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Chapter 5

THERAPEUTIC AND PHARMACEUTICAL APPLICATION OF SEAWEEDS

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ABSTRACT

Our planet is supposed to host 11.213 billion people by the end of the year 2100. Such demographic explosion poses serious problems for human life quality and security. Generally, the term "seaweed" is conventionally used to designate multicellular marine algae. In the last three decades, and due to the high diversity of their metabolites, seaweeds are used in medicine to treat gall stones, stomach ailments, eczema, cancer, renal disorders, scabies, psoriasis, asthma, arteriosclerosis, heart disease, lung diseases, ulcers, etc. Compounds like carotenoid, polysaccharides, fatty acids, glycoproteins, haloforms, halogenated alkanes, alkenes, alcohols, aldehydes, hydroquinones, ketones, phlorotannins, pigments, lectins, alkaloids, terpenoids, sterols and some heterocyclic and phenolic compounds are among the most important seaweed substances that receive attention from pharmaceutical companies for use in drug development, or from scientists in the field of medical

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research. The potential pharmaceutical, medicinal and investigatory applications of these compounds in antibiotic, antiviral, anticancer, antioxidants, anti-inflammatory, anticoagulants, and antidiabetic production are discussed in this chapter.

Keywords: seaweeds, antibiotic, antiviral, anticancer, anticoagulants, antidiabetic, analgesic.

INTRODUCTION

The term "seaweed" is conventionally used to designate multicellular marine algae (red, green and brown algae). However, the unicellular (spores or zygotes) stage seems to be an obligatory present stage in the life cycle of all described seaweeds (Lobban and Harrison 1997). Seaweeds are photosynthetic organisms, able to fix carbon dioxide to form complex organic compounds and release high amounts of oxygen in the atmosphere. Thus, suggesting that algae are the true lungs of earth (Pereira 2016). Based on pigmentation, seaweeds were classified to: 1) Green algae (Chlorophyta), characterized by their photosynthetic pigments such as Chlorophyll a and b, contained in special structures known as chromatophores. 2) Brown algae (Phaeophyta), that varies in color from olive-yellow to deep brown. These colorations are due to fucoxanthine and carotenoid pigments. 3) Red algae (Rhodophyta), characterized by their water-soluble phycoerythrin and phycocyanin pigments, in addition to carotene and chlorophyll (Verlecar and Rathod 2004). The differences between these groups are more important than those indicated by this simple designation; ultra-structural and metabolic characteristics such as photosynthetic pigments, storage compounds, fine structure of chloroplasts and their cell wall composition, are variable from one group to another and even from one species to another in the same group (Rindi et al. 2012).

The world's population is supposed to surpass 9.725 and 11.213 billion habitants by the end of the years 2050 and 2100; respectively. This demographic explosion poses serious problems for human life quality and security (UN 2004, Ashraf et al. 2012, UN 2015). Recently, seaweeds figure prominently among the proposed solutions for sustainability challenges, aiming to unlock seas and oceans potential as primordial sources of food and feed production worldwide. In addition to their use as fertilizers, fungicides, herbicides, condiments, dietary supplements and as resources of phycocolloids such as agar, seaweeds can be a substantial feedstock for biomass, biofuel production,

and for animal feeds. Impressively, and due to the high diversity of their chemistry, seaweeds are used in medicine to treat gall stones, stomach ailments, eczema, cancer, renal disorders, scabies, psoriasis, asthma, arteriosclerosis, heart disease, lung diseases, ulcers, etc.(Smit 2004, Ye et al. 2008, Peng et al. 2015, Tiwari and Troy 2015). Away from medicine, my story with seaweeds started with Pr. Nabti Elhafid in 2013, when we carried interesting works about the role of natural compatible solutes from tow marine chlorophytes "*Ulva lactuca* and *Enteromorpha intestinalis*" in improving both rhizobacterial and plant growth under salt stress. In this chapter, we tried to summarize the most important aspects of therapeutic and pharmaceutical application as well as the principal bioactive molecules of seaweeds used in pharmaceutical area, lightening with examples the major species used in antimicrobial, antitumor, antiviral, antioxidant, anticoagulant and other fabrications worldwide.

SEAWEEDS, A BIG TANK OF ANTIBIOTICS

The famous works of Pasteur and Koch have opened a large window in science, establishing that microorganisms are the causative agents of infectious diseases. In parallel, through the works of Paul Ehrlich on a "magic bullet" that selectively targets microbes but not hosts and his development of anti-syphilis drugs (1904-1909), together with the amazing discovery of Penicillin by Alexander Fleming (1929), it becomes well established the existence of molecules able to attack specifically disease-causing microorganisms in the host. Since that, scientists are continually developing different protocols to synthetize chemicals and purify bioactive molecules from different sources that have inhibitory effects against pathogenic microorganisms (Franklin et al. 2005, Aminov 2010). It is well admitted that chemical composition of seaweeds contains a wide range of molecules having antibiotic activities, especially halogenated molecules such as haloforms, halogenated alkanes and alkenes, alcohols, aldehydes, hydroquinones, ketones, polysaccharides, fatty acids, phlorotannins, pigments, lectins, alkaloids, terpenoids, sterols and some heterocyclic and phenolic compounds (Lincoln et al. 1991, Smit et al. 2004, Pérez 2016).

