Sulfated Polysaccharides from Seaweeds

Subjects: Virology

Contributor: Qiang Wei , Shuliang Song , , Jiarui Zhao , Kai Ji

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.

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].

References

1. Garcia-Jimenez, P.; Mantesa, S.R.; Robaina, R.R. Expression of Genes Related to Carrageenan Synthesis during Carposporogenesis of the Red Seaweed Grateloupia imbricata. Mar. Drugs 2020, 18, 432.
2. Frediansyah, A. The antiviral activity of iota-, kappa-, and lambda-carrageenan against COVID-19: A critical review. Clin. Epidemiol. Glob. Health 2021, 12, 100826.
3. Ghanbarzadeh, M.; Golmoradizadeh, A.; Homaei, A. Carrageenans and carrageenases: Versatile polysaccharides and promising marine enzymes. Phytochem. Rev. 2018, 17, 535–571.
4. Buck, C.B.; Thompson, C.D.; Roberts, J.N.; Muller, M.; Lowy, D.R.; Schiller, J.T. Carrageenan is a potent inhibitor of papillomavirus infection. PLoS Pathog. 2006, 2, e69.
5. Yamada, T.; Ogamo, A.; Saito, T.; Watanabe, J.; Uchiyama, H.; Nakagawa, Y. Preparation and anti-HIV activity of low-molecular-weight carrageenans and their sulfated derivatives. Carbohyd. Polym. 1997, 32, 51–55.
6. Yamada, T.; Ogamo, A.; Saito, T.; Uchiyama, H.; Nakagawa, Y. Preparation of O-acylated low-molecular-weight carrageenans with potent anti-HIV activity and low anticoagulant effect. Carbohyd. Polym. 2000, 41, 115–120.
7. Perino, A.; Consiglio, P.; Maranto, M.; de Franciscis, P.; Marci, R.; Restivo, V.; Manzone, M.; Capra, G.; Cucinella, G.; Calagna, G. Impact of a new carrageenan-based vaginal microbicide in a female population with genital HPV-infection: First experimental results. Eur. Rev. Med. Pharmacol. Sci. 2019, 23, 6744–6752.
8. Shao, Q.; Guo, Q.; Xu, W.; Li, Z.; Zhao, T. Specific Inhibitory Effect of kappa-Carrageenan Polysaccharide on Swine Pandemic 2009 H1N1 Influenza Virus. PLoS ONE 2015, 10, e0126577.
9. Wang, W.; Zhang, P.; Hao, C.; Zhang, X.E.; Cui, Z.Q.; Guan, H.S. In vitro inhibitory effect of carrageenan oligosaccharide on influenza A H1N1 virus. Antiviral. Res. 2011, 92, 237–246.
10. Schutz, D.; Conzelmann, C.; Fois, G.; Gross, R.; Weil, T.; Wettstein, L.; Stenger, S.; Zelikin, A.; Hoffmann, T.K.; Frick, M.; et al. Carrageenan-containing over-the-counter nasal and oral sprays inhibit SARS-CoV-2 infection of airway epithelial cultures. Am. J. Physiol. Lung Cell Mol. Physiol. 2021, 320, L750–L756.
11. Kolender, A.A.; Pujol, C.A.; Damonte, E.B.; Cerezo, A.S.; Matulewicz, M.C. Sulfation of kappa-carrageenan and antiviral activity. An. Asoc. Quim. Argent 1998, 86, 304–311.
12. Luo, Z.; Tian, D.; Zhou, M.; Xiao, W.; Zhang, Y.; Li, M.; Sui, B.; Wang, W.; Guan, H.; Chen, H.; et al. lambda-Carrageenan P32 Is a Potent Inhibitor of Rabies Virus Infection. PLoS ONE 2015, 10, e0140586.

