Algae as Source of Pharmaceuticals

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Abstract Pharmaceuticals or pharmaceutical products are medicinal drugs—of proven safety, effectiveness and high quality, which are prescribed and intended to rational dosage. In general, most of the pharmacologically active compounds were isolated from microorganisms and plants, drug-resistance and identification of new disease entities have imposed to select both new sources and application areas of drug components. There is a broad range of health disorders—including cancer, allergy, diabetes, neurodegenerative diseases and inflammation, against which algae have been widely used. Medicinal application of algae depends on the biochemical diversity which is affected by a number of factors, including location, season, grazing pressure, salinity, water motion, temperature, light climate, biomass density and nutrient availability. Despite algae variability, main groups of compounds—such as polysaccharides, pigments, terpenoids, alkaloids, polyphenols, peptides and polyunsaturated fatty acids—showing pharmaceutical activity are indicated. Algae constitute an abundant source of bioactive compounds which have a great potential to be used as pharmaceuticals. Currently, the growing interest is put on the application of different algal compounds in the civilization diseases treatment and the market for pharmaceuticals based on compounds of natural origin is growing worldwide. The still untapped reservoir of chemically active compounds and potential in the field of pharmaceuticals imply a requirement of increased screening of algae for healthcare chemicals and the isolation methods development.

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B.N. Tripathi and D. Kumar (eds.), *Prospects and Challenges in Algal Biotechnology*, DOI 10.1007/978-981-10-1950-0_11

1 Introduction

Pharmaceuticals or pharmaceutical products are medicinal drugs—of proven safety, effectiveness and high quality, which are prescribed and intended to rational dosage (www.who.in). In general, most of the pharmacologically active compounds were isolated from microorganisms and plants, drug-resistance and identification of new disease entities have imposed to select both new sources and application areas of drug components (Schwartz et al. 1990).

The beneficial effect of algae-based products on human health has been known since antiquity, their use was, however, limited to folk medicine (Hoppe 1979). Due to the problematic transfer of species from natural habitats to the laboratory-scale cultivation and controversies over the results of algae blooms in aquatic life, the introduction of products to the market was difficult (Garham and Carmichael 1979; Moore 1977; Shimizu 1978). Although the first report on algae medicinal application was 'Materia Medica' by Shên-nung in 2700 B.C. (Hoppe 1979), the systematic investigation of algal active compounds—particularly antibiotics, began after World War II (Borowitzka 1995) as lateral direction of studies on unconventional protein sources for increasing human population. Early research verified algae for pharmaceutical activity mainly by in vitro experiments, subjected to public discussion in the late 1960s (Hoppe 1979). In vivo examination, on the other hand, was elaborated in the 1970s at the Roche Research Institute of Marine Pharmacology (Australia) and involved screening of crude extracts, rather than pure compounds, to isolate and identify components with given properties (Baker 1984). At the same time, in vitro screens were advanced and novel designs—assessing enzyme activity variation or cell line behaviour, enabled to develop efficient and low-cost investigation methods. These approaches are commonly used nowadays (Borowitzka 1995; Patterson et al. 1991; Suffness et al.1989). As greater attention was paid to marine source for medicinal application, microalgal biomolecules became products of interest (Borowitzka 1995; Kellam and Walker 1989; Moore et al. 1988; Patterson et al. 1991). At present, algae-based pharmaceuticals belong to small, yet high-value and mid-sized/value markets being appraised for $25–5800 thousand and $2–25 thousand per tonne, respectively (www.biofuelsdigest.com). According to the report of BCC Research from 2011, the global market of the marine-derived drug is expected to increase at compound annual growth rate of 12.5% reaching $8.6 billion by 2016 (BCC Research 2011).

There is a wide range of health disorders—including diseases of the circulatory and digestive systems, goitre and inflammation (Hoppe 1979), against which algae have been traditionally used. Medicinal application of algae depends on biochemical diversity which is affected by a number of factors, including location, season, grazing pressure, salinity, water motion, temperature, light climate (depth, turbidity and UV exposure), biomass density and nutrient availability (Stengel et al. 2011). The main groups of pharmaceutical compounds and their activities are shown (Fig. 1).

