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Review Article

Marine Algae and Their Potential Application as Antimicrobial Agents

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ABSTRACT - The world is becoming overwhelmed with widespread diseases as antibiotic resistance increases at an alarming rate. Hence, there is a demanding need for the discovery and development of new antimicrobial drugs. The ocean is gifted with many organisms like phytoplankton, algae, sponges, cnidarians, bryozoans, mollusk, tunicates and echinoderms, which are known to produce a wide variety of bioactive secondary metabolites with pharmacological properties. Many new therapeutic drugs have emerged from marine invertebrates, although the large algal community is yet to be explored. The bioactivity possessing secondary metabolites of marine algae include polyphenols, phlorotannins, alkaloids, halogenated compounds, sulfated polysaccharides, agar, carrageenan, proteoglycans, alginate, laminaran, rhamnan sulfate, galactosylglycerol, and fucoidan. These metabolites have been found to have great antimicrobial activities against many human aliments. Studies show that the algal community represents about 9% of biomedical compounds obtained from the sea. This review looks at the evolution of drugs from the ocean, with a special emphasis on the antimicrobial activities of marine algae.

Key words : Antimicrobial effect, Bioactive secondary metabolites, Marine algae

Many chemotherapeutic agents have been discovered from a wide variety of chemical classes such as terpenoids, polyketides, acetogenins, peptides, and alkaloids. These agents have been discovered from the marine environment making it a worldwide focus in the effort for the discovery of novel natural products. Reports show that more than 12,000 novel chemicals have been discovered from marine organisms and majority of these chemical compounds have been identified from marine invertebrates such as sponges predominate[1,2]. Marine algae represent a small fraction of these discoveries. However, recent trends in drug research from natural sources have indicated that marine algae are a promising source of novel biochemically active compounds, especially for antiprotozoal, antibiotic, anti-cancer, and antiviral activities[3]. Table 1 shows various biological activities of marine algae and its metabolites[4-17].

Marine macroalgae can be classified as red algae (rhodophyta), brown algae (phaeophyta) or green algae (chlorophyta) depending on their nutrient and chemical composition. Red and brown algae commonly referred to as seaweeds for human food sources also serve as an important source of bioactive natural substance[18]. These red and brown algae are extensively used in Asian diet for centuries due to their natural nutritional value such as carotenoids, dietary fibers, proteins, essential fatty acids, and also huge presence of vitamins and minerals[18]. Apart from their nutritional value, many coastal inhabitants in Asia prepare algae extracts for the treatment of disorders and ailments such as wounds, fever and stomach aches, and for the prevention of arrhythmia[19].

Bio stimulating properties of seaweed are shown to have antimicrobial activities such as antibiotics, laxatives, anticoagulants, anti-ulcer products and suspending agents in radiological preparations, thus making seaweeds a potential source of natural antioxidants. Bioactive metabolites such as sulphated polysaccharides, a macromolecule of seaweed and phlorotannins have also exhibited active response to the treatment of most bacterial and viral diseases and also have anticoagulant activities. Marine algae have consequently become an important source of pharmacologically active metabolites in the discovery of novel drugs.

Antibacterial activity of marine algae

The development of new antibiotics has become a high priority for many biomedical researches due to the high

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Table 1. Marine algae active compounds and their biological activities