Crude extracts from brown, red and green seaweeds have been used all over the world for their antibiotic activities. For example, Varier at al. (2013) tested the effect crude extracts from the Indian red seaweeds *Gelidiella acerosa*, *Gracilaria verrucosa* and *Hypnea musciformis* against *Salmonella*

paratyphi, *Enterococcus aerogenes*, *Staphylococcus epidermidis*, *Salmonella typhi* and *Shigella flexneri*. The results showed different activities from extract to another, from bacteria to another and from extraction solvent to another. Another study realized by Moorthi and Balasubramanian (2015) revealed the antibacterial activity of acetone and chloroform extracts from the seaweed *Sargassum muticum* against human pathogens such as *Micrococcus* sp., *Salmonella paratyphi* and *Shigella flexneri*. In addition, Acetone, Methanol, Chloroform, Diethyl ether, Ethyl acetate, Ethanol and Petroleum ether extracts from the green algae *Codium adherens*, *Ulva reticulata* and *Halimeda tuna* were tested for their antibacterial activities. The results showed that ethanol extract gave better activity against *Staphylococcus* sp., while the tested seaweed showed different inhibitory effects against *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, *Enterococci* sp., *Proteus* sp., *Streptococcus* sp., *Pseudomonas aeruginosa*, *Vibrio parahaemolyticus*, *Salmonella* sp., *Shewanella* sp., *Vibrio flurialis, and Vibrio splendidus.* Extracts efficiency was variable from one solvent to another and from one species to another (Karthikaidevi et al. 2009). Saidani et al. (2012) screened the antifungal activity of four Algerian marine algae *Rhodomella confervoides* (Rodophyceae), *Ulva lactuca* (Chlorophyceae), *Cystoseira tamaricifolia* and *Padina pavonica* (Phaeophyceae) against *Aspergillus niger* (939N), *Candidaalbicans* (ATCC 1024) and *Mucor ramaniannus* (NRRL 1829). Their results suggest that marine algae harvested from Algerian coast present high antifungal activities, making of them interesting sources of natural antibiotic compounds. In addition, antiprotozoal activity of seaweeds also attracts scientific attention, looking for new bioactive molecules against parasites. Thereby, ten Turkish marine algae (*Caulerpa rasemosa*, *Codium bursa*, *Cystoseira barbata*, *Cystoseira crinata*, *Corallina granifera*, *Jania rubens*, *Ceramium rubrum*, *Gracilaria verrucosa*, *Dasya pedicellata* and *Gelidium crinale*) were tested for their antiprotozoal activities against four parasites *Plasmodium falciparum*, *Trypanosoma brucei rhodesiense*, *T. cruzi* and *Leishmania donovani*. The results showed that all seaweed extracts were active against *T. brucei rhodesiense* and *Leishmania donovani*, while the majority of extracts showed antiplasmodial activity, revealing that seaweeds could constitute a potential source of antiprotozoal compounds (Süzgeç-Selçuk et al. 2011). Many other works highlighted the efficiency of crude extracts from seaweeds in inhibiting bacterial, fungal and protozoal growth and the possibility of exploiting them as new sources for antibiotics worldwide (Manivannan et al. 2011, Pandian et al. 2011, Vonthron-Sénécheau et al. 2011,

Oumaskour et al. 2012, Peres et al. 2012, Moorthi and Balasubramanian 2015, Pérez et al. 2016).

Away from crude extracts, researchers are more to more focusing on extraction, isolation and purification of new molecules with antibiotic activities from seaweeds. Fucoidan from the marine macro-algae *Sargassum wightii* revealed interesting antibacterial activity against human pathogens such as *Escherichia coli*, *Klebsiella pneumonia*, *Vibrio cholera*, *Proteus sp.*, *Pseudomonas aeruginosa* and others (Marudhupandi and Kumar 2013). Kantachumpoo and chirapart (2010) found that polysaccharides from the two marine algae *Colpomenia sinuosa* and *Sargassum polycystum*, collected from the province Chon Buri-Thailand, present an inhibitory activity against *Candida albicans*. Furthermore, Alghazeer et al. (2013) found that Alkaloids from the brown marine algae *Cystoseira barbata* could inhibit the growth of the human pathogen Klebsiella spp.They also discussed the inhibitory effect of alkaloid extract from the red seaweed *Dictyopteris membranacea*, showing itsantibacterial activity against *Salmonella typhi*. Concerning phlorotannins, Eom et al. (2012) summarized the antimicrobial activities of compounds such as Eckol, dieckol, dioxinodehydroeckol, fucofuroeckol-A, 7-phloroeckol, Phlorofucofuroeckol-A, 8,8'-Bieckol and phloroglucinol against bacteria and fungi like methicillin-resistant *Staphylococcus aureus* (MRSA), *Trichophyton rubrum, bacillus cereus, Salmonella thyphimurium, Klebsiella pneumonia* and others. Lee et al. (2014) reported the antibacterial activity of a fucofuroeckol-A purified from the brown seaweed *Eisenia bicyclis* against acne-related bacterium *Propionibacterium acnes*. In addition, the antifungal activities of dieckol from the brown alga *Ecklonia cava* against *Trichophyton rubrum*, the most common causative agent of dermatophytic nail infections in humans, was described in the work of Lee et al. (2010). The results obtained with microscopic observation indicated that dieckol exhibited fungicidal activity against *T. rubrum* due to loss of its membrane integrity. Nagayama et al. (2002) studied the bactericidal activity of five phlorotannins (phloroglucinol, eckol, Phlorofucofuroeckol-A, dieckol and 8,8′-bieckol) purified from the brown alga *Ecklonia kurome* against *Staphylococcus aureus* ATCC 25923 (MRSA), *Bacillus cereus* ATCC 19637, *Campylobacter jejuni* CIP 702, *Escherichia coli* ATCC 25922, *Salmonella enteritidis* S-48, *Salmonella typhimurium* ATCC 14028 and *Vibrio parahaemolyticus* KR1151. No toxicity was obtained on mice treated with the same bactericidal concentrations of algal phlorotannins.