13. Jang, Y.; Shin, H.; Lee, M.K.; Kwon, O.S.; Shin, J.S.; Kim, Y.I.; Kim, C.W.; Lee, H.R.; Kim, M. Antiviral activity of lambda-carrageenan against influenza viruses and severe acute respiratory syndrome coronavirus 2. Sci. Rep. 2021, 11, 821.
14. Vissani, A.; Galdo Novo, S.; Ciancia, M.; Zabal, O.A.; Thiry, E.; Bratanich, A.C.; Barrandeguy, M.E. Effects of lambda-carrageenan on equid herpesvirus 3 in vitro. J. Equine Vet. Sci. 2016, 39, S61–S62.
15. Talarico, L.B.; Damonte, E.B. Interference in dengue virus adsorption and uncoating by carrageenans. Virology 2007, 363, 473–485.
16. Liu, Z.; Gao, T.; Yang, Y.; Meng, F.; Zhan, F.; Jiang, Q.; Sun, X. Anti-Cancer Activity of Porphyran and Carrageenan from Red Seaweeds. Molecules 2019, 24, 4286.
17. Gubina-Vakyulyk, G.I.; Gorbach, T.V.; Tkachenko, A.S.; Tkachenko, M.O. Damage and regeneration of small intestinal enterocytes under the influence of carrageenan induces chronic enteritis. Comp. Clin. Pathol. 2015, 24, 1473–1477.
18. Luo, M.; Shao, B.; Nie, W.; Wei, X.W.; Li, Y.L.; Wang, B.L.; He, Z.Y.; Liang, X.; Ye, T.H.; Wei, Y.Q. Antitumor and Adjuvant Activity of lambda-carrageenan by Stimulating Immune Response in Cancer Immunotherapy. Sci. Rep. 2015, 5, 11062.
19. Talarico, L.B.; Noseda, M.D.; Ducatti, D.R.B.; Duarte, M.E.R.; Damonte, E.B. Differential inhibition of dengue virus infection in mammalian and mosquito cells by iota-carrageenan. J. Gen. Virol. 2011, 92, 1332–1342.
20. Morokutti-Kurz, M.; Graf, C.; Prieschl-Grassauer, E. Amylmetacresol/2,4-dichlorobenzyl alcohol, hexylresorcinol, or carrageenan lozenges as active treatments for sore throat. Int. J. Gen. Med. 2017, 10, 53–60.
21. Leibbrandt, A.; Meier, C.; Konig-Schuster, M.; Weinmullner, R.; Kalthoff, D.; Pflugfelder, B.; Graf, P.; Frank-Gehrke, B.; Beer, M.; Fazekas, T.; et al. Iota-carrageenan is a potent inhibitor of influenza A virus infection. PLoS ONE 2010, 5, e14320.
22. Morokutti-Kurz, M.; Konig-Schuster, M.; Koller, C.; Graf, C.; Graf, P.; Kirchoff, N.; Reutterer, B.; Seifert, J.M.; Unger, H.; Grassauer, A.; et al. The Intranasal Application of Zanamivir and Carrageenan Is Synergistically Active against Influenza A Virus in the Murine Model. PLoS ONE 2015, 10, e0128794.
23. Ludwig, M.; Enzenhofer, E.; Schneider, S.; Rauch, M.; Bodenteich, A.; Neumann, K.; Prieschl-Grassauer, E.; Grassauer, A.; Lion, T.; Mueller, C.A. Efficacy of a carrageenan nasal spray in patients with common cold: A randomized controlled trial. Respir. Res. 2013, 14, 124.
24. Morokutti-Kurz, M.; Froeba, M.; Graf, P.; Grosse, M.; Grassauer, A.; Auth, J.; Schubert, U.; Prieschl-Grassauer, E. Iota-carrageenan neutralizes SARS-CoV-2 and inhibits viral replication in vitro. PLoS ONE 2021, 16, e0237480.

