CHAPTER 20

Anti-HIV Activity of Extracts and Compounds from Marine Algae

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Contents

Abstract

In recent years, elucidation of novel bioactive substances from different marine organisms is gaining importance rapidly not only from the research and publications but also from controlled clinical studies of natural product-derived substances. They offer important leads for the development of antiviral drugs against viral infections caused by human immunodeficiency virus type 1 (HIV-1). Regarding this issue, numerous anti-HIV-1 therapeutic agents from marine resources have been reported for their potential medicine/medical application as novel functional ingredients in anti-HIV therapy. In detail, marine macroalgae have attracted much of attention as a reliable source for potential anti-HIV compounds. Up to date, several types of compounds such as tannins, polysaccharides, lectins, and derivatives have been isolated, identified, and reported to possess significant anti-HIV-1 activity.

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I. BACKGROUND

High amounts of secondary metabolites produced by microorganisms, plants, and marine organisms have been of much attention as bioactive substances for disease treatment (Lam, 2007). Among these diseases, acquired immunodeficiency syndrome (AIDS) stands as one of the most important diseases worldwide with about 33.2 million people infected by human immunodeficiency virus type-1 (HIV-1; Unaids Global Report, 2010). HIV is an enveloped retrovirus that belongs to the lentivirus family. The structure of HIV is relatively complex with each virus expressing 160 kDa glycoproteins composed of gp120 and gp41. The gp41 molecule is a transmembrane glycoprotein that crosses the membrane of the viral envelope. There is a noncovalent interaction between gp120 and gp41. The entry of HIV into the host cell requires the interaction of viral envelope glycoprotein, gp120, with the CD4 glycoprotein and a chemokine receptor on the host cell surface (Kwong *et al.*, 1998). The viral envelope is composed of the host cell membrane and naturally contains some host cell membrane proteins, including class I and class II major histocompatibility complex molecules which were previously located on host-cell membrane. Within the envelope, viral core (nucleocapsid) that includes a layer of protein called p17, and an inner layer of protein called p24, is located. The HIV genome is composed of two identical single-stranded RNA (+) and some proteins are attached to the genome such as two molecules of reverse transcriptase (RT), a protease, and an integrase (Reeves *et al.*, 2000).

The knowledge of HIV replication is important for the understanding of its pathogenesis and the development of therapeutic agents. Following entry of HIV into cells and getting into contact with the appropriate receptors and coreceptors, formation of the viral double-stranded DNA genome is followed by the integration of proviral-DNA into the host cell genome, creating a provirus. Attachment of the virus occurs upon the binding of the gp120 on the viral envelope to the CD4+ host cell. Receptors on the host cells could be either one of the following major chemokine receptors: CXCR4 or CCR5. CXCR4 is found on naive T-cells, whereas CCR5 is located on monocytes, macrophages, and activated or memory subset of T-cells. Once in the cytoplasm, the viral RNA is converted to DNA by the action of a viral RNA-dependent DNA polymerase activity and a virus-specified ribonuclease H activity found in the HIV-1 RT enzyme. Following several stages of integration through integrase enzyme activity, new virus particles are started to be synthesized by host cell genome. Forming new virus particles are followed by trimming by HIV protease inside the capsid. This process produces the functioning proteins such as RT, integrase, and protease enzymes. The newly released virions now have the capacity to infect new target cells, starting a new replication cycle as fully mature viruses.

HIV-1 is identified as the causative agent of AIDS, and up to now, there are significant advances in rational drug design and highly active compounds can be synthesized (De Clercq, 2009). However, HIV drug resistance, side effects, and the need for long-term antiviral treatment urge the inevitable development of new anti-HIV agents, targets, and therapies (D'Aquila *et al.*, 2002; Worm *et al.*, 2010). In this regard, naturally occurring products are still known as the richest source of bioactive compounds. Natural products promote excessive availability for discovering anti-HIV treatment, while they contain a massive amount of potential, being a consistent source for successful drug discovery. There are quite big amounts of marine-based natural products, which are reported to have bioactivities such as antifungal and antimicrobial effects. In addition, several natural products from marine organisms have been reported to express bioactivity against prevalent diseases such as cancer, diabetes, and obesity (Mayer *et al.*, 2011). So far, numerous compounds isolated from natural resources have been reported to exhibit significant anti-HIV activity and were able to inhibit HIV-1 activity in almost every stage of the viral life cycle (Jiang *et al.*, 2010). Several compounds of plant origin such as alkaloids, coumarins, carbohydrates, flavonoids, lignans, phenolics, quinines, phospholipids, terpenes, and tannins have been elucidated and reported to possess inhibitory activity against various targets during the viral life cycle of HIV. Considering that the marine species comprise more than half of the total biodiversity of the earth, the sea holds considerably high potential of lead compounds for novel drugs. On this matter, among the terrestrial organisms for compound isolation, the marine organisms present rich resources of diverse compounds with various crucial antiviral activities.

