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Proceeding Paper

Direct and Indirect Effects of Fucoidans as Enhancers of Immunity against Viral Infections: Main Factors Affecting Its Effectiveness †

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Abstract: It is imperative to know how the physical and biological properties affect the survival of pathological organisms, in that way allowing not only to predict their pathological condition, as also the best strategy to prevent it. In this scope, hydrated biological matrices are widely distributed in nature, and understanding the complexity and functionality of such systems has been improving greatly in recent years, particularly considering their potential action over the physical and biological conditions of pathogens. Therefore, it is of great interest to understand the best way to model and study polymer-based systems, such as those represented by hydrocolloids. Besides selecting the best hydrocolloid for a given purpose, as well as the most suitable source under a specific set of circumstances, defining the optimal operational conditions and best chemical and structural features, represent determinant factors. To validate this assumption, different studies employing fucoidan as a potential antiviral were compared. Considering the analysed reports, it was possible to conclude that the antiviral activity of fucoidan depends mainly on the degree of sulfation, molecular weight, natural sources from which it is obtained, purity, monosaccharide structure and extraction methodology (2,3). In either case, fucoidan can be highlighted as promising candidate as a starting material for new natural-based antiviral drug design, meeting some of the current consumers' demands.

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1. Occurrence of Fucoidans in Seaweeds

Seaweeds (a.k.a., macroalgae) are distributed in phyla Chlorophyta (green algae), Rhodophyta (red algae) and Phaeophyta (brown algae). Fucoidan polysaccharide are produced by different brown algae species such as *Ascophyllum nodosum* (Rajauria et al., 2023), *Cladosiphon okamuranus* (Lim et al., 2019), *Ecklonia cava* (Lee et al., 2022), *Fucus evanescens* (Yuguchi et al., 2016), *Fucus serratus* (Wang et al., 2021), *Fucus vesiculosus* (Flórez-Fernández et al., 2023), *Laminaria japonica* (Zhao et al., 2018a), *Saccharina latissima* (Bruhn et al. 2017), *Saccharina japonica* (Ye et al., 2020), *Sargassum ilicifolium* (Lakshmanan et al. 2022), *Sargassum swartzii* (Dinesh et al., 2016), or *Undaria pinnatifida* (Si et al., 2019), which are characterized as being benthic organisms that preferably strive in temperate and cold coastal ecosystems (Kawai and Henry, 2017). Fucoidans are acknowledged as the major sulfated polysaccharide, often reaching percentages of 30% of the algal dry weight. From the structural point of view, fucoidan is characterized by a backbone of α-(1→3)-L-fucopyranosyl residues with α-(1→3) or α-(1→4) glycosidic bonds positions (Yuguchi et al.,

2016). 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) (Ale et al., 2011; Zhao et al., 2018b).

2. Antiviral Activity of Fucoidan from Different Sources

Fucoidan polysaccharides are located in the cell wall of brown algae, representing a cellular matrix component. Fucoidans from different seaweeds have different bioactivities, but these effects are modulated not only by structural aspects, as also by the employed operational conditions. In what concerns their structure, it has been showed that higher biological activities are usually associated with a high degree of sulfation and low molecular weight. In addition, fucoidans interact with other polymers with long range applications due to the presence of sulfate moieties. This is observed for instance in the interaction between the negatively charged fucoidan sulfate groups and the positively charged glycoproteins of the virus cell envelope, which has the capacity to inhibit virus binding to the host cell, preventing virus replication (Tan et al., 2022). Similarly, inhibit the virus attachment to host cells by interfering with the external viral glycoproteins involved in target-cell attachment, besides increasing the immune system response after being absorbed (Lomartire and Gonçalves, 2022).

Furthermore, besides their natural source and operational set up, the structural complexity of fucoidans depends also on the time of harvest, which influences the biological activity of fucoidans as well (Mensah et al., 2023).

In the specific case of their potential antiviral effects, fucoidans 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 has been developed based in the capacity of algae polysaccharides to inhibit the primary stages (attachment, penetration, uncoating, biosynthesis, viral assembly, and release) of virus life cycle (Pereira et al., 2022).

