Seaweed Phenolic Compounds

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Seaweeds are a potential source of bioactive compounds that are useful for biotechnological applications and can be employed in different industrial areas in order to replace synthetic compounds with components of natural origin. Diverse studies demonstrate that there is a solid ground for the exploitation of seaweed bioactive compounds in order to prevent illness and to ensure a better and healthier lifestyle. Among the bioactive algal molecules, phenolic compounds are produced as secondary metabolites with beneficial effects on plants, and also on human beings and animals, due to their inherent bioactive properties, which exert antioxidant, antiviral, and antimicrobial activities.

Keywords: seaweeds ; phenolic compounds ; bioactive compounds ; pharmaceutical application ; nutraceutical application

1. Seaweed Phenolic Compounds

Seaweed phenolic compounds are attracting the attention of the scientific community, as well as several industries, due to their high variety and potential uses [1][2][3]. For instance, the occurrence of phlorotannins (in brown seaweeds) and bromophenols, flavonoids, phenolic terpenoids, and mycosporine-like amino acids (MAAs) in green and red seaweeds has been recorded (Table 1) [4][5].

Phenolic acids consist of a single phenol ring and at least a group of functional carboxylic acids and are typically graded according to the number or the amount of carbon in the chain bound to the phenolic ring. These phenolic acids are also categorized as C6-C1 for hydroxybenzoic acid (HBA; one carbon chain linked to the phenolic ring), C6-C2 for acetophenones and phenylacetic acids (two carbon chains linked to the phenolic ring) and C6-C3 (3 carbon chains attached to the phenol ring) for hydroxycinnamic acid (HCA) [6][7]. HBAs include, among others, gallic acid, p-hydroxybenzoic acid, vanillic acid, syringic acid, and protocatechins, in which there are differences in the basic structure of the HBA, including an aromatic ring hydroxylation and methoxylation [6][7].

Trans-phenyl-3-propenoic acids are hydroxycinnamic acids (HCA), which vary in their ring constitution [6]. These HCA derivatives include caffeic (3,4-dihydroxycinnamic), ferulic (3-methoxy-4-hydroxy), sinapic (3,5-dimethoxy-4-hydroxy), and p-coumaric (4-hydroxy) acids, all of which are commonly distributed as conjugates, primarily as quinic acid esters (chlorogenic acids) [6][7]. In addition, these acids can be subcategorized up into different groups based on the identity, location, and number of the acyl residue: (1) mono-esters of caffeic, ferulic, and p-coumaric acids; (2) bi-, tri-, and tetra-esters of caffeic acids; (3) mixed di-esters of caffeic-ferulic acid or caffeic-sinapic acids; and (4) mixed caffeic acid esters with aliphatic dibasic acids, such as oxalic or succinic acid [6][7].

Some experiments have shown the presence of phenolic acids in marine algae [6][7][8]. For instance, coumarins have been found in green seaweed species such as *Dasycladus vermicularis*, as well as some vanillic acid derivatives in the *Cladophora socialis* (Chlorophyta, green algae) [9]. *Ascophyllum nodosum* (Figure 1A), *Bifurcaria bifurcata* (Figure 1B), and *Fucus vesiculosus* (Figure 1C) (Phaeophyceae, brown algae) have been distinguished by the presence of HBAs, rosmarinic acid, and quinic acid [10]. In addition, in the genus *Gracilaria* (Figure 1I) (Rhodophyta, red alga), phenolic acids have been detected, such as benzoic acid, p-hydroxybenzoic acid, salicylic acid, gentisic acid, protocatechuic acid, vanillic acid, gallic acid, and syringic acid [11][12][13].

Figure 1. Some seaweeds producing phenolic compounds: (**A**)—*Ascophyllum nodosum* (P); (**B**)—*Bifurcaria bifurcata* (P); (**C**)—*Fucus vesiculosus* (P); (**D**)—*Leathesia marina* (P); (**E**)—*Lobophora variegata* (P); (**F**)—*Macrocystis pyrifera* (P); (**G**)—*Asparagopsis armata* (R); (**H**)—*Chondrus crispus* (R); (**I**)—*Gracilaria* sp. (R); (**J**)—*Kappaphycus alvarezii* (R); (**K**)—*Neopyropia* sp. (R); (**L**)—*Palmaria palmata* (R); (**M**)—*Dasycladus vermicularis* (Chl); (**N**)—*Derbesia tenuissima* (Chl); (**O**)—*Ulva intestinalis* (Chl); *P—Phaeophyceae*, R—Rhodophyta; Chl—Chlorophyta.

