Sulfated Polysaccharides from Seaweeds

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Sulfated polysaccharides derived from seaweeds, considered a potential source of bioactive compounds for drug development, have shown antiviral activity against a broad spectrum of viruses, mainly including common DNA viruses and RNA viruses. In addition, sulfated polysaccharides can also improve the body's immunity. Sulfated polysaccharides from seaweeds, including carrageenan, galactan, fucoidan, alginate, ulvan, p-KG03, naviculan, and calcium spirulan, may provide new ideas for the development of COVID-19 therapeutics and vaccines.

Keywords: sulfated polysaccharides ; seaweed ; algae ; antiviral ; COVID-19 ; SARS-CoV-2

1. Red Seaweed

1.1. Carrageenan

Carrageenan is a soluble sulfated galactan isolated from red seaweed where it is a component of the outer cell wall and intracellular matrix, and it accounts for 30–70% of the dry weight of red algae. The galactan backbone is produced in the Golgi apparatus and is subsequently sulfated by sulfotransferases in the cell wall [1]. Commercially, red seaweed is considered more valuable than brown and green algae. Furthermore, the kappa-(κ-), iota-(ι-), and lambda-(λ-) isoforms are most commonly used in industry. These differ in the position and numbers of sulfate groups attached to the hexose scaffold, with the κ, ι, and λ forms containing one, two, and three anionic sulfate ester moieties, respectively, on each disaccharide repeat [2]. The degree of sulfation of the κ-, ι, and λ isoforms is 25–30%, 28–30%, and 32–39%, respectively [3]. The sol-gel transition, chemical cross-linking, mechanical strength, and biological properties vary with the structural changes of carrageenan. Due to its unique properties, carrageenan is mainly used in industries, such as food, cosmetics, printing, textile formulations, and pharmaceuticals [4]. Significantly, a higher degree of sulfation in carrageenan does not necessarily correspond with higher antiviral activity [5], and it appears that both the position and density of the sulfate moieties on the backbone influence the molecule's antiviral capability [6]. This suggests that carrageenan's antiviral activity is not entirely dependent on the sulfate content. In addition, carrageenan is the most studied sulfated polysaccharide in human clinical trials for use against various viral diseases [7].

Kappa-(κ-)carrageenan

Kappa-(κ-)carrageenan inhibits viral replication both through blocking adsorption to the surface and inhibition of protein expression. Low-molecular-weight κ-carrageenan shows a better performance in these aspects [8][9]. Shao et al. investigated the molecular mechanism by which κ-carrageenan protects cells from invasion by H1N2009 influenza (SW731) virus [8]. They treated MDCK cells with κ-carrageenan, observing significant inhibition of SW731 influenza virus replication resulting from interference with viral adsorption and protein expression [8]. Remarkably, low-molecular-weight κ-carrageenan has better antiviral activity because of its better tissue penetration. Wang and colleagues found that 2-kDa-κ-carrageenan (CO-1) prevented the replication of the influenza A (H1N1) virus in MDCK cells more effectively than the 3 and 5 kDa forms (CO-2 and CO-3, respectively), with IC50 values of 32.1, 239, and 519 μg/mL for the 3 isoforms, respectively [9]. Given these results, the authors recommend the use of low-molecular-weight carrageenan oligosaccharides for influenza treatment as an alternative strategy [9]. Schütz et al. showed that both nasal and oral sprays containing κ-carrageenan inhibited SARS-CoV-2 replication in human airway epithelial cells [10]. Furthermore, κ-carrageenan also showed significant inhibitory effects on HSV-2 and HPV16, with IC50 values of 1.6 and 0.044 μg/mL, respectively [4][11].

