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Algal-Derived Hydrocolloids with Potential Antiviral Activity: A Mechanistic Approach †

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Abstract: From a structural point of view, hydrocolloids are characterized as hydrophilic biopolymers with high molecular weight. Hydrocolloids are widely used in the food industry, mainly as thickeners, gelling agents, stabilizers of foams and emulsions, and inhibitors of ice and sugar crystals. Additionally, hydrocolloids are being increasingly used as fat replacers, aiming to produce low-calorie foods. Besides these important functional properties in different food products, hydrocolloids are being progressively recognized for their diverse biological properties, including anticoagulant, antithrombic, hypocholesterolemic, antioxidant, antiviral, antitumor, and immunomodulatory effects. Additionally, some studies have reported that these biopolymers have beneficial effects against a significant number of dermatological problems. Regarding antiviral properties, some hydrocolloids, such as sulfated polysaccharides, exhibit unique structures that exert these effects. This study aims to describe the corresponding underlying mechanisms of this bioactivity. Special attention will be given to the way hydrocolloids may obstruct different phases of the viral life cycle (attachment, penetration, uncoating, biosynthesis, viral assembly, and release) by directly inactivating virions before infection or by inhibiting its replication inside the host cell. The presented information might represent a potential contribution to the discovery and development of new antiviral drugs.

Keywords: sulfated polysaccharides; biological properties; antiviral activity

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1. Occurrence of Sulfated Polysaccharides in Algal Species

1.1. Red Macroalgae

In red macroalgae, sulfated galactans stand out as the major polysaccharides. From a structural point of view, these compounds are characterized by their typical linear backbone with alternating units of β-D-galactopyranose (with the glycosidic bond in carbon 3) and α-galactopyranose (with the glycosidic bond in carbon 4). Sulfated galactans are generally divided in agarans, in which the monomeric unit is α-L-galactose, and carrageenans, which, are formed by linear chains of α-D-galactose [1].

In red algae, carrageenan is located in the outer cell wall and in the intracellular matrix and may correspond to as much as 30–70% of their dry weight. In what concerns its metabolic pathway, carrageenan is initially produced in the Golgi apparatus and later sulfated by sulfotransferases in the cell wall [2].

The carrageenans with the highest commercial relevance, are kappa (κ), which is naturally abundant, for instance, in *Kappaphycus alvarezii* and several *Eucheuma* species [3]; iota (ι), found in high percentages in *Eucheuma denticulatum* [4]; and lambda (λ), which is abundant, together with other red algae, in *Gigartina skottsbergii* and *Chondrus crispus* [5,6].

Aside from carrageenan, agar is also common in red macroalgae. Agar comprises two polysaccharides, agarose and agaropectin, and it is particularly abundant in the genera *Gelidium* and *Gracilaria*. From a structural point of view, agar contains alternating sequences of 1→3-β-D-galactopyranose (which can be substituted by sulfate esters, pyruvic acid acetals, or methoxy groups) and 1→4-α-L-galactopyranose or 3→6-α-L-galactopyranose [7,8].

1.2. Green Macroalgae

Ulvan is the most common polysaccharide in the cell walls of green seaweed, being most commonly found in genera such as *Ulva*, *Gayralia*, and *Monostroma*. Despite representing a less exuberant percentage than carrageenan in red macroalgae, ulvan can reach 8–29% of the algal dry weight [9]. It is mainly constituted by L-rhamnose (5.0–92.2%), D-glucuronic acid (2.6–52.0%), D-xylose (0.0–38.0%), L-iduronic acid (0.6–15.3%), and sulfate [10]. These monomeric units are typically linked by α- and β-(1→4) bonds, forming repeating disaccharide units, such as aldobiuronic acids (or ulvanobiuronic acid) and aldobioses (or ulvanobioses) [11].

1.3. Brown Macroalgae

Among brown macroalgae, fucoidan is acknowledged as the major sulfated polysaccharide, often reaching percentages as high as 30% of its dry weight. Fucoidan is characterized by a backbone of α-(1→3)-L-fucopyranosyl residues with α-(1→3) or α-(1→4) glycosidic bonds positions [12]. Nonetheless, fucoidan is classified as an heterogenous polysaccharide since the pyranose unit may be substituted by sulfate, acetate, or glycosyl (e.g., glucuronic acid) units and, less frequently, other monosaccharides (e.g., D-xylose, D-galactose, D-mannose, or uronic acids) [13].

Fucus evanescens and *Ascophyllum nodosum* are typical sources of fucoidan [12].

2. Antiviral Activity of Algae-Derived of Sulfated Polysaccharides

Owing to their unique chemical structures, algae-sulfated polysaccharides may exert different biological activities.

In the specific case of their potential antiviral effects, these compounds may block different phases of the viral life cycle, either by direct inactivation of virions before infection, or by inhibiting its replication inside the host cell. Accordingly, a significant number of antiviral drugs have been developed based in the capacity of algae polysaccharides to inhibit the primary stages (attachment, penetration, uncoating, biosynthesis, viral assembly, and release) of the virus life cycle [14].

