ISSN 2278-8808 SJIF 2015: 5.403
An International Peer Reviewed & Referred
SCHOLARLY RESEARCH JOURNAL
FOR INTERDISCIPLINARY STUDIES

BIOACTIVE COMPOUNDS FROM MACROALGAE- THE MEDICINAL PROSPECTIVES

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Abstract

Our natural world is extremely rich in resources. Hence, it plays a diverse role in the field of therapeutics. As the Earth's surface is covered by more than 70% of the oceans, marine organisms can therefore be considered as an excellent source of bioactive compounds. Bioactive compound or biologically active compounds are the compounds that are effective on a living organism, tissue or cell. Examples of certain bioactive compounds and flavonoids, carotenoids, polysaccharides, glucosinates, polyphenols, and many more. Numerous bioactive compounds having heterogeneous function such as antiproliferative, antioxidant, and anti-microtubule have been extracted from the marine sources. Macroalgae or Seaweed, a word that includes the macroscopic, multicellular or benthic marine algae, is thought to be an exceptional source of bioactive compounds because they are enriched with different kinds of secondary metabolites exhibiting various biological activities and have extensively been utilized for the treatment of various kinds of diseases. Several unpolished or partly refined polysaccharides from many brown, green and red algae have been confirmed for their diverse curing activities. Recent trends in drug research indicated macroalgaeto be promising as novel and sustainable sources of bioactive compounds for both pharmaceutical and nutraceutical applications. The proper development of marine algae compounds will be helpful in pharmaceutical product development and in the development of the pharmaceutical industry.

Keywords: *Macroalgae, Bioactive compounds, Pharmaceuticals, Polysaccharides, Protein, PUFAs, Polyphenols, Pigments, Phlorotannins*

Introduction

The term 'bioactive' is derived from two words, bio and active (Abdelkarim et al. 2014). Bio from the Greek (βίο-) "bios" refers life and active from the Latin "activus", means energetic or involves an activity (Alain 1994). Bioactive is a substitute term for biologically active which can be defined as a simple substance that has a biological activity (Cammack et al. 2006). The bioactive compounds show a broad range of effects starting from a good maintenance of health even healing effect to the dangerous even deadly effect (Abdelkarim et al. 2014). The multi-cellular plants rising in salt or fresh water are known as macro algae (Kharkwal et al. 2012). They are the large aquatic photosynthetic plants that can be seen without a microscope (Abdelkarim et al. 2012). On the basis of their pigmentation, marine algae are classified as brown seaweed (Phaeophyceae), red seaweed (Rhodophyceae), and green seaweed (Chlorophyceae) (Kharkwal et al. 2012). Marine algae are considered as a source of bioactive compounds as they are competent to produce a great diversity of secondary metabolites categorized by a broad spectrum of biological activities (Jeyanthi et al. 2013). With activities such as antibiotics, antiviral, antioxidant and anti inflammatory the macro algae acts as a source of bioactive molecules (Jeyanthi et al. 2013). Bioactive compounds isolated from marine algae are chemically classified as brominated, aromatics, sterols, proteins, peptides and sulphated polysaccharides (Mtolera et al. 1996; Taskin et al. 2007; Rajasulochana et al. 2012). Macro algae produce a large variety of chemically active metabolites in their surroundings as an aid to protect themselves against the other settling organisms (Jeyanthi et al. 2013). These chemically active metabolites are also known as biogenic compounds, such as halogenated compounds, alcohols, aldehydes, terpenoid etc. (Jeyanthi et al. 2013). Chlorellin derivatives, acrylin acid, halogenated aliphatic compounds, phenolic inhibitors and guianesesquiterpenes and labdanediterpenoids are the antimicrobial agents which were also detected from macroalgae (Chakraborthy 2010 a). Seaweeds are used in the human and animal nutrition. They produce a rich source of bioactive compounds such as carotenoids, dietary fibre, proteins, essential fatty acids, vitamins and minerals (Bocanegra et al. 2009). Polysaccharides such as agar, alginates and carrageenans obtained from seaweeds are used in pharmaceutical purposes (Bocanegra et al. 2009). They produce a rich source of structurally and biologically diverse active secondary metabolities. Those secondary metabolities acts in defense mechanism against herbivores, fouling organisms and pathogens.