In fact, different concentrations of fucoidan were reported as being effective against several RNA and DNA viruses, including HIV (by reducing the p24 antigen and reverse transcriptase levels), herpes simplex virus (HSV), influenza A virus (by blocking neuraminidase activity), SARS-CoV-2, hepatitis, bovine viral diarrhea, and human papilloma virus (Dinesh et al., 2016).

Operational Conditions Effect

The antiviral activity of fucoidan (as other polysaccharides) has been associated to the molecules' anionic features, which are linked to virus adsorption inhibition. As previously stated, this activity might be modulated by the selected operational set up, particularly by the performed extraction methodology. When comparing different extraction processes unitary (hot water, subcritical water, ultrasound, microwave, alcalase, cellulase, flavourzyme, and viscozyme) or combined (alcalase-ultrasound, ultrasound-microwave), it was possible to conclude that the antiviral activities of extracts obtained with alcalase, cellulase, flavourzyme, viscozyme and alcalase-ultrasound, were similar to that measured in extracts prepared with hot water. In turn, the antiviral activity was significantly lower in extracts obtained by microwave, ultrasound, subcritical water, and ultrasound-microwave, when compared to hot water extracts. Interestingly, all extracts (except those obtained with subcritical water or ultrasound combined with microwave) showed higher activity against HSV-2 than acyclovir. This is particularly interesting in we take into account that the antiviral activity of fucoidan was not induced by cytotoxicity (there were no effects in cell viability at the concentrations used in the antiviral assays). This finding confirms the ability of the extracted fucoidan to inhibit the early phase of HSV-2 infection, as reported in cited references (Alboofetileh et al., 2019; Shanthi et al., 2021).

3. Conclusions

Fucoidans are being progressively reported for their antiviral activity, which, conjugated with the observed unique antiviral mechanisms and the high availability and low production costs of brown algae, may result particularly profitable. Actually, fucoidans become part of new natural antiviral treatments, even though they possess pros and cons that need to be considered, and that different fucoidan polysaccharides act in a different way depending on its characteristics and the ones of the target virus; another important factor is the purity of fucoidan. Likewise, different extraction methods resulted in obtaining fucoidans with various chemical compositions and molecular weights, despite the high antiviral activity achieved in all cases (as well as lack of acute cytotoxicity). Overall, it is clear that fucoidans possess a broad antiviral spectrum, making brown algae interesting candidates for starting materials in different pharmaceutical applications.

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Conflicts of Interest:

References

1. Alboofetileh, M.; Rezaei, M.; Tabarsa, M.; Rittà, M.; Donalisio, M.; Mariatti, F.; You, S.; Lembo, D.; Cravotto, G. Effect of different non-conventional extraction methods on the antibacterial and antiviral activity of fucoidans extracted from *Nizamuddinia zanardinii*. *Int. J. Biol. Macromol.* **2019**, *124*, 131–137.
2. Ale, M.T.; Mikkelsen, J.D.; Meyer, A.S. Review of structure-function relations and extraction methods for fucose-containing sulfated polysaccharides from brown seaweeds. *Mar. Drugs* **2011**, *9*, 2106–2130.
3. Bruhn, A.; Janicek, T.; Manns, D.; Nielsen, M.M.; Balsby, T.J.S.; Meyer, A.S.; Rasmussen, M.B.; Hou, X.; Saake, B.; Göke, C.; et al. Crude fucoidan content in two North Atlantic kelp species, *Saccharina latissima* and *Laminaria digitata*-seasonal variation and impact of environmental factors. *J. Appl. Phycol.* **2017**, *29*, 3121–3137.
4. 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.
5. Flórez-Fernández, N.; Pontes, J.F.; Guerreiro, F.; Afonso, I.T.; Lollo, G.; Torres, M.D.; Domínguez, H.; Costa, A.M.R.; Grenha, A. Fucoidan from *Fucus vesiculosus*: Evaluation of the impact of the sulphate content on nanoparticle production and cell toxicity. *Mar. Drugs* **2023**, *21*, 115.
6. Kawai, H.; Henry, E.C. Phaeophyta. In *Handbook of the Protists*; Archibald, J., Simpson, A., Slamovits, C., Eds.; Springer: Cham, Switzerland, 2017; pp. 267–304.
7. Lakshmanan, A.; Balasubramanian, B.; Maluventhen, V.; Malaisamy, A.; Baskaran, R.; Liu, W.-C.; Arumugam, M. Extraction and characterization of fucoidan derived from *Sargassum ilicifolium* and its biomedical potential with in silico molecular docking. *Appl. Sci.* **2022**, *12*, 13010.
8. Lee, H.-G.; Jayawardena, T.J.; Song, K.-M.; Choi, Y.-S.; Jeon, Y.-J.; Kang, M.-C. Dietary fucoidan from a brown marine algae (*Ecklonia cava*) attenuates lipid accumulation in differentiated 3T3-L1 cells and alleviates high-fat diet-induced obesity in mice. *Food Chem. Toxicol.* **2022**, *162*, 112862.
9. Lim, S.J.; Aida, W.M.W.; Schiehser, S.; Rosenau, T.; Böhmdorfer, S. Structural elucidation of fucoidan from *Cladosiphon okamuranus* (Okinawa mozuku). *Food Chem.* **2019**, *272*, 222–226.
10. Lomartire, S.; Gonçalves, A.M.M. Antiviral activity and mechanisms of seaweeds bioactive compounds on enveloped viruses—A review. *Mar. Drugs* **2022**, *20*, 385.
11. Mensah, E.O.; Kanwugu, O.N.; Panda, P.K.; Adadi, P. Marine fucoidans: Structural, extraction, biological activities and their applications in the food industry. *Food Hydrocoll.* **2023**, *142*, 108784.
12. Pereira, C.S.G.P.; Prieto, M.A.; Oliveira, M.B.P.P. Algal-Derived Hydrocolloids with Potential Antiviral Activity: A Mechanistic Approach. *Biol. Life Sci. Forum* **2022**, *18*, 23.
13. Rajauria, G.; Ravindran, R.; Garcia-Vaquero, M.; Rai, D.K.; Sweeney, T.; O'Doherty, J. Purification and molecular characterization of fucoidan isolated from *Ascophyllum nodosum* brown seaweed grown in Ireland. *Mar. Drugs* **2023**, *21*, 315.