2.1. Antiviral Activity of Red Macroalgae Sulfated Polysaccharides

Possibly due to its higher natural occurrence, carrageenan is the most studied sulfated polysaccharide in human clinical trials designed to evaluate its potential effect against various viral diseases [15]. Kappa-(κ-)carrageenan, particularly in low-molecular weight forms, showed capacity to inhibit viral replication, either by blocking adsorption to the surface, or by inhibiting protein expression [16]. This action was reported in different viral species, such as the influenza virus [16], severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [17], herpes simplex virus type 2 (HSV-2), and human papilloma virus subtype 16 (HPV16) [18].

On the other hand, lambda-(λ-)carrageenan inhibits viral internalization by specifically targeting cell surface receptors in which virus attachment occurs or through binding to viral envelope proteins. This effect has been reported in rabies virus infection [19], influenza, SARS-CoV-2 [20], different herpes viruses [20], and dengue virus [21].

Iota-(ι-)carrageenan's antiviral activity has also been well documented, especially against respiratory viruses [22]. Likewise, it seems to contribute to the neutralization of SARS-CoV-2, particularly because of positively charged regions on the glycoprotein envelope and protein aggregation on host cells' surface [23].

Additionally, galactans show good antiviral activity against herpes simplex virus (HSV), dengue virus, hepatitis A virus, and human immunodeficiency virus (HIV) (preventing the interaction between HIV gp120 and the cluster of differentiation (CD)4 + T-cell receptor) [24].

2.2. Antiviral Activity of Green Macroalgae Sulfated Polysaccharides

Ulvan, the major sulfated polysaccharide in green macroalgae, was reported for its in vitro and in vivo antiviral activity [25], for instance, by preventing the infection and replication of the vesicular stomatitis virus [26], by reducing the formation of syncytia in the measles virus [27], by inhibiting cell-to-cell fusion in the Newcastle disease virus [28], or by downregulating protein synthesis in HSV [29].

2.3. Antiviral Activity of Sulfated Brown Macroalgae Polysaccharides

Due to its abundance in these algae species, fucoidan is the most commonly studied polysaccharide, already having been reported as being effective against several RNA and DNA viruses, including HIV (by reducing the p24 antigen and reverse transcriptase levels), HSV, influenza A virus (by blocking neuraminidase activity), and SARS-CoV-2, among others [30,31].

3. Conclusions

Comparing the algae species referred to above, it seems evident that red and brown algae have higher potential as sources of sulfated polysaccharides, which may justify that these species are studied in further depth. Independently of algae source, sulfated polysaccharides showed activity against various DNA and RNA viruses. The associated antiviral mechanisms and corresponding effectiveness appear to be highly dependent on virus species and host cell type. Nevertheless, algae-derived sulfated polysaccharides seem to have a validated antiviral activity, which, conjugated with their high availability, low production costs, broad-spectrum antiviral activities, and unique antiviral mechanisms, suggest that their exploitation for this purpose may be particularly attractive.

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References

1. Al-Alawi, A.A.; Al-Marhubi, I.M.; Al-Belushi, M.S.M.; Soussi, B. Characterization of carrageenan extracted from Hypnea bry-oides in Oman. *Mar. Biotechnol.* **2011**, *13*, 893–899. [CrossRef] [PubMed]
2. 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. [CrossRef] [PubMed]
3. Rudke, A.R.; de Andrade, C.J.; Ferreira, S.R.S. Kappaphycus alvarezii macroalgae: An unexplored and valuable biomass for green biorefinery conversion. *Trends Food Sci. Technol.* **2020**, *103*, 214–224. [CrossRef]
4. Jönsson, M.; Allahgholi, L.; Sardari, R.R.; Hreggviðsson, G.O.; Nordberg Karlsson, E. Extraction and modification of macroalgal polysaccharides for current and next-generation applications. *Molecules* **2020**, *25*, 930. [CrossRef]
5. Zhu, B.; Ni, F.; Sun, Y.; Zhu, X.; Yin, H.; Yao, Z.; Du, Y. Insight into carrageenases: Major review of sources, category, property, purification method, structure, and applications. *Crit. Rev. Biotechnol.* **2018**, *38*, 1261–1276. [CrossRef]
6. Muthukumar, J.; Chidambaram, R.; Sukumaran, S. Sulfated polysaccharides and its commercial applications in food industries—A review. *J. Food Sci. Technol.* **2020**, *58*, 2453–2466. [CrossRef]
7. Usov, A.I. Polysaccharides of the red algae. In *Advances in Carbohydrate Chemistry and Biochemistry*; Horton, D., Ed.; Academic Press: Cambridge, MA, USA, 2011; pp. 115–217.