Lambda-(λ-)carrageenan

Lambda-(λ-)carrageenan inhibits viral activity by inhibiting viral internalization through targeting attachment cell surface receptors and binding to viral envelope proteins [12][13][14]. Luo et al. found that λ-carrageenan P32 screened from different molecular weights (4–350 kDa) carrageenans had the highest inhibitory effect on RABV infection, which was consistent with the low molecular weight (4 kDa), high solubility, and high stability of closely related P32 [12]. These results suggested

that λ-carrageenan P32 was a promising drug to inhibit RABV infection by preventing virus internalization and glycoprotein-mediated cell fusion [12]. In mice, the use of λ-carrageenan nasal drops not only reduced weight loss resulting from influenza viral infection but also prevented infection-related death in a majority of the mice [13]. In addition, λ-carrageenan was also effective against SARS-CoV-2. The EC50 of λ-carrageenan was 0.9 ± 1.1 μg/mL and the principal mechanism involved λ-carrageenan targeting viral attachment to cell surface receptors and subsequent prevention of viral entry [13]. λ-carrageenan extracted from the red alga *Gigantina skotsbergii* was found to be effective in preventing infection by equid herpesvirus 3(EHV3), bovine herpesvirus 1 (BoHV-1), and suid herpesvirus-1 (SuHV-1), most likely because the compound binds to the envelope glycoprotein of the virus, preventing viral attachment to the cell surface receptor [14]. In addition, λ-carrageenan also had a significant inhibitory effect on DENV-3, with an EC50 of 0.14 μg/mL [15]. λ-carrageenan polysaccharide induces the synthesis of interferon and has biological effects on the immune response. Studies have shown that microwave degradation of λ-carrageenan from *Chondrus ocellatus* can inhibit tumor growth, enhance interferon activity, and enhance lymphocyte multiplication [16]. However, it has been reported that λ-carrageenan can induce enteritis in rats after long-term oral administration [17]. Furthermore, these sulfated polysaccharides can be used in the manufacture of carbohydrate-based conjugate vaccines to achieve the desired immunogenicity and potency. Luo et al. proved that λ-carrageenan has increased the efficacy of ovalbumin-based prophylactic and therapeutic cancer vaccines [18].

Iota-(ι-)carrageenan

Iota-(ι-)carrageenan's antiviral activity against a variety of viruses, especially respiratory viruses, has been well documented [19][20][21][22]. Some scholars have proposed to improve the therapeutic effect by combining carrageenan with other clinically common antiviral drugs. A study using a combination of ι-carrageenan and oseltamivir showed that this combination significantly improved the survival rate of infection with the H1N1 virus compared with a single therapy [21]. Ludwig et al. found that patients treated with ι-carrageenan recovered more quickly than those in the placebo group, with a duration of 11.6 days compared with 13.7 days in the placebo group. In addition, the ι-carrageenan group showed significantly faster remission of symptoms than the placebo group, with lower viral loads in the nasal cavity [23]. ι-carrageenan from *Euchema spinosum* was able to neutralize the SARS-CoV-2 Spike pseudotyped lentivirus (SSPL) in a concentration-dependent manner at an MOI of 0.1 and an IC50 of 2.6 μg/mL [24]. In addition, different forms of administration of ι-carrageenan can play a significant role in its antiviral activity. Morokutti et al. found that ι-carrageenan in lozenge form significantly reduced the amount of SARS-CoV-2 virus in saliva, thus limiting interpersonal viral transmission and the transfer of the virus to the lower respiratory tract [25]. In addition, ι-carrageenan can be given directly to infected patients to treat COVID-19 with ivermectin via nasal spray and oral antivirals. The number of people diagnosed with COVID-19 in the treatment group was 3.4%, which was significantly lower than 21.4% in the control group (p = 0.0001) [26]. The Xylitol nasal spray containing ι-carrageenan has been found to prevent SARS-CoV-2 infection in vitro, with an IC50 < 6.0 μg/mL [27]. Graf et al. developed a nasal spray formulation containing 0.05% xylimeta-zoline hydrochloride and 0.12% ι-carrageenan. The formulation was reported to be effective in relieving nasal congestion symptoms while also providing antiviral protection to the respiratory mucosa [28]. Hassanzadeh et al. found that ι-carrageenan can significantly inhibit SARS-CoV-2 in vitro, an effect caused by the effect of positively charged regions on the glycoprotein envelope and protein aggregation in host cells on the surface [29].®