Among thirty-eight seaweeds samples, crude extract from the rhodophyta *Laurencia papillosa* showed the highest antibacterial activity against

Staphylococcus aureus ATCC 25923, *Bacillus subtilis* ATCC 6051, *Escherichia coli* ATCC 8739 and *Pseudomonas aerugenosa* ATCC 9027. The active fraction was identified as a cholesterol derivative (24-propylidene cholest-5-en-3β-ol) using gas chromatography mass spectrometry (GC–MS). The purified compound had a minimum inhibitory concentration that ranged from 1.2 to 1.7 µg/ml against the four clinical isolates *Escherichia coli*, *Pseudomonas aerugenosa*, *Klebsiella pneumoniae* and *Shigella flexneri*. These results suggest the usefulness of the purified sterol as potential lead molecule for broad-spectrum drug development, and confirm the potential of seaweeds as an important natural source of antimicrobial compounds for pharmaceutical industries (Kavita et al. 2014). Similarly, Rajauria et al. (2013) succeeded to isolate and partially identify a bioactive fucoxanthin from the Brown Seaweed *Himanthalia elongata*. The isolated fucoxanthin revealed strong antibacterial activity against the human pathogen *Listeria monocytogenes* (inhibition zone: 10.27 mm, 25μg compound/disc). It is also important to mention the interesting work of Kasanah et al. (2015) that constitute an excellent synthesis of the most important molecules used as antibacterial compounds from red seaweeds, particularly those belonging to bromophycolides and neurymenolides classes.

ANTIVIRAL COMPOUNDS IN SEAWEEDS

Viral infections are in the first line of mortality causes worldwide. For example, hepatitis A virus touch more than 80% of the population in some developing countries, while hepatitis B and C viruses affect about 360 and 123 million persons on the planet respectively and 30 million are attained by HIV. Under pressure of their high mortality, together with the permanent threat of emerging virulent strains, an important number of drugs have been developed face to viral threats. Their effectiveness is limited by viral resistance and drug safety (Dwivedi et al. 2013, Sousa et al. 2016).

Marine macro-algae could be cultured in high volumes without demanding a lot of care. Among a wide range of therapeutic compounds produced by seaweeds, some of them are characterized by antiviral activities (Pinto et al. 2012, Peng et al. 2013, Anbuchezhian et al. 2015, Pérez et al. 2016). Yasuhara-Bell and Lu (2010) summarized the antiviral activities of marine compounds, including those produced by seaweeds, toward a wide range of viruses such as: herpes viruses (HSV-1, HSV-2, HCMV), togaviruses, paramyxoviruses (RSV), rhabdoviruses (VSV), human immune deficiency

viruses (HIV), mumps virus and influenza B virus etc. Hudson et al. (1999) studied the antiviral activity of 13 Korean seaweed against the herpes simplex (HSV), Sindbis virus (SINV) and poliovirus. The *Codium fragile*-extract showed high activity against the three viruses, while *Enteromorpha linza*, *Colpomenia bullosa*, *Scytosiphonlo mentaria*, and *Undaria pinnatifida*-extract were active only against HSV and SINV. The other algae (*Ulvapertusa*, *Ishige okamurai*, *Sargassum sagamianum*, *Carpopeltis affinis*, *Corallina pilulifera*, *Grateloupia turuturu*, *Symphyocladia latiuscula* and *Symphyocladia marchantioides*) were selective against either HSV or SINV. The antiviral activity of aqueous, methanolic, chloroform-methanolic and dichloromethanolic extracts from 16 Moroccan red seaweed was tested against Herpes simplex virus type-1 (HSV-1) using cell viability method. Algal extracts from *Asparagopsis armata*, *Ceramium rubrum*, *Gelidium pulchellum*, *Gelidium spinulosum*, *Halopitys incurvus*, *Hypnea musciformis*, *Plocamium cartilagineum*, *Boergeseniella thuyoides*, *Pterosiphonia complanata* and *Sphaerococcus coronopifolius* inhibited the *in vitro* replication of the virus at an effective concentration (Rhimou et al.2010). Furthermore, Wang et al. (2008) and Koishi et al. (2012) described the antiviral activity of crude extracts from seaweeds such as *Canistrocarpus cervicornis*, *Padina gymnospora*, *Palisada perforate*, *Caulerpa racemose*, *Hydroclathrus clathratus* and *Lobophora variegate* against dengue virus (DENV), HSV-1 and HSV-2.

Polysaccharides (sulfated polysaccharides in particular), poliketides, terpenoids, peptides and glycolipids such as monogalactosyl diacylglycerides (MGDG), digalactosyl diacylglycerides (DGDG), and sulfoquinovosyl diacyl-glycerides (SQDG), constitute the major part of antiviral compounds that have been purified and identified from seaweeds (Adhikari et al. 2006, Bandyopadhyay et al. 2011, Cardozo et al. 2011, de Souza et al. 2012, Kind et al. 2012, Saha et al. 2012). In 2013, Plouguerné et al. isolated and identified the detailed chemical structure of an anti-herpes compound from the Brazilian brown seaweed *Sargassum vulgare*. This active compound was purified from the lipid fraction of the crude extract and identified as sulfoquinovosyl diacyl-glycerols (SQDGs). SQDGs showed high antiviral activity against herpes simplex virus (HSV-1 and HSV-2). Wang et al. (2007) isolated and purified a SQDG with high antiviral activity against both HSV-1, HSV-2 and Coxackie virus B3 (Cox B3) from an n-butanol fraction of an aqueous extract of the green algae *Caulerpa racemosa* collected from the south China sea. In addition, Mandal et al. (2007) analyzed a sulphated-fucan-containing fraction isolated from the brown seaweed *Cystoseira indica*. The main fraction (CiF3)

