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Review

Marine Algae: A Potential Resource of Anti-HSV Molecules

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Abstract: Herpes simplex viruses (HSVs) are common human pathogens belonging to the subfamily *alpha-herpesvirinae* that trigger severe infections in neonates and immunocompromised patients. After primary infection, the HSVs establish a lifelong latent infection in the vegetative neural ganglia of their hosts. HSV infections contribute to substantial disease burden in humans as well as in newborns. Despite a fair number of drugs being available for the treatment of HSV infections, new, effective, and safe antiviral agents, exerting different mechanisms of action, are urgently required, mainly due to the increasing number of resistant strains. Accumulating pieces of evidence have suggested that structurally diverse compounds from marine algae possess promising anti-HSV potentials. Several studies have documented a variety of algal polysaccharides possessing anti-HSV activity, including carrageenan and fucan. This review aimed to compile previous anti-HSV studies on marine algae–derived compounds, especially sulfated polysaccharides, along with their mode of action, toward their development as novel natural anti-HSV agents for future investigations.

Keywords: virus; natural product; green algae; brown algae; red algae; antiviral; human infections; phytochemicals; *Herpesviridae*; sulfated polysaccharides

1. Introduction

Viral infections count as the most predominant cause of death in humans worldwide [1]. Among the different deadly viruses, *Herpesviridae*, belonging to a large family, is responsible for a wide range of mild to severe infections in humans. Out of 130 members of the *Herpesviridae* family, eight human herpesviruses have been considered, based on their biological properties toward host range, genetic make-up, and mode of replication, into three subfamilies, namely *alpha-*, *beta-*, and *gamma-herpesvirinae* [2–4].

The most notable herpes viruses belonging to *alpha-herpesvirinae* are herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2), which have been widely studied. Although HSV-1 and HSV-2 are closely related, they differ at antigenic and biological levels [5]. Typically, HSV-1 is associated

frequently with orofacial infections and encephalitis, while HSV-2 is associated with genital infections that can be transmitted from infected mother to fetus. These viruses can establish persistent, long-term, latent infections in sensory neurons and cause lesions at the entry point of the human body [6,7]. These characteristic features of latency enhance the pathogenicity of HSV and enable it to be used for therapeutic purposes.

Owing to the seriousness of infection caused by the pathogen, it has been considered as the most common microbial infection in humans. Approximately 3.7 billion people worldwide, under the age of 50 years (67%), have been estimated to be a victim of HSV-1, while approximately 417 million aged between 15 and 49 years (11%) are estimated to suffer from HSV-2 infection [8]. Paradoxically, HSV infection has been considered a menace in human immunodeficiency virus (HIV) infection.

The word "herpes" is derived from the Greek word "herpein," meaning "to creep," referring to recurring, lytic, and latent infections [9]. HSV-1 infection is not limited to mucous membranes or skin; it also affects eyes (herpetic keratitis), genital areas, and the central nervous system (meningitis and encephalitis) [10,11]. The viruses are the causative agents of different disease conditions like cold sores, chickenpox, mononucleosis, and warts, and can develop recurring and latent infections in both animals and humans [12]. HSV-1 and HSV-2 of *alpha-herpesvirinae* subfamily are responsible for the pathology of genital and/or oral herpes, herpes labialis (cold sores), and herpes genitalis, whereas varicella-zoster virus (VZV) of the same subfamily is responsible for chickenpox and shingles pathology. The β-herpesvirinae subfamily consists of *Cytomegalovirus* (CMV) and *Roseolovirus* B, which are associated with the pathology of retinitis, an infectious mononucleosis-like syndrome, and Roseola infantum or exanthem subitem. Kaposi's sarcoma-associated herpesvirus (KSHV), of γ-herpesvirinae subfamily, is involved in the pathology of Castleman's disease, Kaposi's sarcoma, and primary effusion lymphoma, while Epstein–Barr virus (EBV) of γ-herpesvirinae subfamily is linked with the pathology of central nervous system, Burkitt's lymphoma, infectious mononucleosis, post-transplant lymphoproliferative syndrome (PTLD), and nasopharyngeal carcinoma [9].

Human herpesviruses have a highly structured icosahedral-shaped nucleocapsid of 100 nm diameter, which encapsulates a linear double-stranded DNA of 120–230 kb, with approximately 80 reported genes. The capsid comprises of a dense matrix with an outer trilaminar lipid envelope upholding the viral proteins as well as host cell origins [13]. Various cellular proteins such as tubulin, actin, annexin, Hsp70, and Hsp90 are present in the herpes virus; however, their role is still unclear [14]. The viral life cycle is divided into different phases, like cellular invasion, viral transport, replication, maturation, assembly, and release [9].

2. Diseases, Symptoms, and Their Mode of Infection

Infections caused by HSV can be either primary or recurrent (reactivation) and are often contagious via infectious secretions. Clinical progression of the infection depends on several factors such as the age and immune level of the host, anatomic site of infection, and virulence type of virus. Primary infections by HSV have been observed with systemic signs, prolonged symptoms being accompanied by a higher rate of complications. In contrast, recurrent infections are usually weaker and smaller. The diseases caused by HSV are acute herpetic gingivostomatitis, acute herpetic pharyngotonsillitis, herpes labialis, herpetic whitlow, herpes gladiatorum, eczema herpeticum, and genital herpes [15–17]. Details of the disease, symptoms, and their mode of infections are given in Table 1.

