European Journal of Pharmaceutical Sciences 44 (2011) 11–20

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Review

Marine organisms as a therapeutic source against herpes simplex virus infection

Thanh-Sang Vo [a], Dai-Hung Ngo [a], Quang Van Ta [a], Se-Kwon Kim [a,b,*]

[a] Department of Chemistry, Pukyong National University, Busan 608-737, Republic of Korea
[b] Marine Bioprocess Research Center, Pukyong National University, Busan 608-737, Republic of Korea

ARTICLE INFO

Article history:
Received 1 May 2011
Accepted 6 July 2011
Available online 12 July 2011

Keywords:
Herpes simplex virus
Marine organisms
Sulfated polysaccharides
Algae
Marine invertebrates

ABSTRACT

Herpes simplex virus (HSV) is a member of the Herpesviridae family that causes general communicable infections in human populations throughout the world, the most common being genital and orolabial disease. The current treatments for HSV infections are nucleoside analogs such as acyclovir, valacyclovir and famciclovir. Despite the safety and efficacy, extensive clinical use of these drugs has led to the emergence of resistant viral strains, mainly in immunocompromised patients. To counteract these problems, alternative anti-HSV agents from natural products have been reported. Recently, a great deal of interest has been expressed regarding marine organisms such as algae, sponges, tunicates, echinoderms, mollusks, shrimp, bacteria, and fungus as promising anti-HSV agents. This contribution presents an overview of potential anti-HSV agents derived from marine organisms and their promising application in HSV therapy.

Contents

1. Introduction

Viral diseases are still the leading cause of death in humans worldwide (Kitazato et al., 2007). Meanwhile, Herpesviridae, a large family of several pathogenic viruses, are able to cause a variety of inapparent, mild or severe human infections. Among more than 130 different members, nine different human herpes viruses have

* Corresponding author at: Department of Chemistry, Pukyong National University, Busan 608-737, Republic of Korea. Tel.: +82 516297097; fax: +82 516297099.
E-mail address: sknkim@pknu.ac.kr (S.-K. Kim).

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doi:10.1016/j.ejps.2011.07.005

been described and divided into three subfamilies, such as *alpha-*, *beta-*, and *gamma-herpesviridae*, based on their biological characteristics (Roizmann et al., 1992). Notably, herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2), a subfamily of *alpha-herpesviridae*, are the most widely studied human herpes viruses. 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; Esmann, 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). Moreover, HSV infections were reported to be recognized as a risk factor for human immunodeficiency virus (HIV) infection (Celum, 2004). Effective anti-herpes drugs, such as acyclovir, valacyclovir, penciclovir, famciclovir, trifluridine, cidofovir, and vidarabine are available for treatment. These drugs act as nucleoside inhibitors of DNA polymerase (Brady and Bernstein, 2004). Acyclovir is the first selective antiviral agent introduced, and is the drug commonly employed in the treatment of HSV infection (Furman et al., 1981). However, the prolonged therapies with the available anti-herpes drugs have resulted in some undesirable effects and also induced the emergence of drug-resistant strains (Bacon et al., 2003; Morfin and Thouvenot, 2003). Resistance to acyclovir and related nucleoside analogs can occur following mutation in either HSV thymidine kinase or DNA polymerase (Pielop et al., 2000). For this reason, the search for new types of anti-herpes 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 (Faulkner, 2002; Blunt et al., 2010). Products from marine organisms show many interesting activities, such as anti-cancer, anti-diabetic, anti-fungal, anti-coagulant, anti-inflammatory, and other pharmacological activities (Gul and Hamann, 2005; Mayer and Hamann, 2005). In relation to antiviral properties, the marine environment is believed to be able to provide novel leads against pathogenic viruses that are evolving and developing resistance to existing pharmaceuticals (Vo and Kim, 2010; Donia and Hamann, 2003; Yasuhara-Bell and Lu, 2010). Thus, marine organisms are regarded as a promising source for the production of therapeutic drugs against viral diseases (Che, 1991). This paper focuses on anti-herpes virus therapeutic agents derived from marine organisms and their potential medical application as novel functional ingredients in anti-herpes virus therapy.

2. Potential anti-herpes virus agents from marine organisms

2.1. Marine algae

Marine algae are a large and diverse group of simple, typically autotrophic organisms, ranging from unicellular to multicellular forms. Two major types of marine algae can be identified as macroalgae (seaweeds) and microalgae. Macroalgae occupy the littoral zone, which included red macroalgae, brown macroalgae, and green macroalgae, whereas microalgae are found in both benthic and littoral habitats and also throughout the ocean waters as phytoplankton. Phytoplankton comprises organisms such as diatoms, dinoflagellates, green and yellow-brown flagellates, and blue-green algae (Gamal, 2010). Marine algae are one of the most important producers of biomass in the marine environment. They produce a wide variety of chemically active metabolites in their surroundings as an aid to protect themselves against other settling organisms (Bhadury and Wright, 2004). So far, it was evidenced that marine algae are potential anti-herpes virus agents (Deig, 1974; Richards et al., 1978). Up to now, numerous studies have confirmed the anti-HSV activity of algae that increase the interest in algae as a source of antiviral compounds.

2.1.1. 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, anti-HSV activities of *Symphyocladia latiuscula* were evidenced by Park et al. (2005). A MeOH extract of *S. 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. 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., 2007b). 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. Recently, various marine red macroalgae from Morocco also have been evaluated for their potential against HSV-1 replication *in vitro* (Rhimou et al., 2010). It was revealed that the aqueous extracts of *Asparagopsis armata*, *Ceramium rubrum*, *Gelidium pulchellum*, *Gelidium spinulosum*, *Halopitys incurvus*, *Hypnea musciformis*, *Plocamium cartilagineum*, *Boergeseniella thuyoides*, *Pterosiphonia complanata*, and *Sphaerococcus coronopifolius* were capable of inhibiting the replication of HSV-1 at an EC_{50} range of 2.5–75.9 μg/ml without any cytotoxic effect. 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 (McCandless and Craigie, 1979; 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). Furthermore, the xylomannan sulfate of *Scinaia hatei*, which contained a backbone of α-(1→3)-linked D-mannopyranosyl residues substituted at position 2, 4, and 6 positions with single stubs of β-D-xylopyranosyl residues, 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 indentified to have a similar backbone, but it differed from *N. fastigiata* xylomannan in the position of xylopyranosyl residues and from *S. hatei* polymer in the location of sulfate group (Ghosh et al., 2009). Thus, its activity against HSV-1 exhibited a different effect that showed more strong inhibition than the known sulfated xylomannan with IC_{50} range of 0.35–2.8 μg/ml. The appreciable inhibition produced by sulfated xylomannan was similar to that of standard anti-herpetic 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.