14. Shanthi, N.; Arumugam, P.; Murugan, M.; Sudhakar, M.P.; Arunkumar, K. Extraction of fucoidan from *Turbinaria decurrens* and the synthesis of fucoidan-coated AgNPs for anticoagulant application. *ACS Omega* **2021**, *46*, 30998–31008.
15. Si, H.; Koh, A.; Jun Lu, Zhou, W. Structure characterization and antioxidant activity of fucoidan isolated from *Undaria pinnatifida* grown in New Zealand. *Carbohydr. Polym.* **2019**, *212*, 178–185.
16. Tan, M.; Gorji, M.; Toh, J.; Park, A.; Li, Y.; Gong, Z.; Li, D. Fucoidan from *Fucus vesiculosus* can inhibit human norovirus replication by enhancing the host innate immune response. *J. Funct. Foods* **2022**, *95*, 105149.
17. Wang, F.; Xiao, Y.; Neupane, S.; Ptak, S.H.; Römer, R.; Xiong, J.; Ohmes, J.; Seekamp, A.; Fretté, X.; Alban, S.; et al. Influence of fucoidan extracts from different *Fucus* species on adult stem cells and molecular mediators in in vitro models for bone formation and vascularization. *Mar. Drugs* **2021**, *19*, 194.
18. Ye, J.; Chen, D.; Ye, Z.; Huang, Y.; Zhang, N.; Lui, E.M.K.; Xue, C.; Xiao, M. Fucoidan Isolated from *Saccharina japonica* Inhibits LPS-Induced Inflammation in Macrophages via Blocking NF-κB, MAPK and JAK-STAT Pathways. *Mar. Drugs* **2020**, *18*, 328.
19. 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 crassifolium* and *Padina australis*. *Carbohydr. Polym.* **2016**, *147*, 69–78.
20. Zhao, D.; Xu, J.; Xu, X. Bioactivity of fucoidan extracted from *Laminaria japonica* using a novel procedure with high yield. *Food Chem.* **2018**, *245*, 911–918.
21. Zhao, Y.; Zheng, Y.; Wang, J.; Ma, S.; Yu, Y.; White, W.L.; Yang, S.; Yang, F.; Lu, J. Fucoidan extracted from *Undaria pinnatifida*: Source for nutraceuticals/functional foods. *Mar. Drugs* **2018**, *16*, 321.