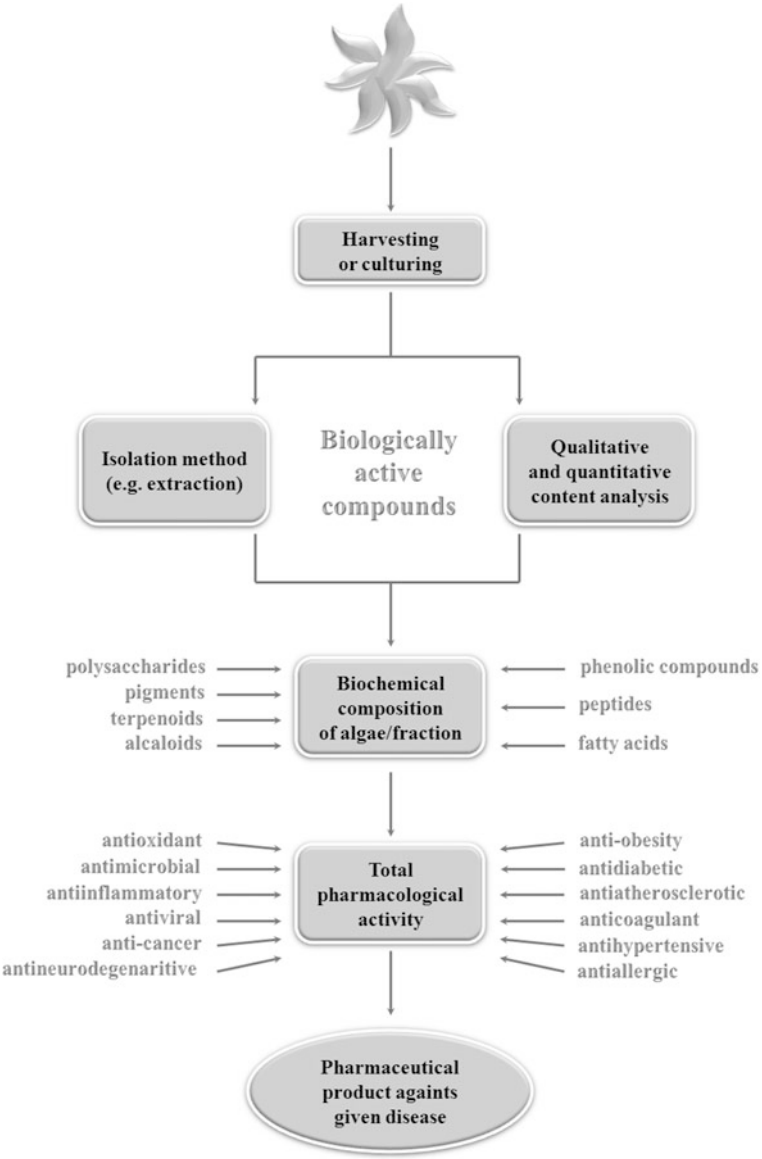

Fig. 1 Scheme of obtaining pharmaceutical products from algal biomass

It is a common practice to evaluate the applicability of selected source, based on total biological activity assessed, and pharmaceutical products comprised of pure components rather than a mixture of given properties. Thus, in the current work, review section was divided into seven subsections, each of which described one group of algae-derived compounds.

2 Compounds with Pharmaceutical Potential

2.1 Polysaccharides

Polysaccharides constitute the most widespread group of chemically active compounds found in algae and demonstrating pharmaceutical properties. Antiinflammatory activity of polysaccharides was shown to be a feature dependent on the type of molecule and its biological source. Polysaccharides are able to bind to the surface of leukocytes and decrease inflammation by interference with the migration of white blood cells (Raposo et al. 2015).

Yang et al. (2008) extracted fucoidans from *Undaria pinnatifida* and observed the anticancer activity of isolated polysaccharides. It was also shown that partial depolymerization of fucoidans in mild conditions significantly improved the anticancer activity of extracted biomolecules (Yang et al. 2008).

The activity of fucoidan from *U. pinnatifida* towards PC-3 prostate cancer cells was examined by Boo et al. (2013). Extracted polysaccharide induced apoptosis and inhibited the growth of tumour cells through the activation of ERK1/2 MAPK and inactivation of p38MAPK pathways (Boo et al. 2013).

Fucoidan obtained from *Cladosiphon novae-caledoniae* enhanced activity of chemotherapeutic agents such as cisplatin, tamoxifen and paclitaxel in breast cancer treatment. Its application induced apoptosis and reduced expression of Bcl-xL and Mcl-1 (Zhang et al. 2013).

In another study, fucoidan led to apoptosis induction in MCF-7 tumour cells by the activation of caspase 8 (Yamasaki et al. 2012).

Fucoidans extracted from *Laminaria cichorioides* and *Fucus evanescens* were examined for their influence on blood coagulation system. Dose-dependent inhibition of thrombin and Xa factor as a result of different sulfation degree of polysaccharides was observed (Drozd et al. 2006).

Fucoidan was also shown to be a factor able to inhibit binding formation between host cell and virus and hence a great antiviral agent towards HSV, RSV and HIV (Smit 2004).

Fucoidan was also recognized to be effective against allergic response. Polysaccharides isolated from *U. pinnatifida* caused the reduced concentration of interleukins in bronchoalveolar lavage fluid and suppressed production of IgE in airway hypersensitivity (Maruyama et al. 2005).

The treatment of mouse thymocytes with different concentrations of laminarin extracted from *Laminaria japonica* led to apoptosis suppression and genes responsible for the production of immune response proteins were activated (Kim et al. 2006a).

Laminarin produced by *Laminaria digitata* was examined for human colon cancer treatment. It was observed that extracted polysaccharide induced apoptosis of HT-29 cells and activated ErbB2 phosphorylation (Park et al. 2013).

Inhibited proliferation and induced apoptosis after the application of laminarin for prostate cancer PC-3 cells was observed in the study conducted by Zou et al. (2010). Also, increased expression of P27kip1 and PTEN was investigated.

Laminarin showed also beneficial effect against RIF-1 tumour cells. In vitro experiments proved its influence on the prevention of tubule formation. Reduced tumour growth as a result of laminarin application was also observed in the in vivo experiments (Hoffman et al. 1996).

Among algal polysaccharides with pharmacological potential, alginate should also be mentioned. Experiments carried out by Asada et al. (1997), alginate occurring in brown seaweeds inhibited release of hyaluronidase and histamine from mast cells.

Alginate was shown to be able to stimulate Toll-like receptors and activate production of cytokines (Draget and Taylor 2011).

Another possible application of alginate in pharmacology is due to its significant role as a base for the production of controlled-release drug products (Lee and Mooney 2012).

Antiallergic activities of alginic acid were shown to be a result of its suppressive effect on histidine cocarboxylase, interleukin and TNF-α production and reduce systemic anaphylaxis (Jeong et al. 2006).

The pharmacological activity of other polysaccharides from algae was also proved and described in the literature. Porphyran isolated from *Porphyratenera* was shown to be effective against different allergic responses and reduced contact hypersensitivity reaction by decreasing of IgE in Balb/c mice (Ishikara et al. 2005).

Carrageenans from *Gigartina skottsbergii* demonstrated potential activity against different strains of HSV (Smit 2004). Similar properties were observed for some agaroids from *Gracilaria corticata* (Mazumder et al. 2002).

Galactan from red seaweed *Cryptonemia crenulata* was described as a selective inhibitor of DENV-2 acting through the prevention from virus multiplication during infection (Talarico et al. 2007).

In another study, anticoagulant activity of sulfated galactans isolated from *Gellidium crinale* and *Botryocladia occidentalis* was examined. It was observed that proportion of 2,3-di-sulfated α-units in galactan chain is crucial for interaction between protease and coagulation inhibitor (Pereira et al. 2005).

Galactans from *Callophyllis variegata* were shown to possess antiviral activity against HSV and DENV (Rodriguez et al. 2005).

Matsuhiro et al. (2005) isolated galactans by aqueous extraction of *Schizymeniabinderi*. Extracted polysaccharides revealed high antiviral activity against HSV types 1 and 2. It was concluded that antiviral activity of galactans was due to the fact that polysaccharides interfere with the initial adsorption of the virus.