Marine algae	Biological activity	Active compound	Classification	Reference
Botryocladiaoccidentails	Anticoagulant	Sulfated galactan	Red algae	[4]
Bryopsissp	Anticancer	Kalalalide F	Green algae	[5]
Chondria. sp	Anti-herpes simplex virus type II	Condriamide A	Red algae	[6]
Chondriaatropurpurea	Anthelmintic	Chondriamide B	Red algae	[7]
Cladosiphonokamuramus	Antiviral	Fucan	Brown algae	[8]
Eiseniabicyclis	Antioxidant	Polyphenols, Pholorotannins	Brown algae	[9]
Fucusvesiculosus	Anticoagulant	Fucoidans	Brown algae	[10]
Kappaphycus striatum	Anticancer	Kappa-carrageenan	Red algae	[11]
Laurenciabrongniartii	Antibacterial	Brominated indoles	Red algae	[12]
Martensiafragilis	Antioxidant	Alkaloids	Red algae	[13]
Rhodophyllismembranacea	Antifungal	Polyhalogenated indoles	Red algae	[14]
Sargassum vulgare	Anticancer	Alginate	Brown algae	[15]
Schizymeniadubyi	Antiviral	Sulfated glucuronogalactan	Brownish-red algae	[16]
Stypodium sp.	Cytotoxity	Stypoldione	Brown algae	[17]

resistance to current antibacterial agents to the treatment of infectious disease and food borne pathogens. Many studies on compounds such as terpenoids, phlorotannins, acrylic acid, phenolic, steroids, halogenated ketones and alkanes, and cyclic polysulphide present in marine algae have been reported as promising bactericidal agents[20]. The presence of these compounds suggests a number of alternative mechanisms for antimicrobial action. Among the tested algae the extracts of *Scenedesmus obliquus* showed a strong inhibition against Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*Salmonella* spp., *Escherichia coli*, and *Pseudomonas aeruginosa*)[21]. Phlorotannins extracted from Marine brown algae (*Ecklonia cava, E. kurome, E. stolonifera, Eiseniaaborea, Eiseniabicyclis, Ishigeokamurae,* and *Pelvetiasiliquosa*) have also been reported to show an antibacterial activity against *S. aureus*, methicillin resistant *S. aureus* (MRSA), *Salmonella* spp., and *E. coli*[22].

Polyphenols, carotenoids, amino acids, and catechinsare extracted from Marine algae *Gracilariopsislongissima* have an antibacterial activity against *Vibrio* spp.[23]. Demirel et al.[24] also reported that hydrocarbons, terpenes, phenols, sulfur-containing compound, and aldehydes extracted from the brown algae *Colpomeniasinuosa, Dictyota dichotoma, Dictyota dichotoma* var. *implexa, Petaloniafascia*, and *Scytosiphon lomentar* have an antibacterial activity against *Bacillus subtilis* and *S. aureus*. Phytochemicals such as saponins, tannins, carotenoids, flavonoids, alkaloids, and glycosides extracted from the green algae *Chlorococcum-humicola* have an antibacterial activity against *E. coli, S. aureus, Salmonella* Typhimurium*, P. aeruginosa* and *Vibrio cholerae*[25]. Phytol, fucosterol, neophytadiene or palmitic, palmitoleic and oleic acids from the brown algae *Himanthalia elongate* have an antibacterial activity against *E. coli* and *S. aureus*[26]. Lipophilic compounds (pyrrole-2-carboxylic acid, pentadecanoic acid, and octadecanoic acid) from the red algae *Asparagopsis taxiformis, Laurenciaceylanica, Laurencia-brandenii,* and *Hypneavalentiae* have an antibacterial activity against pathogenic *Vibrio* strains[27].

Similarly, Etahiri et al.[28] reported that *Sphaerococcus-coronopifolius*, a cosmopolitan red alga, contains diterpene and bromosphaerone, and shows an antibacterial activity against *S. aureus* with an MIC of 0.047 μg/mL. It has been also reported that a marine fungus isolated from the surface of the brown alga *Rosenvingea* sp. cultured with a unicellular marine bacterium to yield pestalone has a potent antibiotic activity against MRSA with an MIC of 0.037 μg/mL and vancomycin-resistant *Enterococcus faecium* with an MIC of 0.078 μg/mL[29]. 95% ethanol extract from whole dried *Gracilariacervicornis* algae was active against *S. aureus* at a concentration of 5.0 mg/mL and ethanol extracts from *Gracilariadomigensis* and *G. sjoestedii* showed antibacterial activity against *E. coli* and *S. aureus*[30,31]. The phlorotannin, dieckol, extracted from the brown marine algae has shown a potent antimicrobial activity against MRSA in the range of 125-250 μg/mL[32]. Eom et al.[33] also reported that fermentation broth of *Eiseniabicyclis* with *Candida utilis* YM-1 exhibited enhanced antimicrobial activity against MRSA and food-borne pathogenic bacteria. In addition, 2,3,5,6-tetrabromo-1-methylindole, a bromoindole isolated from the red algae *Laurenciabrongniartii* possess an antibacterial activity against *B. subtilis* and *Saccharomyces cerevisiae* and themethanol extract of fresh