8. Lee, W.K.; Lim, Y.Y.; Leow, A.T.C.; Namasivayam, P.; Ong Abdullah, J.; Ho, C.L. Biosynthesis of agar in red seaweeds: A review. *Carbohydr. Polym.* **2017**, *164*, 23–30. [CrossRef]
9. Lahaye, M.; Robic, A. Structure and functional properties of ulvan, a polysaccharide from green seaweeds. *Biomacromolecules* **2007**, *8*, 1765–1774. [CrossRef]
10. Kim, S.K. *Springer Handbook of Marine Biotechnology*; Springer: Berlin/Heidelberg, Germany, 2015; pp. 941–953.
11. Kidgell, J.T.; Magnusson, M.; de Nys, R.; Glasson, C.R.K. Ulvan: A systematic review of extraction, composition and function. *Algal Res.* **2019**, *39*, 101422. [CrossRef]
12. Yuguchi, Y.; Bui, L.M.; Takebe, S.; Suzuki, S.; Nakajima, N.; Kitamura, S.; Thanh, T.T.T. Primary structure, conformation in aqueous solution, and intestinal immunomodulating activity of fucoidan from two brown seaweed species Sargassum crassifo-lium and Padina australis. *Carbohydr. Polym.* **2016**, *147*, 69–78. [CrossRef]
13. Ale, M.T.; Mikkelsen, J.D.; Meyer, A.S. Important Determinants for Fucoidan Bioactivity: A Critical Review of Structure-Function Relations and Extraction Methods for Fucose-Containing Sulfated Polysaccharides from Brown Seaweeds. *Mar. Drugs* **2011**, *9*, 2106–2130. [CrossRef] [PubMed]
14. Wang, W.; Wang, S.-X.; Guan, H.-S. The Antiviral Activities and Mechanisms of Marine Polysaccharides: An Overview. *Mar. Drugs* **2012**, *10*, 2795–2816. [CrossRef] [PubMed]
15. 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 experi-mental results. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 6744–6752.
16. 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. *Antivir. Res.* **2011**, *92*, 237–246. [CrossRef] [PubMed]
17. Schütz, 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 epi-thelial cultures. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2021**, *320*, 750–756. [CrossRef]
18. Buck, C.B.; Thompson, C.D.; Roberts, J.N.; Muller, M.; Lowy, D.R.; Schiller, J.T. Carrageenan is a potent inhibitor of papillo-mavirus infection. *PLoS Pathog.* **2006**, *2*, 69. [CrossRef]
19. Luo, Z.; Tian, D.; Zhou, M.; Xiao, W.; Zhang, Y.; Li, M.; Sui, B.; Wang, W.; Guan, H.; Chen, H.; et al. lamb-da-carrageenan P32 is a potent inhibitor of rabies virus Infection. *PLoS ONE* **2015**, *10*, 0140586. [CrossRef] [PubMed]
20. 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 lamb-dacarrageenan against influenza viruses and severe acute respiratory syndrome coronavirus 2. *Sci. Rep.* **2021**, *11*, 821. [CrossRef]
21. Talarico, L.B.; Damonte, E.B. Interference in dengue virus adsorption and uncoating by carrageenans. *Virology* **2007**, *363*, 473–485. [CrossRef]
22. Morokutti-Kurz, M.; Graf, C.; Prieschl-Grassauer, E. Amylmetacresol/2,4-dichlorobenzyl alcohol, hexylresorcinol, or carra-geenan lozenges as active treatments for sore throat. *Int. J. Gen. Med.* **2017**, *10*, 53–60. [CrossRef]
23. 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. [CrossRef] [PubMed]
24. 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. [CrossRef] [PubMed]
25. Hardouin, K.; Bedoux, G.; Burlot, A.S.; Donnay-Moreno, C.; Bergé, J.P.; Nyvall-Collén, 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. [CrossRef]
26. 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. [CrossRef] [PubMed]
27. Morán-Santibañez, K.; Cruz-Suárez, L.E.; Ricque-Marie, D.; Robledo, D.; Freile-Pelegrín, Y.; Peña-Hernández, M.A.; Rodríguez-Padilla, C.; Trejo-Avila, L.M. Synergistic effects of sulfated polysaccharides from Mexican seaweeds against measles virus. *Biomed. Res. Int.* **2016**, *2016*, 8502123. [CrossRef] [PubMed]
28. Aguilar-Briseño, J.A.; Cruz-Suárez, L.E.; Sassi, J.F.; Ricque-Marie, D.; Zapata-Benavides, P.; Mendoza-Gamboa, E.; Rodríguez-Padilla, C.; Trejo-Avila, L.M. Sulphated polysaccharides from Ulva clathrata and Cladosiphon okamuranus sea-weeds both inhibit viral attachment/entry and cell-cell fusion, in NDV infection. *Mar. Drugs* **2015**, *13*, 697–712. [CrossRef]
29. 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. [CrossRef]
30. 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. [CrossRef]
31. Jiao, G.; Yu, G.; Wang, W.; Zhao, X.; Zhang, J.; Ewart, S.H. Properties of polysaccharides in several seaweeds from Atlantic Canada and their potential anti-influenza viral activities. *J. Ocean Univ. China* **2012**, *11*, 205–212. [CrossRef]