II. COMPOUNDS FROM MARINE ALGAE WITH ANTI-HIV ACTIVITY

A. Phlorotannins

Tannins are naturally occurring water-soluble polyphenolic compounds, and it has been reported that they show their anti-HIV activity by inhibiting polymerase and ribonuclease activities of HIV-1 RT. Phlorotannins are tannin derivatives which contain several phloroglucinol units linked to each other in different ways and formed by the polymerization of phloroglucinol (1,3,5-trihydroxybenzene) monomer units and biosynthesis through the acetate–malonate pathway. So far, phlorotannins mostly have been isolated from red and brown alga. Numerous bioactivities of phlorotannins have been reported up to date such as antioxidant, anti-inflammatory, antibacterial, and anti-MMP activities (Kim *et al.*, 2006; Nagayama *et al.*, 2002).

For the first time, seaweeds extracts have been tested for their anti-HIV-1 activity in terms of inhibiting RT, protease, and integrase of HIV-1 (Ahn *et al.*, 2004). Following the mentioned research, two phlorotannins from brown alga *Ecklonia cava* Kjellman have been isolated and reported to inhibit the HIV-1 protease and RT. These pholorotannins, 8,8′-bieckol and 8,4‴-dieckol, which are dimers of eckol, isolated from *E. cava*, inhibited the RT and protease activity efficiently. In case of inhibition of HIV-1 RT, 8,8′-bieckol which has a biaryl linkage showed a 10-fold higher activity than that of 8,4‴-dieckol which has a diphenyl ether linkage with the IC_{50} values of 0.5 and 5.3 μM, respectively. Hence the significant RT inhibitory activity of 8,8′-bieckol was favorable against its protease inhibition and comparable to the positive control nevirapine which has an IC_{50} value of 0.28 μM. In the light of recent reports, 8,8′-bieckol might be employed as a drug candidate for development of new generation therapeutic agents against HIV. In addition to these results, in another report, 6,6′-bieckol from *E. cava* reduced the cytopathic effects of HIV-1 including HIV-1-induced syncytia formation and viral p24 antigen levels, as well as inhibited RT and HIV-1 entry activity (Artan *et al.*, 2008). It has been strongly suggested that 6,6′-bieckol is a safe tannin derivative exhibiting a relatively lower cytotoxicity in comparison to other polyphenols and significant anti-HIV-1 activity. In detail, 6,6′-bieckol protected 96% of the HIV-1 infected cells from infection-induced lytic effects and inhibited the syncytia formation up to 88% with an EC_{50} value of 1.72 μM. Moreover, 6,6′-bieckol inhibited the RT activity and p24 production with IC_{50} values of 1.07 and 1.26 μM, respectively. The performed studies also clearly showed that addition of 6,6′-bieckol successfully prevented the HIV-1 entry dependent on the inhibition of production of specific proteins such as p55 and p41. These results were strengthening by coculture assays which again show clear inhibitory effect against HIV-1 infection *in vitro*. This important anti-HIV activity in various stages of viral cycle including viral entry and RT activity, however, excluding a sufficient protease inhibition, promotes 6,6′-bieckol as a significant lead for further drug design on the way to a full inhibition of HIV-1 activity.