Phlorotannins are well-known phenolic compounds synthesized by brown seaweeds. These compounds are constituted by oligomeric units of phloroglucinol [14][15]. Commonly, these secondary metabolites have a molecular weight ranging from 10 to 100 kDa, due to the high variability that these molecules can present in the structural bonds between phloroglucinol and the hydroxyl groups [16][17]. In this context, phlorotannins can be categorized into six categories: (1) fucols (aryl–aryl bonds), (2) phloretols (aryl–ether bonds), (3) eckols (dibenzo-1,4-dioxin bonds), (4) fucophloretols (ether or phenyl linage), (5) carmalols (dibenzodioxin moiety), and (6) fuhalols (ortho-/para- arranged ether bridges containing an additional hydroxyl group on one unit) [14][16][17]. Moreover, the complexity of these molecules classify them, by each category, into linear or branched phlorotannins [16][17]. Due to its biotechnological properties, dieckol is the most exploited phlorotannin, and it can be found in the species *Ecklonia cava* (Phaeophyceae) [18].

Flavonoids are structurally characterized as phenolic compounds with a heterocyclic oxygen bound to two aromatic rings, which can then differ according to the degree of hydrogenation [19][20]. However, there is a generalized lack of studies regarding algal flavonoids' isolation and characterization. Nevertheless, some research has shown that seaweeds are a rich source of flavonoids. Several species of the Chlorophyta, Rhodophyta phyla, and Phaeophyceae class were found to have flavonoids such as rutin, quercitin, and hesperidin [14][21]. For instance, *Chondrus crispus* (Figure 1H) and *Porphyra*/*Pyropia* spp. (Rhodophyta) and *Sargassum muticum* and *Sargassum vulgare* (Phaeophyceae) can synthesize isoflavones, likewise daidzein or genistein [22]. Moreover, many flavonoid glycosides have also been recorded in the brown seaweeds *Durvillaea antarctica*, *Lessonia spicata*, and *Macrocystis pyrifera* (also known as *Macrocystis integrifolia*) (Figure 1F) [14]. Furthermore, green (*Acetabularia ryukyuensis*), brown (*Eisenia bicyclis*—as *Ecklonia bicyclis*, *Padina arborescens*, *Padina minor*), and red seaweeds (*Neopyropia yezoensis*—also known as *Porphyra yezoensis*—Figure 1K, *Gelidium elegans*, and *Portieria hornemannii*—also known as *Chondrococcus hornemannii*) proved to be a valuable source of catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate, or epigallocatechin gallate [23].

Bromophenols are brominated phenolic compounds characterized by the presence of one or more benzene rings and hydroxyl substituents [24][25]. These compounds can be found in green [26][27][28][29], red [30][31][32] and brown seaweeds [33][34]. Nevertheless, red seaweeds often exhibit a higher content of these molecules [35]. However, due to the low content of bromophenols in seaweeds, there are just a few studies regarding the isolation and characterization of these compounds.

Phenolic terpenoids are secondary metabolites that have already been identified in seaweeds [15]. For instance, meroditerpenoids (such as plastoquinones, chromanols, and chromenes) were found in brown seaweeds, mainly from the family Sargassaceae (Phaeophyceae). These compounds are partially derived from terpenoids and are characterized for having a polyprenyl chain linked to a hydroquinone ring moiety [36]. Red seaweeds also synthesize phenolic terpenoids, such as diterpenes and sesquiterpenes in Rhodomelaceae. For example, the species *Callophycus serratus* synthesizes a specific diterpene, bromophycolide [37].

Table 1. Seaweed phenolic compounds recorded, according to phyla and phenolic compound group.

