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Chapter

Major Natural Vegetation in Coastal and Marine Wetlands: Edible Seaweeds

Ilknur Babahan, Birsen Kirim and Hamideh Mehr

Abstract

For thousands of years, seaweeds grown in coastal and marine have been used as food, materials and medicines by the people. Edible seaweeds directly consumed, especially in Asian, are used for preparing food due to the their components containing minerals, essential trace elements, and various natural compounds. At the last decades, they have been getting more and more attention in food and pharmaceutical industries because of their biological activities such as anti-cancer, anti-obesity, anti-diabetes, anti-microbial, and anti-oxidant activity. Therefore, in the present study, we have worked on to understand the structure of edible seaweeds. It is worthy to mention that they can be considered as source of some proteins, polyunsaturated fatty acids, minerals, vitamins, dietary fibers, antioxidants, and phytochemicals.

Keywords: edible seaweeds, polysaccharides, anti-cancer, anti-obesity, anti-diabetes, anti-oxidant, anti-microbial

1. Introduction

Macroalgae or called seaweeds are multicellular, marine species and are considered as non-vascular plants. Although term seaweed is widely used but these species are characteristically far from "weeds" but the fact is, seaweeds are the main productive species in the oceans and food chain basis. Seaweeds are used directly or indirectly in food and household products without being tasted or smelled. They are vastly used in food industry due to their valuable elements, vitamin, and proteins [1]. Sea or brackish water is the main habitat for seaweeds (macroalgae), and are referred as benthic marine algae or sea vegetables due their choice of habitat in the sea [2-4]. These simple unique organisms are one of the major productions of Asian industries, and main goal for these industries is to use the production to the maximum extent [2, 5]. Since seaweeds are main part of the diet in east Asia and to some extent being used as snacks and delicacies in other countries. Although seaweeds are as part of food in Far East countries, western countries use them as sources of phycocolloids, thickening and gelling agents for various industrial applications including food. Different applications are due to various chemical composition of seaweeds with habitats, maturity, salinity, environmental habitat, and temperature [2, 6].

Seaweeds are produced more than million tons per year, while microalgae are being produced almost 20,000 tons annually. This has to be mentioned the

macroalgae have higher biomass sells in comparison with seaweeds. Seaweeds are mostly cultivated in near shores in China, Philippines and Japan [7, 8]. The total aquatic production in 2004 passed 15.36 million tons while 93% of the contribution belonged to seaweeds. Among this, 6000 species of seaweeds are harvested which fall into three categories as, green (Chlorophytes), brown (Phaeophytes) and red (Rhodophytes). Regarding the abundancy, the human consumption is mainly on brown algae (66.5%), red algae (33%), and green algae (5%) in Asia [2, 9]. The main producers in Asia are focusing on specific algae such as, in China, Japan and Korea are Nori (Porphyra, red algae), Konbu (Laminaria, brown algae) and Wakame (Undaria, brown algae). Among 6000 species discovered about 150 species are known as food source and 100 for phycocolloid production. The total revenue for edible algae passed 1 billion US dollars only in Japan and this estimation is the value of 1.4 kg seaweed per person consumption.

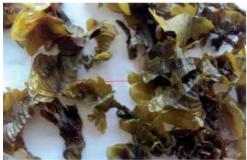
Marine algae, in addition of being used in food, dairy, pharmaceutical, cosmetic and medicine industries, they can also be used in biodiesel, bioethanol, and hydrogen gases preparation. They can also be applied as antioxidant, antibiotics, and virostatic agents [10, 11] application of algae in food industry either for human or animal consumption has brought some negative perspectives due to some toxic elements such as cadmium or fucotoxins. The amount of toxin in algae is related to the contents of fiber and bioactive compounds present. This has direct impact on digestibility and application in food industry. Digestibility has connections mainly with the nitrogen consumption before and after digestion by using specific enzymes called pepsin [10, 12].