Gracilariacorticata was also active against *B. subtilis*, *B. megaterium, S. aureus*, and *Streptococcus viridians*[12,31]. Plaza et al.[26] reported the antimicrobial activity of algae *Himanthalia elongate* and microalgae *Synechocystis* spp. against *E. coli* and *S. aureus*.

Antifungal activity of marine algae

Fungal infections have become common and many researchers are focusing on novel drugs for treating these infections. The algae community has become a promising lead in the discovery and development of novel drugs for fungal infections. The antifungal activity of seaweed extracts can be explained by the presence of phenolic compounds and their impact on spore germination. Some algal extracts have also shown to inhibit fungal enzyme activity due to the presence of bioactive metabolites. Ethanol extracts from *Gracilariadebilis, G. domingensis*, and *G. sjoestedii* were active against *Candida albicans* shown by agar plate method[31]. Also, the ethanol extract of *G. domigensis* was active against *Mycobacterium smegmatis* and *Neurospora crassa*[12]. Alarif et al.[34] also reported that isolauraldehyde isolated from the organic extract of the red alga *Laurencia obtuse* had significant antifungal activity against *C. albicans* with MIC of 70 mg/mL, and showed medium activity against *Aspergillus fumigatus* and *Aspergillus flavus* with a MIC of 100 and 1,000 mg/mL, respectively. Dieckol purified from *E. cava* has fungicidal activity against *Trichophyton rubrum* associated with dermatophytic nail infections in humans[35].

Antiprotozoal activity

Diseases caused by protozoan parasites lead to high rates of mortality and morbidity worldwide. The traditional use of algae for antiparasitic treatment has gained the attention of several research groups around the world, and marine secondary metabolites are now being evaluated as drug leads for the treatment of neglected diseases such as leishmaniasis, Chagas disease, and human African trypanosomiasis. To date, no marine natural products or any derivatives have entered pre-clinical assessment for trypanosomatid diseases, but numerous antiprotozoal therapeutic extracts or fractions and a few compounds from several seaweed species have been studied for potential lead compound isolation, medicinal applications or for modifications. Compounds such as terpenes, acetogenins, polyphenols, and alkaloids from algae are noted to have antiprotozoal activity with the halogenated terpenoids and acetogenins from the genera *Bifurcaria*, *Laurencia*, *Dictyota*, and *Canestrocarpus* showing a leishmanicidal and trypanocidal activity[36-40].

The red algae *Mastocarpusstellatus* which shares phylogenetic origins with *Plasmodium falciparum*, showed the best antiplasmodial activity[41]. Gallé et al.[42] also reported that organic extracts of 20 species of French seaweed showed antiprotozoal activity against *Trypanosoma brucei*, the parasite responsible for sleeping sickness. These extracts have previously shown potent antiprotozoal activities *in vitro* against *P. falciparum* and *Leishmaniadonovani*. Süzgeç-Selçuk et al.[43] showed that methanolic extracts of algae belonging to Chlorophyta (*Caulerparacemosa* and *Codium bursa*), Phaeophyta (*Cystoseirabarbata* and *Cystoseiracrinata*) and Rhodophyta (*Corallinagranifera*, *Janiarubens*, *Ceramiumrubrum*, *Gracilariaverrucosa*, *Dasyapedicellata*, and *Gelidiumcrinale*) were active against *T. bruceirhodesiense*. Further studies also showed that the *n*-hexane and dichloromethane fractions of *Bostrychiatenella* (Rhodophyta) from the Sao Paulo Coast, Brazil, showed activity against *Trypanosoma cruzitrypomastigotes* and *Leishmania amazonensis promastigotes*[44].