2. Bioactive Compounds from Several Algal Extracts

2.1. Polysaccharides

Macroalgae or Seaweeds encompass various diverse groups of polysaccharides and the resultant taxonomic categorization of algae in addition to their cell structure is associated to their chemical structure (Ferreira et al. 2012;Wijesinghe and Jeon 2012). The activity of numerous bacterial species along with viruses is found to be inhibited by sulfated polysaccharides (Leonard et al. 2010). Polysaccharides can act as the substances that encourage the growth of beneficial bacteria in the digestive tract i.e. prebiotics, hence results in the effects that stimulate growth and improve health (Vidanarachchi et al. 2009). Alginic acid is among the several soluble dietary fibers that exhibits positive effect on the digestive tract of animals. Such polysaccharides derived from seaweeds are more effective and are non-toxic antioxidants (Li and Kim 2011; Souza et al. 2012). Seaweeds comprises of up to 76% of dry weight of these compounds (Holdt and Kraan 2011). Thefurthermostchiefalgal polysaccharides among all others are galactans, fucoidan, laminarin and alginates (Ferreira et al. 2012).

Both the intercellular matrix and the cell wall contain the sulfated galactans. Galactan is basically a macromolecule that is made up of disaccharide-based repeating units: [□ 3)-β-D-Galp-1□] and either [□ 4)-α-Galp-(1□] or 3,6-anhydro-α-Galp (Ferreira et al. 2012).Agarans (D) and carrageenans (L) are differentiated according to the optical conformation of the second unit. Sulfategroups, methoxyl groups, pyruvic acid acetals and glucosyl side chains are the substituents of the main chain of the galactans. An unequal distribution of these groups is observed in the macromolecule (Ferreira et al. 2012). Galactansexhibit anti-tumor as well as antiviral properties.

Brown seaweeds contain a sulfated polysaccharide called as fucoidan. The macromolecule's main sugar unit contains α-1,3-linked sulphated L-fucose, and sulfate ester groups (Song et al. 2012; Synytsya et al. 2010). Algae have about 10% of dry mass of fucoidan. The molecular weight of fucoidan determines its absorption and bioavailability. The bioavailabilty of low molecular fucoidan (LMF) is much more in comparison to high molecular fucoidan (HMF), (Song et al. 2012). Most of the biological effects of these polysaccharides are linked to their capability to modify surface properties of the cell. These compounds show anti-inflammatory, antiviral, anti-tumor and antioxidative activities (Song et al. 2012; Synytsya et al. 2010). In case of antiviral activity, fucoidan inhibits the viral-induced syncytium formation.

Brown algae also containlaminarin as one of their major polysaccharides or bioactive compound. The chemical structure of laminarin is composed of β-(1□ 3)-linked glucose in the main chain along with unsystematic β-(1□ 6)-linked side-chains [10]. Seaweeds have about 10% of dry weight of laminarin and the content can stretch up to 32% depending on the various seasons (Holdt and Kraan 2011). Laminarin can be considered as a prebiotic because it is also a dietary fibre. Italso exhibits antiviral and antibacterial properties (O'Doherty et al. 2010). Antioxidativeacitivity of laminarin depends on its molecular weight and chemical structure (Li and Kim 2011).

Even though alginates are absent in terrestrial plant but they can be derived from brown seaweeds. The content of the alginates in brown seaweeds is about 47% of dry biomass (Holdt and Kraan 2011). Both acidic and salt forms of alginates are known. Alginic acid, which is the acidic form, is a polymer that is composed of two types of hexuronic acid monomers linked by 1–4 bonds (Andriamanantoanina and Rinaudo 2010): β-D-mannuronic acid and α-L-guluronic acid. The properties of thickening, stabilizing and general colloidal are shown by these compounds (Aliste et al. 2000) along with strong antibacterial and anti-inflammatory activities.