1.1 Marine seaweeds

Three main categories of marine seaweeds are Chlorophyta (green algae), Rhodophyta (red algae) and Phaeophyta (brown algae) [13]. Each class is explained in different section in this review.

1.1.1 Brown seaweeds

Brown algae also known as phaeophyta are the seaweeds mainly grow in cold waters at Northern Hemisphere. Marine is their main habitat and it plays a great role in their properties. Macrocystic is a kelp which grows underwater forests and may extend 60 m (200 ft) in length and has high level of biodiversity [14, 15]. Sargassum, another brown algae is an example of singular floating mats of seaweed in tropical waters. Many other brown algae grow along rocky shores and they have been used as food by humans since 2000 years [14].



Padina boerengsnii



Dictyota ciliolata

Figure 1. Some example of brown seaweeds [13].

Brown algae is a great source of iodine and is the most commonly used alginates. They have thickening property, which is greatly used in food products such as salad dressings, in oil industry for oil-drilling muds and in coatings. The color of brown algae is from green and yellow pigments coming from xanthophyll and chlorophyll, respectively. The ranges of colors in brown algae species are due to the variable blending of these two pigments [13, 16, 17]. Some example of brown seaweeds are shown in **Figure 1**.

1.1.2 Red seaweeds

Red algae are also classified as phylum Rhodophyta. They are the most abundant and commercial value of sea algae. The term Rhodophyta refers to the algae group with red pigments due to phycoerythrin and phycocyanin. These pigments mask chlorophyll a, which do not contain chlorophyll b, β -carotene and a number of unique xanthophylls [13, 18].

Red algae are found on rocky shores. Some species are much deeper than brown or green algae. It is known that there are 550 species of red seaweed in the world and so they are the largest seaweed group [13, 17]. Two of them are shown in **Figure 2**. For example, a total of 128 varieties of red algae had been recorded in Red Sea so far [13, 16]. The main reserves in red seaweeds are typically floridean starch, and floridoside. The walls of these algae are made of cellulose and agar and carrageenans, both of which are long chained polysaccharides. Cellulose, agar and carrageenans are widely used commercially and have a large number of uses. Some red algae cells are different because, they are not good enough in amoeboidly, but none of the algae contain flagella, so none can swim quickly [13, 17].

1.1.3 Green seaweeds

The green algae are classified in the phylum Chlorophyta and are usually grown in the intertidal zone which has the high and low water marks, and in shallow water where there is plenty of sunlight. Due to the similarity of pigments, it is thought that they are the most closely related algae. Many types of green algae found on the surface of the ocean or near rocky surfaces. Some species of green seaweeds, *Halimeda macroloba*, *Ulva lactuca*, *Enteromorpha clathrata* and *Caulerpa trifara* are shown in **Figure 3** [13]. Approximately 140 species were recorded on the shores of the world. On the coast of Eritrea, there are about 50 species in the Red Sea.

Sea lettuce is one of the most widely known species. Green algae with bright green leaves up to 30 cm are called sea lettuce (*Ulva lactuca*). Green algae are deeply bound to the lower layers and are not usually cast by waves on the beach. Sometimes exceptionally, some green algae can tear through their substrate during storms and with heavy wave motion.

1.2 Edible seaweeds

Seaweed as a fundamental diet matter are known in Asia since prehistoric times. Some 21 species are used in daily cuisine in Japan and even six of them have been used since the eighth century. Kaiso, one of the edible seaweeds, accounted for 10% of the Japanese cuisine until recently. Using seaweeds in the kitchens extend an average of 3.5 kg per household in 1973, an increase of 20% over 10 years [19–22]. The 12 largest countries, using seaweeds in the kitchens in the world, are China, France, UK, Japan, Chile, Philippines, Korea, Indonesia, Norway, USA, Canada and Ireland. The seaweed production and the health of the sea algae is growing



Figure 3.

Some species of green seaweeds [13].

increasingly important, the world seaweed production in 2000, including wild and softened, has reached about 10 million tons [21, 22].