Seaweed Species	Phenolic Compound Group	Compound	Reference
		Chlorophyta	
Acetabularia ryukyuensis *Dasycladus vermicularis*	Flavonoids	Catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate, or epigallocatechin gallate Coumarin	[9][26]
Dasycladus vermicularis *Cladophora socialis* *Nitella hookeri*	Phenolic acids Flavonoids	Coumarin Vanillic acid C-glycosides	[9][23]
		Rhodophyta	
Gracilaria sp.	Phenolic acids	Benzoic acid, p-hydroxybenzoic acid, salicylic acid, gentisic acid, protocatechuic acid, vanillic acid, gallic acid, and syringic acid	[12]
Chondrus crispus	Flavonoids	Isoflavones; daidzein or genistein	[22]
Porphyra/*Pyropia* spp.	Flavonoids	Isoflavones; daidzein or genistein	[22]
Neopyropia yezoensis (as *Porphyra yezoensis*) *Gelidium elegans* *Portieria hornemannii* (as *Chondrococcus hornemannii*)	Flavonoids	Catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate, or epigallocatechin gallate	[23]
Callophycus serratus	Phenolic terpenoids	Bromophycolides	[37]
Palmaria palmata	Mycosporine-like amino acids	Palythine, shinorine, asterina-330, palythinol, and porphyra-334	[38]
Falkenbergia rufolanosa (tetrasporophyte phase of *Asparagopsis armata*)	Mycosporine-like amino acids	Palythine and shinorine	[39]
		Ochrophyta, Phaeophyceae	
Ascophyllum nodosum *Bifurcaria bifurcata* *Fucus vesiculosus*	Phenolic acids	Rosmarinic acid; quinic acid	[10]
Ecklonia cava *Cystoseira* sp. *Fucus spiralis* *Ishige okamurae* *Ascophyllum nodosum* *Bifurcaria bifurcata*	Phlorotannins	Dieckol Eckol Fucophloroethol-type Diphlorethohydroxycarmalol Fucaphlorethol-type Tetrafuhalol B	[18][40][41][42][43]

Seaweed Species	Phenolic Compound Group	Compound	Reference
Durvillaea antarctica *Lessonia spicata* *Macrocystis pyrifera* (as *Macrocystis integrifolia*)	Flavonoids	C-glycosides	[14]
Eisenia bicyclis (as *Ecklonia bicyclis*) *Padina arborescens* *Padina minor*		Catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate, or epigallocatechin gallate	[23]
Sargassum muticum *Sargassum vulgare*		Daidzein or genistein	[22]
Sargassaceae	Phenolic terpenoids	Plastoquinones, chromanols, and chromenes	[36]
Stypopodium zonale		Stypofuranlactone; 10,18-dihydroxy-5′a-desmethyl-5′-acetylatomaric acid; 10-keto-10-deisopropyliden-5′a-desmethyl-5′-acetylatomaric acid; 10-keto-10-deisopropyliden-atomaric acid	[44]

Mycosporine-like amino acids (MAAs) are secondary metabolites that, despite being synthesized by several organisms, were found to be more often produced by marine organisms [45][46][47]. Such compounds present a low molecular weight (<400 kDa) and are soluble in water. Moreover, they present a cyclohexanone or cyclohexenine ring, with amino acid moieties in their chemical structure [45][48]. Thus, these compounds can be found mainly in red seaweeds. For example, it was found that the edible red seaweed *Palmaria palmata* (Figure 1L) biosynthesizes the MAA palythine, shinorine, asterina-330, palythinol, and porphyra-334 [38]. In addition, the tetrasporophyte phase of *Asparagopsis armata* (Figure 1G) was found to produce palythine and shinorine [39].

2. Phenolic Compounds Application in Biotechnology

Biological compounds extracted from seaweeds exert several activities that can be exploited for the production of food, animal feed, and new drugs, substituting synthetic compounds with natural-origin compounds.