Studies showed that *Dictyotapfaffii* and *Canistrocarpuscervicornis*, brown alga have an antileishmanial activity and that the diterpene [8,10,18-trihydroxy-2,6-dolabelladiene(5)] obtained from *Dictyotapfaffii*, exhibited a leishmanicidal activity against intracellular amastigotes (IC_{50} = 44 μM) and anti-human immunodeficiency virus (HIV)-1 activity. HIV-1 is known to exacerbate the Leishmania load in macrophage infection. Therefore, the leishmanicidal and anti-HIV-1 activities of dolabelladienetriol (5) make it a promising candidate for leishmaniasis chemotherapy, either in isolated cases or in cases associated with HIV-1[37,39].

Antiviral activity of marine algae

Viral diseases, caused by pathogenic virus infections, are still one of the leading causes of death in humans worldwide. Although many antiviral agents have been developed and are used for treatment of viral infections, emergence of drug resistance, side effects, and the necessity for extensive clinical use are the main reasons for failure of antiviral therapy[45]. Therefore, the development of new antiviral agents with diverse kinds of antiviral actions is required. The search for new antiviral agents focuses on not only synthetic compounds but also natural products such as plants, insects, animal organs, and their components[45]. Recently, a great deal of interest has been expressed regarding marine algae as potential antiviral agents. This contribution focuses on anti-herpes virus therapeutic agents derived from marine algae which are considered as novel functional ingredients in anti-herpes virus therapy. Sulfated polymannuroguluronate (SPMG) a polysaccharide with an average molecular weight

of 8.0 kDa isolated from brown algae, recently entered Phase II clinical trial in China as the first anti-acquired immune deficiency syndrome (AIDS) drug candidate and was initially reported to bind to 28 amino acids located in the HIV viral glycoprotein gp120 V3 loop[46].

Witvrouw and De Clercq[47] have reported that fucoidans and sulfated polysaccharides (SPs) extracted from some marine brown seaweeds show an antiviral activity against infectious diseases, such as HIV, herpes simplex virus types (HSV-1 and HSV-2) and cytomegalovirus. It has been also reported that some seaweed-derived SPs such as carrageenans, fucoidans, and sulfated rhamnogalactans have inhibitory effects on the entry of enveloped viruses including herpes and HIV into cells[48-51]. Ono et al.[52] and Talarico et al.[53] have also reported that the SPs of some seaweed extract from *Undariapinnatifida*, *Splachnidiumrugosum*, *Gigartinaatropurpurea*, and *Plocamiumcartilagineum* have an antiviral activity against HSV-I and HSV-II. Beress et al.[54] have demonstrated that seaweed-derived SPs could be used as vaginal antiviral formulations without disturbing essential functions of the vaginal epithelial cells and normal bacterial flora.

Summary

Marine environments provide a rich and an invaluable source of new natural products of chemically diverse compounds that have a promising lead in the development of novel, potential, and useful therapeutic agents. Many marine algae have been reported to exhibit antimicrobial effects against several pathogens and human infections thus making them the focus for the discovery of novel drugs, however more Studies need to be done on the bioactivity of marine natural products especially marine algae as these group of marine natural products have exhibited great potential for novel drugs.

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국문요약

해양생물에는 육상생물자원에서는 존재하지 않는 다양한 화합물이 많이 존재하는데 이들 화합물은 새로운 치료제 및 대체 치료법을 개발하는데 유용하게 이용될 수 있다. 현재 해조류의 다양한 생리활성에 대한 연구가 진행되고 있으며 최근에는 여러 병원성 및 인체 감염균에 대한 항균효과를 나타내어 신약개발의 보고로 다양한 연구가 진행이 되고있다. 즉, 해조류는 천연물신약 또는 새로운 치료제 개발에 중요한 생물자원이다.