Besides the brown alga *E. cava*, another phlorotannin, diphlorethohydroxycarmalol has been isolated from *Ishige okamurae* Yendo (Ahn *et al.*, 2006). This phlorotannin was assayed for its inhibitory activity against HIV-1 RT, integrase, and protease while any study for its HIV-1 activity *in vitro* has not been carried out. Diphlorethohydroxycarmalol inhibited the RT and protease activity with IC_{50} values of 9.1 and 25.2 μM, respectively; however, it failed to show any efficiency against HIV-1 protease. Therefore, this phlorotannin also can be regarded as an important compound for anti-HIV drug designing, or nutraceutical and pharmaceutical industries.

B. Polysaccharides

Biological effects of polysaccharides have been observed by several researches. Activities such as anticoagulant, anti-inflammatory, antitumor, and antiviral stand as the main bioactivities of polysaccharides from different natural sources. In this respect, marine algae are abundant sources of different type of plant-originated bioactive polysaccharides. The chemical structure, amount and bioactivity of these polysaccharides vary according to marine algae species and divisions such as Chlorophyta (green algae), Rhodophyta (red algae), and Phaeophyta (brown algae). In recent studies, numerous saccharides isolated from marine algae have attracted quite attention in the fields of biochemistry and pharmacology due to their efficiency as anti-HIV-1, antiadhesive, anticoagulant, anticancer, and anti-inflammatory agents (Schaeffer and Krylov, 2000; Wijesekara *et al.*, 2010). Moreover, polysaccharides have attracted much of attention as antiviral compounds since the inhibitory activities of algal polysaccharides against mumps and influenza virus were firstly reported (Gerber *et al.*, 1958). Further, a comparative study has been reported on the inhibition of herpes simplex virus and other viruses by polysaccharide fractions from the extracts of 10 red algae (Ehreshmann *et al.*, 1977). It is proposed that polysaccharides are quite efficient in disrupting the viral peptide attachments which are supposed to be highly preserved in the drug-resistance mutation process. Therefore, polysaccharides are directed to affect these peptides as potential anti-HIV targets.

Fucans are sulfated polysaccharides of high molecular weight which can be found widely in various brown algae species. They have fucose as their main repeating unit; however, they can include other sugars as well such as glucose, mannose, galactose, and uronic acid. Several fucans from the seaweed species *Dictyota mertensii*, *Lobophora variegata*, *Spatoglossum schroederi*, and *Fucus vesiculosus* were reported to successfully inhibit the activity of HIV RT (Queiroz *et al.*, 2008). An isolated galactofucan which is mainly formed by galactose-linked fucose and with lower sulfate content from *L. variegate* inhibited the 94% HIV-1 RT activity at a concentration of 1.0 μg/mL. Another isolated fucan with a higher sulfate content and containing mostly fucose units exerted a high inhibitory effect on RT as well. Same fucan from two different algae, *S. schroederi* and *D. mertensii*, showed similar inhibition ratios which are 99.03% and 99.30%, respectively, at 1.0 mg/mL concentration. However, a higher sulfate containing fucan from *S. schroederi* with the units of galactose and fucose could only show a 53.90% inhibitory against the RT activity at the same concentration. As a part of this comparative approach, a homofucan containing only sulfated fucose units have been isolated and surprisingly exhibited a strong RT inhibitory effect. At a concentration of 0.5 mg/mL, this fucan

inhibited 98.10% of the RT activity with poly(rA)-oligo(dT) nucleotides. In order to possess more information regarding the structure–activity relationship of fucans, chemical modifications were carried out. Fucans which were modified by carboxyreduction and desulfation showed approximately fourfold lower inhibitory activities for RT under same conditions. Detailed comparison regarding the chemical structure and the inhibitory activity, RT inhibition of fucans are suggested to be dependent on both the ionic changes and the sugar rings that act to spatially orientate the charges in chemical configuration and recognizes the enzyme, therefore defining the specificity of the enzyme–compound binding.

In addition, a recent study has exhibited that galactofucan fractions from the brown algae *Adenocystis utricularis* showed *in vitro* anti-HIV-1 activity (Trinchero *et al.*, 2009). Two fractions among five had strong inhibitory effects on HIV-1 replication with IC_{50} values of 0.6 and 0.9 μg/mL, respectively. Moreover, these fractions showed their activity against both wild-type and drug-resistant viral strains. Researchers suggest that this inhibitory effect of galactofucan fractions is due to blocking of viral infection and early steps of replication rather than inactivating the viral particle production.