25. Morokutti-Kurz, M.; Unger-Manhart, N.; Graf, P.; Rauch, P.; Kodnar, J.; Grosse, M.; Setz, C.; Savli, M.; Ehrenreich, F.; Grassauer, A.; et al. The Saliva of Probands Sucking an Iota-Carrageenan Containing Lozenge Inhibits Viral Binding and Replication of the Most Predominant Common Cold Viruses and SARS-CoV-2. Int. J. Gen. Med. 2021, 14, 5241–5249.
26. Chahla, R.E.; Medina Ruiz, L.; Ortega, E.S.; Morales, M.F.; Barreiro, F.; George, A.; Mancilla, C.; D'Amato, S.P.; Barrenechea, G.; Goroso, D.G.; et al. A Randomized Trial-Intensive Treatment Based in Ivermectin and Iota-Carrageenan as Pre-Exposure Prophylaxis for COVID-19 in Healthcare Agents. medRxiv 2021.
27. Bansal, S.; Jonsson, C.B.; Taylor, S.L.; Figueroa, J.M.; Dugour, A.V.; Palacios, C.; Vega, J.C. Iota-carrageenan and xylitol inhibit SARS-CoV-2 in Vero cell culture. PLoS ONE 2021, 16, e0259943.
28. Graf, C.; Bernkop-Schnurch, A.; Egyed, A.; Koller, C.; Prieschl-Grassauer, E.; Morokutti-Kurz, M. Development of a nasal spray containing xylometazoline hydrochloride and iota-carrageenan for the symptomatic relief of nasal congestion caused by rhinitis and sinusitis. Int. J. Gen. Med. 2018, 11, 275–283.
29. Hassanzadeh, K.; Pena, H.P.; Dragotto, J.; Buccarello, L.; Iorio, F.; Pieraccini, S.; Sancini, G.; Feligioni, M. Considerations around the SARS-CoV-2 Spike Protein with Particular Attention to COVID-19 Brain Infection and Neurological Symptoms. ACS Chem. Neurosci. 2020, 11, 2361–2369.
30. Froba, M.; Grosse, M.; Setz, C.; Rauch, P.; Auth, J.; Spanaus, L.; Munch, J.; Ruetalo, N.; Schindler, M.; Morokutti-Kurz, M.; et al. Iota-Carrageenan Inhibits Replication of SARS-CoV-2 and the Respective Variants of Concern Alpha, Beta, Gamma and Delta. Int. J. Mol. Sci. 2021, 22, 13202.
31. Ahmadi, A.; Moghadamtousi, S.Z.; Abubakar, S.; Zandi, K. Antiviral potential of algae polysaccharides isolated from marine sources: A review. Biomed. Res. Int. 2015, 2015, 825203.
32. Delattre, C.; Fenoradosoa, T.A.; Michaud, P. Galactans: An Overview of their Most Important Sourcing and Applications as Natural Polysaccharides. Braz. Arch. Biol. Techn. 2011, 54, 1075–1092.
33. Yasuhara-Bell, J.; Lu, Y. Marine compounds and their antiviral activities. Antiviral. Res. 2010, 86, 231–240.
34. Ohta, Y.; Lee, J.B.; Hayashi, K.; Hayashi, T. Isolation of sulfated galactan from Codium fragile and its antiviral effect. Biol. Pharm. Bull. 2009, 32, 892–898.
35. Witvrouw, M.; Este, J.A.; Mateu, M.Q.; Reymen, D.; Andrei, G.; Snoeck, R.; Ikeda, S.; Pauwels, R.; Bianchini, N.V.; Desmyter, J.; et al. Activity of a Sulfated Polysaccharide Extracted from the Red Seaweed Aghardhiella-Tenera against Human-Immunodeficiency-Virus and Other Enveloped Viruses. Antivir. Chem. Chemoth. 1994, 5, 297–303.