As it was mentioned above, seaweeds are categorized into three classes of Rhodophyta (red), Phaeophyta (brown) and Chlorophyta (green) marine macroalgae. Some reported common edible Brown algae (Phaeophycae) are divided as Kelp, Fucales and Ectocarpales, given in **Table 1** [23]. Common edible Red algae (Rhodophyta) are Carola (*Callophyllis* spp.), Carrageen moss (*Mastocarpus stellatus*), Dulse (*Palmaria palmata*), *Eucheuma (Eucheuma spinosum* and *Eucheuma cottonii*), Gelidiella (*Gelidiella acerosa*), Ogonori (*Gracilaria*), Grapestone *Mastocarpus papillatus*, *Hypnea*, Irish moss (*Chondrus crispus*), Laverbread (*Porphyra laciniata/Porphyra umbilicalis*), Gim (*Pyropia*, *Porphyra*) and Nori (*Porphyra*) [23]. Common edible Green algaes are Chlorella (*Chlorella* sp.), Gutweed (*Ulva intestinalis*), Sea grapes or green caviar (*Caulerpa lentillifera*), Sea lettuce (*Ulva* spp.) [23].

1.2.1 Biological activity of edible seaweeds

There two categories of algae as macro-algae (macroscopic) and micro-algae (microscopic) [10, 24]. Although algeas are great source and producers of vitamins,

Kelps	Fucales	Ectocarpales
Arame (<i>Eisenia bicyclis</i>)	Bladderwrack (Fucus vesiculosus)	Mozuku (Cladosiphon okamuranus)
Badderlocks (Alaria esculenta)	Channelled wrack (<i>Pelvetia</i> canaliculata)	
Cochayuyo (Durvillaea antarctica)	Hijiki or Hiziki (<i>Sargassum</i> fusiforme)	
Ecklonia cava	Limu Kala (Sargassum echinocarpum)	
Kombu (Saccharina japonica)	Sargassum	$\left[\begin{array}{c} \\ \end{array} \right] \left[\end{array} \right] \left[\begin{array}{c} \\ \end{array} \\ \end{array} \left[\end{array} \right] \left[\begin{array}{c} \\ \end{array} \right] \left[\end{array} \\ \\ \end{array} \left[\begin{array}{c} \\ \end{array} \right] \left[\end{array} \\ \\ \end{array} \left[\end{array} \right] \left[\end{array} \\ \\ \\ \end{array} \left[\end{array} \left[\end{array} \right] \left[\end{array} \\ \\ \\ \end{array} \left[\end{array} \left[\end{array} \\ \\ \end{array} \left[\end{array} \\ \\ \\ \end{array} \left[\end{array} \left[$
Oarweed (Laminaria digitata)	Spiral wrack (Fucus spiralis)	
Sea palm (<i>Postelsia</i> palmaeformis)	Thongweed (Himanthalia elongata)	
Sea whip (Nereocystis luetkeana)		
Sugar kelp (Saccharina latissima)		
Wakame (Undaria pinnatifida)		
Hiromi (Undaria undarioides)		

Table 1.

The list of the common edible Brown algae types (Kelps, Fucales and Ectocarpales).

minerals and proteins and fatty acids but not great efforts have been allocated on the research of these plant like organisms [10, 25, 26]. Seaweeds are considered as source of soluble dietary fibers, proteins, minerals, vitamins, antioxidants, phytochemicals, and polyunsaturated fatty acids, with low caloric value. These nutrient factors are directly influenced by external environmental factors such as geographic location, temperature and season [27, 28]. Although their main application is gelling agent, thickened and stabilizers in food industries but currently studies are focused on medicinal usage and their anticancer, diabetes, inflammation, obesity and other ailments treatments [27].