The glucoronogalactan from red algae *Schizymenia dubyi* was also reported to exhibit anti-HIV activity (Bourgougnon *et al.*, 1996). Glucoronogalactan from *S. dubyi* successfully protected the MT4 cells from the cytopathic effects of HIV-1 infection by means of reducing the syncytia formation almost to 1% of untreated infected control at a concentration of 5 μg/mL. At same concentration, HIV-1 RT activity was also inhibited significantly without any cytotoxic effect. *In vitro* studies on glucoronogalactan suggest that the disturbing virus–host cell linkage and inhibiting early steps of HIV infection can be regarded as the possible action mechanism of this polysaccharide

In addition to *S. dubyi*, *Grateloupia filicina* and *Grateloupia longifolia* are also sources for two sulfated galactans (Wang *et al.*, 2007), GFP and GLP, respectively, which have been shown to possess anti-HIV activity *in vitro*. The sulfate contents of the GFP and GLP were confirmed as 25.7% and 18.5%, respectively. The sulfated galactan GFP has sulfate ester groups at carbon 2 and at carbon 2 and 6 for GLP. The anti-HIV activities of these polysaccharides have been tested on a primary isolate of HIV-1 and human peripheral blood mononuclear cells, and both GFP and GLP showed strong anti-HIV activity with low cytotoxicity. EC_{50} values for the HIV-1 infection protective effect of GFP and GLP addition were calculated as 0.010 and 0.003 μM, respectively.

Moreover, a variety of potential bioactive polysaccharides are also isolated from brown algae where some of them exhibit anti-HIV activity with different mechanism of action. Sulfated polymannurogluronate

(SPMG) is a novel member of polysaccharides extracted from brown algae (Meiyu *et al.*, 2003; Miao *et al.*, 2005). It has 8 kDa average molecular weight and is rich in 1,4-linked β-D mannuronate with 1.5 sulfated and 1.0 carboxyl groups per sugar residue. Studies suggested a possible linkage between SPMG and gp120 of HIV-1. It has been reported that binding of SPMG to gp120 alone or gp120-CD4 complex occurred through V3 loop region of the protein. SPMG showed partial suppression of gp120 binding to CD4 when treated prior to infection. However, SPMG addition to preinfected cells did not show any significant suppression of virus–host cell linkage. Therefore, it is suggested that SPMG either shares common binding sites on gp120 with CD4 or masks the docking sites of gp120 for CD4.

As stated in recent studies, the various advantages of natural-based antiviral drugs, such as relatively low-production costs, broad range of activity, low cytotoxicity, safety, and novel modes of action suggest that polysaccharides from marine algae are promising drug candidates and lead for novel drug design in the near future.

C. Lectins

Lectins are carbohydrate-binding proteins which are found in a variety of species ranging from prokaryotes to corals, algae, fungi, plants, invertebrates, and vertebrates. Due to their specific carbohydrate-binding properties, they are highly involved in crucial biological processes such as host–pathogen interaction, cell–cell communication, induction of intracellular signaling cascades, and cell targeting. In this regard, lectins are showed to have potential to block the binding between HIV-1 and host cells, preventing the viral infection and dissemination. Evidently, HIV-1 envelope glycoprotein gp120 is extensively glycosylated with numerous N-linked glycosylation sites. Glycans which are seated in these glycosylation sites are rich in mannose and can easily serve as ligands for lectins. The importance of gp120 in viral infection of the target cell makes this protein suitable target for anti-HIV treatment or prophylaxis. In this manner, there are several types of lectins which were isolated from marine sources with potential anti-HIV activity (Sato and Hori, 2009).

Griffithsin is a novel lectin isolated from the red algae *Griffithsia* sp. with a molecular weight of 12.7 kDa. This 121 amino acid protein is reported to display promising anti-HIV activity (Mori *et al.*, 2005). Griffithsin is completely novel with no cysteine residues and does not have any homology to any of the proteins or translated nucleotide sequences. Studies showed that Griffithsin potently prevented the T-lymphoblastic cells from the cytopathic effects of both laboratory strains and clinical primary isolates of HIV-1. It was also exhibited to be active against both T-cell tropic and macrophage-tropic strains of HIV-1 at concentrations as

low as 0.043 μM. More importantly, Griffithsin blocked cell–cell fusion between chronically infected and uninfected cells at subnanomolar concentrations without any cytotoxic effect. In connection with predicted mode of action, this lectin disturbed the binding of CD4 host cell membrane receptor to gp120 in a glycosylation-dependent manner and prevented HIV-1 infection. On the other hand, gp120-Griffithsin bond was inhibited by higher glucose and mannose but not by galactose, xylose, or sialic acid-containing glycoproteins. In a structure–activity relationship perspective, the linker sequences of Griffithsin, Gly-Gly-Ser-Gly-Gly is credited to its unusually potent activity.

