CHAPTER 19

Potential Application of Marine Algae as Antiviral Agents in Medicinal Foods

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Abstract

Viral diseases, caused by pathogenic virus infections, are still the leading cause of death in humans worldwide. Although many antiviral agents have been developed and are used for treatment of infectious diseases, emergence of drug resistance, side effects, and the necessity for extensive clinical use are the main reasons for failure of antiviral therapy. 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. Recently, a great deal of interest has been expressed regarding marine algae as potential antiviral agents. This contribution focuses on antiherpes virus therapeutic agents

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derived from marine algae which are considered as novel functional ingredients in antiherpes virus therapy.

I. INTRODUCTION

Herpes is a family of viruses of which herpes simplex virus 1 and herpes simplex virus 2 (HSV-1 and HSV-2) are the most serious human pathogens. HSV-1 is more frequently associated with oral–facial infections and encephalitis, whereas HSV-2 usually causes genital infections and can be transmitted from infected mothers to neonates. Both viruses establish long-term latent infections in sensory neurons and lesions at or near point of entry into the body (Whitley and Roizman, 2001). HSV infections are among the most common diseases of humans, with an estimated 60–95% of the adult population being infected by at least one of them (Brady and Bernstein, 2004). Effective antiherpes drugs, such as acyclovir, valacyclovir, penciclovir, famciclovir, trifluridine, cidofovir, and vidarabine, are available for treatment. However, the prolonged therapies with the available antiherpes drugs have resulted in some undesirable effects and also induced the emergence of drug-resistant strains (Morfin and Thouvenot, 2003). For this reason, the search for new types of antiherpes virus agents with high efficacy on resistant mutant viral strains is urgently needed.

The marine environment, which represents approximately half of the global biodiversity, contains a rich source of structurally diverse and biologically active metabolites. Specially, products from marine algae show many interesting activities, such as anticancer, antidiabetic, antifungal, anticoagulant, anti-inflammatory, and other pharmacological activities (El Gamal, 2010). In relation to antiviral properties, marine algae are believed to be able to provide novel leads against pathogenic viruses that are evolving and developing resistance to existing pharmaceuticals (Vo and Kim, 2010). Thus, marine algae are regarded as a promising source for the production of therapeutic drugs against viral diseases. This chapter focuses on antiherpes virus therapeutic agents derived from marine algae and their potential medical application as novel functional ingredients in antiherpes virus therapy.

II. POTENTIAL ANTIHERPES VIRUS AGENTS FROM MARINE ALGAE

A. Red macroalgae

The importance of red macroalgae as a source of novel anti-HSV agents has been recognized and reported by many researchers. According to Serkedjieva (2000), the water extract of *Polysiphonia denudate* exhibited

selective inhibition on the reproduction of HSV-1 and HSV-2 at their effective concentration 50% (EC_{50}) range of 8.7–47.7 mg/ml. The inhibition affected adsorption as well as intracellular stages of viral replication. Likewise, methanol extract of *Symphyocladia latiuscula* and its fractions was effective against acyclovir and phosphonoacetic acid-resistant HSV-1 (AP^r HSV-1), thymidine kinase deficient HSV-1 (TK HSV-1), and wild-type HSV-1 *in vitro* without cytotoxicity (Park *et al.*, 2005). Specially, the major component of CH_2Cl_2-soluble fraction, 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether (TDB), inhibited wild-type HSV-1, as well as (AP^r HSV-1) and (TK HSV-1) with their inhibitory concentration 50% (IC_{50}) values of 5.48, 4.81, and 23.3 μg/ml, respectively. Moreover, the oral administrations of TDB significantly delayed the development of skin lesions and suppressed virus yields in HSV-1-infected mice. In another study, Persian Gulf *Gracilaria salicornia* was elucidated for its capability against HSV-2 (Zandi *et al.*, 2007). The antiviral activity of water extract from *G. salicornia* displayed not only before attachment and entry of virus to the Vero cells but also on post attachment stages of virus replication. Accordingly, the extracts of marine red macroalgae can be a rich source of potential antiviral components. Interestingly, it has known that marine red macroalgae contain significant quantities of sulfated polysaccharides that may be responsible for anti-HSV properties (Damonte *et al.*, 2004).