36. Bouhlal, R.; Haslin, C.; Chermann, J.C.; Colliec-Jouault, S.; Sinquin, C.; Simon, G.; Cerantola, S.; Riadi, H.; Bourgougnon, N. Antiviral activities of sulfated polysaccharides isolated from Sphaerococcus coronopifolius (Rhodophytha, Gigartinales) and Boergeseniella thuyoides (Rhodophyta, Ceramiales). Mar. Drugs 2011, 9, 1187–1209.
37. Matsuhiro, B.; Conte, A.F.; Damonte, E.B.; Kolender, A.A.; Matulewicz, M.C.; Mejias, E.G.; Pujol, C.A.; Zuniga, E.A. Structural analysis and antiviral activity of a sulfated galactan from the red seaweed Schizymenia binderi (Gigartinales, Rhodophyta). Carbohydr. Res. 2005, 340, 2392–2402.
38. Rodriguez, M.C.; Merino, E.R.; Pujol, C.A.; Damonte, E.B.; Cerezo, A.S.; Matulewicz, M.C. Galactans from cystocarpic plants of the red seaweed Callophyllis variegata (Kallymeniaceae, Gigartinales). Carbohydr. Res. 2005, 340, 2742–2751.
39. Talarico, L.B.; Duarte, M.E.; Zibetti, R.G.; Noseda, M.D.; Damonte, E.B. An algal-derived DL-galactan hybrid is an efficient preventing agent for in vitro dengue virus infection. Planta Med. 2007, 73, 1464–1468.
40. Skriptsova, A.V. Fucoidans of brown algae: Biosynthesis, localization, and physiological role in thallus. Russ. J. Mar. Biol. 2015, 41, 145–156.
41. Cardoso, S.M.; Carvalho, L.G.; Silva, P.J.; Rodrigues, M.S.; Pereira, O.R.; Pereira, L. Bioproducts from Seaweeds: A Review with Special Focus on the Iberian Peninsula. Curr. Org. Chem. 2014, 18, 896–917.
42. Kim, B.S.; Kang, H.J.; Park, J.Y.; Lee, J. Fucoidan promotes osteoblast differentiation via JNK- and ERK-dependent BMP2-Smad 1/5/8 signaling in human mesenchymal stem cells. Exp. Mol. Med. 2015, 47, e128.
43. Sapharikas, E.; Lokajczyk, A.; Fischer, A.M.; Boisson-Vidal, C. Fucoidan Stimulates Monocyte Migration via ERK/p38 Signaling Pathways and MMP9 Secretion. Mar. Drugs 2015, 13, 4156–4170.
44. Kim, S.Y.; Joo, H.G. Evaluation of adjuvant effects of fucoidan for improving vaccine efficacy. J. Vet. Sci. 2015, 16, 145–150.
45. Dinesh, S.; Menon, T.; Hanna, L.E.; Suresh, V.; Sathuvan, M.; Manikannan, M. In vitro anti-HIV-1 activity of fucoidan from Sargassum swartzii. Int. J. Biol. Macromol. 2016, 82, 83–88.
46. Jiao, G.L.; Yu, G.L.; Wang, W.; Zhao, X.L.; Zhang, J.Z.; Ewart, S.H. Properties of polysaccharides in several seaweeds from Atlantic Canada and their potential anti-influenza viral activities. J. Ocean U China 2012, 11, 205–212.
47. Mandal, P.; Mateu, C.G.; Chattopadhyay, K.; Pujol, C.A.; Damonte, E.B.; Ray, B. Structural features and antiviral activity of sulphated fucans from the brown seaweed Cystoseira indica. Antivir. Chem. Chemother. 2007, 18, 153–162.

48. Thuy, T.T.; Ly, B.M.; Van, T.T.; Quang, N.V.; Tu, H.C.; Zheng, Y.; Seguin-Devaux, C.; Mi, B.; Ai, U. Anti-HIV activity of fucoidans from three brown seaweed species. Carbohydr. Polym. 2015, 115, 122–128.

49. Queiroz, K.C.; Medeiros, V.P.; Queiroz, L.S.; Abreu, L.R.; Rocha, H.A.; Ferreira, C.V.; Juca, M.B.; Aoyama, H.; Leite, E.L. Inhibition of reverse transcriptase activity of HIV by polysaccharides of brown algae. Biomed. Pharmacother. 2008, 62, 303–307.

50. Lee, J.B.; Hayashi, K.; Hashimoto, M.; Nakano, T.; Hayashi, T. Novel antiviral fucoidan from sporophyll of Undaria pinnatifida (Mekabu). Chem. Pharm. Bull. 2004, 52, 1091–1094.

51. Wang, W.; Wu, J.; Zhang, X.; Hao, C.; Zhao, X.; Jiao, G.; Shan, X.; Tai, W.; Yu, G. Inhibition of Influenza A Virus Infection by Fucoidan Targeting Viral Neuraminidase and Cellular EGFR Pathway. Sci. Rep. 2017, 7, 40760.