In a recent study, a high-mannose-binding lectin (BCA) is isolated from green alga *Boodlea coacta* with potent antiviral activity against HIV-1 and influenza viruses (Sato *et al.*, 2011). Carbohydrate-binding specificity determination of BCA evidently showed that this lectin has strong specificity for α1-2 linked mannose at nonreducing terminal. The potent anti-HIV-1 activity of BCA was easily predicted from carbohydrate-binding propensity and similarity with formerly reported antiviral lectins. Studies showed that BCA inhibited the HIV-1 infection with EC_{50} value of 8.2 nM. In addition, surface plasmon resonance analysis reported a high affinity between BCA and the HIV envelope glycoprotein gp120 with an association constant of $3.71 \times 10^8\ M^{-1}$.

D. Other

As a part of wide screening of seaweed extracts, 47 marine macroalgae extracts were tested for their ability to inhibit HIV-1 RT and integrase (Ahn *et al.*, 2002). Results clearly showed that one of four Chlorophyta, eight of 17 Phaeophyta, and six of 26 Rhodophyta species showed inhibitory activity against HIV-1 RT. In addition, among these 47 algae extracts, five species (*E. cava, I. okamurae, Sargassum confusum, Sargassum hemiphyllum, Sargassum ringgoldianum*) were able to inhibit the activity of HIV-1 integrase. Moreover, *in vitro* studies confirmed that extracts of *Bossiella sp.* and *Chondria crassicaulis* successfully prevented the MT4 cells from HIV-1 induced cytopathic effects in case of noncytotoxic concentrations. Following these screening results, a carmalol derivative, diphlorethohydroxycarmalol, was isolated from brown alga, *I. okamurae* (Ahn *et al.*, 2006), as mentioned earlier which urges the further isolation processes for elucidation of active compounds of these extracts.

Further, two diterpenes, named (6R)-6-hydroxydichotoma-3,14-diene-1,17-dial (DT1) and (6R)-6-acetoxydichotoma-3,14-diene-1,17-dial (DT2), were isolated from the brown alga *Dictyota menstrualis* (Pereira *et al.*, 2004). It has been reported that DT1 and DT2 inhibited the virus replication with EC_{50} values of 40 and 70 μM, respectively, in addition to HIV-1 RT inhibitory activity with IC_{50} values of 10 and 35 μM. Another study

reported a dolabellane diterpene, 8,10,18-trihydroxy-2,6-dolabelladiene, from brown alga *Dictyota pfaffii* with a HIV-1 infection inhibitory effect with an EC_{50} of 8.4 and 1.7 μM in peripheral blood mononuclear cells and macrophages, respectively. Moreover, this diterpene inhibited the HIV-1 RT activity with an IC_{50} of 16.5 μM (Barbosa *et al*., 2004).

III. CONCLUSION

Recent studies have evidently proved that marine-derived anti-HIV agents may play a vital role against HIV. There are promising results in the way to discover or design new drug candidates and pharmaceuticals to support reducing or regulation HIV-1 infection and related complications. Moreover, these results promote agents from marine macroalgae with beneficial health effects and potential anti-HIV activity on the road to novel highly effective HIV-1 treatment. Further studies including human subjects will reveal the true anti-HIV potential of marine algae-derived compounds in near future.

REFERENCES

Ahn, M. J., Yoon, K. D., Kim, C. Y., Min, S. Y., Kim, Y. U., Kim, H. J., Kim, J. H., Shin, C. G., Lee, C. K., Kim, T. G., Kim, S. H., Huh, H., *et al*. (2002). Inhibition of HIV-1 reverse transcriptase and HIV-1 integrase and antiviral activity of Korean seaweed extracts. *J. Appl. Phycol.* **14**, 325–329.