Indeed, numerous sulfated polysaccharides from red macroalgae have been determined to possess significant inhibition on herpes virus. Xylomannan, a sulphated polysaccharide from *Nothogenia fastigiata*, was found to inhibit efficiently the replication of HSV-1 and HSV-2 under various experimental conditions (Damonte *et al.*, 1994; Pujol *et al.*, 1995). Further, the xylomannan sulfate of *Scinaia hatei* exhibited potent antiviral activity against reference strains, syncytial formation, and TK acyclovir-resistant strains of HSV-1 and HSV-2 at IC_{50} range of 0.5–4.6 μg/ml (Mandal *et al.*, 2008). Additionally, the sulfated xylomannan from *Sebdenia polydactyla* was identified to have a stronger inhibition than the known sulfated xylomannan with IC_{50} range of 0.35–2.8 μg/ml (Ghosh *et al.*, 2009). The appreciable inhibition produced by sulfated xylomannan was similar to that of standard antiherpetic polysulfates, such as heparin and dextran sulfate. Notably, the inhibitions of *in vitro* HSV replication by these xylomannans were observed at concentrations, which did not have any effect on cell viability. These sulfated xylomannans represent a potential candidate for further clinical studies.

Similar to xylomannan, galactans were found to be highly selective antiviral substances against the replication of the different strains of herpes viruses. Remarkably, *Gymnogongrus griffithsiae* and *Cryptonemia crenulata* have known to represent an interesting source of galactans with selective and potent antiviral action against reference strains,

syncytial variants, and acyclovir-resistant strains of HSV-1 and HSV-2 at IC_{50} values in the range of 0.5–5.6 μg/ml (Talarico *et al.*, 2004). The active galactans that extracted from *C. crenulata* exhibited a more effective antiviral action higher than the reference compounds heparin and dextran sulfate. Further, the crude galactan of *C. crenulata* showed a significant protective effect *in vivo* against HSV-2 vaginal infection in a murine model, suggesting the potential use of this low-cost product, easy to obtain in large quantities, for prophylaxis of virus infection. On the other hand, the strong antiherpetic activity of galactan sulfate obtained from *Grateloupia indica* has been shown in recent study (Chattopadhyay *et al.*, 2007). The isolated galactan exhibited potent anti-HSV effect on reference strains, syncytial variants, and TK ACV-resistant strains at low value of IC_{50} (0.12–1.06 μg/ml), mainly affecting virus adsorption to the host cells.

The natural carrageenans isolated from the red seaweed have recently identified as potent and selective inhibitors of HSV-1 and HSV-2. Carrageenans isolated from *Meristiella gelidium* were found to be among the most potent sulfated polysaccharides obtained from red seaweeds according to their inhibitory activity against herpes virus. The most active fraction obtained from *M. gelidium* showed a selectivity index against HSV-2 of 25,000, a value high enough to regard this carrageenan as a potential agent to be evaluated for the treatment of genital HSV-2 infection (De S-F-Tischer *et al.*, 2006). Additionally, the inhibition of *in vivo* HSV by carrageenan has been investigated in model of murine infection (Carlucci *et al.*, 2004; Pujol *et al.*, 2006). Among them, the λ-carrageenan extracted from the red seaweed *Gigartina skottsbergii* revealed 100% protection against HSV-2 mortality and replication in a very strict model of murine infection at a high dose of virus. Further, virus or neutralizing antibodies against HSV-2 was not detected in serum of λ-carrageenan-treated animals until 3 weeks after infection. These evidences warrant the availability of λ-carrageenan to protect the whole infectable surface of the mouse vagina.

B. Brown macroalgae

Besides red macroalgae, brown macroalgae also provide useful additional therapy for treating several enveloped viruses infections. Fucoidans, a complex sulfated polysaccharide found mainly in brown macroalgae, have been reported in many papers for their anti-HSV activities. Feldman and colleagues isolated fucoidan fractions (Ee, Ec, and Ea) from *Leathesia difformis* and determined their selective antiviral abilities against HSV-1 and HSV-2 (Feldman *et al.*, 1999). Fucoidan Ea was shown to be the most active agent, with IC_{50} value in the range of 0.5–1.9 μg/ml. Continually, fucoidans were found in different marine brown macroalgae due to their

