palstra et al., 2018), neuroprotective (Silva et al., 2018), tissue healing (Premarathna et al., 2019b) and thyroid-stimulating properties have been demonstrated in red, brown, and green seaweeds (Khalid et al., 2018). Furthermore, seaweeds are used in the cosmetic and pharmaceutical industries (Hentati et al., 2020). They are now a possible energy source as biofuels (Del Río et al., 2020) and important as biobased goods (Nakhate & van der Meer, 2021) and biopolymers (Jumaidin et al., 2018). In addition, Seaweeds are also employed in aquaculture as probiotics (Vatsos & Rebours, 2015; Nazarudin et al., 2020) animal feed additive (Makkar et al., 2016; Morais et al., 2020), water purifier (Arumugam et al., 2018), bio-elicitors (Agarwal et al., 2021), plant fertilizer (Ruban & Govindasamy, 2018), biostimulants (Pereira & Cotas, 2019) and as seaweed-based liquid oganic fertilizer to other seaweed such as to stimulate the growth and quality of *G. verrucosa* (Nasmia et al., 2020).

Extraction of Seaweeds

To extract novel metabolites from seaweed without causing degradation, modern techniques such as Enzyme Assisted Extraction (EAE), Microwave Assisted Extraction (MAE), Ultrasound-Assisted Extraction (UAE), Supercritical Fluid Extraction (SFE), and Pressure Solvent Extraction (PSE) have been employed (Table 6) due to its advantages over the traditional techniques. However, to generate extracts containing the necessary bioactive components, the process parameters of each technique must be modified (Cikoš et al., 2018).

Table 6 shows the seaweed extraction process (common bioactive compounds extracted, advantages and limitations of green extraction method). Table 6 also shows the differences, advantages and limitations of the modern (green) techniques. EAE has advantages for industrial applications since it can be scaled up, it has a high catalytic efficiency and specificity, and it is a safe method of extraction because the enzymes utilized are food grade level. However, the full benefits of this extraction process can only be realized if the limitations such as expensive cost, lengthy extraction time that can range from hours to days, lack of substrate specific enzyme availability, and enzymatic hydrolysis efficacy are overcome. UAE on the other hand, is an extraction approach that has been employed in the industrial extraction of bioactive chemicals from many natural resources, and it has recently been shown that it can also be used in the extraction of new metabolites from seaweeds. For SFE, this approach is quite expensive for the extraction due to the high pressure equipment requirements, but it can also be utilized for the extraction of new metabolites from seaweeds. In fact, it is a very promising method of extraction because it produces extracts with great purity and no residues. MAE and PLE, on the other hand, are quite risky because they require high

Table 6. Seaweed extraction process (adapted from Admassu et al. (2018), Kadam et al. (2015), Praveen et al. (2019))

Extraction Method	Procedure	Bioactive Components	Advantages	Limits
Enzyme-Assisted Extraction (EAE)	*Incorporating food-grade enzymes such as *cellulase, a-amylase, pepsin, viscozyme, cellucast, termamyl, ultraflo, carrageenase, agarase, xylanase, kojizyme, neutrase, alcalase, and umamizyme* into seaweeds. * Degradation of glycosidic bonds and other internal bonds	*Fucoxanthin *Lipids *Phlorotannins *Phenolic compounds	*Time efficiency *High catalytic efficiency & specificity *Enzymes employed are eco-friendly, non-toxic, and food grade level *High yield *High possibility for industrial scale-up	*Slow extraction procedure (takes hours to days) *Enzymatic hydrolysis effectiveness is very low if the material's moisture content is very low *Limited owing to its costly price
Microwave-Assisted Extraction (MAE)	*Most researched extraction technique. *Microwave energy was used to heat solvent-containing samples. *Dielectric and total volumetric heating by microwaves. *2.45 GHz	*Sulfated polysaccharides, such as fucoidan, ulvan, and rhamnan sulfate.	*Short treatment time *Can utilize organic solvents and water *Ideal for thermally labile chemicals *Better than traditional and Soxhlet methods	*The only solvent that can be used is one with a high dielectric constant, and a low dissipation factor *High capital cost *Potential explosion danger, especially with MAE closed vessels
Ultrasound-Assisted Extraction (UAE)	*Ultrasonic radiation pressure was used to generate intense mixing and agitation, which promotes Extraction. *Compression and rarefaction (pressure variation and cavitation) *20 kHz *50-60 kHz	*Polyphenols * Fucose and uronic acid * Laminarin *Phycobiliary proteins *Taurine *Antioxidants	*Short treatment time *Less solvent usage *High extraction yields *Low cost	*Extraction efficiency varies according to plant matrix *Solvents with low surface tension, viscosity, and vapor pressure are preferred *Excessive sonication may degrade extract quality
Supercritical Fluid Extraction (SFE) Pressurized	*The supercritical fluid's temperature and pressure are both greater than the critical point.	*Fatty acids (ω-3) *Carotenoids, * Fucoxanthin, *Fluorotannins * Volatile compounds *Polyphenols, *Cytokinins, * Auxins, Microelements, and macro elements	*Technology for green Extraction *Extracts with excellent purities and no residues *Extracts made without the use of solvents *Extraction of thermolabile compounds requires a short extraction period.	*Expensive high-pressure equipment is required. *Polar chemicals may be difficult to remove. *Processing costs and energy usage are both high.
Pressurized Solvent Extraction (PSE)/ Pressurized Liquid Extraction (PLE) Reaction	*To extract analytes, a relative amount of solvent (toluene, hexane, or acetone) was used at high temperatures and pressure.	*Polyphenols *Fluorotannins *Neo antioxidants, *Amino acids *Polysaccharides *Fucoidan *Total organic carbon *Minerals	*Green extraction method (water can be used as solvents) *Extraction efficiency is high, using fewer solvents. *Extraction time is limited.	*The cost of the required high-pressure equipment is too expensive. *High-temperature extraction may cause thermolabile compounds to degrade.