Table 1. Details of the diseases caused by herpes simplex viruses (HSVs) with symptoms and mode of infections.

Disease	Virus	Symptoms	Mode of Infection	Age Group	Course of Infection	Incubation Period	Ref.
Acute herpetic gingivostomatitis	HSV-1	High body temperature (102–104 °F), lethargy, swollen erythematous, anorexia, friable gums, vesicular lesions (on the oral mucosa, tongue, lips and later rupture and coalesce, leaving ulcerated plaques) and regional lymphadenopathy.	Through infected saliva.	>0.6 to >5 years and in adult.	5–7 days	3–6 days	[18]
Acute herpetic pharyngotonsillitis	HSV-2	Headache, fever, malaise, sore throat, ulcerative lesions on tonsils and pharynx showing grayish exudates.	Through infected saliva and mucous.	>0.6 to >5 years and in adult.	5–7 days	3–6 days	[19]
Herpes labialis	HSV-1	Lesions with pain, burning, and tingling at a face, around the lips, erythematous papules.	Through infected saliva and mucous.	All age groups.	0–14 days	3–6 days	[20]
Herpetic whitlow	HSV-1 and HSV-2	Infections and lesions in fingers associated with swelling, tenderness, and reddening of the infected finger. Occasionally with fever and swollen lymph nodes.	Transmitted from primary orofacial and genital infected victims. May also be transmitted from self or other infected victims. Healthcare personnel's, including dentists during oral examinations oral care with ungloved hands	Thumb-sucking children with primary HSV-1 oral infection Adults aged 20 to 30 following contact with HSV-2-infected genitals.	10–14 days	2–20 days	[21]
Herpes gladiatorum	HSV-1	Infection of the face, arms, neck, and upper trunk. Fever. Swollen lymph glands. The affected area suffers a tingling feeling. A bunch of clear, fluid-filled blisters surrounded by redness lesions which may or may not provoke painfully.	Typically seen in wrestlers and participants in some contact sports such as rugby. Infection is promoted by trauma to the skin sustained during matches.	Males and females of all ages of athletes.	<8 days	7–10 days	[22]
Eczema herpeticum	HSV-1 or HSV-2	Clusters of itchy and/or painful blisters with uncontrolled atopic dermatitis, which may end up in increased morbidity, and mortality, if it prolongs further.	Through infected saliva and contact.	Males and females of all ages but is more common in infants and children with atopic dermatitis.	5 to 12 days	7 to 10 days	[23]

3. Pathogenesis of HSV

Infectivity of HSV ranges from the host epithelial cells, fibroblasts, and lymphocytes to neuronal cells. Thus, HSV is termed a "broad cell tropic" [5]. The pathogenesis of HSV-1 is massive, since it causes primary infection in the non-keratinized mucosa as well as keratinized regions, such as gingiva, hard plate, and dorsum of the tongue [24]. Soon after the establishment of primary infection, the virus moves up to sensory nerve axons to cause chronic latent infection in trigeminal ganglia. Later, the latent viruses are reactivated by several triggering factors and cause recurrent lesions at the site of primary infection (Figure 1) [25].