The most exploited phenolic compounds are phlorotannins, which are exclusively present in high concentration in brown seaweeds [49][50] and are involved in defense activities [51][52][53], showing strong antioxidant properties and antimicrobial activity, which help to inhibit bacterial growth [49]. Phlorotannins can be exploited in different biotechnological sectors. They exert a powerful antioxidant activity, as in the case of phlorotannins extracted from *Sirophysalis trinodis* (formerly known as *Cystoseira trinodis*, Phaeophyceae), which makes considering this species a potential source of phenolic compounds for diverse applications [54].

The synthesis of these compounds is driven by different factors. For example, seaweeds are particularly sensitive to external stressors; consequentially, they produce phenolic compounds, which develop multiple activities in order to protect seaweeds [54][55][56][57][58][59]. Due to several biological activities that involve phenolic compounds, they have been found interesting to be applied in the nutraceutical, pharmaceutical, medical, and industrial areas [60][40][61].

2.1. Medical and Pharmaceutical Applications

The consumption of seaweeds can prevent diseases or help the healing. Their bioactive compounds have positive effects on human health. For example, Tanniou et al. [62] identified the brown alga *Sargassum muticum* as a potential source of bioactive phenolic compounds: this species showed a strong antioxidant activity [51] and anti-proliferative activity in breast cancer cells [63] that may suggest the involvement of *S. muticum* in biotechnological applications.

Shibata et al. [64] compared the antioxidant activity of phlorotannins extracted from *Eisenia bicyclis* (Phaeophyceae) in vitro to available and active compounds such as vitamin C (ascorbic acid) and vitamin E (α-tocopherol). This study demonstrates that the antioxidant activity of phlorotannin was 10 times higher than that of other biological compounds.

The isolation and studies on phlorotannin derivates demonstrate that their high anti-proliferation activity is able to induce growth inhibition and apoptosis in human breast cancer cells [65][66]. For example, the red seaweed *Kappaphycus alvarezii* (also known as *Eucheuma cottonii*) (Figure 1J) polyphenol in vitro extracts were analyzed to evaluate antiproliferative, apoptotic, and cell cycle effects. Results showed an effect of these compounds against cancer cells [67].

The uptake of phlorotannins has also been related to the reduction in cardiovascular diseases and hypercholesterolemia [68][69].

Phlorotannins are responsible for the absorption of UV-B radiation [70][71][72][73], acting as photoprotective agent for algal cells [3][74], to avoid DNA damage [75][76][77]. This property is also effective for human and animal skin, reducing the probability of skin cancer due to UV-B radiation [71]. Additionally, phlorotannins prevent the production of matrix metalloproteinases (MMPs), enzymes that encourage the presence of wrinkles by degrading the extracellular matrix. For this purpose, seaweed phenolic compounds may be involved in the production of anti-aging creams and skin products [78].

Phlorotannins are also involved in the development of therapies to treat diverse allergic diseases. In Korean traditional medicine, phlorotannin extracts from the brown alga *Sargassum hemiphyllum* and the red alga *Polyopes affinis* (formerly known as *Carpopeltis affinis*) have been confirmed to have effective antiallergic properties in vitro [79]. The Japanese brown alga *Ecklonia arborea* (formerly known as *Eisenia arborea*) has been found to contain effective inhibitors of histamine; the presence of phlorofucofuroeckol B (phlorotannin) may be the reason for the anti-allergic activity shown in rats. *Ecklonia arborea* is popular in Japan since it has been consumed for years as healthy food and folkloristic therapies [80].

Among phenolic compounds, bromophenol and its derivates are widely investigated due to their potential activities. Studies conducted with *Leathesia marina* (formerly known as *Leathesia nana*) (Figure 1D) (Phaeophyceae) indicate that bromophenol derivatives respond positively to the inhibition of human cancer cells proliferation in vitro [81]. Alongside the ideal exploitation of bromophenol derivates for the development of new therapies for tumor treatment, these biological compounds reported antiviral activity against Herpes Simplex Viruses-1. For instance, extracts from the red alga *Symphyocladia latiuscula* (Figure 1N), which is abundant in Korea, demonstrate antiviral activity against HSV-1, likely due to the presence of its bromophenols, the major compounds [82].

Moreover, researchers have proven the antimicrobial effect of bromophenols extracted from the red alga *Rhodomela confervoides*, which act against some *Staphylococcus* and *Pseudomonas aeruginosa* strains [83].