Edible seaweeds are fundamental part of the cuisine for people living by the seas in areas such as Asia, Hawaii, South America and Africa, as well as marine products obtained from the sea, which are the source of protein from the sea, and in recent years a focus of interest in Europe and America due to the increasing interest in healthy nutrition. Edible seaweeds are a very good source of vitamins such as A, B₁, B₂, B₆, B₁₂, niacin and C and also rich in iodine, potassium, iron, magnesium and calcium. They are nutritious as a component in food [4, 13, 21, 22, 29–32].

In addition to being source of food, seaweeds have antibacterial, antiviral and antifungal properties [2, 33]. In ancient researches, there are tracks of seaweed applications specially in 2500 years old Chinese literature [34, 35]. For instance, Japanese were using seaweed as one of the main ingredients in recipe for Nori in addition to raw fish and sticky rice. It is also well known in Europe and North America that seaweeds have therapeutic powers in treatment of tuberculosis, arthritis, colds and influenza. Very early discovery in 1990s, marine bacteria, invertebrates and algae were used in bioactive compounds [34, 36]. Major milestone in pharmaceutical industries during 1980–1995 was research on seaweed [34, 37]. The discoveries showed that many types of seaweed have anti-inflammatory and anti-microbial agents. These agents are able to be used in treatment of wounds, burns and rashes and some evidences have suggested the algae have been used in treatment of breast cancer in ancient Egypt [38, 39]. Seaweeds are known to contain strong natural anti-oxidants, since algae contain a lot of secondary metabolites such as tocopherol, carotenoids, polyphenols, flavonoids, tannins, lignans, and mycosporine-like amino acids (MAA), vitamin C, and glutathione [40].

The studies have shown that seaweeds possess anticancer agents and there are hopes they can be effective in treatment of tumors and leukemia [34]. As the efforts have continued, scientists successfully isolated chemical compounds from brown seaweed with anticancer and antitumor activities [38, 39]. It has been reported that fucoidan from *U. pinnatifida* shows very good anti-cancer activity against human lung cancer cell line which is known A549 cell line [41].

Some studies in last decades show that fucoxanthin and fucoxanthinol from *U. pinnatifida* shows also anti-obesity activity. As obesity is known a serious health issue and has cost significant economic problem, that edible seaweeds possess anti-obesity activity, is very notable because; it is well known that obesity cost to some chronic diseases, such as liver steatosis, cardiovascular disease, osteoarthritis, type 2 diabetes, and some types of cancer. Alongside having anti-obesity activity, some reports show that fucoxanthin and fucoxanthinol from *U. pinnatifida* possesses anti-diabetic activity [41]. Therefore, it can be considered that anti-obesitity activity and anti-diabetic activity are related each other. It is expected that if seaweeds have anti-obesity activity, they can able to show anti-diabetic activity.

2. Chemical components of edible seaweeds

2.1 Polysaccharides

Polysaccharides are the main components of green, brown and red seaweed. Algae cell walls contain numerous polysaccharides such as, alginates, alginic acid, carrageenans, agar, laminarans, fucoidans, ulvans and derivatives with storage and structural functions (Perez et al., 2016; [42, 43]). As it is shown in **Figure 4** [44], agar polysaccharides have complex molecular structure with alternating composition of 3-linked-D-galacropyranose (G unit) and 4-linked-3,6-anhydro-L-galactopyranose (LA unit) [45]. Substitution of hydroxyl group by ester sulfate, methyl groups and pyruvic acid at various positions have direct impact on physical and rheological properties of polysaccharides [44, 46–50].

Polysaccharides have noticeable effects in immunomodulatory and anti-cancer as one of the most important macromolecules. These effects are driving force for wide research in biochemical and medical areas. As it was mentioned above, polysaccharides are abundant in cell walls and their composition is under the influence of season, age, species and geographical location. Their main goal in plants are food reservoir, however they can provide strength, and flexibility encountering wave actions and also balancing the ionic equilibrium inside the cell. Other structural benefits of polysaccharides, such as regularity of the hydroxyl group, can increase the ion interactions our of cell walls and interchain hydrogen bonding and causing gelation.