obtained by anion exchange chromatography of the crude aqueous extract had strong antiviral activity against the two viruses HSV-1 and HSV-2. The major polysaccharide in the fraction (CiF3) was identified as a sulfated fucan with a molecular mass of 35 kDa. It contains a backbone of α-(1→3)-linked fucopyranosyl residues substituted at C-2 with fucopyranosyl and xylopyranosyl residues. In the last few years, many other sulfated polysaccharides have been isolated from seaweeds like *Adenocystis utricularis*, *Sphaerococcus coronopifolius*, *Boergeseniella thuyoides* and *Cladosiphon okamuranus*. Such compounds were identified as antiviral molecules against a wide range of viruses such as Newcastle Disease Virus (NDV), Herpes simplex virus (HSV-1, HSV-2) and Human immunodeficiency virus (HIV) etc.(Ponce et al. 2003, Trinchero et al. 2009, Bouhlal et al. 2011, Elizondo-Gonzalez et al. 2012). Furthermore, Soares et al. (2007) showed that extract from the Brazilian seaweed *Stypopodium zonale* contains compounds such as meroditerpenoids aromatic acid, epitaondiol and peroxylactone with high antiviral activity against the herpes simplex virus (HSV-1).

PLACE OF SEAWEEDS IN THE FIGHT AGAINST CANCER

Historically, seaweeds were used for a long time in both traditional Chinese and Folk Japanese medicine to treat tumors. In such populations, where seaweeds constitute a regular part of their diet, the rates of tumors development are dramatically lower (Teas et al. 2013). In Europe, the first reported use of seaweed was in 1970, when an English physician used ash from kelp to treat goiter (Hayes 2015). An interesting study realized by Yang et al. (2010) on the relation between two seaweed consumption (*Porphyra* sp. and *Undaria pinnatifida*) and breast cancer. In this study, 362 Korean women aged between 30 and 65 years old, were histologically confirmed to have breast cancer and compared to control cases visiting the same hospital. Among other characters, controls were matched to cases based on their diet, estimated by the quantitative FFQ with 121 items, including the two studied seaweeds. The results showed high inverse correlation between *Porphyra* sp. intake and the risk of breast cancer. Namvar et al. (2013) highlighted several *in vivo* and *in vitro* pharmacological studies describing Seaweed anticancer effects and underlined the possibility that these therapeutic properties may be attributed to the biologically active metabolites produced by seaweeds. In 1989, Fernandez et al. isolated and characterized an antitumor active agar-type polysaccharide from the red macro-algae *Gracilaria dominguensis* using a cold-water

extraction followed by cetyltrimethylammonium bromide fractionation. The obtained sulfated galactan (CT-1) presented high inhibition of the Ehrlich ascites carcinoma transplantation in mice. Ye et al. (2008) succeeded to obtain two polysaccharide fractions SP-3-1 and SP-3-2 from the brown seaweed *Sargassum pallidum*. These fractions showed high antitumor activity against the human hepatoma cell line "HepG2 cells," human lung cancer cell line "A549 cells," and human gastric cancer cell line "MGC-803 cells." The authors attributed this antitumor activity to the molecular weight of the fractions and their high sulfate content. Mhadhebi et al. (2014) tested the antioxidant, anti-inflammatory and antiproliferative effects of aqueous extracts of three Mediterranean brown seaweeds of the genus *Cystoseira*. Aqueous extracts from the algae *Cystoseira crinita*, *C. sedoides* and *C. compressa* showed a significant antiproliferative effect against Human tumor cell lines HCT15 and MCF7. This pharmacological property was positively correlated with the total phenol content and the antioxidant activity of the extracts. Other works suggested the implication of compounds such as phlorotanins, fucoidans and terpenes (diterpene mediterraneol, usneoidone E and Z etc.)in the antitumoral, antiproliferative and anticancer activities that characterize algal extracts (Francisco et al. 1985, Urones et al. 1988, Fisch et al. 2003, Huicheng 2010, Lowenthal and Fitton 2015). In addition, Boominathan and Mahesh (2015) underlined the important role of carotenoid compounds such as β-carotene, astaxanthin and fucoxanthin in suppressing carcinogenesis. Being highly effective as antioxidant (oxidative stress is putatively involved in cancer development), carotenoids such β-carotene, α-carroten, fucoxanthin, astaxanthin, canthaxanthin, zeaxanthin and lutein could constitute important additive or drugs for cancer prevention (Kotake-Nara et al. 2005, Boominathan and Mahesh 2015). Otherwise, seaweeds belonging to the genera *Bryopsis*, *Sargassum* and *Kappaphycus* are able to produce compounds like kahalalide F, alginate and kappa-carrageenan, known for their impressive anticancer activities (Pereira and Costa-Lotufo 2012). Kim et al. (2014) investigated the cytotoxic and apoptotic effects of an ethanol extract derived from the marine brown alga *Dictyopteris undulata* against human colon adenocarcinoma cells. The obtained result showed that this algal extract induced apoptotic cell death in three colon-cancer cell lines SW480, SNU407 and HT29, and proved its usefulness as a therapeutic agent for colon cancer attenuation.

ANTIOXIDANTS FROM SEAWEEDS

Recently, due to knowledge accumulation about production and metabolism of reactive oxygen and nitrogen species (ROS and RNS), and understanding damages related to free radicals and their derivatives, oxidative stress has become one of the most alarming topics between researchers. The imbalanced generation of ROS and RNS (pro-oxidants) in a system, exceeding its ability to neutralize and eliminate them, produces oxidative stress (Rahman et al. 2012, Rahal et al. 2014). For more than four decades, oxidative stress remained known to be implicated in various forms of pathophysiology of inflammation, neurodegenerative disorders, diabetes mellitus, atherosclerosis, fibrosis, cancer, and reperfusion injury (Hybertson et al. 2011, Vadlapudi et al. 2012). In response to oxidative stress, the body synthesize and/or accumulate antioxidants such as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, minerals like Se, Mn, Cu and Zn, and vitamins like vitamin A, C and E (Irshad and Chaudhuri 2002).Antioxidant compounds from seaweeds constitute a potential source of antioxidant compounds in nature such as ascorbate, glutathione, carotenoids, mycosporine-like amino acids, catechins, gallate, phlorotannins, eckol, ascorbic acid, tocopherols etc. (Mariya and Ravindran 2013, Farasat et al. 2014).