Advantages of Phenolic Compounds Consumption for Human Health

Benefits of phenolic compounds are very common in human diet, since they can be ingested as food or food supplements and provide the human organisms with multiple positive effects [84]. They can be found in food and beverages from natural origin such as plants, seaweeds, fruits, coffee, black tea, and chocolate [85][86], but they can be also added to our daily diet as colorants or as antioxidants [87].

Many synthetic antioxidants have been developed to retard the oxidation in foods. However, synthetic compounds may have collateral effects [88] that could be avoided by the intake of natural antioxidant compounds, such as phenolic compounds extracted from seaweeds [89]. Phenolic acids present in food are also responsible for organoleptic properties, influencing color, flavor, and nutritional values [90].

Brown algae have already been exploited as food in Asia in the past 15 centuries; phlorotannin extracts from *Ecklonia cava* are already available in the market since 2018, when the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) attested that these extracts are indicated for diet due to their nutritional properties. *Ecklonia cava* thallus is consumed as salad and as a component of soups, while *E. cava* powder is also used to dye food, especially sweets, such as candies or rice cakes [91].

Phlorotannins have anti-diabetic effects: Roy et al. [92] assessed the in vitro inhibitory activity of phlorotannins extracted from *Ascophyllum nodosum* and *Fucus vesiculosus*, and their effect on rat blood glucose and insulin levels. It has been noticed that, 20 min after the consumption of animal feed enriched in phlorotannins, the normal increase in postprandial blood glucose was reduced by 90%, with a consequential reduction by 40% of insulin secretion [92].

As different classes of polyphenols from seaweeds can assure health benefits, it is suggested to consume the whole algae in order to uptake a higher quantity of bioactive compounds, instead of consuming only algae extracts as food supplements [93].

Flavonoids have been investigated for a long time for their powerful antioxidant activities. Their uptake has been linked with a reduced risk of lung cancer [84].

2.2. Aquaculture and Industrial Applications

Bromophenols are also investigated for the flavor they give to seafood [94][95][96]. Studies attested that bromophenols are responsible for the typical iodine-like flavor of marine fish [96], prawns, and marine algae [94]. It is quite likely that bromophenols detected in marine fish and prawns derived from their diet based on seaweeds that can synthesize these compounds [94][97].

The Japanese brown algae *Padina* spp., *Sargassum* spp., and *Lobophora* spp. (Figure 1E) have been detected as sources of bromophenols for local fish. It is likely that fish assimilate the typical marine flavor after the ingestion of these algae [34].

The presence of bromophenols in the diet of prawns may be useful for aquaculture [94][96]: crustaceans used as fish feed in aquaculture systems have low amounts of bromophenols due to their diet, with a consequential absence of iodine-like flavor in farmed fish [96]. The inclusion of seaweeds in prawns feed may thus increase the sea-like flavor of aquaculture seafood, enhancing their taste [34]

Moreover, other compounds, such as flavonoids, play an important role in retarding lipid oxidation that occurs in muscle, especially in fish, in order to delay the deterioration of seafood [89][98].

Over the last years, textile industries dedicated more attention towards medical textiles since their usage is not restricted to medical centers and care facilities: it is also present in other fields where hygienic conditions are required, e.g., hotels or restaurants [99]. Natural fibers such as cotton or silk are limited; therefore, medical textile industries started to use synthetic fibers, such as polyester, viscose, polyamides, and polypropylene [99]. A critical problem with synthetic fibers is the risk of spreading infections. To overcome this problem, seaweeds' bio-compounds may be utilized for textile production. Due to the properties of phenolic compounds, new biological textiles may be developed. The new textiles could have antioxidant and antimicrobial properties [100] with the advantage of being natural and not irritating to the skin and being biodegradable and biocompatible [101][102]. The natural bioactive agents are non-toxic and skin and eco-friendly. From the extraction and treatment of cellulose-based polyphenols, these textiles can be brought into contact with the human skin and tissues and body fluids [99].

Moreover, the use of flavonoids to obtain UV-protective clothing has been suggested, since they show UV protection ability linked with antibacterial and anti-inflammatory properties [99].

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