2.2 Pigments

Carotenoids, one of the most abundant group of molecules in algae were found to exhibit different biological activities. There is growing interest in their isolation from microalgae mainly due to their potentially beneficial characteristics for pharmacology (Crupi et al. 2013). Carotenoids isolated from algae are famous mainly for antioxidant properties. Currently, an emphasis is put on different groups of carotenoids such as fucoxanthin, astaxanthin, zeaxanthin due to the high potential for the use as pharmaceuticals. It was postulated that the application of algal carotenoids in modern pharmacology can lead to the development of cancer or cardiovascular diseases treatment (Gammone et al. 2015).

The antioxidant properties of fucoxanthin were examined in the in vitro experiments. High radical scavenging activity of isolated marine carotenoids was assumed to be a result of the presence of allenic bonds (Sachindra et al. 2007).

Fucoxanthin was presented as an efficient inhibitor of the cyclin-dependent kinase in the treatment of melanoma cells. Beneficial properties of this pigment were proved in the in vitro and in vivo experiments (Kim et al. 2013).

In another study, the same carotenoid produced by *E. bicyclis* and *Undaria pinnatifida* was shown to possess inhibitory activity against PTP1B—negative regulator of the insulin-signaling pathway (Matsuno 2001).

Among many beneficial health effects of fucoxanthin, anti-obesity properties seem to be the best examined (Apostolidis and Lee 2011). Ability of fucoxanthin to decrease glucose levels in blood led to comprehensive studies over its application in diabetes and obesity treatment (Jung et al. 2012). Fucoxanthin from *U. pinnatifida* was recognized for its inhibitory effect against pancreatic lipase (Matsumoto et al. 2010). In another study, it was demonstrated that the main health care action of fucoxanthin was based on the reduction of cardiovascular risk factors (obesity, cholesterol concentration and hypertension) (D'Orazio et al. 2012).

The antioxidative potential of astaxanthin was shown to be even higher than vitamin E and β-carotene. Pigments found mainly in microalgae such as microalgae *Haematococcus pluvialis*, *Chlorella zofingiensis*, and *Chlorococcum* sp. promotes immune response in liver and kidney diseases. Also, its extraordinary potential in the protection against cancers, diabetes and gastrointestinal diseases was proved (Yuan et al. 2011).

Another algal carotenoid—violaxanthin—was shown to be the major factor detected in dichloromethane extract from *Dunaliella tertiolecta*, which demonstrated strong antiproliferative activity against two cell lines of human mammary cancer (MCF-7 and LNCaP) (Pasquet et al. 2011). Violaxanthin was also isolated from *Chlorella ellipsoidea* and examined for its antiinflammatory activity with the use of lipopolysaccharide (LPS)—stimulated RAW 264.7 mouse macrophage cells. As the result of the test, inhibition of NO and prostaglandin E2 was revealed. It was shown that violaxanthin acts mainly on the NF-κB pathway (Soontornchaiboon et al. 2012).

In another study, hepatoprotective properties of the carotenoid-rich extract obtained from Spirulina sp. were examined on rats. Obtained results revealed that carotenoids from microalgae were characterized by the greater antihepatotoxic effect in comparison with synthetic compounds (Murthy et al. 2005).

Inhibitory effects of carotenoids on the increase of ROS levels in gastric cells induced by H_2O_2 were reported. Furthermore, the application of carotenoids led to the activation of NF-κB and interleukin 8 expressions. It was claimed that supplementation of carotenoids significantly reduced the risk of gastric cancer (Kim et al. 2011). Administration of β-carotene to OVA-immunized mice decreased serum histamine level and hence inhibited an anaphylactic response (Vo et al. 2012).

Another important pigment isolated from microalgae with well-documented pharmaceutical potential is phycoyanin. It is one of the major pigments from *Spirulina sp.* Its inhibitory activity of allergic responses, such as ear swelling, skin reactions and histamine release from mast cells was documented (Ramirez et al. 2002). Phycoyanin poses also antiinflammatory activity through enhancement of IgA antibody response and suppression of allergivIgE antibody response (Nemoto-Kawamura et al. 2004).

The possible application of phycobilin pigments, such as phycocyanin or phycoerythrin, unique for algae, in photodynamic therapy during cancer treatment was pointed out by Borowitzka (2013).

2.3 Terpenoids

Among organic compounds with high potential for the use in pharmaceuticals and isolated from algae, terpenoids should be also listed.

Methanolic extract from *Sargassum micracanthum* was shown to be rich in benzoquinone-type compounds and poses great inhibitory activity on lipid peroxidation. Strong antiviral activity against MCMV of the obtained extract was also investigated (Iwashima et al. 2005). Terpenoids extracted from *Dictyotapfaffii* were presented as potential anti-HIV-1 agents. Conducted experiments showed that *Dolabella dienetriol* can act as HIV-1 reverse transcriptase enzyme inhibitor (Crime-Santos et al. 2008).

Quinone metabolites isolated from *Sargassum sagamianum* revealed antibacterial activity against *Staphylococcus aureus* (Horie et al. 2008). Rhipocephalin, sesquiterpenoid from green algae exhibited high activity in the inhibition of phospholipase A2 from bee venom (Mayer et al. 1993).

Ji et al. (2008) investigated the possibility of the application of triterpenoids isolated from marine algae *Laurencia mariannensis* in cancer treatment. Obtained results revealed the cytotoxic effect of lauren mariannol and hydroxythyrsiferol against P-388 tumour cells. Triterpenoids extracted from *Laurencia viridis* displayed cytotoxic activity against murine leukaemia cell lines. Inhibitory activity on protein phosphatase was also determined (Souto et al. 2003).

2.4 Alkaloids

Despite the content of alkaloids in algae is relatively low in comparison with terrestrial plants, they were indicated as factors with high potential for the use in health protection. Alkaloids isolated from marine algae are known for antifungal, antioxidant and antibacterial activity. There are also some reports about the application of alkaloids as pharmaceuticals for effective neuromodulation, growth regulation and neurotransmission (Barbosa et al. 2014; De Souza et al. 2009).