Although the three types of carrageenan, namely, κ-, ι-, and λ-carrageenan, showed antiviral action against SARS-CoV-2, including the alpha, beta, gamma, and delta variants of concern [10][13][24], ι-carrageenan showed the strongest antiviral activity with an IC50 value approximately ~1 log-stage lower than either λ-or κ-carrageenan [30]. Therefore, ι-carrageenan is a potential respiratory virus inhibitor that can be used to prevent and treat SARS-CoV-2 infection, irrespective of the viral variant.

In addition, the combined use of antiviral drugs often has a multiplier effect. Morokutti-Kurz et al. showed that carrageenan and Zanamivir act synergistically against several influenza A virus strains (H1N1(09)pdm, H3N2, H5N1, H7N7) in vitro; therefore, by acting synergistically, they can provide a broader spectrum of anti-influenza activity [22]. When using ι- and k-carrageenan at the same time, the physical interaction of carrageenan with the virus did not interfere with the inhibitory effect of zanamivir, and the spray effect was increased [22]. Xylimidazolines have been used for over 50 years to relieve vasoconstriction and acute nasal edema. Graf et al combine this vasoconstrictor and ι-carrageenan in a scientific formulation. The experimental results show that ι-carrageenan does not reduce the efficacy and safety of the drug, and the antiviral effect of iota-carrageenan is also not affected [28]. Therefore, the most successful antiviral formulation of carrageenan may be the recently developed nasal spray formulation for use against rhinoviruses and SARS-CoV-2 [27][28].

1.2. Galactan

Sulfated galactans are the principal extracellular polysaccharides found in red seaweed. With few exceptions, they consist mainly of linear chains of galactose. These polysaccharides show good antiviral activity against HSV, DENV, HIV, and HAV [31][32][33][34]. Galactan from the red alga *Agardhiella tenera* has been shown to inhibit HIV-1 and HIV-2 infection by preventing the interaction between HIV gp120 and the CD4 + T cell receptor [33][35]. Similarly, 12.5 μg/mL galactan isolated from *Schizymenia binderi* was found to inhibit HIV replication in vitro, and block the replication of HSV-1 in Vero cells [36]. Matsuhiro et al. found that *Schizymenia binderi* galactan showed strongly selective antiviral activity against HSV-1 and HSV-2, with EC50 values of 0.76 and 0.63 μg/mL, respectively [37]. Similarly, 3 galactan (F1, F2, and F3) isolated from Callophyllis variegate are effective inhibitors of HSV-1 and HSV-2, with IC50 values ranging from 0.16 to 2.19 μg/mL, and are effective against DENV-2 with IC50s in the range of 0.10–0.41 μg/mL [38]. The galactan (C2S-3) extracted from *Cryptonemia crenulata* can inhibit the proliferation of DENV-2 in Vero cell lines [39]. The result of the experiment showed that C2S-3 blocked the initial binding of the virus to cells and its subsequent penetration, preventing DENV-2 from RNA replication and other biomacromolecule synthesis functions in host cells. Moreover, compared with heparin, C2S-3 was more effective as an antiviral against various DENV-2 strains [39]. Therefore, galactan is a very promising antiviral drug.