Ismail and Hong (2002) studied the antioxidant potential of crude extracts from the marine algae *Porphyra* sp. *Laminaria* sp. *Undaria* sp. and *Hijikia* sp. Water extract from *Porphyra* sp. *Laminaria* sp. and *Hijikia* sp. exhibited higher radical scavenging activity than *Undaria* sp. this last exhibited the highest antioxidant and free radical scavenging activities when extracted with ethanol. Likewise, aqueous and ethanolic extracts from the Thailand Gulf seaweeds *Sargassum binderi* Sonder, *Amphiroa* sp., *Turbinaria conoides* (J. Agardh) Küzting and *Halimeda macroloba* showed high antioxidant and scavenging activity of both ABTS [2, 2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)] and DPPH (2, 2- diphenyl-1-picrylhydrazyl) radicals (Boonchum et al. 2011). Other studies discussed the total antioxidant activity of crude extracts from seaweeds such as *Dictyota dichotoma*, *Dictyota indica*, *Iyengaria stellata*, *Padina pavonica*, *Sargassum swartzii*, *Sargassum variegatum*, *Stoechospermum marginatum*, *Stokeyia indica*, *Jolyna laminarioides*, *Caulerpa taxifolia*, *Halimeda tuna*, *Ulva* sp., *Solieria robusta*, *Melanothamnus afaqhusainii*, *Eucheuma cottonii*, *Padina* sp., *Chaetomorpha linum*, *Grateloupia lithophila*, *Sargassum wightii*, *Jania rubens* and *Pterocladia capillacea*. For this, different protocols were used like total antioxidant assays, reducing power, DPPH radical scavenging activity, ABTS

radical scavenging activity, Deoxyribose scavenging activity, H2O2 radical scavenging assay, Lipoxygenase activity and Nitric oxide radical inhibition assay (Farasat et al. 2013, Foon et al. 2013, Indu and Seenivasan 2013, Khairy and El-Sheikh 2015, Tariq et al. 2015).

The efficiency of polysaccharides, especially sulfated polysaccharides, from marine algae such as *Dictyopteris Justii, Sargassum graminifolium, Padina gymnospora, Gracilaria birdiae, Gigartina skottsbergii, Schizymenia binderi, Lessonia vadosa* and *Fucus vesiculosus*, was largely studied in the last few years (Rupérez et al. 2002, Barahona et al. 2011, de Souza et al. 2007, Souza et al. 2012).Melo et al. (2013) extracted and purified four sulfated polysaccharides [fucoglucoxyloglucuronan (DJ-0.3v), heterofucan (DJ-0.4v), and two glucans (DJ-0.5v and DJ-1.2v)]from the brown seaweed *Dictyopteris Justii*. The polysaccharides DJ-0.4v and DJ-0.5v showed high antioxidant activity in some in vitro tests (determination of total antioxidant capacity, reducing power, and hydroxyl radical scavenging activity, superoxide radical scavenging activity, ferrous and copper chelation assays). The antioxidant activities of polysaccharides from the brown seaweed *Sargassum graminifolium* were assayed by determining their reducing power, their ability to scavenge superoxide radicals, and their activity in the DPPH assay. The ability of these polysaccharides to inhibit calcium oxalate crystallization, together with their antioxidant activities suggest their usefulness in treating urinary stones (Zhang et al. 2012).

Phlorotannins are phenolic compounds restricted to polymers of phloroglucinol. Among other characters, phlorotannins from marine algae have an important antioxidant activity. Sathya et al. (2013) isolated a dichloromethane fraction with high antioxidant activity from the crud extract of the brown seaweed *Cystoseira trinodis*. It was further fractionated using column chromatography. The column-purified fractions were subjected to thin-layer chromatography to obtain seven sub-fractions. Most of the fraction, analyzed and identified as phlorotannins, had antioxidant activity. Furthermore, Kim et al. (2011) tested the hepatoprotective effect of phlorotannins from the seaweed *Eisenia bicyclis* against oxidative stress induced by *tert*-Butyl Hyperoxide (*t*-BHP). For this, crude ethanol extract and its serial solvent fractions were screened. Five phlorotannin compounds (eckol, 6,6'-bieckol, 8,8'-bieckol, dieckol and phlorofucofuroeckol A), purified from the ethyl acetate fraction, and showed high hepatoprotective effect against *t*-BHP-induced cell death in HepG2 cells, suggesting their possible development as potential candidates for natural hepatoprotective agents. Antioxidant activity of phlorotannins from seaweeds like *Eisenia*

bicyclis, *Ecklonia cava*, *Ecklonia kurome*, *Fucus vesiculosus*, *F. spiralis*, *Cystoseira nodicaulis*, *C. tamariscifolia* and *C. usneoides*, was also discussed by researchers such as Ahn et al. (2007), Shibata et al. (2008), Ferreres et al. (2012), Wang et al. (2012), and others. Elsewhere, fucoxanthin from the seaweed *Hijikia fusiformis* was its richest carotenoid compound. This fucoxanthin also revealed high radical scavenging efficiency (Yan et al. 1999). Airanthi et al. (2011) assayed antioxidant activities of some edible seaweed in Japan (*Eisenia bicyclis*, *Kjellmaniella crassifolia*, *Alaria crassifolia*, *Sargassum horneri* and *Cystoseira hakodatensis*). Their results suggest that the antioxidant activity of the seaweed *C. hakodatensis* is mainly due to its fucoxanthin and phenolics compounds with high radical scavenging activities.