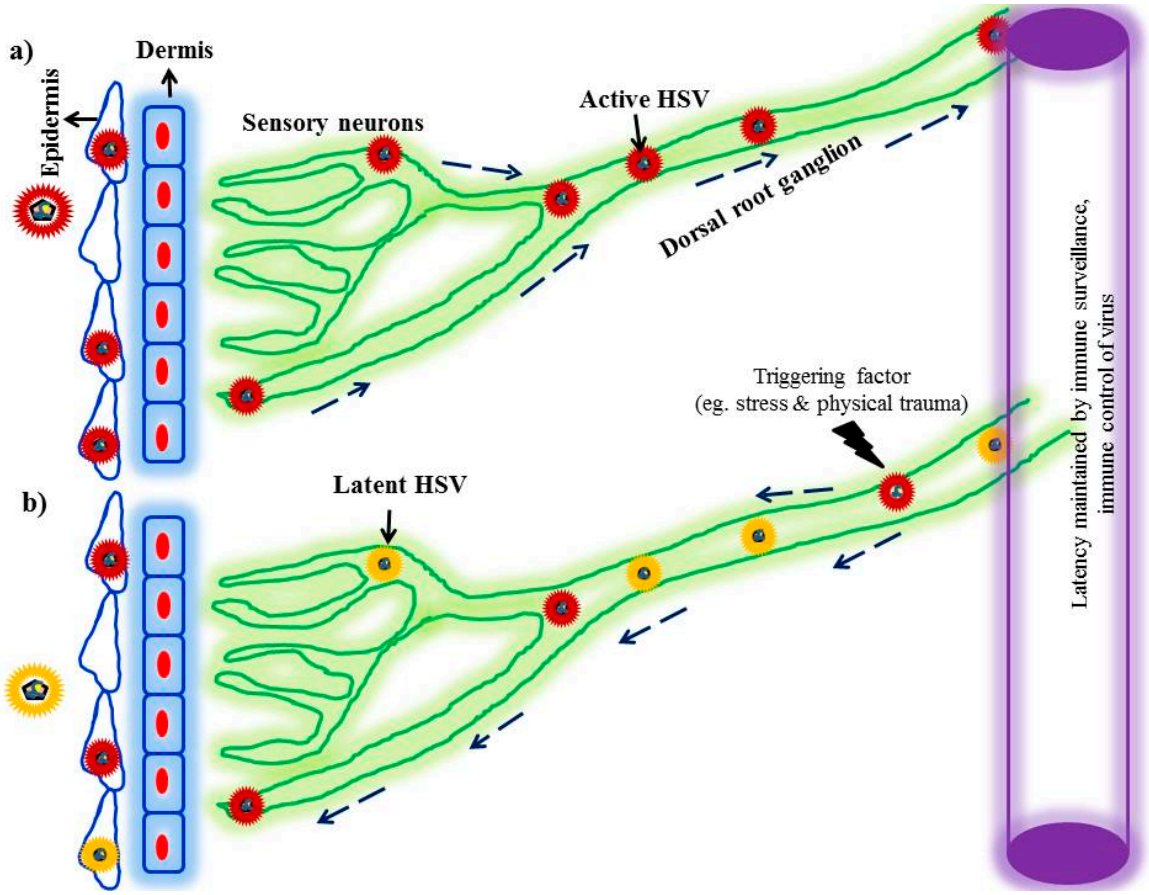

Figure 1. Model of herpes simplex virus (HSV) establishing infection in host. (**a**) HSV enters the sensory nerve terminals and is transferred to the dorsal root ganglion, which is situated within the epidermal-dermal junction. (**b**) In chronic cases, the virus which is already present inside the ganglion and reaches the tissues by penetrating through the sensory nerves.

Generally, HSV is more specific to sensory neurons and triggers an infection in the external layers of the skin and mucosa [26]. Hence, repeated infections are predominantly found in keratinized surfaces of mucosal membranes and skin [24].

The primary cause and ubiquitous pathogen for genital herpes is HSV-2. In the last couple of decades, an association of HSV-2 with HIV has also been observed, and HSV-2 infection was found to be associated with a threefold elevated risk of sexually acquired HIV [27]. A frequent, recurrent, and painful genital lesion, along with psychological stress, is observed in immunocompetent people with HSV-2 infections.

4. Establishment of Primary Infection

Primary infection is usually asymptomatic and is mostly seen in children and teenagers [28]. Susceptibility of individuals to HSV infection is altered by the polymorphism in genes coding for human leukocyte antigen (HLA) class-I with killer immunoglobulin-like receptors (KIR) and FcγRIIIA (CD16A) molecules, which are critical in regulating the effector functions of cytotoxic T and NK lymphocytes [29]. The low frequency of HLA class-I and B18 allele was found to be common amongst patients with herpes. However, the B35 allele renders protection against HSV infection [30]. The severity of primary infection caused by HSV is determined chiefly by the host immune response and its potential to interact with the viral genes [31]. Initiation of primary HSV-1 infection is mainly caused by the virion host shutoff protein, followed by the devastation of natural killer cells, key HLA complex class-I and class-II molecules, complementary proteins, and antibodies produced by the host immune defense mechanisms [32].

5. Involvement of Virion Host Shutoff Protein in Causing Infection

Virion host shutoff (Vhs) is a protein involved primarily in provoking the cellular gene expression of the host after the initial attack. It is one of the vital members involved in virulence, pathogenesis, and multiplication of HSV. Vhs, being a part of the tegument, is secreted mainly during the early and immediate-early phase of infection. It exhibits endoribonuclease activity by encoding the gene UL41, and hence, it has the potential to degrade all types RNA. Nevertheless, it degrades only the mRNA inside the host [33,34]. Cellular degradation of mRNA enhances the viral competition for translation and thus promotes the succession of viral infection. Meanwhile, by stabilizing the gE/gI complex, Vhs eventually stabilizes the viral mRNA that plays a crucial role in cell-to-cell spread [35]. Reduction of innate and adaptive immune response proteins by Vhs demonstrated the blockage of synthesis of type-I interferon, dendritic cells, and proinflammatory cytokines and chemokines [36–38] (Figure 2).