52. Elizondo-Gonzalez, R.; Cruz-Suarez, L.E.; Ricque-Marie, D.; Mendoza-Gamboa, E.; Rodriguez-Padilla, C.; Trejo-Avila, L.M. In vitro characterization of the antiviral activity of fucoidan from Cladosiphon okamuranus against Newcastle Disease Virus. Virol. J. 2012, 9, 307.

53. Sansone, C.; Brunet, C.; Noonan, D.M.; Albini, A. Marine Algal Antioxidants as Potential Vectors for Controlling Viral Diseases. Antioxidants 2020, 9, 392.

54. Singh, K.K.; Chaubey, G.; Chen, J.Y.; Suravajhala, P. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. Am. J. Physiol. Cell Physiol. 2020, 319, C258–C267.

55. Zinovkin, R.A.; Zamyatnin, A.A. Mitochondria-Targeted Drugs. Curr. Mol. Pharmacol. 2019, 12, 202–214.

56. Diaz-Resendiz, K.J.G.; Toledo-Ibarra, G.A.; Ruiz-Manzano, R.; Giron Perez, D.A.; Covantes-Rosales, C.E.; Benitez-Trinidad, A.B.; Ramirez-Ibarra, K.M.; Hermosillo Escobedo, A.T.; Gonzalez-Navarro, I.; Ventura-Ramon, G.H.; et al. Ex vivo treatment with fucoidan of mononuclear cells from SARS-CoV-2 infected patients. Int. J. Environ. Health. Res. 2021, 1–19.

57. Kwon, P.S.; Oh, H.; Kwon, S.J.; Jin, W.; Zhang, F.; Fraser, K.; Hong, J.J.; Linhardt, R.J.; Dordick, J.S. Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro. Cell Discov. 2020, 6, 50.

58. Zhang, W.; Oda, T.; Yu, Q.; Jin, J.O. Fucoidan from Macrocystis pyrifera has powerful immune-modulatory effects compared to three other fucoidans. Mar. Drugs 2015, 13, 1084–1104.

59. Kuznetsova, T.A.; Zaporozhets, T.S.; Persianova, E.V.; Khotimchenko, Y.S.; Besednova, N.N. Prospects for the use of sulfated polysaccharides from brown seaweeds as vaccine adjuvants. Russ. J. Mar. Biol. 2016, 42, 443–450.

60. Sachan, N.K.; Pushkar, S.; Jha, A.; Bhattcharya, A. Sodium alginate: The wonder polymer for controlled drug delivery. J. Pharm. Res. 2009, 2, 1191–1199.