Ahn, M. J., Yoon, K. D., Min, S. Y., Lee, J. S., Kim, J. H., Kim, T. G., Kim, S. H., Kim, N. G., Huh, H., and Kim, J. (2004). Inhibition of HIV-1 reverse transcriptase and protease by phlorotannins from the brown alga *Ecklonia cava*. *Biol. Pharm. Bull.* **27**, 544–547.

Ahn, M. J., Yoon, K. D., Kim, C. Y., Kim, J. H., Shin, C. G., and Kim, J. (2006). Inhibitory activity on HIV-1 reverse transcriptase and integrase of a carmalol derivative from a brown alga, *Ishige okamurae*. *Phytother. Res.* **20**, 711–713.

Artan, M., Li, Y., Karadeniz, F., Lee, S. H., Kim, M. M., and Kim, S. K. (2008). Anti-HIV-1 activity of phloroglucinol derivative, 6,6′-bieckol, from *Ecklonia cava*. *Bioorg. Med. Chem.* **16**, 7921–7926.

Barbosa, J. P., Pereira, R. C., Abrantes, J. L., Cirne Dos Santos, C. C., Rebello, M. A., and Texeira, V. L. (2004). *In vitro* antiviral diterpenes from the Brazilian brown alga *Dictyota pfaffii*. *Planta Med.* **70**, 856–860.

Bourgougnon, N., Lahaye, M., Quemener, B., Chermann, J. C., Rimbert, M., Cormaci, M., Furnari, G., and Komprobst, J. M. (1996). Annual variation in composition and *in vitro* anti-HIV-1 activity of the sulfated glucuronogalactan from *Schizymenia dubyi* (Rhodophyta, Gigartinales). *J. Appl. Phycol.* **8**, 155–161.

D'Aquila, R. T., Brun-Vézinet, F., Clotet, B., Md, R. T. D., Demeter, L. M., Grant, R. M., Schapiro, J. M., and Telenti, A. (2002). Drug resistance mutations in HIV-1. *Top. HIV Med.* **10**, 21–25.

De Clercq, E. (2009). Anti-hiv drugs: 25 compounds approved within 25 years after the discovery of HIV. *Int. J. Antimicrob. Agents* **33**, 307–320.

Ehreshmann, D. W., Dieg, E. F., Hatch, M. T., DiSalvo, L. H., and Vedros, N. A. (1977). Antiviral substances from California marine algae. *J. Phycol.* **13**, 37–40.

Gerber, P., Dutcher, J. D., Adams, E. V., and Sherman, J. H. (1958). Inhibition of herpes virus replication by marine algae extracts. *Proc. Soc. Exp. Biol. Med.* **99**, 590–593.

Jiang, Y., Ng, T. B., Wang, C. R., Zhang, D., Cheng, Z. H., Liu, Z. K., Qiao, W. T., Geng, Y. Q., Li, N., and Liu, F. (2010). Inhibitors from natural products to HIV-1 reverse transcriptase, protease and integrase. *Mini Rev. Med. Chem.* **10**, 1331–1344.

Kim, M. M., Ta, Q. V., Mendis, E., Rajapakse, N., Jung, W. K., Byun, H. G., Jeon, Y. J., and Kim, S. K. (2006). Phlorotannins in *Ecklonia cava* extract inhibit matrix metalloproteinase activity. *Life Sci.* **79**, 1436–1443.

Kwong, P. D., Wyatt, R., Robinson, J., Sweet, R. W., Sodroski, J., and Hendrickson, W. A. (1998). Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature* **393**, 648–659.

Lam, K. S. (2007). New aspects of natural products in drug discovery. *Trends Microbiol.* **15**, 279–289.

Mayer, A., Rodríguez, A., Berlinck, R., and Fusetani, N. (2011). Marine pharmacology in 2007–8: Marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis and antiviral activities; affecting the immune and nervous system and other miscellaneous mechanisms of action. *Comp. Biochem. Physiol. C: Toxicol. Pharmacol.* **153**, 191–222.