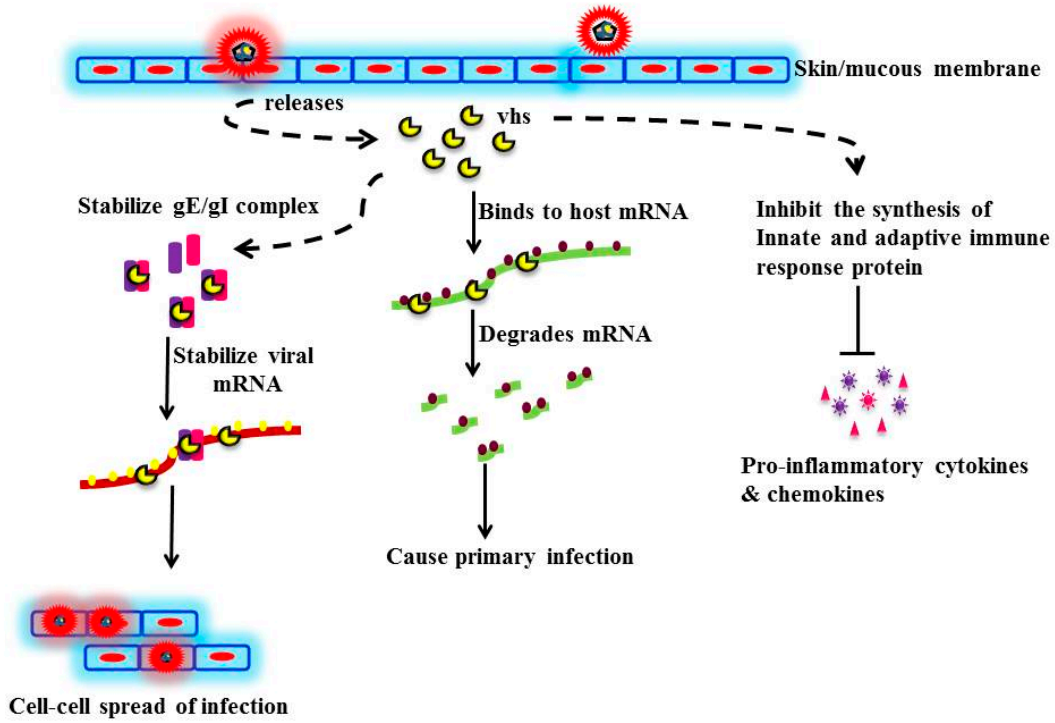

Figure 2. Schematic representation of the mechanism of virion host shutoff (Vhs) in establishing viral infection in host.

6. Immune Evading Strategies of HSV

To evade the host immune system and cause persistent primary infection, HSV adopts a multitude of strategies directed toward overcoming all mucosal barriers [39]. Usually, the mechanism of evasion targets the immune components like complementary proteins, major histocompatibility complex (MHC) class-I or class-II molecules, killer cells, and antibodies [40]. Glycoproteins that are found to be embedded in the outer lipid envelope mediate the attachment of HSV to the host cell receptors, blending of viral and host cell membranes, envelopment, and occurrence of the virus as newly formed nucleocapsids bud from host cell nuclei [41]. However, these glycoproteins are majorly targeted by humoral and cellular immune responses [42]. Instead, the glycoproteins bind with C3b, gE, and IgG Fc domain, and block the complement activation and antibody-mediated cellular cytotoxicity. Additionally, the regulation of ICP0 by HSV demonstrated higher resistance of the virus against immune attack by the interferon system of the host [43].

7. State of Viral Latency and Reactivation

In a viral infection, latency is characterized by the silent persistence of pathogen inside the body, existing in non-replicating and non-pathogenic mode [44]. Once it is exposed to certain triggering factors, it becomes active to cause infection or recurrence. Commonly, the sites of latency differ across herpes virus types. The type of virus and its specific latency site is shown in Table 2.

Table 2. Types of virus and its specific site of latency.

Family of Herpes Virus	Name of the Virus	Site of Latency	References
Gammaherpesvirinae	Epstein-Barr Virus (EBV) or human herpesvirus 4 (HHV-4)	Lymphocytes	[45]
Betaherpesvirinae	Murine cytomegalovirus	Salivary gland, spleen, and lymphocytes	[46]
Alphaherpesvirinae	Herpes simplex virus	Nervous site, especially trigeminal ganglion	[47]

After establishing a primary infection, HSV-1 penetrates the nerve terminals of sensory neurons located at the periphery and reaches trigeminal nerve ganglion through the retrograde axon. It passes through the neuronal cell and blends the plasma membrane with an external envelope by exploiting the pH-dependent endocytic pathway [48]. The capsid proteins are essential for such site-specific fusion of viral particles with the infected cells. Later, the viral particle establishes latency inside neuronal cells by down-regulating the α-gene expression and DNA replication [49].

Upon favorable conditions, the HSV at the latent stage becomes active through activating factors such as sun exposure, stress, and trauma. The triggered HSV in the dorsal root ganglion establishes its recurrent infection by passing through the sensor nerves present in the junction of the epidermal-dermal layer. This recurrent infection is asymptomatic, which persists with no systemic sign. Most often, the mucocutaneous junction of lips is recurrently infected, which appears as cold sores, commonly known as recurrent herpes labialis [50].

8. Role of Keratin in Primary Recurrent Lesions

Unlike the other parts of human body, the oral cavity possesses a large number of keratinized and unkeratinized cells. These keratinized cells cover themselves by secreting keratin. Such types of cells are found abundantly in the mucocutaneous junction of the lip and tongue (especially on the hard palate, gingiva, and dorsum) [24]. In general, HSV causes primary lesions on unkeratinized tissues, such as labial and buccal mucosa. However, it can also cause lesions on keratinized tissues [51]. The keratin layer found on the surface of the cell wall reduces permeability of the cell for viral penetration. Hence, primary and recurrent lesions are more predominant in non-keratinized cells. Interestingly, in recurrent lesions, the HSV is already present in the ganglion, and hence, the need for viral penetration in such cases is not required, and keratin plays a protecting role for virus against immune response [24].

9. Anti-HSV Molecules from Marine Algae

Among the different marine resources, marine algae are considered to be one of the prominent primary producers in marine food webs, being rich in essential nutrients and bioactive molecules. Marine algae are functionally and morphologically diverse chlorophyll-containing organisms, composed of one cell or grouped into colonies, or as multi-cellular organisms, sometimes collaborating as simple tissues. These unicellular or multi-cellular organisms are classified into two major groups according to their size—macroalgae and microalgae [52,53].