Depending on seaweeds, different polysaccharides can be produced by alginates, fucoidans, and laminarans. Laminarans, fucoidans as water soluble and high molecular mass alginic acids as alkali soluble polysaccharides are main products of brown seaweeds [51]. Main components of brown algae wall are cellulose microfibrils merged in amorphous polysaccharide while they relate to each other via proteins. There are two kinds of acid polysaccharides in extracellular structure of brown algae, sulfated fucans and alginic acid (Perez et al., 2016).

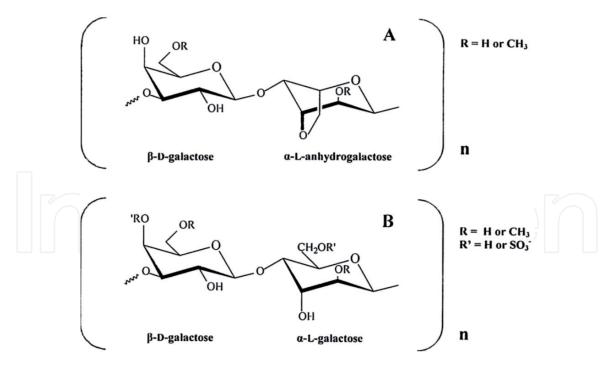


Figure 4.

Chemical structure of agar polysaccharides with the different types of monomers [44].

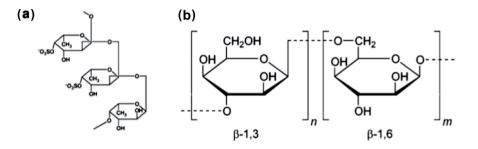


Figure 5.

(a) Structure of fucoidan [51] and (b) structure of laminaran [51].

2.1.1 Fucans

Fucans as one of the acid polysaccharides present in extracellular structure of brown algae (**Figure 5**) are categorized into three major groups: fucoidans, xylofucoglycuronans and glycorunogalactofucans [51].

2.1.2 Fucoidans

Fucoidan is a branched sulfate ester polysaccharide with branching. The major branches in this polysaccharide are L-fucose-4 sulfate or sulfate ester at C₃. Fucoidan has molecular weight ranging from 100 kDa [52] to 1600 kDa [53]. Main components of Fucoidan are fucose, uronic acids, galactose, xylose and sulfated fucose. Fucoidan structure contains sulfated fucans backbone, which is made of different sugars, fucose, or uronic acid. The backbone also has different degrees of branching. This structure is highly dependent on the algae's species. Due to the complex structure, especially due to branching, it is very difficult to study the whole molecule [54].

As a known fact, fucoidan has solubility in water and acid solution [53] and acid hydrolysis can result various amounts of D-xylose, D-galactose, and uronic acid. Algal fucoidans as very common sulfated polysaccharide present in all brown algae are mainly found in Fucales and Laminariales, also present in Chordariales, Dictyotales, Dictyosiphonales, Ectocarpales, and Scytosiphonales. Although algal is present in brown algae but it seems to be absent in green algae, red algae, as well as in freshwater algae and terrestrial plants [55].

Study the structural composition of polysaccharides showed that xylofucoglycuronans or ascophyllans have polyuronide backbone, fundamentally poly-b-(1,4)-D-mannuronic acid branched with 3-O-D-xylosyl-L-fucose-4-sulfate or sometimes uronic acid. While, glycuronogalactofucans are composed of linear chains of (1,4)-D-galactose branched at C₅ with L-fuco-syl-3-sulfateoroccasionallyuronicacid [56]. This backbone consists of $(1 \rightarrow 3)$ -linked α -L-fucopyranose residues (type 1, **Figure 6A**) or alternating $(1 \rightarrow 3)$ -linked α -L-fucopyranose, $(1 \rightarrow 4)$ -linked α -L-fucopyranose residues (type 2, **Figure 6B**), and fucose and sulfate branching (**Figure 6C**) [54].