2. Brown Seaweed

2.1. Fucoidan

Fucoidan is an intercellular or mucilage matrix component of brown seaweed, accounting for approximately 5–20% of the dry weight of the plant [40][41]. Fucoidan is documented to be effective against a wide variety of viruses, including HIV, HSV, and SARS-CoV-2, and numerous other RNA and DNA viruses [42][43][44][45][46][47][48]. Dinesh et al. extracted fucoidan (CFF, FF1, and FF2) from *Sargassum swartzii*, observing that the FF2 fraction was effective against HIV-1 at concentrations between 1.56 and 6.25 μg/mL, shown by significant reductions in the p24 antigen levels (95.6 ± 1.1%) and reverse transcriptase (78.9 ± 1.43%) at a concentration of 25 μg/mL [45]. Fucoidans isolated from *Dictyota mertensii, Lobophora variegate, Fucusvesiculosus,* and *Spatoglossum schroederi* were found to inhibit HIV reverse transcriptases, thus preventing infection; it was further observed that the antiviral action was positively associated with the numbers of sulfate moieties on the compound [49]. Lee et al. demonstrated that the fucoidan extracted from Mekabu and *Sargassum trichophyllum* significantly inhibited HSV-1, HSV-2, H5N3, and influenza A viral infection together with enhancing the immune function [50]. High-molecular-weight fucoidan (KW) from the brown alga *Kelmanella crassifolia* was shown to bind and block influenza A virus neuraminidase activity, inhibiting the release of viral particles. Fucoidan was also found to block EGFR and subsequent activation of downstream PI3K/Akt and NF-κB signaling [51]. In addition, fucoidan also inhibits NDV La Sota infection (IS_{50} > 2000), significantly reducing the number of syncytia (inhibition rate of 70%), suggesting specific binding of fucoidan to the F0 protein [52]. Fucoidan is considered a possible candidate for treating COVID-19 as it has significant antiviral activity [53]. Recovery of the mitochondrial membrane potential Δψm was observed in the PBMCs of patients after recovery from COVID-19, showing that fucoidan has strong antioxidant activity and can restore cellular homeostasis [54][55][56]. RPI-27 extracted from Saccharina japonica is a high-molecular-weight fucoidan similar in structure to glycosaminoglycans on the surfaces of host cells [57]. This could provide opportunities for binding the S protein of SARS-CoV-2, resulting in competitive inhibition with the virus, with an EC50 value of 8.3 ± 4.6 μg/mL [57].

Fucoidan has a variety of immunomodulatory effects, such as stimulating the production of NK (natural killer) cells, promoting cell development and other functions of dendritic cells. In addition, it enhances Th1-type immune responses by producing antibodies against specific antigenic determinants and generating memory T cells against specific viruses [58]. Sulfated polysaccharides could provide an important approach to designing therapeutic vaccines based on their desired physicochemical properties and easily modifiable structural features. Fucoidan is reported to have the best adjuvant quality for future vaccine production and can elicit strong cell-mediated and humoral immune responses [59].

2.2. Alginate

Alginate is a soluble acidic polysaccharide found in the cell walls of brown seaweed, especially *Macrocystis pyrifera, Laminaria hyperborea*, and *Ascophyllum nodosum*, amongst others [60]. Alginate is a linear polymer formed by 1,4-linked β-D-mannuronic acid and 1,4 α-L-guluronic acid moieties assembled in blocks [61]. The compound has both antiviral and immunomodulatory activities [62][63][64][65][66]. Serrano-Aroca et al. summarized and analyzed the effects of biomaterials constructed of alginate on 17 viruses, finding that these materials were essentially non-toxic and effective against a variety of viruses [67]. In vivo results showed that oral administration of marine polysaccharide drug 911 reduced viral infection and the plasma RNA copy number. In addition, the introduction of 911 has a protective effect on CD4 cells [68][69]

[70]. Furthermore, the inhibitory effect of 911 on HIV-1 is dose dependent with low toxicity. Moreover, it can also inhibit HBV viral replication by inhibiting DNA replication [71].