The inhibition of Aβ-induced SH-SY5Y cell damage by racemosins A and B from *C. racemosa* was evaluated by Liu et al. (2013) in the in vitro experiments.

Alkaloids isolated from *Caulerpa taxifolia* (Vahl) C. Agardh. displayed inhibitory activity against PTP1B and hPTP1B (Mao et al. 2006).

2.5 Phenolic Compounds

Polyphenols, beside polysaccharides, are one of the most common secondary metabolites produced by algae. Although high content of phenolic compounds in terrestrial plants has been reported, there are fundamental differences in the chemical structure—plant molecules are derivatives of gallic and ellagic acids (Haslam and Cai 1994), whereas most frequently studied polyphenols from algae are composed of polymerized 1,3,5-trihydroxybenzene (phloroglucinol) units. Various algal polyphenols have been isolated, such as: phenolic acids, tannins, flavonoids, catechins, phlorotannins (Kadam et al. 2013); yet, scientific works concerning pharmaceuticals usually focus only on the latter group from marine brown seaweeds, particularly *Ecklonia* sp. (Singh and Bharate 2006). Beside phloroglucinol, eckol, dieckol, bieckols, phlorofucofuroeckol A and B were suggested, among other phlorotannis, for pharmacological activities (Li et al. 2009; Nagayama et al. 2008; Yoon 2008; Yoon et al. 2008).

Algal phenolic compounds are known for their strong radical scavenging effect, meaning inhibition of H_2O_2—induced DNA damage in particular (Heo and Jeon 2008). Efficacy of eckol, phlorofucofuroeckol A, dieckol, and 8,8'-bieckol—derived from *Ecklonia* species, against O_2^- and 1,1-diphenyl 1,2-picrylhydrazyl was comparable to L-ascorbic acid and α-tocopherol (Shibata et al. 2008). Moreover, *E. cava* dieckol was proved to exceptionally mitigate the results of photo-oxidative stress (Heo et al. 2009; Xie et al. 2009). Kim et al. (2006b) showed phlorotannis isolated from *E. cava* to inhibit matrix metalloproteinase enzymes responsible for chronic inflammation.

Ecklonia-derived phlorotannins were also verified for antimicrobial activity against *Campylobacter jejuni*, *Vibrio parahaemolyticus*, *Staphylococcus aureus* (Eom et al. 2008; Nagayama et al. 2002), while supplementation with phenolic compounds from *Ascophyllum nodosum* reduced the prevalence of *Escherichia coli* O157:H7 among feedlot steers (Braden et al. 2004).

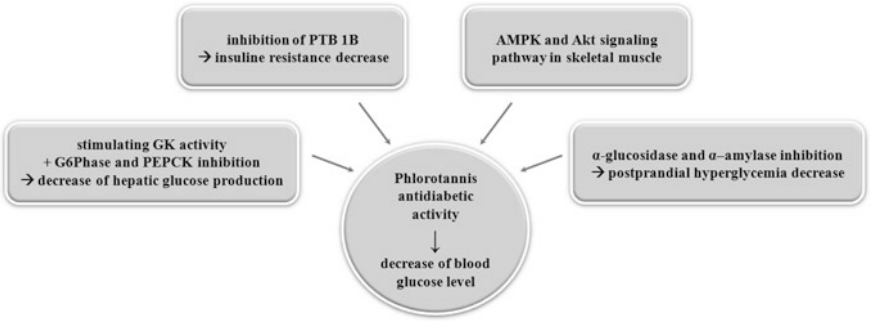

Fig. 2 Mechanisms of phlorotannis antidiabetic activity; GK—hepatic glucokinase, G6Phase—glucose-6-phosphatase, PEPCK—phosphoenolpyruvate carboxykinase, AMPK—5′ adenosine monophosphate-activated protein kinase, Akt—protein kinase B (Lee and Jeon 2013)

Antiviral effect of extracts from brown seaweeds—besides *E. cava*, such as *Dictyota pfaffi*, *Ishige okamurage*, *Peyssonelia* sp.,—were investigated against human immunodeficiency virus type-1 (HIV-1) and inhibition of HIV-1 reverse transcriptase, HIV-1 integrase and protease were observed (Lee and Jeon 2013).

Currently, a great attention is paid to examine phlorotannins for antidiabetic and anti-obesity activity. The former involves mechanisms shown in Fig. 2, while the latter is correlated with inhibition of pancreatic lipase—a key enzyme for triglyceride absorption in the small intestine (Lowe 1994, 2002).

The most recent trend to phlorotannis from *Ecklonia maxima* and *Ishigeo kamurae* pharmacological application is to inhibit acetylcholinesterase to protect the neurons from neurodegeneration—especially Alzheimer's disease—by the enhancement of cholinergic neurotransmission in the brain and, simultaneously, ß-amyloid formationdecrease (Hodges 2006; Kannan et al. 2013; Yoon et al. 2009). Yoon et al. (2008) showed *E. maxima* extract to affect both acetyl and butylcholinesterase, while the activity of phenolic compounds from *Sargassum* species were proved against cholinesterase (Choi et al. 2007; Kusumi et al. 1979a, b; Ryu et al. 2003).

3 Peptides and Proteins

Due to intensive studies on the correlation between exposure to oxidative stress and chronic diseases, algal peptides as stress-response compounds have been investigated (Bondu et al. 2015). In vitro examination showed components derived from both micro—*Chlorella vulgaris*, *C. ellipsoidea* and *Navivulla incerta* (Kang et al. 2011, 2012; Ko et al. 2012; Sheih et al. 2009) and macroalgae—*Solieria chordalis*, *Palmaria palmata*, *Ulva lactuca* and *Saccharina longicruris*, to have activity against radicals, particularly hydroxyl radicals (Fan et al. 2014).

Most peptides showed activation when released from the parent protein molecule by hydrolysis (Fan et al. 2014). At the same time, the use of peptides is limited by their susceptible to degradation in the gastrointestinal tract and chemical modification or encapsulation of biomolecules is required (Shen et al. 2010; Walsh et al. 2004; Wang and Zhang 2013). Regardless of the application issues, algal peptides are also tested for blood pressure control, antiatherosclerotic and anticancer activity.