2.1.3 Carrageenans

Carrageenan as linear sulfated polysaccharides are extracted from edible red seaweeds. Carrageenan name is from *Chondrus crispus* species of seaweed known as Carrageen Moss or Irish Moss in England, and Carraigin in Ireland [57]. This large and highly flexible polysaccharide contain 15–40% of ester-sulfate as the main component of sulfated polygalactan with average molecular weight of 100 kDa. The structural composition shows alternate units of anhydrogalactose (3,6-AG) and D-galactose. These units are joint by α -1,3 and β -1,4-glycosidic linkage. There are different classes of carrageenan such as λ , κ , ι , ε , μ . All these classes have sulfate groups in range of 22–35%. The number and position of the ester sulfate is the key for the primary differences in different types of carragenans. It must be mentioned that these nomenclatures have no reflect on the chemical structures. Kappa and lota type have ester sulfate content around 25–30% and 3,6-AG content of about 25–30%. While, Lambda type has higher ester sulfate content of about 32–39% and no content of 3,6-AG (**Figure 7**) [57, 58].

2.1.4 Alginic acids

Alginic acid or algin is a linear polysaccharide with 1,4-linked, b-D-mannuronic and a-L-guluronic acid (**Figure 8**) as building blocks which are arranged in nonregular and different sequences fashion [59]. Alginic acid is derived from brown seaweed in form of sodium and calcium alginate with main application in food and pharmaceutical industries. Structural functionalities make them able to bind with

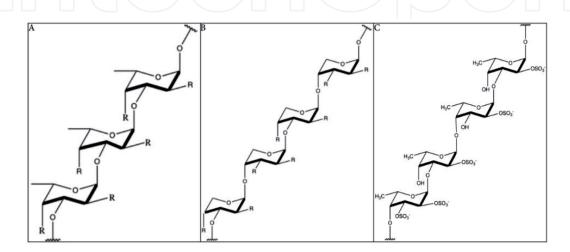
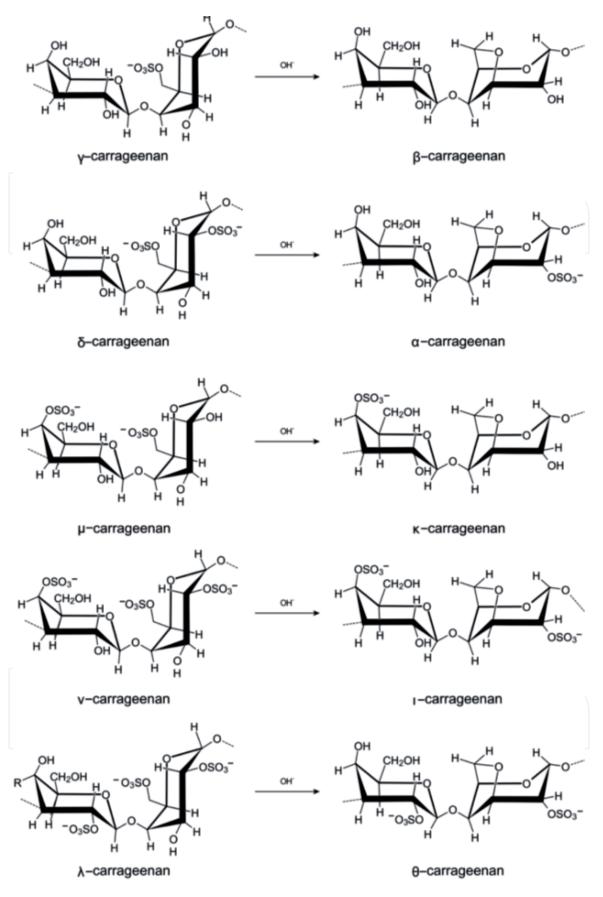
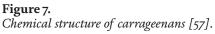


Figure 6. *Structure of fucoidans* [54].





metal ions and obtained very viscous solutions when hydrated. This water absorption property makes alginate suitable for different applications specially in biological studies with potential application as anti-coagulant, anti-tumor, anti-viral and anti-oxidant [55, 60, 61].