References

1. Donia M., Hamann M.T.: Marine natural products and their potential applications as anti-infective agents. *Lancet Infect. Dis.,* **6**, 338-348 (2003).
2. Lie J., Zhou J.: A marine natural product database. *J. Chem. Inf. Comput. Sci.,* **42**, 742-748 (2002).
3. Barbosa M., Valentão P., Andrade P.B.: Bioactive compounds from macroalgae in the new millennium: implications for neurodegenerative diseases. *Mar. Drugs,* **12**, 4934-4972 (2014).
4. Farias W.R., Valente A.P., Pereira M.S., Mourão P.A.: Structure and anticoagulant activity of sulfated galactans. Isolation of a unique sulfated galactan from the red algae *Botryocladiaoccidentalis* and comparison of its anticoagulant action with that of sulfated galactans from invertebrates. *J. Biol. Chem.,* **275**, 29299-2307 (2000).
5. Nuijen B., Bouma M., Talsma H., Manada C., Jimeno J.M., Lopez-Lazaro L., Bult A., Beijnen J.H.: Development of a lyophilized parenteral pharmaceutical formulation of the investigational polypeptide marine anticancer agent kahalalide F. *Drug Dev. Ind. Pharm.,* **27**, 767-780 (2000).
6. Palermo J.A., Flower B.P., Seldes A.M.: Chondriamides A and B new indolic metabolites from red algae *Chondria* sp. *Tetrahedron Lett.,* **33**, 3097-3100 (1992).
7. Davyt D., Entz W., Fernandez R., Mariezcurrena R., Mombrú A.W., Saldaña J., Domínguez L., Coll J., Manta E.: A new indole derivative from the red alga *Chondriaatropurpurea*. Isolation, structure determination, and anthelmintic activity. *J. Nat. Prod.,* **61**, 1560-1563 (1998).
8. Hidari K.I., Takahashi N., Arihara M., Nagaoka M., Morita K., Suzuki T.: Structure and anti-dengue virus activity of sulfated polysaccharide from a marine alga. *Biochem. Biophys. Res. Commun.,* **376**, 91-95 (1981).
9. Shibata T., Fujimoto K., Nagayama K., Yamaguchi K., Nakamura T.: Inhibitory activity of brown algal phlorotannins against hyaluronidase. *Int. J. Food Sci. Tech.,* **37**, 703-709 (2002).
10. Bernardi G. and Springer G.F.: Properties of highly purified fucan. *J. Biol. Chem.,* **237**, 75-80 (1962).
11. Yuan H., Song J., Li X., Li N., Dai J.: Immunomodulation and antitumor activity of κ-carrageenan oligosaccharides. *Cancer Lett.,* **243**, 228-234 (2006).
12. Carter G.T., Rinehart K.L. Jr., Li L.H. Kuentzel S.L., Connor J.L.: Brominated indoles from *Laurenciabrongniartii*. *Tetrahedron Lett.,* **46**, 4479-4482 (1978).
13. Takamatsu S., Hodges T.W., Rajbhandari I., Gerwick W.H., Hamann M.T., Nagle D.G.: Marine natural products as novel antioxidant prototypes. *J. Nat. Prod.,* **66**, 605-608 (2003).
14. Woolner V.H., Jones C.M., Field J.J., Fadzilah N.H., Munkacsi A.B., Miller J.H., Keyzers R.A., Northcote P.T.: Polyhalogenated indoles from the red alga *Rhodophyllis-*