ANTI-INFLAMMATORY, IMMUNOMODULATORY AND ANALGESIC COMPOUNDS

Oxidative stress is implicated in various forms of pathophysiology of inflammation. A wide range of brow, red and green seaweed are known to contain antioxidants with anti-inflammatory activity. Studies of anti-inflammatory compounds in seaweeds range from the revelation of seaweed crude extracts to the study of certain isolated, purified, and characterized molecules (polysaccharides, carotenoids, phlorotannins, polyunsaturated fatty acids etc.) (Lee et al. 2013). Vázquez et al. (2011) studied Anti-inflammatory and analgesic activities of the red seaweed *Dichotomaria obtusata*. In the classical tests used on mice (ear edema induced by TPA and writhing induced by acetic acid), aqueous extract of the algae inhibited ear edema in a dose-dependent manner and reduced abdominal writhes in mice, suggesting that this algal extract possesses therapeutic potential in the treatment of peripheral painful or/and inflammatory symptoms. Several studies have focused on anti-inflammatory activities of complete fractions or crude extracts from red, green and brown marine macroalgae (*Capsosiphon fulvescens*, *Codium fragile*, *Colpomenia sinuosa*, *Ishige okamurae*, *Chondrus ocellatus*, *Carpopeltis cornea*, *Cystoseira sedoides*, *Padina tertastomatica*, *Sargassum wightii*, *Spatoglossum schroederi*, *Dichotomaria obtusata* etc.) (Khan et al. 2008, Mhadhebi et al. 2011, Delgado et al. 2013, Radhika et al. 2013, Júnior et al. 2014).

The Algal sulfated polysaccharide from the seaweed *Eckloniacava* significantly inhibited nitric oxide production, prostaglandin-E2 (PGE2)

production and suppressed inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression when tested in LPS-stimulated RAW 264.7 macrophages. Suggesting that this polysaccharide could be used as an effective immunomodulatory mediator with a variety of beneficial effects, implicated in anti-inflammatory agents-modulation (Kang et al. 2011). Sulfated polysaccharides from the red algae *Gracilaria cornea* (Gc-TSP) showed significant analgesic and anti-inflammatory effects when tested in mice model. Thus, weak doses of Gc-TSP (3 and 9 mg ⁄ kg) significantly inhibited paw edema induced by carrageenan, especially at 3 hour after treatment. In addition, Gc-TSP significantly reduced nociceptive responses, as measured by the number of writhes, at all tested doses, indicating that Gc-TSP possesses important analgesic and anti-inflammatory activities (Coura et al. 2012). Fucans fraction from the brown seaweed *Ascophyllum nodosum* was termed (BS8) and tested for its ability to modulate complement activation. BS8 inhibited the formation of classical pathway C3 convertase by inhibiting C1 activation, C4 cleavage, suppressing the binding B-C3b and by interfering with the stabilizing function of Properdin. BS8 was more efficient than heparin in inhabiting complement activation and exhibiting lesser anticoagulant activity. These results suggest that sulfated polysaccharides from *Ascophyllum nodosum* could play an important role as immunomodulatory compounds (Blondin et al. 1994). De Araújo et al. (2011) studied the role of a sulfated polysaccharide (SP-Sf), isolated from the red seaweed *Solieria filiformis*, as analgesic and anti-inflammatory compound. For this, they treated mal Swiss mice with the polysaccharide 30 minutes before the injection of 0.8% acetic acid, 1% formalin or 30 min prior to a thermal stimulus. 1, 3 or 9 mg/kg of SP-Sf significantly reduced the number of writhes and the second phase of the formalin test. In addition, SP-Sf did not cause a significant antinociceptive effect in the hot plate test, suggesting that its antinociceptive action occurs through a peripheral mechanism, suggesting that this sulfated polysaccharide may be a key tool for studying inflammatory processes associated with nociception.

In an interesting study, a blend of three extracts from different species of brown seaweeds (*Fucus vesiculosis*, *Macrocystis pyrifera* and *Laminaria japonica*) was administrated, together with some nutritional additives, to 10 randomized participants that receive either a 100 mg (n = 5) or 1000 mg (n = 5) dose over 4 weeks. The objective was to investigate the changes in lymphocyte subsets (primary outcome measures), and to follow the changes in T-lymphocyte (CD4 and CD8) activation, phagocytosis of granulocytes and monocytes, T helper 1/T helper 2 cytokines, and serum oxygen radical

absorbance capacity (secondary outcome measures). The mixture used in this experiment was safe for administration during four week and was demonstrated to have significant potential as an immune modulator of the studied parameters (Myers et al. 2011). Kim and Joo, (2008) highlighted the Immunostimulatory effects of fucoidan from the brown seaweed *Fucus vesiculosus* on bone marrow-derived dendritic cells. This polysaccharide significantly increased the viability of DCs, the production of interleukin-12 and tumor necrosis factor-α, and the expression of major histocompatibility complex class I, class II, CD54, and CD86 molecules. In fucoidan treated dendritic cells, p65 molecules of nuclear factor-κB translocated from the cytosol to the nucleus, suggesting that Immunostimulatory and maturing effects of this fucoidan on dendritic cells, via a pathway involving at least the nuclear factor-κB. Furthermore, the important role of sulfated polysaccharides from seaweed (*Cauler pamexicana*, *Cauler pacupressoides*, *Nemalion helminthoides* etc.) as anti-inflammatory, analgesic and as immune-reactions modulators was widely studied (Patel 2012, Rodrigues et al. 2012, Carneiro et al. 2014, Pérez-Recalde et al. 2014, Raposo et al. 2015).