Macroalgae are commonly known as seaweeds and are grouped into three major categories according to their pigmentation—green seaweeds (Chlorophyta), brown seaweeds (Phaeophyta), and red seaweeds (Rhodophyta) [54]. The pigment characteristics of macroalgae are related to their sea habitat, since not all of them need the same amount of light to perform photosynthesis. Therefore, green macroalgae, which can absorb a large amount of light energy, are distributed in coastal regions, while red and brown macroalgae occur at greater depths, where penetration of sunlight is limited. The microalgae consist of a wide range of autotrophic organisms, with the majority existing as small cells of approximately 3–20 μm [53].

Over the past decades, marine algae have stimulated significant economic interest as agar, fertilizer, food, source of iodine, and potash [55]. Amongst the marine natural products available in the market, approximately 9% of biomedical compounds have been isolated from algae. The marine organisms produce a myriad of bioactive compounds, including polysaccharides, chlorophyll, acetogenins, fatty acids, vitamins, xanthophylls, amino acids, and halogenated compounds [56,57].

The marine source is one of the most potent resources for antiviral compounds. Gerber et al. [58] first confirmed the possible anti-viral effect of an algal polysaccharide, obtained from *Gelidium cartilagineum* (Linnaeus) Gaillon, against influenza B virus and mumps. Polysaccharides obtained from various algae are being rigorously studied for structure exploration and biological effects, for a long time. Sulfated polysaccharides possess a variety of therapeutic activities, namely anticoagulant effect, antiviral effects on the immune system, and antitumor activity (Table 3) [59]. Different pharmacological activities of these high molecular weight sulfated polysaccharides are evaluated through their chemical structure, which includes molecular weight, degree of sulfation, conformation, dynamic stereochemistry, and constituent sugars. Despite the known HIV inhibitory activity of sulfated polysaccharides [60–62], application of cellulose sulfate has shown no protection in women with HIV [63].

The interaction between negatively charged molecules of the polysaccharides, including different sulfated polysaccharides with the positive charge present either in viruses or their cell surfaces, exhibits the preventive effect in the permeation of virus into the host cell [64,65].

9.1. Green Algae

A sulfated polysaccharide consisting of a huge quantity of L-rhamnose accompanied by a small amount of D-glucose was isolated from *Monostroma nitidum* Wittrock (family: Ulvophyceae) and referred to as rhamnansulfate [66]. Various studies have revealed that different rhamnan-types of sulfated polysaccharides exhibit strong antiviral activities against several enveloped viruses, like HSVs and HIV. These include rhamnansulfate from *Monostroma latissimum* Wittrock (Chlorophyta) and sodium spirulan obtained from *Spirulina platensis* (Gomont) Geitler (Cyanophyta) [67,68]. Additionally, few sulfated polysaccharides derived from seaweeds have been observed to cause nitric oxide (NO) production [69,70]. On the contrary, in some cases, rhamnansulfate was found to not induce NO production when evaluated in RAW264.7 cell lines [66]. Sulfated polysaccharides also act as heparan sulfate mimetics, thus targeting the attachments of the viruses and preventing their adherence to cells [60].

Several green algae have grown along the coastlines of India, and one of the predominant species is *Scinaia hatei* Børgesen, which contains sulfated xylomannan [71]. Various chemically altered structures, mainly polysaccharides, have been studied from this alga, by different researchers, for their antiviral activities. Ray et al. assessed the antiviral activity of sulfated xylomannan obtained from *S.*

hatei and demonstrated potent antiviral efficacy of the chemically engineered sulfated xylomannan with limited degree of cytotoxicity. They observed that the compounds with higher sulfate content and lesser substitution of xylose with a greater molecular mass depicted more anti-HSV effect [72]. Anti-HSV effect of seven chemically altered polysaccharides, obtained from *Enteromorpha compressa* (Linnaeus) Nees, has been evaluated; out of these seven compounds, one derivative, namely SU1F1, which was a 22% (*w*/*w*) sulfated heteroglycuronan, exhibited acceptable inhibitory effect on the virus through a wide-ranging mechanism of action [73]. Sulfated polysaccharide fraction isolated from *Caulerpa racemosa* (Forsskål) J. Agardh was considered to be a selective inhibitor of thymidine kinase (TK) acyclovir-resistant HSV-1 and HSV-2 strains in Vero cells and reference strains with EC_{50} of approximately 2.2–4.2 µg/mL [60]. Further study on this green alga has shown the presence of a sulfoquinovosyldiacylglycerol compound, which was potent against standard and clinical HSV-2 strains at IC_{50} of 15.6 µg/mL [74].

9.2. Red Algae

The significance of red algae, as a potential novel source of anti-HSV agents, is well-known [75–77]. Serkedjieva [78] reported that the *Polysiphonia denudata* (Dillwyn) Greville ex Harvey aquatic extract from the Bulgarian Black Sea coast demonstrated selective inhibition of HSV-1 and HSV-2 reproduction with IC_{50} ranging between 8.7 and 47.7 mg/mL. This inhibition was effective against intracellular viral replication and adsorption. Similarly, the anti-HSV effect of Persian Gulf *Gracilaria salicornia* (C. Agardh) E. Y. Dawson was demonstrated by Zandi et al. [79]. *G. salicornia* aqueous extract exhibited antiviral effect against HSV-2, not only prior to virus attachment and entry into Vero cells, but also on viral replication and post-attachment stages. In a study carried out by Rhimou et al. [80], the aqueous extracts of *Ceramium rubrum* C. Agardh, *Pterosiphonia complanata* (Clemente) Falkenberg, *Asparagopsis armata* Harvey, *Gelidium spinulosum* (C. Agardh) J. Agardh, *Halopitys incurvus* (Hudson) Batters, *Gelidium pulchellum* (Turner) Kützing, *Hypnea musciformis* (Wulfen) J. V. Lamouroux, *Boergeseniella thuyoides* (Harvey) Kylin, *Plocamium cartilagineum* (Linnaeus) P.S. Dixon, and *Sphaerococcus coronopifolius* Stackhouse were demonstrated to be effective at constraining HSV-1 replication at an EC_{50} of 2.5–75.9 µg/mL, deprived of any cytotoxic effect.