Table 7. Extraction method of different species of seaweeds

Extraction Method	Species	References
Enzyme-Assisted Extraction (EAE)	*Macrocystis pyrifera, C. chamissoi, S. boveanum, S. anguistifolium, F. irregularis, P. palmata, C. crispus, C. fragile, S. muticum, O. pinnatifida, C. tomentosum, U. armoricana, S. ilicifolium, S. polycystum*	Kulshreshtha et al., 2015; Rodrigues et al., 2015; Hardouin et al., 2016; Naseri et al., 2020; Vásquez et al., 2019; Sabeena et al., 2020
Microwave-Assisted Extraction (MAE)	*Gelidiella. acerosa, U. pinnatifida, S. fusiformis, L. japonica, F. vesiculosus, G. vermiculophylla, G. racemosa, E. prolifera, F. virsoides, C. barbata, E. radiata*	Rodriguez-Jasso et al., 2011; Michalak et al., 2015; Charoensiddhi et al., 2015; Singh et al., 2017; Dobrinčić et al., 2021
Ultrasound-Assisted Extraction (UAE)	*Ascophyllum nodosum, S. muticum, O. pinnatifida, C. tomentosum, S.binderi , T. ornate, K. alvarezii, E. denticulatum, S. mcclurei, G. turuturu*	Cecile et al., 2015; Kadam et al., 2015; Rodrigues et al., 2015; Youssouf et al., 2017; Thao My et al., 2020
Supercritical Fluid Extraction (SFE)	*Ulva flexuosa, D. membranacea D. lingulatus, S. hemiphyllum, L. vadosa, S. muticum, U. pinnatifida, G. tenax, Z. marina, P. oceana, C. glomerata, U. clathrata, P. fucoides, G. mammillaris*	Zheng et al., 2012; Quitain et al., 2013; Pérez-López et al., 2014; Becerra et al., 2015; Michalak et al., 2016; Machmudah et al., 2018; Sevimli-Gur & Yesil-Celiktas, 2019
Pressurized Solvent Extraction (PSE)	*Ulva intestinalis, U. lactuca, F. vesiculosus, D. dichotoma, C. baccata, H. elongate, S. japonica, S. muticum*	Sánchez-Camargo et al., 2017; Otero et al., 2018

temperatures. Thermolabile chemicals may deteriorate as a result of high-temperature extraction (Kadam et al., 2015; Admassu et al., 2018; Cikoš et al., 2018; Praveen et al., 2019). Table 7 shows the different species of seaweeds that has been extracted using these novel green methods of extraction.

Purification of seaweed extracts

Given that every biological matrix, including seaweeds, is a complicated combination of different macromolecules and micromolecules, it is critical to eliminate all extra materials while retaining those containing the biomolecules of interest. As a result, it is vital to use analytical methods to characterize these bioactive chemicals. This is usually achieved by first preparing the sample and then extracting it by various methods using the required solvents and within each phase of the procedure, the necessary number of substeps is determined by the matrix's complexity and the type of target biomolecule under investigation. Finally, the extracted bioactive chemicals are subjected to various types of chromatography as well as identification procedures such as mass spectrometry (Misra et al., 2015; Batool & Menaa, 2020).

Conclusion

Seaweeds, are regarded as an economically important biological resource because they contain a diverse range of bioactive compounds, such as different pigments, phenolic compounds, lipids, vitamins, proteins, minerals, polysaccharides, polyunsaturated fatty acids, and other essential bioactive compounds with a wide range of biological functions. Seaweeds are commercially sold as fresh and extracts, mainly in the food industry, pharmaceutical industry, cosmetics industry, and many other industries. Although seaweeds are generally healthy and safe, they may still pose significant risks, notably high iodine concentration, heavy metals, and arsenic exposure. However, there is still a lacked of information on this manner because the epidemiological study is still inconclusive. Furthermore, various green extraction techniques were employed to isolate bioactive components, then purified using chromatographic analysis to confirm the extract's purity.

Compliance With Ethical Standards

Authors' Contributions

The study was conceptualized by MQA and SY, and MQA wrote the original draft of the article. SY then edited the manuscript for additional corrections. Finally, the authors reviewed and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical Approval

For this type of study, formal consent is not required.

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