membranacea: The first isolation of bromo-chloro-iodo secondary metabolites. *J. Nat. Prod.,* **79**, 463-469 (2016).
15. de Sousa A.P.A., Torres M.R., Pessoa C., deMoraes M.O., Filho F.D.R., Alves A.P.N.N., Costa-Lotufo L.V.: *In vivo* growth-inhibition of sarcoma 180 tumor by alginates from brown seaweed *Sargassum vulgare*. *Carbohydr. Polym.,* **69**, 7-13 (2007).
16. Bourgougnon N., Lahaye M., Quemener B., Chermann J.C., Rimbert M., Cormaci M., Furnari G., Komprobst J.M.: Annual variation in composition and in vitro anti-HIV-1 activity of the sulfated glucuronogalactan from *Schizymeniadubyi* (Rhodophyta, Gigartinales). *J. Appl. Phycol.,* **8**, 155-161 (1996).
17. Gerwick W.H., Fenical W.: Ichthyotoxic and cytotoxic metabolites of the tropical brown alga, *Stypopodiumzonale*. *J. Org. Chem.,* **46**, 22-27 (1981).
18. Rajasulochana P., Krishnamoorthy P., Dhamotharan R.: Isolation, identification of bromophenol compound and antibacterial activity of *Kappaphycus* sp. *Int. J. Pharm. Bio. Sci.,* **3,** 173-186 (2012).
19. Torres F.A.E., Passalacqua T.G., Velasquez A.M.A., Souza R.A., Colepicolo P., Graminha M.A.S.: New drugs with antiprotozoal activity from marine algae: a review. *Rev. Bras. Farmacog.,* **24**, 265-276 (2014).
20. Pérez M.J., Falqué E., Domínguez H.: Antimicrobial action of compounds from marine seaweed. *Mar. Drugs,* **14**, E52 (2016).
21. Guedes A.C., Barbosa C.R., Helena M.A., Cláudia I.P., Francisco, X.M.: Microalgal and cyanobacterial cell extracts for use as natural antibacterial additives against food pathogens. *Int. J. Food Sci. Technol.,* **46**, 862-870 (2011).
22. Eom S.H., Kim Y.M., Kim S.K.: Antimicrobial effect of phlorotannins from marine brown algae. *Food Chem. Toxicol.,* **50**, 3251-3255 (2012).
23. Cavallo R.A., Acquaviva M.I., Stabili L., Cecere E., Petrocelli A., Narracci M.: Antibacterial activity of marine macroalgae against fish pathogenic *Vibrio* species. *Cent. Eur. J. Biol.,* **8**, 646 (2013).
24. Demirel Z., Yilmaz-Koz F.F., Karabay-Yavasoglu U.N., Ozdemir G., Sukatar A.: Antimicrobial and antioxidant activity of brown algae from the Aegean Sea. *J. Ser. Chem. Soc.,* **74**, 619-628 (2009).
25. Bhagavathy S., Sumathi P., Jancy Sherene Bell I.: Green algae *Chlorococcumhumicola* a new source of bioactive compounds with antimicrobial activity. Asian Pac. *J. Trop. Biomed.,* **1**, S1-7 (2011).
26. Plaza M., Santoyo S., Jaime L, García-Blairsy R.G., Herrero M., Señoráns F.J., Ibáñez E.: Screening for bioactive compounds from algae. *J. Pharm. Biomed. Anal.,* **51**, 450-455 (2010).
27. Manilal A., Sujith S., Selvin J., Shakir C., Seghal G.: Antibacterial activity of *Falkenbergiahillebrandii* (Born) from the Indian coast against human pathogens. *Int. J. Exp. Bot.,* **78**, 161-166, (2009).
28. Etahiri S., Bultel-Poncé V., Caux C., Guyot M.: New bromoditerpenes from the red alga *Sphaerococcuscoronopifolius. J. Nat. Prod.,* **64**, 1024-1027 (2001).