Cha et al. (2006) verified peptides isolated from *Ecklonia cava* for affecting hypertensive rats by ACE inhibition. The same mechanism of decreasing blood pressure was observed for microalgal peptides (Ko et al. 2012; Samarakoon et al. 2013). *Chlorella* and *Spirulina*-derived peptides were also reported to inhibit the production of adhesion molecules, and thus prevent atherogenesis (Shih et al. 2013; Vo and Kim 2013).

In the work of Zhang and Zhang (2013), anti-tumour peptide from *Spirulina platensis* with activity against human liver cancer MCF-7 and HepG2 cells is reported. On the other hand, *Chlorella* sp. components showed cytotoxicity towards both HepG2 cells and gastric cancer (AGS cells), their effectiveness was, however, lower by 80% (Sheih et al. 2010; Wang and Zhang 2013).

4 Fatty Acids

Algae are proved to surpass terrestrial plants in content of essential fatty acids, which, besides being well known dietary supplements of mainly antiatherosclerotic and immune-enhancing effect (Kay 1991; Khotimchenko 1993; Sanchez-Machado et al. 2002), show antiallergic activity by limiting the production and/or the release of allergic response mediator. Polyunsaturated fatty acids—stearidonic acid (C18:4, n-3) and hexadecatetraenoic acid (C16:4, n-3)—from *Undaria pinnatifida* and *Ulva pertusa* effectively decreased content of leukotriene B4, leukotriene C4 and 5-hydroxyeicosatetraenoic acid in MC/9 mouse mast cells (Ishihara et al. 1998). Histamine production was efficiently inhibited by treatment of RBL-2H3 cells with both α- and γ-linolenic acid (C18:3, n-3 and n-6, respectively) (Gueck et al. 2003; Kawasaki et al. 1994). Gueck et al. (2003, 2004) verified α- and γ-linolenic acid and docosahexaenoic acid (C22:6, n-3) to affect PGE2 production and histamine release in the canine mastocytoma cell line C2.

5 Conclusions

Algae constitute an abundant source of bioactive compounds, which have a great potential to be used as pharmaceuticals. Currently, the growing interest is put on the application of different algal compounds in the civilization diseases treatment. The market for pharmaceuticals based on compounds of natural origin is growing

worldwide. Still untapped reservoir of chemically active compounds and potential in the field of pharmaceuticals imply requirement of increased screening algae for healthcare chemicals. Equally important is development of isolation methods.

Acknowledgments This project is financed in the framework of a grant entitled *Innovative technology of seaweed extracts—components of fertilizers, feed and cosmetics* (PBS/1/A1/2/2012) attributed by The National Centre for Research and Development in Poland.

References

Apostolidis E, Lee CM (2011) Brown seaweed-derived phenolic phytochemicals and their biological activities for functional food ingredients with focus on *Ascophyllum nodosum*. In: Kim SK (ed) Handbook of marine macroalgae: biotechnology and applied phycology, 1st edn. Wiley-Blackwell, Wiley, Chichester, pp 356–370

Asada M, Sugie M, Inoue M et al (1997) Inhibitory effect of alginic acids on hyaluronidase and on histamine release from mast cells. Biosci Biotechnol Biochem 61(6):1030–1032

Baker JT (1984) Seaweeds in pharmaceutical studies and applications. Hydrobiologia 116/117 (1):29–40

Barbosa M, Valentão P, Andrade PB (2014) Bioactive compounds from macroalgae in the new Millennium: implications for neurodegenerative diseases. Mar Drugs 12(9):4934–4972

BCC Research (2011) Global Markets for Marine-Derived Pharmaceuticals. Report No. PHM101A. http://www.bccresearch.com/market-research/pharmaceuticals/marine-derived-pharma-markets-phm101a.html. Accessed 27 April 2016

Bondu S, Bonnet C, Gaubert J et al (2015) Bioassay-guided fractionation approach for determination of protein precursors of proteolytic bioactive metabolites from macroalgae. J Appl Phycol 27:2059–2074

Boo HJ, Hong JY, Kim SC (2013) The anticancer effect of fucoidan in PC-3 prostate cancer cells. Mar Drugs 11(8):2982–2999

Borowitzka MA (1995) Microalgae as sources of pharmaceuticals and other biologically active compounds. J Appl Phycol 7(1):3–15

Borowitzka MA (2013) High-value products from microalgae-their development and commercialisation. J Appl Phycol 25(3):743–756

Braden KW, Blanton JR, Allen VG et al (2004) Ascophyllum nodosum supplementation: a preharvest intervention for reducing *Escherichia coli* O157:H7 and *Salmonella* spp. in feedlot steers. J Food Prot 67:1824–1828

Cha SH, Ahn GN, Heo SJ et al (2006) Screening of extracts from marine green and brown algae in Jeju for potential marine angiotensin-I converting enzyme (ACE) inhibitory activity. J Korean Soc Food Sci Nutr 35:307–314

Choi BW, Ryu G, Park SH et al (2007) Anticholinesterase activity of plastoquinones from *Sargassum sagamianum*: lead compounds for Alzheimer's disease therapy. Phytother Res 21:423–426

Cirne-Santos CC, Souza TML, Teixeira VL et al (2008) The dolabellanediterpene Dolabelladienetriol is a typical noncompetitive inhibitor of HIV-1 reverse transcriptase enzyme. Antivir Res 77(1):64–71

Crupi P, Toci AT, Mangini S et al (2013) Determination of fucoxanthin isomers in microalgae (*Isochrysis* sp.) by high-performance liquid chromatography coupled with diode-array detector multistage mass spectrometry coupled with positive electrospray ionization. Rapid Commun Mass Sp 27(9):1027–1035

D'Orazio N, Gemello E, Gammone MA et al (2012) Fucoxantin: a treasure from the sea. Mar Drugs 10(3):604–616

De Souza ET, De Lira DP, De Queiroz AC et al (2009) The antinociceptive and antiinflammatory activities of caulerpin, a bisindole alkaloid isolated from seaweeds of the genus Caulerpa. Mar Drugs 7:689–704

Draget KI, Taylor C (2011) Chemical, physical and biological properties of alginates and their biomedical implications. Food Hydrocolloid 25(2):251–256