The*ω*-3 polyunsaturated fatty acid (PUFA) of stearidonic acid (SA), *ω*-3 PUFA of eicosapentaenoic acid (EPA) and *ω*-6 PUFA of arachidonic acid (AA) were extracted and purified from the Brown seaweed *Undaria pinnatifida*, then tested for their anti-inflammatory activity using BALB/c mice. The effect of these compounds was revealed by comparing ear edema and erythema after application of Phorbol 12-myristate 13-acétate (PAM). Indomethacin was used as positive control. The three molecules showed significant anti-inflammatory activities and were active against edema, erythema, and blood flow in mice (Khan et al. 2007). Moreover, Heo et al. (2010) evaluated the anti-inflammatory effect extract from the brown algae *Myagropsis myagroides*, using lipopolysaccharide-stimulated RAW 264.7 macrophages. The extract possesses high ability to inhibit nitric (NO) oxide production. The active compound was later identified as fucoxanthin. Therefore, it inhibited NO production, reduced inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) protein expressions, and slightly reduced the prostaglandin E2 (PGE2) production. Their results suggest that the studied fucoxanthin may be useful in therapeutic approach for inflammatory diseases. Jaswir and Monsur (2011) also reviewed the diversity of anti-inflammatory compounds of macro-algae origin (*Sargassum swartzii*, *Ulva reticulate*, *Dichotomaria obtusata*, *Turbinaria conoides*, *Sargassum micracanthum*, *Galaxaura marginata* etc.).

ANTICOAGULANTS AND ANTI-THROMBIC ACTIVITIES

Anticoagulants are a class of drugs that work to prevent blood coagulation (clotting). They are used to treat and prevent blood clots that may occur in your blood vessels (Thrombosis) (Ekanayake et al. 2008). Seaweeds are known to be an exploitable source of anticoagulant compounds. Sulfated polysaccharides, particularly fucose containing polysaccharides, are the main source of such activity in seaweeds (Millet et al. 1999, Smit 2004, Yende et al. 2014). During the nineties, Takashi Nishino and his colleagues published a series of works on molecules with anticoagulant activity, including sulfated polysaccharides, and having as source the brown seaweed *Ecklonia kurome*. In 1989, his work "isolation, purification and characterization of fucose-containing sulfated polysaccharides from the brown seaweed *Ecklonia kurome* and their blood anticoagulant activities" opened. Compared to heparin (a standard anticoagulant), the four purified polysaccharides (B-I, B-II, C-I, C-II) showed a blood anticoagulant activity between 24 and 85%, with respect to APTT (activated partial thromboplastin time) (Nishino et al. 1989). Later, they published another work discussing the composition the anticoagulant C-II, previously isolated from the same marine algae *Ecklonia kurome*. Their analysis results suggested a structure of a highly branched, new type of fucan sulfate containing a backbone of (1+3)-linked L-fucosyl residues having sulfate groups mainly attached to c-4 (Nishino et al. 1991). At the same year, they discussed the influence of sulfate content in the same polysaccharide (C-II) on its anticoagulant activity. For this, they prepared fucans having different sulfate content by solvolytic desulfation of C-II and compared chemical, physical and anticoagulant activities of the product. Their results suggest that the sulfate content strongly affect anticoagulant activity of the fucan, and that fucans having a ration "sulfate/total sugar" < 0.3 had no anticoagulant activity (Nishino and Nagumo 1991). In 1999, they analyzed the effect of the molecule C-II on generating inhibitory effect of thrombin and factor Xa by measuring the amidolytic activities using the respective specific chromogenic substrates in both plasma and purified systems. C-II significantly inhibited the factor Xa generation, blocked prothrombinase formation and preventing intrinsic factor Xa generation. Moreover, C-II was more efficient in inhibiting thrombin generation than in inhibiting its activity (Nishino et al. 1999). Li et al. (2015) characterized a sulfated polysaccharide from the green algae *Codium divaricatum*. This polysaccharide, designated CP2-1, revealed to be a galactan, which is highly sulfated and substituted with pyruvic acid ketals. Its backbone was mainly composed of (1→3)-β-D-galactopyranose residues, branched by

single (1→)-β-D-galactopyranose units attached to the main chain at C-4 positions. The APTT assay demonstrated that the pyruvated galactan sulfate CP2-1 is very efficient as anticoagulant may be a potential source of anticoagulant polysaccharide with novel structure. Other studies showed the possibility of extracting and purifying sulfated polysaccharides with anticoagulant activities from seaweeds such as *Sargassum fulvellum* and *Pachymeniopsis elliptica* used as substrate for fermentation (Ekanayake et al. 2008, Zoysa et al. 2008). Seaweeds like *Turbinaria ornata*, *Dictyo pterisdelicatula*, *Codium divaricatum*, *C. adhaerence*, *C. latum*, *C. fragile* and *Padina gymnospora* have also been screened for their polysaccharides having anticoagulant activities (Silva et al. 2005; Ciancia et al. 2010; Arivuselvan et al. 2011; Magalhaes et al. 2011).

ANTIDIABETIC COMPOUNDS IN SEAWEED

Diabetes is a significant cause of continued bad health and premature mortality. It claims more lives per year than HIV with almost one death every ten seconds. The glucose levels regulation in blood is principally based on a negative feedback loop that acts through insulin and glucagon release by both β and α cells of the pancreas, respectively. Thus, diabetes reduces the individual ability to regulate glucose levels in the blood stream, producing various major and minor complications (Kaul et al. 2013).