29. Cueto M., Jensen P.R., Kauffman P., Fenical W., Lobkovsky E., Clardy J.: Pestalone a new antibiotic produced by a marine fungus in response to bacterial challenge. *J. Nat. Prod.,* **64**, 1444-1446 (2001).
30. Perez R.M., Avila J.G., Perez S., Martinez A., Martinez G.: Antimicrobial activity of some American algae. *J. Ethnopharmacol.,* **29**, 111-116 (1990).
31. Albuquerque M.R., Takaki C., Koening M.L.: Detection of antimicrobial activity in marine seaweeds. *Rev.Inst. Antibiot. Univ. Fed. Pernambuco Recife.,* **21**, 127-138 (1983).
32. Choi J.G., Kang O.H., Brice O.O., Lee Y.S., Chae H.S., Oh Y.C., Sohn D.H., Park H., Choi H.G., Kim S.G., Shin D.W., Kwon D.Y.: Antibacterial activity of *Ecklonia cava* against methicillin-resistant *Staphylococcus aureus* and *Salmonella* spp. *Foodborne Pathog. Dis.,* **7**, 435-441 (2010).
33. Eom S.H., Lee D.S., Kang Y.M., Son K.T., Jeon Y.J., Kim Y.M.: Application of yeast *Candida utilis* to ferment *Eiseniabicyclis* for enhanced antibacterial effect. *Appl. Biochem. Biotechnol.,* **171**, 569-582 (2013).
34. Alarif W.M., Al-Lihaibi S.S., Ayyad S.E., Abdel-Rhman M.H., Badria F.A.: Laurene-type sesquiterpenes from the Red Sea red alga *Laurenciaobtusa* as potential antitumoreantimicrobial agents. *Eur. J. Med. Chem.,* **55**, 462-466 (2012).
35. Lee M.H., Lee K.B., Oh S.M., Lee B.H., Chee H.Y.: Antifungal activities of dieckol isolated from the marine brown alga *Ecklonia cava* against *Trichophyton rubrum*. *Food Sci. Biotechnol.,* **53**, 504-507 (2010).
36. da Silva Machado F.L., Pacienza-Lima W., Rossi-Bergmann B., de Souza Gestinari L.M., Fujii M.T. de Paula J.C., Costa S.S., Lopes N.P., Kaiser C.R., Soares, A.R.: Antileishmanialsesquiterpenes from the brazilian red alga *Laurenciadendroidea*. *Planta Med.,* **77**, 733-735 (2011).
37. dos Santos A.O., Britta E.A., Bianco E.M., Ueda-Nakamura T., Filho B.P., Pereira R.C., Nakamura C.V.: 4-Acetoxydolastane diterpene from the Brazilian brown alga *Canistrocarpuscervicornis* as antileishmanial agent. *Mar. Drugs,* **9**, 2369-2383 (2011).
38. dos Santos A.O., Veiga-Santos P., Ueda-Nakamura T., Sudatti D.B., Bianco E.M., Pereira R.C., Nakamura C.V.: Effect of elatol, isolated from red seaweed *Laurenciadendroidea*, on *Leishmaniaamazonensis*. *Mar. Drugs,* **8**, 2733-2743 (2010).
39. Soares D.C., Calegari-Silva T.C., Lopes U.G., Teixeira V.L., de Palmer Paixão I.C.N., Cirne-Santos C., Bou-Habib D.C., Saraiva E.M.: Dolabelladienetriol, a compound from *Dictyotapfaffii* algae, inhibits the infection by *Leishmaniaamazonensis. PLOS Neglect. Trop. D.,* **6**, e1787 (2012)
40. Veiga-Santos P., Pelizzaro-Rocha K.J., Santos A.O., Ueda-Nakamura T., Dias Filho B.P., Silva S.O., Sudatti D.B., Bianco E.M., Pereira R.C., Nakamura C.V.: *In vitro* anti-trypanosomal activity of elatol isolated from red seaweed *Laurenciadendroidea*. *Parasitology,* **137**, 1661-1670 (2010).
41. Vonthron-Sénécheau C., Kaiser M., Devambez I., Vastel A.,