Polymannuroguluronate

Polymannuroguluronate (PMG) is a common low-molecular-weight alginate. Polymannuroguluronate sulfate (PMGS) is capable of inactivating HPV particles and of blocking virus capsid L1 protein binding, and downregulating the levels of the E6 and E7 viral oncogenic proteins [72]. In addition, sulfated polymannuronate (SPMG) inhibits the interaction between the HIV-1 gp120 protein and the CD4 + T lymphocyte receptor, thus preventing entry of the virus into the lymphocyte [73]. In addition, Miao et al. suggested that the interaction between SPMG and the CD4 + T lymphocyte may provide a mechanistic explanation for the immunoenhancement and anti-AIDS activity of SPMG in HIV-infected individuals [74]. Therefore, PMGS deserves further study as a novel candidate for the prevention of HPV infection, treatment of genital warts or cervical cancer, and HIV infection.

Polyguluronate

Polyguluronate (PG) is another low-molecular-weight alginate. Polyguluronate sulfate (PGS) significantly reduces the levels of HBsAg (51.8%) and HBeAg (36.2%), showing dose- and time-dependent inhibitory effects [75]. PGS likely binds to HepG2.2.15 cells, upregulating the NF-κB and RAF/MEK/ERK pathways to promote interferon-β production and thus interfering with HBV transcription and exerting an anti-HBV effect [75]. In addition, PGS can significantly reduce oxidative stress induced by H_2O_2 and improve the survival rate of HepG2 hepatocytes due to its strong antioxidant activity [76].Therefore, PGS, as a new anti-HBV drug designed to regulate the host's natural immune system, deserves further study.

3. Green Seaweed

Ulvan

Ulvan is the most common polysaccharide in the cell walls of green seaweed, making up to 8–29% of the algal dry weight[77].Both in vitro and in vivo investigations have shown that ulvan has anticoagulant, antibacterial, antiviral, and immunomodulatory activities[78][79][80][81][82].Several low-molecular-weight ulvan isoforms (ULVAN-F1, ULVAN-F2, and ULVAN-F3) were purified from *Ulva pertusa*, which were found to be effective in preventing the infection and replication of vesicular stomatis virus[83].The antiviral activity of ulvan is not, however, consistently related to its molecular weight. The antiviral effect of SU1F1 is mainly via inhibition of DNA replication and transcription while downregulating HSV protein synthesis[84].The polysaccharide extract containing ulvan blocks the adsorption of JEV (Japanese encephalitis virus) and inhibits the entry of the virus into the host cell. In addition, they effectively reduce the production of proinflammatory cytokines[85].In addition to antiviral activity, ulvan also has certain immunomodulatory activity. Ulva extract from *Ulva armoricana* can induce the release of proinflammatory cytokines by activating avian heterophile and monocytes in vitro, ultimately enhancing the innate immune system of chickens[86].

4. Microalgae

4.1. p-KG03

p-KG03 is a homogeneous polysaccharide derived from *Gyrodiniumimpudicum* and complexed by galactose with uronic and sulfonic acid groups[31].p-KG03 extracted from the dinoflagellate *Gyrodinium impudicum* is the first marine compound (EC50 = 26.9 μg/mL) reported to significantly inhibit encephalomycarditis RNA virus (EMCV) infection in vitro[87].

4.2.Naviculan

Naviculan is derived from the diatom *Navicula directa*. Lee and colleagues reported that naviculan reduced virus infection by inhibiting the binding and internalization of HSV-1, HSV-2, HIV, and INF A, with IC50 values in the 7.4–170 μg/mL range[88].

4.3.Calcium Spirulan

Calcium spirulan is obtained from the alga *Arthrospira platensis*. Due to the chelation of calcium ions with the sulfate groups on the polysaccharide, it has high antiviral activity against coated viruses[89][90][91][92].Hayashi and colleagues found that calcium spirulan (Ca-SP) from *Spirulina platensis* is an inhibitor of several viruses. It can inhibit replication and infiltration of HSV-1, HCMV, MeV, MUV, INF A, and HIV-1, with EC50 values in the 0.92–23 μg/mL range[93].

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