2.2. Protein

Unlike polysaccharides, the structure and biological properties of proteins extracted from seaweeds are not broadlyknown. Seaweeds contain only 5% of protein (Leonard et al. 2010). Brown seaweeds have the lowest amount of protein. Almost all the essential amino acids are contained in most of the species of algae. For example, as compared to the corresponding weight of the soybeans, the *Enteromorpha*spp. showed 9 of the 10 essential amino acids required in vertebrates in greater levels (Aguilera-Morales et al. 2005).Lectins are the most important biologically active proteins derived from macroalgae that helps in intercellular communication by binding to carbohydrates. Several activities such as antibacterial, antiviral or anti-inflammatory activities are exhibited by these compounds (Cunningham and Joshi 2010).

2.3. Polyunsaturated Fatty Acids (PUFAs)

Thecore classes of lipids found in seaweeds are the phospholipids and glycolipids. Poly-unsaturated fatty acids (PUFAs) are accumulated in seaweeds with the decrease in environmental temperature. The species living in hotter regions contain less PUFAs than species living in colder temperatures (Holdt and Kraan 2011). Plant manufactures long chain PUFAs (LC-PUFAs), which are significant for maintaining human health (Pulz and Gross 2004) and is composed of at least 20 carbon atoms with at least two double bonds. The lipid molecule is referred to as omega-3 (n-3 LC-PUFA) when the first double bond is located in the third carbon atom. According to a study (Aguilera-Morales et al. 2005), Enteromorpha spp. contains about 10.38% of the n-3 LC-PUFA of the total fatty acids content.

2.4. Pigments

Chlorophylls, carotenoids and phycobiliproteins constitute the three key groups of pigments in seaweeds. Chloroplasts and chromoplasts contain the organic pigments i.e. carotenoids (Wijesinghe and Jeon 2012). Carotenoid is the most wide-spread pigment in the nature and is manufactured by marine algae, plants, fungi and by some bacteria (Li and Kim 2011;Liaua et al. 2010). Pigments are referred to as polyenes soluble in lipids. Various Carotenoids are possessed bydiverse species of algae. Carotenoids are very strong antioxidants; hence they are able to cause the reduction of singlet oxygen and scavenging of free radicals (Li and Kim 2011). β-carotene, fucoxanthin and tocopherol are the major carotenoid pigment molecules.

The algal dry mass 36 to 4500 mg/kg ofβ-carotene. However, 70% of total carotenoid content is constituted byFucoxanthin (Holdt and Kraan 2011). These compounds are extracted from different sea-weeds e.g. *Chlorella vulgaris,* or *Dunaliellasalina* due to supercritical CO_2 extraction with extraction yield ranging up to 90% (Crampon et al. 2011).

Cyanobacteria (blue-green algae), red algae and crypto-monads produce phycobiliproteins, which are the water soluble pigments(Mihovet al. 1996) andset up a scarce percent of algal dry weight. Phycobiliproteins act as an antioxidant, anti-inflammatory, antiviral and neuroprotectivecompound (Holdt and Kraan 2011).

2.5. Polyphenols

Seaweeds in addition to most of the plants produce polyphenols (Antonisamy and Raj 2011). Phenolic acids, flavonoids, isoflavones, cinnamic acid, benzoic acid, quercetin and lignans are among the important polyphenols(Keyrouz et al. 2011). Polyphenols exhibit tough antioxidant activity (Gumulet al. 2011). Such compounds are produced by the seaweeds in order to defend them from stress and herbivores (Li et al. 2011). As reactive oxygen species arecreated in organisms as a fundamental part of metabolism, and are extremely reactive causing cellular dysfunction and cytotoxicity (Alviano and Alviano 2009).Polyphenols can donate hydrogen to free radicals and generate non-reactive radicals (Gupta and Abu-Ghannam2011). Even thoughsubstantialquantities of polyphenols are contained in seaweed extracts, but their content is mainly reliant on the extraction technique. Significant amount of polyphenols is found in *Ascophyllum*spp., whereasthe lowermost content of these compounds is present in *Ulva* spp. (Keyrouz et al. 2011; Craige 2011).