Indeed, numerous polysaccharides from red algae possess substantial antiviral activity against several animal viruses [64,81–83]. Reports are available for polysulfates, either naturally-occurring or chemically produced against a broad assortment of viruses, together with HSV-1, HSV-3, HIV, respiratory syncytial virus, influenza, and human cytomegalovirus [59,62,84]. An in-vitro and in-vivo study was performed by Huheihel et al. [85] in order to explore antiviral potency of a cell wall polysaccharide obtained from *Porphyridium* species. Results revealed the extracted polysaccharide to expressively inhibit infection of Vero cells caused by herpes simplex virus when evaluated in newborn rabbits and rats. This sulfated polysaccharide consisted of xylose, glucose, and galactose [86]. Although the exact mechanism of their anti-herpes activity is not yet clear, they are believed to exert inhibitory effect at an initial stage of the infection cycle, involving virus penetration into the host cell or virus adsorption onto cell, mainly due to interaction of the polysaccharide with the virus [85,87].

Acyclovir, along with some of its recently licensed nucleoside analogues (usually targets viral DNA synthesis), is still the drug of choice for systemic or topical delivery against herpes virus [6,88]. Many polysaccharides, with sulfated galactans representing the chief matrix polysaccharides, are present in red seaweed. The potent anti-HSV-2 effect was also recorded from a galactan preparation obtained from *Cryptonemia crenulata* (J. Agardh) J. Agardh in an in vivo murine model of HSV [59]. Alkali-extracted xylan (with a molecular weight of 12 kDa) from a red algae *Scinaia hatei* showed potent anti-HSV activity with a prominent effect on viral entry [89]. Another polysaccharide fraction obtained from the alga *Lithothamnion muelleri* inhibited HSV-1 and HSV-2 mainly due to viral adsorption inhibition and virus entry prevention into host cells [90]. Carrageenans are anionic sulfated polysaccharides classified into three groups, based on the existence of 3, 6-anhydrogalactopyranose and allocation of sulfate groups on the main structures, namely λ-, κ-, and ι-carrageenan (Figure 3). Carrageenans

isolated from *Meristiella gelidium* had also been reported for their anti-HSV potentials [91]. Recently, the work done by Boulho et al. [92] demonstrated that iota-carrageenan fraction of *Solieria chordalis* (C. Agardh) J. Agardh is potent against HSV-1 (EC_{50} 3.2 to 54.4 µg/mL) without cytotoxicity in that range of concentration.

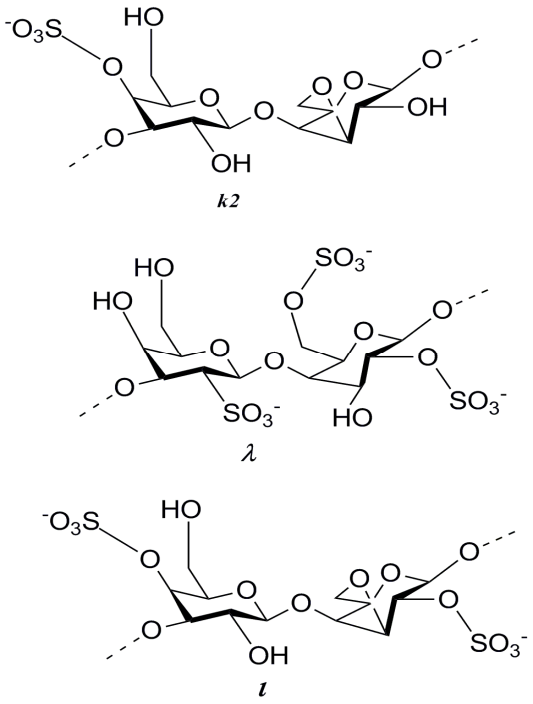

Figure 3. Chemical structure of carrageenan units, namely, kappa, lambda, and iota, isolated from red seaweeds.

Apart from carbohydrates, some proteins like griffithsin, which are lectin derivatives from red algae of *Griffithsia* genus, are among the most potent inhibitors of viral entry discovered [93]. Several reports of griffithsin are also available for anti-HSV activity. An in vitro study revealed griffithsin to demonstrate an IC_{50} at nanomolar range, and exhibit mild to moderate HSV-2 blocking effect [94,95]. The anti-HSV-2 effect of griffithsin is also reported in in vivo murine models [95]. The HSV-2 blocking effect was due to its interaction with glycoprotein D, which is involved in HSV-2 entry [94].