Drozd NN, Tolstenkov AS, Makarov VA et al (2006) Pharmacodynamic parameters of anticoagulants based on sulfated polysaccharides from marine algae. B Exp Biol Med + 142 (5):591593

Eom SH, Kang MS, Kim YM (2008) Antibacterial activity of the *Phaeophyta Ecklonia* stolonifera on Methicillin-resistant *Staphylococcus aureus*. J Fish Sci Technol 11:1–6

Fan X, Bai L, Zhu L et al (2014) Marine algae-derived bioactive peptides for human nutrition and health. J Agric Food Chem 62:9211–9222

Gammone MA, Riccioni G, D'Orazio N (2015) Marine carotenoids against oxidative stress: effects on human health. Mar Drugs 13(10):6226–6246

Gorham PR, Carmichael WW (1979) Phycotoxins from blue-green algae. Pure Appl Chem 52 (1):165–174

Gueck T, Seidel A, Baumann D et al (2004) Alterations of mast cell mediator production and release by gamma-linolenic and docosahexaenoic acid. Vet Dermatol 15:309–314

Gueck T, Seidel A, Fuhrmann H (2003) Effects of essential fatty acids on mediators of mast cells in culture. Prostaglandins Leukot Essent Fatty Acids 68:317–322

Haslam E, Cai Y (1994) Plant polyphenols (vegetable tannins): gallic acid metabolism. Nat Prod Rep 11:41–66

Heo SJ, Jeon YJ (2008) Radical scavenging capacity and cytoprotective effect of enzymatic digests of Ishige okamurae. J Appl Phycol 20:1087–1095

Heo SJ, Ko SC, Cha SH et al (2009) Effect of phlorotannins isolated from Ecklonia cava on melanogenesis and their protective effect against photo-oxidative stress induced by UV-B radiation. Toxicol In Vitro 23:1123–1130

Hodges JR (2006) Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects. Brain 129:2811–2822

Hoffman R, Paper DH, Donaldson J et al (1996) Inhibition of angiogenesis and murine tumour growth by laminarin sulphate. Brit J Cancer 73(10):1183–1186

Hoppe HA (1979) Marine algae and their products and constituents in pharmacy. In: Hoppe HA, Levring T, Tanaka Y (eds) Marine algae in pharmaceutical science, vol 1. Walter de Gruyter, Berlin, New York, pp 25–119

Horie S, Tsutsumi S, Takada Y et al (2008) Antibacterial quinone metabolites from the brown alga. Sargassum sagamianum. B Chem Soc Jpn 81(9):1125–1130

Ishihara K, Murata M, Kaneniwa M et al (1998) Inhibition of icosanoid production in MC/9 mousemast cells by n-3 polyunsaturated fatty acids isolated from edible marine algae. Biosci Biotechnol Biochem 62:1412–1415

Ishihara K, Oyamada C, Matsushima R et al (2005) Inhibitory effect of porphyran, prepared from dried "Nori", on contact hypersensitivity in mice. Biosci Biotechnol Biochem 69(10):1824–1830

Iwashima M, Mori J, Ting X et al (2005) Antioxidant and antiviral activities of plastoquinones from the brown alga *Sargassum micracanthum*, and a new chromene derivative converted from the plastoquinones. Biol Pharm Bull 28:374–377

Jeong HJ, Lee SA, Moon PD et al (2006) Alginic acid has anti-anaphylactic effects and inhibits inflammatory cytokine expression via suppression of nuclear factor-kappaB activation. Clin Exp Allergy 36(6):785–794

Ji NY, Li XM, Xie H et al (2008) Highly oxygenated triterpenoids from the marine red alga *Laurencia mariannensis* (Rhodomelaceae). Helv Chim Acta 91:1940–1946

Jung HA, Islam MN, Lee CM et al (2012) Promising antidiabetic potential of fucoxanthin isolated from the edible brown algae *Eisenia bicyclis* and *Undaria pinnatifida*. Fisheries Sci 78 (6):1321–1329

Kadam SU, Tiwari BK, O'Donnell CP (2013) Application of novel extraction technologies for bioactives from marine algae. J Agr Food Chem 61(20):4667–4675

Kang KH, Qian ZJ, Ryu B et al (2012) Antioxidant peptides from protein hydrolysate of microalgae *Navicula incerta* and their protective effects in HepG2/CYP2E1 cells induced by ethanol. Phytother Res 26(10):1555–1563

Kang KH, Qian ZJ, Ryu B et al (2011) Characterization of growth and protein contents from microalgae *Navicula incerta* with the investigation of antioxidant activity of enzymatic hydrolysates. Food Sci Biotechnol 20(1):183–191

Kannan RRR, Aderogba MA, Ndhlala AR et al (2013) Acetylcholinesterase inhibitory activity of phlorotannins isolated from the brown alga, Ecklonia maxima (Osbeck) Papenfuss. Food Res Int 54:1250–1254

Kawasaki M, Toyoda M, Teshima R et al (1994) Effect of alphalinolenic acid on the metabolism of omega-3 and omega-6 polyunsaturated fatty acids and histamine release in RBL-2H3 cells. Biol Pharm Bull 17:1321–1325

Kay RA (1991) Microalgae as food and supplement. Crit Rev Food Sci Nutr 30:555–573

Kellam SJ, Walker JM (1989) Antibacterial activity from marine microalgae. Br Phycol J 24 (2):191–194

Khotimchenko SV (1993) Fatty acids of green macrophytic algae from the sea of Japan. Phytochem 32:1203–1207

Kim KH, Kim YW, Kim HB et al (2006a) Anti-apoptotic activity of laminarin polysaccharides and their enzymatically hydrolyzed oligosaccharides from *Laminaria japonica*. Biotechnol Lett 28 (6):439–446

Kim KN, Ahn G, Heo SJ et al (2013) Inhibition of tumor growth in vitro and in vivo by fucoxanthin against melanoma B16F10 cells. Environ Toxicol Phar 35(1):39–46

Kim MM, Ta QV, Mendis E et al (2006b) Phlorotannins in *Ecklonia cava* extract inhibit matrix metalloproteinase activity. Life Sci 79:1436–1443