The polyphenolic substancespossessthe group of tannin compounds called phlorotannins.Phlorotannins, eg. eckol or dieckol, have been found only in brown seaweeds even though tannins are prevalent amongst both terrestrial and marine plants (Antonisamy and Raj 2011;Gupta and Abu-Ghannam 2011). Polymerization of phloroglucinol via the acetate-malonatepathwayproduces the polyphenols, phlorotannins(Wijesinghe and Jeon 2012;Li et al. 2011) that are polymers having biological activities in organisms and are involved in host defense mechanisms (Swanson and Druehl 2002). The algal dry mass contains variedamount i.e. 1 to 10% ofPhlorotannin(Swanson and Druehl 2002). A total of 8 phenol rings makes up the molecular skeleton of phlorotannins(O'Sullivan et al. 2011), however terrestrial plants only 3 to 4 ringed tannins (Antonisamy and Raj 2011). Free radicals are electronically captured by the phenol rings (Gupta and Abu-Ghannam 2011). Because of their distinctive structure, phlorotannins have very resilient anitioxidant properties (Antonisamy and Raj 2011). For example, in comparison with ascorbic acid and αtocopherol, the phlorotannins isolated from *Eiseniabicyclis* have shown even 10 times higher antioxidant activity(Gupta and Abu-Ghannam 2011).Phlorotanninscan attack microbiological proteins resulting in inhibition of bacteria as they are known to possess strong antimicrobial activities (Table 1) (Gupta and Abu-Ghannam 2011).

Table 1.Biologically Active Substances in Seaweed Extracts (Ref: Chojnacka et al. 2012)

Bioactive compound	Activity
Polysaccharides	Prebiotics (Vidanarachchi et al. 2009) antimicrobial activity (Leonard et al. 2010) growth-promoting activity (Vidanarachchi et al. 2009) health-improving activity (Vidanarachchi et al. 2009) antiviral activity (Song et al. 2012) anti-tumor activity (Song et al. 2012) anti-inflammatory activity (Song et al. 2012) source of soluble dietary fibers (Song et al. 2012; O'Doherty et al. 2010) antioxidants (Song et al. 2012) antithrombotic activity (Wijesinghe and Jeon2012) anticoagulant activity (Wijesinghe and Jeon2012)
Proteins	source of essential amino acids (Aguilera-Morales et al. 2005) elements of intercellular communication (Cunningham and Joshi 2010) antiviral activity (Cunningham and Joshi 2010) antimicrobial activity (Cunningham and Joshi 2010) anti-inflammatory activity (Cunningham and Joshi 2010) antioxidants (Wijesinghe et al. 2011)
Polyunsaturated fatty acids	health-improving activity (Pulz and Gross2004) antibiotic activity (Bhagavathy et al.2011) antifungal activity (Bhagavathy et al.2011)
Pigments	Antioxidants (Heo et al. 2005) anti-inflammatory activity (Pangestuti and Kim 2011) antiviral activity (Holdt and Kraan2011) neuroprotective activity (Pangestuti and Kim 2011) anti-obesity activity (Dufossé et al. 2005) anti-angiogenic activity (Pangestuti and Kim 2011) Anticancer activity (Moreau et al. 2006)
Polyphenols	host defense activity (Swanson and Druehl2002) strong antioxidants (Gumul et al. 2011) antimicrobial activity (Gupta and Abu-

	Ghannam2011) antiviral activity (Gupta and Abu-Ghannam2011) anti-photo aging activity (Mao and Guo 2010) anti-obesity activity (Nwosu et al. 2011) antiallergic activity (Vo et al. 2012) anticancer activity (Nwosu et al. 2011)

3. Macroalgae used for medicinal purposes

3.1. Antioxidant property of marine algae

Antioxidants play a major role in the treatment of later stages of cancer development. Efficient antioxidants found in algae are polyphenols, phycobilins and vitamins (Plaza et al. 2008). Oxidation promotes carcinogenesis whereas antioxidants cause the regression of premalignant lesions and inhibits cancer development. The mechanism involves the scavenging of free radicals of active oxygen (Richardson 1993). Polyphenols extracted from marine brown algae are called as phlorotannins which act as potential antioxidants (Pooja 2014).