Mussio I., Rusig A.M.: Antiprotozoal activities of organic extracts from French marine seaweeds. *Mar. Drugs,* **9**, 922-933 (2011).

42. Galle J.B., Attioua B., Kaiser M., Rusig A.M., Lobstein A., Vonthron-Senecheau C.: Eleganolone, a diterpene from the French marine alga *Bifurcariabifurcata* inhibits growth of the human pathogens *Trypanosoma brucei* and *Plasmodium falciparum*. *Mar. Drugs,* **11**, 599-610 (2013).
43. Süzgeç-Selçuk S., Mericli A.H., Guven K.C., Kaiser M., Casey R., Hingley-Wilson S., Lalvani A., Tasdemir D.: Evaluation of Turkish seaweeds for antiprotozoal, antimycobacterial and cytotoxic activities. *Phytother. Res.,* **25**, 778-783 (2011).
44. de Felício R., de Albuquerque S., Young M.C., Yokoya N.S., Debonsi H.M.: Trypanocidal, leishmanicidal and antifungal potential from marine red alga *Bostrychiatenella* J. Agardh (Rhodomelaceae, Ceramiales). *J. Pharm. Biomed. Anal.,* **52**, 763-769 (2010).
45. Richards J.T., Kern E.R., Glasgow L.A., Overall J.C. Jr., Deign E.F., Hatch M.T.: Antiviral activity of extracts from marine algae. *Antimicrob. Agents Chemother.,* **14**, 24-30 (1978).
46. Meiyu G., Fuchuan L., Xianliang X., Jing L., Zuowei Y., Huashi G.: The potential molecular targets of marine sulfated polymannuroguluronate interfering with HIV-1 entry. Interaction between SPMG and HIV-1 rgp120 and CD4 molecule. *Antiviral Res.,* **59**, 127-135 (2003).
47. Witvrouw M., De Clercq E.: Sulfated polysaccharides extracted from sea algae as potential antiviral drugs. *Gen. Pharmacol.,* **29**, 497-511 (1997).
48. Ponce N.M., Pujol C.A., Damonte E.B., Flores M.L., Stortz C.A.: Fucoidans from the brown seaweed *Adenocystisutricularis*: extraction methods, antiviral activity and structural studies. *Carbohydr. Res.,* **338**, 153-165 (2003).
49. Pujol C.A., Estevez J.M., Carlucci M.J., Ciancia M., Cerezo A.S., Damonte E.B.: Novel DL-galactan hybrids from the red seaweed *Gymnogongrustorulosus* are potent inhibitors of herpes simplex virus and dengue virus. *Antivir. Chem. Chemother.,* **13**, 83-89 (2002).
50. Schaeffer D.J., Krylov V.S.: Anti-HIV activity of extracts and compounds from algae and cyanobacteria. *Ecotoxicol. Environ. Saf.,* **45**, 208-227 (2000).
51. Thompson K.D.Dragar C.: Antiviral activity of *Undariapinnatifida* against herpes simplex virus. *Phytother. Res.,* **18**, 551-555 (2004).
52. Ono L., Wollinger W., Rocco I.M., Coimbra T.L., Gorin P.A., Sierakowski M.R.: *In vitro* and *in vivo* antiviral properties of sulfated galactomannans against yellow fever virus (BeH111 strain) and dengue 1 virus (Hawaii strain). *Antiviral Res.,* **60**, 201-208 (2003).
53. Talarico L.B., Pujol C.A., Zibetti R.G., Faría P.C., Noseda M.D., Duarte M.E., Damonte E.B.: The antiviral activity of sulfated polysaccharides against dengue virus is dependent on virus serotype and host cell. *Antiviral Res.,* **66**, 103-110 (2005).
54. Béress A., Wassermann O., Tahhan S., BruhnT., Béress L., Kraiselburd E.N., Gonzalez L.V., de Motta G.E., Chavez P.I.: A new procedure for the isolation of anti-HIV compounds (polysaccharides and polyphenols) from the marine alga *Fucusvesiculosus*. *J. Nat. Prod.,* **56**, 478-488 (1993).