9.3. Brown Algae

Brown algae of the Dictyotaceae family are representative of over 40 species and are known to produce various secondary metabolites, especially of Diterpenes category. These are mainly divided into groups such as dolabellanes, extended sesquiterpenes, and xenicanes, based on the first formal cyclization of the geranyl-geraniol precursor. [96]. This family is among the most abundant seaweeds of prominent marine habitats like the Indian and Atlantic oceans [97–99]. Fifteen metabolites isolated from *Dictyota linearis* (Ag.) Grev. and 19 from *Dictyota dichotoma* (Huds.) Lam. did not show considerable effect against HSV-I and poliomyelitis virus I [96]. In another study by Garrido et al., dolabellane diterpene dolabelladienetriol and one diacetoxy-derivative obtained from *Dictyota pfaffii* Schnetter (Phaeophyceae) [100] were evaluated for sub-chronic toxicities and their anti-HSV effect [101]. Their study revealed that dolabelladienetriol exhibits anti-HIV activity with low toxicity; thus, it was concluded as a possible molecule for drug development against herpes infection [101]. Vallim et al. [97] had reported dolastane diterpenes 4-hydroxy-9,14-dihydroxydolasta-1(15), 7-diene (1) and 4,7,14-trihydroxydolasta-1(15), 8-diene (2), from *Canistrocarpus cervicornis* (Kützing) De Paula and De Clerck to repress HSV-1 infection in Vero cells (Figure 4).

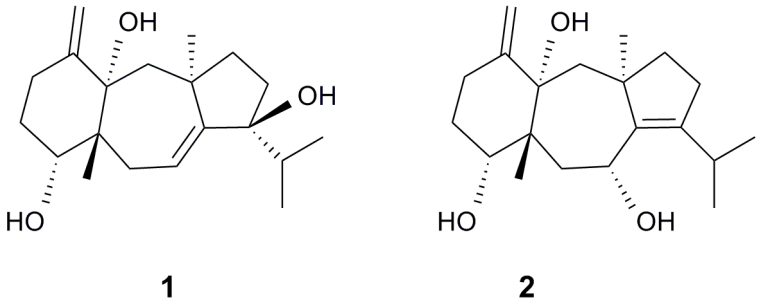

Figure 4. Dolastane diterpenes 1 and 2 isolated from *C. cervicornis*.

Fucoidans or fucan sulfates, predominantly found in brown macroalgae, possess anti-HSV activities [102–104]. A general structural feature of fucoidans is the presence of a sufficient quantity of α-l-fucose residues and sulfate ester groups, along with a small quantity of other residues of monosaccharides including xylose, mannose, galactose, rhamnose, and glucuronic acid (Figure 5) [105]. In 2015, Thuy et al. extracted fucoidan fractions from *Sargassum polycystum* C. Agardh, *Sargassum mcclurei* Setchell, and *Turbinara ornata* (Turner) J. Agardh and estimated their selective antiviral activities against HSV-1. The extracted fucoidans were equally potent against HSV-1 with IC_{50} from 0.33 to 0.7 μg/mL, although they exhibited no cytotoxicity. Fucoidan isolated from *Undaria pinnatifida* (Harvey) Suringar has displayed activity against HSV-1 by directly inhibiting replication of the virus and/or stimulating innate and adaptive immune defenses [103]. Fucoidans isolated from different brown macroalgae such as *Sargassum horneri* (Turner) C. Agardh, *Cystoseira indica* (Thivy and Doshi) Mairh, *Adenocystis utricularis* (Bory) Skottsberg, *Stoechospermum marginatum* (C. Agardh) Kützing, and *Sargassum tenerrimum* J. Agardh have been continually found to exhibit anti-HSV activity [106–110]. Chattopadhyay et al. isolated polysaccharide fractions from *Grateloupia indica* Børgesen, which have shown anti-HSV activity (IC_{50} 0.12–1.06 μg/mL), mainly owing to the inhibition of virus adsorption to host cell [111].

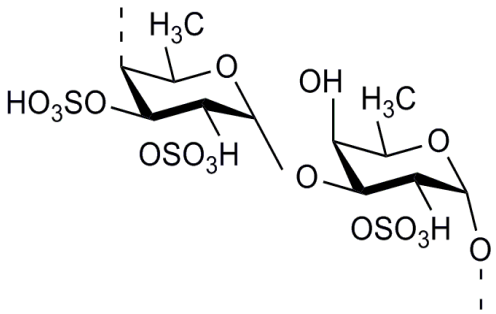

Figure 5. Chemical structure of fucoidan unit.

Alginates are the main acidic polysaccharides of the cell wall widely distributed in brown algae. They are linear anionic polysaccharides, composed of the main backbone of poly-D-glucuronic acid (G blocks) and poly-D-mannuronic acid (M blocks), together with alternate D-guluronic acid and D-mannuronic acid (GM blocks) (Figure 6) [56]. Peng et al. [112] had reported the polysaccharides from cultivated *Sargassum naozhouense* possess strong antiviral activity against HSV-1 strain F in-vitro with EC_{50} value of 8.29 μg/mL. Fourier Transform infrared spectroscopy (FT-IR) spectroscopy analysis revealed the polysaccharides from the studied *S. naozhouense* to possibly be alginates and fucoidan. A fraction of polysaccharide xylogalactofucan and alginic acid were separated from *Sphacelaria indica* Reinke and evaluated for anti-HSV activity. The compound showed potent anti-HSV effect, and the authors demonstrated sulfate content of the polysaccharides to be responsible for the anti-HSV effect [112].