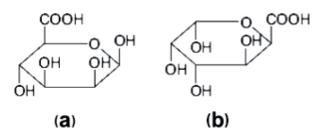


Figure 8.

(a) b-D-mannuronic acid in alginic acid and (b) a-L-guluronic acid in alginic acid (a and b adapted from [51, 62]).

2.1.5 Laminarans

Laminarans, the nutritional reserve of all brown algae, was first detected in Laminaria species. The molecular weight of the laminaran is about 5000 Da depending on the degree of polymerization. The main sugar, structure and composition of the laminaria species is the laminar, which varies according to the algae species. Laminaran is a polysaccharide, which is soluable in water and consisting 20–25 glucose units including of (1,3)-b-D-glucan including of (1,3)-b-D-glucan, b (1,6) branched (**Figure 8b**). There are two kinds of laminar chain, called M or G, which are different at the reduction ends. While the M chains ends with a mannitol residue, the G chains end with a glucose residue. Most of the laminates, which are impervious to hydrolysis in the upper gastrointestinal tract (GIT) and which are considered to be dietary fiber, are stabilized by cross-chain hydrogen bonds [63]. The activity of structure of laminarans, which are affected by environmental factors such as water temperature, nutrient salt, salinity, waves, sea flow and plunge depth, vary. Besides the role of laminar as a prebiotic and dietary fiber, it is also interesting to have anti-microbial and anti-cancer activities [63].

2.2 Alkaloids

Alkaloids are organic compounds, which contains nitrogen atom in their structures. Various structures of amines, cyclic nitrogen and halogenated containing organic compounds exist in the plants and natural materials. Cyclic nitrogen containing alkaloids are only be found in marine organisms and marine algae and are classifies in three main categories [64].

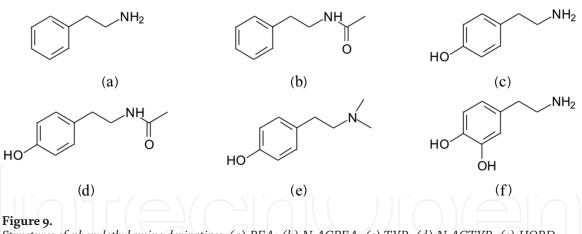
2.2.1 Phenylethylamine alkaloids (PEA)

 β /2-phenylethylamine, phenethylamine also known as PEA is made of benzene ring with different ethylamine side chains (**Figure 9a**). These important alkaloids are precursors for making natural and synthetic compounds. Many pharmaceutical precursors can be achieved from substituted PEAs present in plant and animals, such as, simple phenylamine (tyramine, hordenine) and catecholamine (dopamine) [64].

Some type of brown algae, *Gracilaria bursa-pastoris*, *Halymenia floresii*, *Phyllophora crispa*, *Polysiphonia morrowii* and *Polysiphonia tripinnata*, have PEA in their structures [65].

2.2.2 Indole and halogenated indole alkaloids

Morales-Ríos et al. recorded that the alkaloids produced by *Flustra foliacea*, possessing an unusual pyrroloindoline skeleton, are divided into simple indoles (1–6)



Structures of phenylethylamine derivatives: (a) PEA; (b) N-ACPEA; (c) TYR; (d) N-ACTYR; (e) HORD; (f) DOP (adapted from [65]).

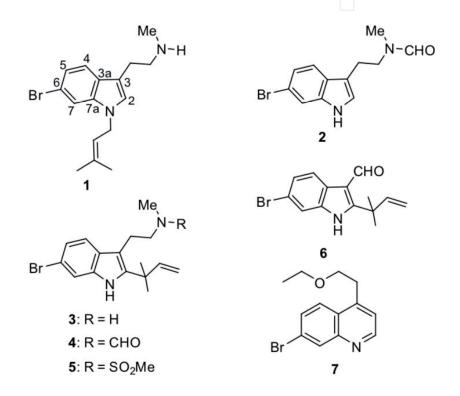


Figure 10.