61. Szekalska, M.; Pucilowska, A.; Szymanska, E.; Ciosek, P.; Winnicka, K. Alginate: Current Use and Future Perspectives in Pharmaceutical and Biomedical Applications. Int. J. Polym. Sci. 2016, 2016, 1–17.
62. Peng, Y.; Xie, E.; Zheng, K.; Fredimoses, M.; Yang, X.; Zhou, X.; Wang, Y.; Yang, B.; Lin, X.; Liu, J.; et al. Nutritional and chemical composition and antiviral activity of cultivated seaweed Sargassum naozhouense Tseng et Lu. Mar. Drugs 2012, 11, 20–32.
63. Zheng, L.X.; Chen, X.Q.; Cheong, K.L. Current trends in marine algae polysaccharides: The digestive tract, microbial catabolism, and prebiotic potential. Int. J. Biol. Macromol. 2020, 151, 344–354.
64. Shapiro, S.E.; Zelenskaia, M.I. On cases of botulism in the Khabarovsk district. Gig. Sanit. 1965, 30, 90–91.
65. Yudiati, E.; Isnansetyo, A.; Murwantoko; Triyanto; Handayani, C.R. Alginate from Sargassum siliquosum Simultaneously Stimulates Innate Immunity, Upregulates Immune Genes, and Enhances Resistance of Pacific White Shrimp (Litopenaeus vannamei) Against White Spot Syndrome Virus (WSSV). Mar. Biotechnol. 2019, 21, 503–514.
66. Tran, N.M.; Dufresne, M.; Helle, F.; Hoffmann, T.W.; Francois, C.; Brochot, E.; Paullier, P.; Legallais, C.; Duverlie, G.; Castelain, S. Alginate hydrogel protects encapsulated hepatic HuH-7 cells against hepatitis C virus and other viral infections. PLoS ONE 2014, 9, e109969.
67. Serrano-Aroca, A.; Ferrandis-Montesinos, M.; Wang, R. Antiviral Properties of Alginate-Based Biomaterials: Promising Antiviral Agents against SARS-CoV-2. Acs Appl. Bio. Mater. 2021, 4, 5897–5907.
68. Xianliang, X.; Hua, D.; Meiyu, G.; Pingfang, L.; Yingxia, L.; Huashi, G. Studies of the anti-AIDS effects of marine polysaccharide drug 911 and its related mechanisms of action. Zhongguo Hai Yang Yao Wu Chin. J. Mar. Drugs 2000, 19, 4–8.
69. Xianliang, X.; Meiyu, G.; Guiling, L.; Huashi, G.; Zelin, L. Effects of marine polysaccharide 911 on HIV-1 proliferation in vitro. Zhongguo Hai Yang Yao Wu Chin. J. Mar. Drugs 2000, 19, 8–11.
70. Xianliang, X.; Meiyu, G.; Huashi, G.; Zelin, L. Study on the mechanism of inhibitory action of 911 on replication of HIV-1 in vitro. Zhongguo Hai Yang Yao Wu Chin. J. Mar. Drugs 2000, 19, 15–18.
71. Jiang, B.-f.; Xu, X.-f.; Li, L.; Yuan, W. Study on ‘911’anti-HBV effect in HepG2. 2.15 cells culture. Mod. Prev. Med. 2003, 30, 517–518.
72. Wang, S.; Lu, Z.; Wang, S.; Liu, W.; Gao, J.; Tian, L.; Wang, L.; Zhang, X.; Zhao, X.; Wang, W.; et al. The inhibitory effects and mechanisms of polymannuroguluronate sulfate against human papillomavirus infection in vitro and in vivo. Carbohydr. Polym. 2020, 241, 116365.

73. Meiyu, G.; Fuchuan, L.; Xianliang, X.; Jing, L.; Zuowei, Y.; Huashi, G. The potential molecular targets of marine sulfated polymannuroguluronate interfering with HIV-1 entryInteraction between SPMG and HIV-1 rgp120 and CD4 molecule. Antivir. Res. 2003, 59, 127–135.
74. Miao, B.; Geng, M.; Li, J.; Li, F.; Chen, H.; Guan, H.; Ding, J. Sulfated polymannuroguluronate, a novel anti-acquired immune deficiency syndrome (AIDS) drug candidate, targeting CD4 in lymphocytes. Biochem. Pharmacol. 2004, 68, 641–649.
75. Wu, L.; Wang, W.; Zhang, X.; Zhao, X.; Yu, G. Anti-HBV activity and mechanism of marine-derived polyguluronate sulfate (PGS) in vitro. Carbohydr. Polym. 2016, 143, 139–148.
76. Gao, Y.; Liu, W.; Wang, W.; Zhao, X.; Wang, F. Polyguluronate sulfate (PGS) attenuates immunological liver injury in vitro and in vivo. Int. J. Biol. Macromol. 2018, 114, 592–598.
77. Lahaye, M.; Robic, A. Structure and functional properties of ulvan, a polysaccharide from green seaweeds. Biomacromolecules 2007, 8, 1765–1774.
78. Ngo, D.H.; Wijesekara, I.; Vo, T.S.; Ta, Q.V.; Kim, S.K. Marine food-derived functional ingredients as potential antioxidants in the food industry: An overview. Food Res. Int. 2011, 44, 523–529.
79. Wijesekara, I.; Pangestuti, R.; Kim, S.K. Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae. Carbohyd. Polym. 2011, 84, 14–21.
80. Hardouin, K.; Bedoux, G.; Burlot, A.-S.; Donnay-Moreno, C.; Berge, J.-P.; Nyvall-Collen, P.; Bourgougnon, N. Enzyme-assisted extraction (EAE) for the production of antiviral and antioxidant extracts from the green seaweed Ulva armoricana (Ulvales, Ulvophyceae). Algal. Res. 2016, 16, 233–239.
81. Berri, M.; Olivier, M.; Holbert, S.; Dupont, J.; Demais, H.; le Goff, M.; Collen, P.N. Ulvan from Ulva armoricana (Chlorophyta) activates the PI3K/Akt signalling pathway via TLR4 to induce intestinal cytokine production. Algal. Res. 2017, 28, 39–47.
82. Song, L.; Chen, X.; Liu, X.; Zhang, F.; Hu, L.; Yue, Y.; Li, K.; Li, P. Characterization and Comparison of the Structural Features, Immune-Modulatory and Anti-Avian Influenza Virus Activities Conferred by Three Algal Sulfated Polysaccharides. Mar. Drugs 2015, 14, 4.
83. Chi, Y.; Zhang, M.; Wang, X.; Fu, X.; Guan, H.; Wang, P. Ulvan lyase assisted structural characterization of ulvan from Ulva pertusa and its antiviral activity against vesicular stomatitis virus. Int. J. Biol. Macromol. 2020, 157, 75–82.
84. Lopes, N.; Ray, S.; Espada, S.F.; Bomfim, W.A.; Ray, B.; Faccin-Galhardi, L.C.; Linhares, R.E.C.; Nozawa, C. Green seaweed Enteromorpha compressa (Chlorophyta, Ulvaceae) derived sulphated polysaccharides inhibit herpes simplex virus. Int. J. Biol. Macromol. 2017, 102, 605–612.