3.2. Anticancer activity of marine algae

Antibiotic substances produced by marine algae inhibit bacterial, viral, fungal and other epibionts (Pooja 2014). The antibiotic property mostly depends on the factor like that particular algae, the microorganism, the season and the growth conditions (Centeno and Ballantine 1999). Antioxidants like β-carotene, shows a good effect in the treatment of precancerous condition such as oral leukoplakia, an oral cancer (Boopathy and Kathirean 2010).

3.3. Antiviral properties of marine algae

Several different species of brown algae were tested for antiviral activity. Then it was discovered that those algal species contain some antiviral properties. The discovery of the activity of the interferon as cellular antiviral systems and the characterization of differences between normal cellular metabolism and viral replication had led to a new pathway in antiviral chemotherapy (Pooja 2014).

3.4. Seaweeds against obesity and diabetes

Naturally existing hypolipidemicagents causes obesity which is a leading cause of death worldwide as it causes various diseases like heart disease, diabetes, obstructive sleep apnea, cancer and osteoarthritis (Mohapatra 2013). The major reason behind the consequence is the typical modern diet having high amount of refined and processed products which lacks the necessary levels of dietary fiber, minerals and vitamins which are necessary for keeping the body healthy (Mohapatra 2013). The incorporation of dietary fiber into the food leads to a healthy body. The dietary content of seaweed is as high as 75% of the total dry weight which consists of structural polysaccharides (alginate and fucoidans) from brown seaweeds, carrageenan, agar and porphyran (red seaweed) and ulvan (green seaweeds) (Mohapatra 2013). Those compounds produce hypocholesterolemic and hypolipidemic responses as they show reduction in cholesterol absorption in the gut (Jimenez-Escrig and Sanchez-Muniz 2000). Adding to this, seaweeds have low fat content (less than 2%) and are good sources of PUFAs including the essential omega- (n)-3s LNA EPA and DHA and omega-(n)-LNA (linolenic acid). Brown algal pigment, fucoxanthin and its precursor metabolite fucoxanthinol induces the expression of UCP_1, a protein which suppresses fat accumulation mostly in rats and mice (Aca et al. 2002).

Obesity causes insulin resistance which leads to diabetes (Mohapatra 2013). As suggested by some dialectologists, alpha-glucosidase inhibitors are a cost-effective means to prevent the gradual increase of diabetes as this enzyme reduces the absorption glucose from the gut (Mohapatra 3013). Methanolic extract of a brown alga, *Ecloniastolonifera*, contains high contentof polypohenols, which inhibits alpha-glucosidase in vitro (Imai 2008). In case of rat, an aqueous ethanolic extract of *Ascophylumnodosum* is found to be effective in inhibiting rat intestinal alpha-glucosidase (Zhang et al. 2007). Polyphenol extracts from edible seaweed have antidiabetic effect and the mechanism is thought to involve the inhibition of both the enzyme activity i.e., alpha amylase and alpha-glucosidase(Nwosu et al. 2011). Fucoxanthin found in edible brown seaweeds such as *Undariapinnatifida*, *Hijikiafusiformis*, *Sargassummuticum* extracts shows hypoglycemic effect. The mechanism involves the enhancement of glucose transporter for mRNA expression of L-6 myotubules by fucoxanthin which is responsible for glucose transport in adult muscle tissue. It enhances the synthesis of docosahexanoicaicd (DHA) in the liver which further increase the insulin sensitivity thereby improving triglycerides and reducing LDL and cholesterol.

3.5. Seaweeds as antithrombotic and anticoagulant activity

Fucoidans present in brown algae shows in vivo and in vitro heparin- like antithrombic and anti- coagulant activities that are carried by blood coagulation inhibitors such as heparin cofactor II or antithrombin III (Matou et al. 2002). The activity further increases with the amount of sulphation (Nishino and Nagumo 1992). Laminarian, acompoundextractedfrom seaweed also shows anticoagulant activity (Table 2).