Kim Y, Seo JH, Kim H (2011) β-Carotene and lutein inhibit hydrogen peroxide-induced activation of NF-κB and IL-8 expression in gastric epithelial AGS cells. J Nutr Sci Vitaminol 57(3):216–223

Ko SC, Kim D, Jeon YJ (2012) Protective effect of a novelm antioxidative peptide purified from a marine *Chlorella ellipsoidea* protein against free radical-induced oxidative stress. Food Chem Toxicol 50(7):2294–2302

Kusumi T, Ishitsuka M, Nomura Y et al (1979a) New farnesylacetone derivatives from *Sargassum micracanthum*. Chem Lett 1:1181–1184

Kusumi T, Shibata Y, Ishitsuka M et al (1979b) Structures of new plastoquinones from the brown alga *Sargassum serratifolium*. Chem Lett 3:277–278

Lee KY, Mooney DJ (2012) Alginate: properties and biomedical applications. Prog Polym Sci 37 (1):106–126

Lee SH, Jeon YJ (2013) Anti-diabetic effects of brown algae derived phlorotannins, marine polyphenols through diverse mechanisms. Fitoterapia 86:129–136

Li Y, Qian ZJ, Ryu BM et al (2009) Chemical components and its antioxidant properties *in vitro*: an edible marine brown alga, *Ecklonia cava*. Bioorg Med Chem 17:1963–1973

Liu DQ, Mao SC, Zhang HY et al (2013) Racemosins A and B, two novel bisindole alkaloids from the green alga Caulerparacemosa. Fitoterapia 91:15–20

Lowe M (1994) Pancreatic triglyceride lipase and colipase: insights into dietary fat digestion. Gastroenterology 107:1524–1536

Lowe ME (2002) The triglyceride lipases of the pancreas. J Lipid Res 43:2007–2016

Mao SC, Guo YW, Shen X (2006) Two novel aromatic valerenane-type sesquiterpenes from the Chinese green alga Caulerpataxifolia. Bioorg Med Chem Lett 16(11):2947–2950

Maruyama H, Tamauchi H, Hashimoto M et al (2005) Suppression of Th2 immune responses by mekabu fucoidan from *Undaria pinnatifida* sporophylls. Int Arch Allergy Immunol 137 (4):289–294

Matsuhiro B, Conte AF, Damonte EB et al (2005) Structural analysis and antiviral activity of a sulfated galactan from the red seaweed *Schizymenia binderi* (Gigartinales, Rhodophyta). Carbohyd Res 340(15):2392–2402

Matsumoto M, Hosokawa M, Matsukawa N (2010) Suppressive effects of the marine carotenoids, fucoxanthin and fucoxanthinol on triglyceride absorption in lymph duct-cannulated rats. Eur J Nutr 49(4):243–249

Matsuno T (2001) Aquatic animal carotenoids. Fisheries Sci 67(5):771–783

Mayer AM, Paul VJ, Fenical W et al (1993) Phospholipase A2 inhibitors from marine algae. Fourteenth international seaweed symposium. Springer, Netherlands, pp 521–529

Mazumder S, Ghosal PK, Pujol CA et al (2002) Isolation, chemical investigation and antiviral activityof polysaccharides from *Gracilaria corticata* (Gracilariaceae, Rhodophyta). Int J Biol Macromol 31:87–95

Moore RE (1977) Toxins from blue-green algae. Bioscience 27(2):797–802

Moore RE, Patterson ML, Carmichael WW (1988) New pharmaceuticals from cultured blue-green algae. In: Fautin DG (ed) Biomedical importance of marine organisms. California Academy of Sciences, San Francisco, pp 143–150

Murthy KN, Rajesha J, Swamy MM et al (2005) Comparative evaluation of hepatoprotective activity of carotenoids of microalgae. J Med Food 8(4):523–528

Nagayama K, Iwamura Y, Shibata T et al (2002) Bactericidal activity of phlorotannins from the brown alga *Ecklonia kurome*. Antimicrob Agents Chemother 50:889–893

Nagayama K, Shibata T, Fujimoto K et al (2008) Algicidal effect of phlorotannins from the brown alga *Ecklonia kurome* on red tide microalgae. Aquaculture 218:601–611

Nemoto-Kawamura C, Hirahashi T, Nagai T et al (2004) Phycocyanin enhances secretary IgA antibody response and suppresses allergic IgE antibody response in mice immunized with antigen-entrapped biodegradable microparticles. J Nutr Sci Vitaminol 50(2):129–136

Park HK, Kim IH, Kim J et al (2013) Induction of apoptosis and the regulation of ErbB signaling by laminarin in HT-29 human colon cancer cells. Int J Mol Med 32(2):291–295

Pasquet V, Morisset P, Ihammouine S et al (2011) Antiproliferative activity of violaxanthin isolated from bioguided fractionation of *Dunaliella tertiolecta* extracts. Mar Drugs 9(5):819–831

Patterson GML, Baldwin CL, Bolis CM et al (1991) Antineoplastic activity of cultured blue-green algae (Cyanophyta). J Phycol 27(4):530–536

Pereira MG, Benevides NM, Melo MR et al (2005) Structure and anticoagulant activity of a sulfated galactan from the red alga, *Gelidium crinale*. Is there a specific structural requirement for the anticoagulant action? Carbohyd Res 340(12):2015–2023

Raposo MDJ, De Morais AM, De Morais RM (2015) Marine polysaccharides from algae with potential biomedical applications. Mar Drugs 13(5):2967–3028

Remirez D, Ledón N, González R (2002) Role of histamine in the inhibitory effects of phycocyaninin experimental models of allergic inflammatory response. Mediat Inflamm 11 (2):81–85

Rodríguez MC, Merino ER, Pujol CA et al (2005) Galactans from cystocarpic plants of the red seaweed *Callophyllis variegata* (Kallymeniaceae, Gigartinales). Carbohyd Res 340(18):2742–2751

Ryu G, Park SH, Kim ES et al (2003) Cholinesterase inhibitory activity of two farnesylacetone derivatives from the brown alga *Sargassum sagamianum*. ArchPharm Res 26:796–799

Sachindra NM, Sato E, Maeda H et al (2007) Radical scavenging and singlet oxygen quenching activity of marine carotenoid fucoxanthin and its metabolites. J Agric Food Chem 55 (21):8516–8522