anti-HSV property, including *Adenocystis utricularis*, *Sargassum horneri*, *Cystoseira indica*, *Stoechospermum marginatum*, and *Sargassum tenerrimum* (Adhikari *et al*., 2006; Mandal *et al*., 2007; Ponce *et al*., 2003; Preeprame *et al*., 2001; Sinha *et al*., 2010). Noticeably, *Undaria pinnatifida*, the most commonly eaten brown seaweed in Japan, contains sulphated polyanions and other components with appreciable anti-HSV effect. Galactofucan, the major component of an aqueous extract of *U. pinnatifida*, was evaluated for antiviral activity against 32 clinical strains of HSV, including 12 ACV-resistant strains (4 HSV-1 and 8 HSV-2) and 20 ACV-susceptible strains (10 HSV-1 and 10 HSV-2). The median IC_{50} of galactofucan for the 14 strains of HSV-1 and 18 strains of HSV-2 was 32 and 0.5 μg/ml, respectively. The mode of action of the galactofucan was shown due to the inhibition of viral binding and entry into the host cell (Thompson and Dragar, 2004). In addition, a fucoidan from sporophyll of *U. pinnatifida* (Mekabu) was examined for its antiviral activity. The IC_{50} values for HSV-1 and HSV-2 were 2.5 and 2.6, respectively, under conditions in which the fucoidan was added at the same time as viral infection (Lee *et al*., 2004a). In the *in vivo* conditions, ingestion of fucoidan from *U. pinnatifida* was associated with increased healing rates in patients with active infections (Cooper *et al*., 2002). Moreover, oral administration of the fucoidan from *U. pinnatifida* could protect mice from infection with HSV-1 as judged from the survival rate and lesion scores (Hayashi *et al*., 2008). Substantially, natural killer and cytotoxic T lymphocytes activity in HSV-1-infected mice was enhanced by oral administration of the fucoidan. The production of neutralizing antibodies in the mice inoculated with HSV-1 was significantly promoted during the oral administration of the fucoidan for 3 weeks. According to these results, fucoidan from *U. pinnatifida* was suggested as a topical microbicide for the prevention of transmission of HSV through direct inhibition of viral replication and stimulation of both innate and adaptive immune defense functions.

In recent years, anti-HSV activity of brown macroalgae was known due to their diterpene and glycolipid components. Two compounds of diterpenes, 8,10,18-trihydroxy-2,6-dolabelladiene (1) and (6*R*)-6-hydroxy-dichotoma-4,14-diene-1,17-dial (2), were isolated from *Dictyota pfaffii* and *Dictyota menstrualis* (Abrantes *et al*., 2009). It was observed that compounds 1 and 2 inhibited HSV-1 replication in a dose-dependent manner at EC_{50} values of 5.10 and 5.90 μM, respectively. Similarly, the dolastane diterpenes 4-hydroxy-9,14-dihydroxydolasta-1(15),7-diene and 4,7,14-trihydroxydolasta 1(15),8-diene isolated from *Canistrocarpus cervicornis* also exposed the suppressive effect on replication of HSV-1 (Vallim *et al*., 2010). In an investigation of El-Baroty *et al*. (2011), they revealed that glycolipid achieved from brown alga *Dilophys fasciola* possessed noticeable effect against HSV-1. At concentration range of 25–100 μg/ml, glycolipid of *D. fasciola* caused remarkably inhibition % of HSV-1 with various

degrees (78.5–100%). The IC_{50} value was 10 μg/ml, compared to that 55 μg/ml for acyclovir. A suggestion for active mechanism of glycolipid might involve in the binding of the virus glycoprotein to algal glycolipid and cause an irreversible denaturation that blocks the viral infectivity. In general, many of natural lipid classes have been shown to have high virucidal activity and are being developed as microbicidal ingredient in drug formulas to kill viruses (Hilmarsson *et al*., 2006).