85. Chiu, Y.H.; Chan, Y.L.; Li, T.L.; Wu, C.J. Inhibition of Japanese encephalitis virus infection by the sulfated polysaccharide extracts from Ulva lactuca. Mar. Biotechnol. 2012, 14, 468–478.
86. Guriec, N.; Bussy, F.; Gouin, C.; Mathiaud, O.; Quero, B.; le Goff, M.; Collen, P.N. Ulvan Activates Chicken Heterophils and Monocytes Through Toll-Like Receptor 2 and Toll-Like Receptor 4. Front. Immunol. 2018, 9, 2725.
87. Yim, J.H.; Kim, S.J.; Ahn, S.H.; Lee, C.K.; Rhie, K.T.; Lee, H.K. Antiviral effects of sulfated exopolysaccharide from the marine microalga Gyrodinium impudicum strain KG03. Mar. Biotechnol. 2004, 6, 17–25.
88. Lee, J.B.; Hayashi, K.; Hirata, M.; Kuroda, E.; Suzuki, E.; Kubo, Y.; Hayashi, T. Antiviral sulfated polysaccharide from Navicula directa, a diatom collected from deep-sea water in Toyama Bay. Biol. Pharm. Bull. 2006, 29, 2135–2139.
89. Karkos, P.D.; Leong, S.C.; Karkos, C.D.; Sivaji, N.; Assimakopoulos, D.A. Spirulina in clinical practice: Evidence-based human applications. Evid Based Complement Altern. Med. 2011, 2011, 531053.
90. Ayehunie, S.; Belay, A.; Baba, T.W.; Ruprecht, R.M. Inhibition of HIV-1 replication by an aqueous extract of Spirulina platensis (Arthrospira platensis). J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 1998, 18, 7–12.
91. Lee, J.B.; Srisomporn, P.; Hayashi, K.; Tanaka, T.; Sankawa, U.; Hayashi, T. Effects of structural modification of calcium spirulan, a sulfated polysaccharide from Spirulina platensis, on antiviral activity. Chem. Pharm. Bull. 2001, 49, 108–110.
92. Mader, J.; Gallo, A.; Schommartz, T.; Handke, W.; Nagel, C.H.; Gunther, P.; Brune, W.; Reich, K. Calcium spirulan derived from Spirulina platensis inhibits herpes simplex virus 1 attachment to human keratinocytes and protects against herpes labialis. J. Allergy Clin. Immunol. 2016, 137, 197–203.e193.
93. Hayashi, T.; Hayashi, K.; Maeda, M.; Kojima, I. Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga Spirulina platensis. J. Nat. Prod. 1996, 59, 83–87.