Meiyu, G., Fuchuan, L., Xianliang, X., Jing, L., Zuowei, Y., and Huashi, G. (2003). The potential molecular targets of marine sulfated polymannuroguluronate interfering with HIV-1 entry: Interaction between SPMG and HIV-1 rgp120 and CD4 molecule. *Antivir. Res.* **59**, 127–135.

Miao, B., Li, J., Fu, X., Gan, L., Xin, X., and Geng, M. (2005). Sulfated polymannuroguluronate, a novel anti-AIDS drug candidate, inhibits T cell apoptosis by combating oxidative damage of mitochondria. *Mol. Pharmacol.* **68**, 1716–1727.

Mori, T., O'Keefe, B. R., Sowder, R. C., Bringans, S., Gardella, R., Berg, S., Cochran, P., Turpin, J. A., Buckheit, R. W., McMahon, J. B., and Boyd, M. R. (2005). Isolation and characterization of Griffithsin, a novel HIV-inactivating protein, from the red alga *Griffithsia* sp. *J. Biol. Chem.* **280**, 9345–9353.

Nagayama, K., Iwamura, Y., Shibata, T., Hirayama, I., and Nakamura, T. (2002). Bactericidal activity of phlorotannins from the brown alga *Ecklonia kurome*. *J. Antimicrob. Chemother.* **50**, 889–893.

Pereira, H. S., Leão-Ferreira, L. R., Moussatché, N., Teixeira, V. L., Cavalcanti, D. N., Costa, L. J., Diaz, R., and Frugulhetti, I. C. P. P. (2004). Antiviral activity of diterpenes isolated from the Brazilian marine alga *Dictyota menstrualis* against human immunodeficiency virus type 1 (HIV-1). *Antiviral Res.* **64**, 69–76.

Queiroz, K. C. S., Medeiros, V. P., Queiroz, L. S., Abreu, L. R. D., Rocha, H. A. O., Ferreira, C. V., Jucá, M. B., Aoyama, H., and Leite, E. L. (2008). Inhibition of reverse transcriptase activity of HIV by polysaccharides of brown algae. *Biomed. Pharmacother.* **62**, 303–307.

Sato, T. and Hori, K. (2009). Cloning, expression, and characterization of a novel anti-HIV lectin from the cultured cyanobacterium, *Oscillatoria agardhii*. *Fish. Sci. (Tokyo Jpn.)* **75**, 743–753.

Sato, Y., Hirayama, M., Morimoto, K., Yamamoto, N., Okuyama, S., and Hori, K. (2011). High mannose-binding lectin with preference for the cluster of α 1-2-mannose from the green alga *Boodlea coacta* is a potent entry inhibitor of HIV-1 and influenza viruses. *J. Biol. Chem.* **286**, 19446–19458.

Schaeffer, D. J. and Krylov, V. S. (2000). Anti-HIV activity of extracts and compounds from algae and cyanobacteria. *Ecotoxicol. Environ. Saf.* **45**, 208–227.

Trinchero, J., Ponce, N. M. A., Córdoba, O. L., Flores, M. L., Pampuro, S., Stortz, C. A., Salomón, H., and Turk, G. (2009). Antiretroviral activity of fucoidans extracted from the brown seaweed *Adenocystis utricularis*. *Phytother. Res.* **23**, 707–712.

Unaids Global Report, (2010). UNAIDS report on the global AIDS epidemic 2010. *WHO Library Cataloguing* **2010**, 1–3.

Wang, S. C., Bligh, S. W. A., Shi, S. S., Wang, Z. T., Hu, Z. B., Crowder, J., Branford-White, C., and Vella, C. (2007). Structural features and anti-HIV-1 activity of novel polysaccharides from red algae *Grateloupia longifolia* and *Grateloupia filicina*. *Int. J. Biol. Macromol.* **41**, 369–375.

Wijesekara, I., Pangestuti, R., and Kim, S. K. (2010). Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae. *Carbohydr. Polym.* **84**, 14–21.

Worm, S. W., Sabin, C., Weber, R., Reiss, P., El-Sadr, W., Dabis, F., De Wit, S., Law, M., Monforte, A. D. A., Friis-Møller, N., Kirk, O., Fontas, E., *et al*. (2010). Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: The data collection on adverse events of anti-HIV drugs (D:A:D) study. *J. Infect. Dis.* **201**, 318–330.