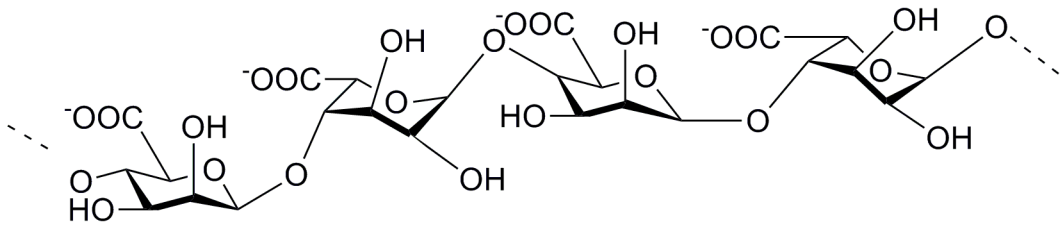

Figure 6. Chemical structure of alginate polysaccharide (GM blocks).

A sulfated xylogalactofucan, along with alginic acid fractions, was extracted from *Laminaria angustata* Kjellman and evaluated for anti-HSV activity. The HSV-1 inhibitory effect was found to be enhanced upon the introduction of sulfate groups, and the effect was due to the direct interaction of polysaccharide with virus particles [113]. Various fractions of sulfated polysaccharides were obtained from *Dictyota dichotoma*, out of which, the ones rich in galactofucan showed moderate inhibitory effect against HSV-1, and some others, like xylomannan-rich fractions, showed activity against HSV-1 [114].

Table 3. Polysaccharide extracts from green, red, and brown algae with activity against HSV-1 and HSV-2.

Species	Extracts/Compounds	Activity (IC50 = μg/mL)		References
		HSV-1	HSV-2	
Green Algae				
Caulerpa brachypus	SP-rhamnan type and galactan type	1.9 (rhamnan type) & 0.65 (galactan type)	-	[115]
Caulerpa okamurai	SP-galactan type	0.55	-	[115]
Caulerpa racemosa	SP fractions	4.2	3.0	[116]
Caulerpa scapelliformis	SP-galactan type	1.6	-	
Chaetomorpha crassa	SP-arabinoxylogalactan type	0.85	-	[115]
Chaetomorpha spiralis	SP-arabinoxylogalactan type	1.9	-	[115]
Codium fragile	SP-arabinan type	0.86	-	[115]
Codium latum	SP-arabinan type	0.38	-	[115]
Enteromorpha compressa	sulphated heteroglycuronan	28.2	-	[73]
Monostroma nitidum	SP-rhamnan type	0.4	-	[115]
Red Algae				
Acanthophora specifira	Carrageenan	80.5	-	[117]
Bostrychia montagnei	Sulfated galactan	13	11	[118]
Callophyllis variegata	Sulfated galactan	0.2	0,2	[76]
Gigartina skottsbergii	Lambda-type carrageenan	0.6	0.4	[119]
Grateloupia indica	Sulfated galactan	0.3	0.3	[120]
Gymnogongrus torulosus	DL-hybrid sulfated galactan		0.6	[121]
Meristiella gelidium	Mixture of iota/kappa/nu-carrageenans		2–0.04	[122]
Scinaia hatei	Sulfated xylomannan	0.5	0.5	[71]

Table 3. *Cont.*

Species	Extracts/Compounds	Activity (IC50 = μg/mL)		References
		HSV-1	HSV-2	
	Brown Algae			
Adenocystis utricularis	Sulfated galactofucan	0.3	0.5	[106]
Cystoseira indica	Sulfated fucan	2.8	1.3	[108]
Hydroclathrus clathratus	Carrageenan	100.5		[117]
Laminaria angustata	Xylogalactofucan	0.2–25		[123]
Stoechospermum marginatum	Sulfated fucan	3.6	0.5	[109]
Undaria pinnatifida	Galactofucan sulfate	32	0.5	[103,114]

10. Concluding Remarks and Future Prospects

Herpesviruses are accountable for causing various diseases in humans. With increasing seroprevalence rates, treatment of HSV infections remains a challenge, irrespective of the availability of various drugs with outstanding intrinsic antiviral activities. The present treatment for HSV infections is fairly safe and efficient. Nevertheless, long-term treatment with these drugs is frequently linked with toxicities and drug resistance, especially in immune-compromised patients, which restrict their utility and ultimate druggability. Hence, there is an apparent need to develop new antiviral drugs [5]. Since several new compounds are presently in clinical development, it would be useful if these compounds are screened not only for their antiviral properties but also for their potential use in combination with existing antivirals as multidrug regimens.

Algae constitute the richest source of well-known and novel biologically active compounds. All anti-HSV compounds, especially the sulfated polysaccharides summarized in this review, appear to be promising and potential leads for novel therapies in HSV infections. However, the number of species screened for anti-HSV so far is comparatively small, and there are numerous polysaccharides and bioactive compounds with antiviral properties that remain untapped. Although marine algae form a repertoire of an array of chemicals with noteworthy diversity, it is difficult to obtain high quantity preferred compounds. In this context, combinatorial genetic and metabolic engineering remain a solution for the large-scale commercial production of bioactive compounds of interest. Besides, aquaculture, chemical synthesis, and fermentation processes also present as options for large-scale production of a desired compound with anti-HSV properties [124].

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