C. Green macroalgae

As expected, green macroalgae also emerged as novel antiviral agents. Herein, Lee *et al*. (2004b) have estimated anti-HSV-1 activity of natural sulfated polysaccharides from 10 green macroalgae (*Enteromorpha compressa*, *Monostroma nitidum*, *Caulerpa brachypus*, *Caulerpa okamurai*, *Caulerpa scapelliformis*, *Chaetomorpha crassa*, *Chaetomorpha spiralis*, *Codium adhaerens*, *Codium fragille*, and *Codium latum*). Except for one from *E. compressa*, other sulfated polysaccharides displayed strong anti-HSV-1 activities with IC_{50} range of 0.38–8.5 μg/ml, while having low cytotoxicities with 50% inhibitory concentrations of >2900 μg/ml. In the delineation of the drug-sensitive phase, the polysaccharides of SX4 and SP4 from *C. brachypus* and SP11 from *C. latum* showed potent anti-HSV-1 activities with IC_{50} values of 6.0, 7.5, and 6.9 μg/ml, respectively, even when added to the medium 8 h postinfection. Subsequently, a polysaccharide from *M. nitidum*, rhamnan sulfate, was found to be effective against HSV-2 via blockade of virus adsorption and penetration steps onto host cell surface (Lee *et al*., 2010). Thus, it was indicated that some sulfated polysaccharides from green macroalgae not only inhibited the early stages of HSV replication, such as virus binding to and penetration into host cells, but also interfered with late steps of virus replication. Likewise, sulfated polysaccharide fraction isolated from the hot water extract of the green alga *Caulerpa racemosa* was regarded as a selective inhibitor of reference strains and TK^- acyclovir-resistant strains of HSV-1 and HSV-2 in Vero cells, with EC_{50} values in the range of 2.2–4.2 μg/ml (Ghosh *et al*., 2004).

D. Microalgae

In fact, microalgae are attracting enormous attention, and the topics have been discussed by a number of researchers. Microalgae have been recognized to provide chemical and pharmacological novelty and diversity, and they are considered as the actual producers of some highly bioactive compounds found in marine resources (Shimizu, 1996). Among the different compounds with highly biological activities, microalgae present attraction due to antiviral profile. According to Hayashi and coworkers,

the water extract of *Spirulina platensis* was shown to inhibit the replication *in vitro* of HSV-1 in HeLa cells within the concentration range of 0.08–50 mg/ml (Hayashi *et al.*, 1993). Addition of the *S. platensis* extract (1 mg/ml) at 3 h before infection causes blockade of virus-specific protein synthesis at 50% effective inhibition dose (ED_{50}) value of 0.173 mg/ml without affecting host cell protein synthesis. Moreover, it was observed that food containing the *S. platensis* extract effectively prolonged the survival time of infected hamsters at doses of 100 and 500 mg/kg per day. Subsequently, Hayashi *et al.* (1996a,b) isolated from *S. platensis* a novel sulfated polysaccharide, calcium spirulan (Ca-SP), which inhibits the replication *in vitro* of several enveloped viruses including HSV-1, human cytomegalovirus, measles virus, mumps virus, influenza A virus, and HIV-1 virus. The anti-HSV-1 activity of Ca-SP was determined to be fivefold higher than that of dextran sulfate (Hayashi *et al.*, 1996a,b). While *S. platensis* was efficient for anti-HSV-1, *Spirulina maxima* exposed inhibitory activity against HSV-2. A hot water extract of *S. maxima* showed appreciable suppression HSV-2 infection at the initial events of adsorption and penetration (ED_{50}, 0.069 mg/ml; Hernández-Corona *et al.*, 2002). Otherwise, blue-green alga *Aphanothece sacrum* and red microalga *Porphyridium* sp. exhibited significant inhibitions in both *in vitro* and *in vivo* model. Specially, cyanovirin-N, a protein produced from blue-green alga *Nostoc ellipsosporum*, was demonstrated to block HSV-1 entry into cells and inhibited membrane fusion mediated by HSV glycoproteins (Tiwari *et al.*, 2009). This compound was suggested as a stronger potential for antiviral therapy against HSV-1.

III. CONCLUSION

The infections with HSV can lead to a variety of skin and mucosal diseases. Despite intensive research, no prophylactic HSV vaccine has proven to be effective because the viruses establish latency and reactivations occur in the presence of humoral and cell-mediated immunity. The suggested options for treatment of HSV infections include oral acyclovir, valacyclovir, and famciclovir. However, the further discovery of new drugs as well as the adaptation of current drugs is very necessary for the war against viral infection and drug-resistant viruses. As expected, a large number of anti-HSV components from marine algae have been identified based on the specific assay system or screening approach. The extensive studies of marine algae with anti-HSV activity will contribute to the development of novel antiviral agents. Thus, it is believed that the marine algae play a vital role in the pharmaceutical industry to develop novel drugs against herpes simplex virus.

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