As time goes on, seaweeds showed significant performance in decreasing or attenuating diabetes complications as important sources of antidiabetic compounds. Thennarasan et al. (2015) studied the hyperglycemic activity of methanolic extracts from the seaweeds *Ulva lactuca*, *Grateloupia lithophila* and *Stoechospermum marginatum*, using an *in vitro* enzymatic assay (α-glucosidase inhibition). Compared to the positive control Acarbose, the two seaweeds *G. lithophila* and *U. lactuca* were more efficient in inhibiting α-glucosidase, with IC_{50} = 427 μg/mL and highest IC_{50} = 760 μg/mL, respectively. The effect of extracts from the brown seaweed *Sargassum polycystum* on Type 2 diabetic rat model (T2DM), compared to that induced by the medicament metformin, was screened by Motshakeri et al. (2014). After 22 days of treatment, the pathological lesions of the livers and kidneys in the diabetic rats were alleviated by both algal extracts (150mg/kg body weight) and by metformin. Oral administration of algal crude extract (300mg/kg body weight) and metformin revealed pancreas protective or restorative effects. Lamela et al. (1989) assayed the hypoglycemic resulting in oral

administration of ethanolic extract from the algae *Laminaria ochroleuca*, *Saccorhiza polyschides* and *Fucusvesiculosus*,as well as the intravenous administration of crude polysaccharides and protein solutions from *Himanthaliu elongata* and *Codium tomentosum*, using normal alloxan-diabetic male New Zealand rabbits, respectively. Oral administration of 10 g/kg of F. vesiculosus extract caused significant reduction of blood glucose. *S. polyschides* extracts increased serum triglyceride levels by 36%, 6 h after administration of a 20 g/kg dose. Crude polysaccharides and protein solutions from *H. elongata* showed significant drop in the glycemia of normal animals.

Hardoko et al. (2014) performed an investigation of laminaran ability, fucoidan and alginic fractions from the two brown seaweeds *Sargassum duplicatum* and *Turbinaria decurens* brown seaweed as an antidiabetic agent using the α-glucosidase inhibition-assay. Alginic fraction showed no inhibition activity, while laminaran fractions were more active against α-glucosidase than fucoidans. Laminaran fraction from *Sargassum duplicatum* was the most active (IC50 = 36.13 ppm), followed by laminaran of Turbinaria (IC50 = 44.48 ppm), fucoidan of Turbinaria (IC50 = 63.39 ppm) and fucoidan of Sargassum (IC50 = 75.10 ppm), respectively. Rafiquzzaman et al. (2014) succeeded to purify a hypoglycemic glycoprotein from the edible brown seaweed *Undaria pinnatifida*, through monitoring α-glucosidase inhibition and glucose transport across yeast cell. Their results suggest that this glycoprotein may be used as bioaccessible food additives for controlling postprandial hyperglycemia. After screening α-glucosidase inhibition and glucose uptake stimulatory activities in several species of marine algae from Atlantic Canada, Zhang et al. (2007) highlighted the antidiabetic activity of polysaccharides- and polyphenolic-enriched fractions from the brown seaweed *Ascophyllum nodosum*. Crude polyphenol extract, enriched polyphenolic fraction and polysaccharide extract were prepared from *A. nodosum* powder and administrated to streptozotocin-diabetic mice for up to 4 weeks (200 mg/kg body mass). Crude polyphenol extract and enriched polyphenolic fraction improved abstaining serum glucose level in diabetic mice. Crude polyphenol extract also normalized the reduction in liver glycogen level in diabetic mice. The three fractions enhanced antioxidant capacity in animal's blood. Crude extracts from different seaweeds such as *Padina boergesenii, Halimeda macroloba, Padina sulcata, Sargassum binderi, Turbinaria conoides, Ulva lactuca, Grateloupia lithophila, Stoechospermum marginatum Symphylocladia latiuscula, Laminaria japonica, Sargassum binderi*, *Padina sulcata*, *Turbinaria conoides* etc., and different compounds such as poly-, monounsaturated fatty acids and polysaccharides were tested for their antidiabetic activities. These studies are mostly based on

extracts or fractions ability to reduce glucose levels via inhibition of α-glucosidase and α-amylase activities or via miscellaneous mechanisms (AGE formation inhibition, Aldose reductase inhibition, Stimulation of GIP and GLP-1 secretion, increasing glucokinase activity etc.). Some seaweed compounds are indirectly implicated in antidiabetic activity due to anti-obesity and anti-inflammatory properties (Chin et al. 2014, Senthilkumar et al. 2014, Murugesan et al. 2015, and Sharifuddin et al. 2015).

CONCLUSION

Human life on earth is facing several problems such as global warming, resource depletion and uncontrollable industrial practices. To meet its increasingly growing requirements, humanity was found obliged to exploit new resources on the globe, seeking for renewable and ecofriendly alternatives to avoid environment degradation. In marine environments, seaweeds are the most important biomass producers that represent potential source of new diverse and unique compounds. For long-time, and especially in the last few years, marine algae were used in several areas such as food, chemical, medical and pharmaceutical industry. Therefore, the compounds cited in this chapter do not cover all the existing neither the discovered algal compounds that could be used in pharmaceutical application, but they do cover the most frequently encountered part of them. In addition, a large portion of these same molecules is used in other domains such as ecofriendly pesticides production, agrochemical compounds, drugs and tools for use in chemical, biochemical and medical research etc. However, (1) improving extraction methods, (2) standardizing analytical protocols for fractionation and safety-evaluation of the purified compounds, (3) identifying active molecules from the already studied crude extracts, (4) seeking for new compounds from new algal material and (5) paying more attention to develop innovative projects constitute essential practices to ensure better use of marine algae in pharmaceutical industry.

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