Table 2.Examples of bioactivity exhibited by chemicals produced by seaweeds (Ref:Renato and Leticia 2012)

Seaweed	Chemical	Activity	Reference
Stypopodium sp.	stypoldione	cytotoxicity	Gerwick and Fenical1981
Chondria sp.	condriamide A	cytotoxicity	Palermo et al. 1992
Chondria sp.	condriamide A	against HSV type II	Palermo et al. 1992
Eiseniabicyclis	polyphenols	antioxidant	Shibata et al. 2002;Heo et al. 2005
Gracilariaedulis	crude extract	antibacterial	Vallinayagam et al. 2009
Martensiafragilis	alkaloids	antioxidant	Takamatsu et al. 2003
Martensiafragilis	alkaloids	NAPDPH-depending lipid peroxidation	Takahashi et al. 1997
Rhodophyllismembranacea	Polyhalogenatedin doles	antifungal	Brennan and Erickson 1978
Bryopsissp	kahalalide F	anticancer	Nuijen et al. 2000; Sparidans et al. 2001
Chondriaatropurpurea	chondriamide B	anthelmintic	Davyt et al. 1998
Fucusvesiculosus	fucoidan	anticoagulant	Bernardi and Springer 1962
Botryocladiaoccidentalis	sulfated galactan	anticoagulant	Farias et al. 2000
Sargassumvulgare	alginate	anticancer	Sousa et al. 2007
Kappaphycus striatum	kappa-carrageenan	anticancer	Yuan et al. 2006
Cladosiphonokamuranus	fucan	antiviral	Hidari et al. 2008
Schizymeniadubyi	sulfated glucuronogalactan	antiviral	Bourgougnon et al. 1996
Undariapinnatifida	crude extract	anti-inflammatory	Khan et al. 2008
Lobophoravariegata	lobophorolide	antifungal	Kubanek et al. 2003
Canistrocarpuscervicorni s	diterpenes	against *Pernaperna* settlement	Bianco et al. 2009
Sargassumtenerrimum	polyphenols	against *Hydroideselegans*settlem ent	Lau and Qian 1997
Plocamiumbrasiliense	monoterpenes	against *Balanusamphitrite*settlem ent	Konig et al. 1999

Deliseapulchra	furanones	against epibiosis	Dworjanyn et al. 1999
Laurenciamajuscula	terpenoid	anti-bacteria	Vairappan et al. 2001
Laurenciarigida	elatol	against *Bugulaneritina*settlement	Konig and Wright 1997
Ulvareticulata	polysaccharides	against *Hydroideselegans*settlement	Harder et al. 2004

Future prospective

The survey of the compounds manufactured by macroalgae or seaweeds for pharmaceutical tenacities has exposed chemical frameworkssignificant for the detection of new agents via the expenditure of refined techniques and formation of new compounds having biomedical application (Cardozo et al. 2007). The amino acid content, kainic acid, sequestered from the tropical species *Digenea simplex* (Rhodophyta, Ceramiales) confirms the pharmacological prospective of marine algae as sources of novel cures for parasitic disease and is acknowledged for its anti-helminthic and insecticidal properties in East-Asian countries for more than 1000 years (Nitta et al. 1958; Moo- Puc et al. 2008). Seaweeds are undeniably the appropriate natural agents for generating and supplying the bioactive products grounded on the multifunctional characteristics of secondary metabolites found in seaweeds and the manifestation of an extensive diversity of related non-toxic antioxidants (Smit 2004). The bioavailability of seaweed based antioxidantshould be the principal study in research possibilities (Frankel and Finley 2008). Organisms do not normally function in isolation at any metabolic level, and oxidation-reduction reactions and subsequent cellular exposures to reactive species are fundamental to all living things. Homeostasis is compromised by an unevenness caused by the reactive species and the impacts of cellular damage can be alleviated and lessened by the host of significant seaweed antioxidants (Cornish and Garbary 2010).

Conclusion

From centuries marine algae has been used as food and medicines (Pooja 2014). Efforts have been made by pharmaceutical companies and academic institutions to separate and spot new marine derived, natural products especially from faunal species (Pooja 2014). The marine resources offer vital bioactive molecules that have advantages on human body (Hamed et al. 2015). They can be applied on several fields such as drugs, cosmetics and food industries.

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