Samarakoon KW, Kwon ON, Ko JY et al (2013) Purification and identification of novel angiotensin-I converting enzyme (ACE) inhibitory peptides from cultured marine microalgae (*Nannochloropsis oculata*) protein hydrolysate. J Appl Phycol 25(5):1595–1606

Sanchez-Machado DI, Lopez-Cervantes J, Lopez-Hernandez J et al (2002) Fatty acids, total lipid, protein and ash contents of processed edible seaweeds. Food Chem 85:439–444

Schwartz RE, Hirsch CF, Sesin DF et al (1990) Pharmaceuticals from cultured algae. J Ind Microbiol 5(2):113–124

Sheih IC, Fang TJ, Wu TK et al (2010) Anticancer and antioxidant activities of the peptide fraction from algae protein in waste. J Agric Food Chem 58:1202–1207

Sheih IC, Wu TK, Fang TJ (2009) Antioxidant properties of a new antioxidative peptide from algae protein hydrolysate in different oxidation systems. Biores Technol 100:3419–3425

Shen B, Makley DM, Johnston JN (2010) Umpolung reactivity in amide and peptide synthesis. Nature 465(7301):1027–1032

Shibata T, Ishimaru K, Kawaguchi S et al (2008) Antioxidant activities of phlorotannins isolated from Japanese *Laminariaceae*. J Appl Phycol 20:705–711

Shih MF, Chen LC, Cherng JY (2013) Chlorella 11-peptide inhibits the production of macrophage-induced adhesion molecules and reduces endothelin-1 expression and endothelial permeability. Mar Drugs 11(10):3861–3874

Shimizu Y (1978) Dinoflagellate toxins. In Scheuer PJ (ed) Marine natural products, chemical and biological perspectives, vol. 1, p 1–42

Singh IP, Bharate SB (2006) Phloroglucinol compounds of natural origin. Nat Prod Rep 23:558–591

Smit AJ (2004) Medicinal and pharmaceutical uses of seaweed natural products: a review. J Appl Phycol 16(4):245–262

Soontornchaiboon W, Joo S, Kim SM (2012) Anti-inflammatory effects of violaxanthin isolated from microalga *Chlorella ellipsoidea* in RAW 264.7 macrophages. Biol Pharm Bull 35 (7):1137–1144

Souto ML, Manrıquez CP, Norte M et al (2003) The inhibitory effects of squalene-derived triterpenes on protein phosphatase PP2A. Bioorg Med Chem Lett 13:1261–1264

Stengel DB, Connan S, Popper Z (2011) Algal chemodiversity and bioactivity: sources of natural variability and implications for commercial application. Biotechnol Adv 29(5):483–501

Suffness M, Newman DJ, Snader K (1989) Discovery and development of antineoplastic agents from natural sources. In: Scheuer PJ (ed) Bioorganic marine chemistry, 1st edn. Springer Verlag, Berlin, pp 131–168

Talarico LB, Duarte ME, Zibetti RG et al (2007) An algal-derived DL-galactan hybrid is an efficient preventing agent for in vitro dengue virus infection. Planta Med 73(14):1464–1468

Vo TS, Kim SK (2013) Down-regulation of histamine-induced endothelial cell activation as potential anti-atherosclerotic activity of peptides from *Spirulina maxima*. Eur J Pharm Sci 50 (2):198–207

Vo TS, Ngo DH, Kim SK (2012) Marine algae as a potential pharmaceutical source for anti-allergic therapeutics. Proc Biochem 47(3):386–394

Walsh DJ, Bernard H, Murray BA et al (2004) *In vitro* generation and stability of the lactokinin β-lactoglobulin fragment (142—148). J Dairy Sci 87(11):3845–3857

Wang X, Zhang X (2013) Separation, antitumor activities, and encapsulation of polypeptide from *Chlorella pyrenoidosa*. Biotechnol Prog 29(3):681–687

Xie Z, Wang Y, Liu Y et al (2009) Ultraviolet-B exposure induces photo-oxidative damage and subsequent repair strategies in a desert cyanobacterium *Microcoleus vaginatus* Gom. Eur J Soil Biol 45:377–382

Yamasaki Y, Yamasaki M, Tachibana H et al (2012) Important role of β1-integrin in fucoidan-induced apoptosis via caspase-8 activation. Biosci Biotech Bioch 76(6):1163–1168

Yang C, Chung D, Shin I et al (2008) Effects of molecular weight and hydrolysis conditions on anticancer activity of fucoidans from sporophyll of *Undaria pinnatifida*. Int J Biol Macromol 43(5):433–437

Yoon NY (2008) Cholinestarase and lens aldose reductase inhibitory activities of phlorotannins from *Ecklonia stolonifera* and their protective effects on tacrineinduced hepatotoxicity and hyperlipidemic rat models. Pukyong National University, Disertation

Yoon NY, Chung HY, Kim HR et al (2008) Acetyl- and butyryl-cholinesterase inhibitory activities of sterols and phlorotannins from *Ecklonia stolonifera*. Fisheries Sci 74:200–207

Yoon NY, Lee SH, Kim SK (2009) Phlorotannins from Ishige okamurae and their acetyl-and butyrylcholinesterase inhibitory effects. J Funct Foods 1:331–335

Yuan JP, Peng J, Yin K et al (2011) Potential health-promoting effects of astaxanthin: A high-value carotenoid mostly from microalgae. Mol Nutr Food Res 55(1):150–165

Zhang B, Zhang X (2013) Separation and nanoencapsulation of antitumor polypeptide from *Spirulina platensis*. Biotechnol Prog 29:1230–1238

Zhang Z, Teruya K, Yoshida T et al (2013) Fucoidan extract enhances the anti-cancer activity of chemotherapeutic agents in MDA-MB-231 and MCF-7 breast cancer cells. Mar Drugs 11 (1):81–98

Zou MC, Cui FL, Sheng YQ et al (2010) Effects of laminarin sulphate on the expressions of PTEN and P271kip1 in prostate cancer PC-3 cells. Zhonghua Nan Ke Xue/National Journal of Andrology 16(6):498–503 [in Chinese]