Structure of indoles (1–6) and quinoline (7) extracted from F. foliacea (adapted from [66]).

and a quinoline 7 (**Figure 10**), and those with a pyrrolo[2,3-b]indole framework (8–23), including hexahydro-1,2-oxazino[5,6-b]indole (24) (**Figure 11**). Main metabolites in marine seaweeds such bryozoan *Flustra foliacea* are brominated indoles. The structure of these seaweeds have number of brominated indoles with prenyl or isoprenyl substituents at different positions [66].

The marine cheilostome bryozoan *Flustra foliacea* contain an order of brominated pyrroloindolines and indoles, terpenes, and a kind of quinoline, having a variety of biological activities, including anti-microbial, anti-tumor and some biological activities, as secondary metabolites [66].

2.2.3 Other alkaloids

Main alkaloids achieved form algae are from family of 2-phenylethylamine and indole with different substitutions and functionalities. 2,7-naphthyridine derivatives are also alkaloids. Substitutions such as bromide and chloride are specifically seen in Chlorophyta (Perez et al., 2016; [67]). Regarding to the medical properties

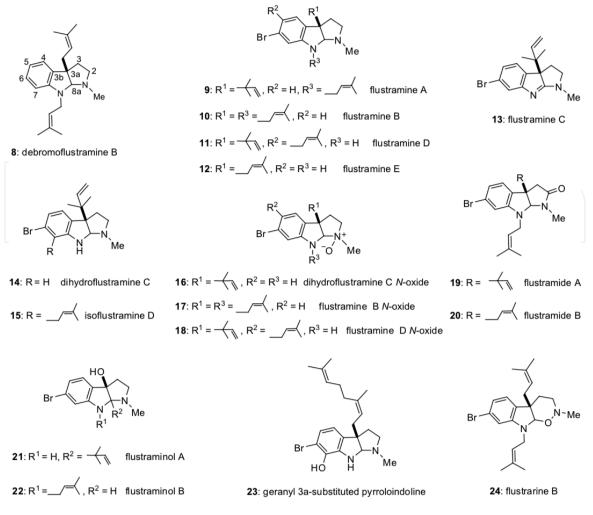


Figure 11.

Indolines 8–24, including indolenine (13), isolated from F. foliacea (adapted from [66]).

of marine alkaloids, further research and study successfully separated sufficient amount of pure organic derivatives for biological testing [66].

2.3 Terpenes

Terpenes known as main algae metabolites, have chemical structure including five-carbon precursor. They are classified into, hemiterpenes, including five carbons (C5); monoterpenes, including ten carbons (C10); sesquiterpenes, including fifteen carbons (C15); diterpenes, including twenty carbons (C20); sesterterpenes, including twenty-five carbons (C25); triterpenes, including thirty carbons (C30) and polyterpenes, including above thirty carbons (>C30). It is known that some seaweeds contains terpenes. Chlorophyceae is one of them. It contains cyclic and linear sesqui-, di-, and triterpenes. The other one is Rhodophyceae and contains high structural diversity of halogenated secondary metabolites whose polyhalogenated monoterpenes show a variety of antibacterial properties (Perez et al., 2016; [68]).

3. Conclusion

In recent decades, seaweed was thought as an abundant and renewable natural resource. Especially, edible seaweeds are rich in polysaccharides, unsaturated fatty acids, protein composition, vitamins, and minerals, as well as natural bioactive compounds such as alkaloids. Their main component, polysaccharides may vary

depending on seaweeds and growth conditions. Because of their components, edible seaweeds possess various bioactivities such as anti-oxidant, anti-cancer, anti-obesity, and anti-diabetes activity.

Conflict of interest

The authors declare no conflict of interest.

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