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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 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, immunomodulatory effects. Also, 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.

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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, in turn, are formed by linear chains of α-D-galactose (Al-Alawi et al., 2011).

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 (Garcia-Jimenez et al., 2020).

The carrageenans with highest commercial relevance, are kappa (κ), naturally abundant, for instance, in *Kappaphycus alvarezii* and several *Eucheuma* species (Rudke et al., 2020); iota (ι), found in high percentages in *Eucheuma denticulatum* (Jönsson et al., 2020) and lambda (λ), abundant, among other red algae, in *Gigartina skottsbergii* and *Chondrus crispus* (Zhu et al., 2018; Muthukumar et al., 2021).

Aside from carrageenan, agar is also common in red macroalgae. Agar comprises two polysaccharides, agarose and agaropectin, and it is particularly abundant in genera *Gelidium* and *Gracilaria*. From the 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 (Usov, 2011; Lee et al., 2017).

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 (Lahaye and Robic, 2007). 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 (Kim, 2015). 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) (Kidgell et al., 2019).

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 (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).

Fucus evanescens and *Ascophyllum nodosum* are typical sources of fucoidan (Yuguchi et al., 2016).

2. Antiviral Activity of Algae-Derived of Sulfated Polysaccharides

Owing 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 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 (Wang et al., 2012).

2.1. Antiviral Activity of Red Macroalgae Sulfated Polysaccharides

Probably 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 (Perino et al., 2019). Kappa-(κ-)carrageenan, particularly low-molecular weight forms, showed capacity to inhibit viral replication, either by blocking adsorption to the surface, as well as inhibiting protein expression (Wang et al., 2011). This action was reported in different viral species, such as influenza virus (Wang et al., 2011), SARS-CoV-2 (Schütz et al., 2021), HSV-2 and HPV16 (Buck et al., 2006).

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 (Luo et al., 2015), influenza, SARS-CoV-2 (Jang et al., 2021), different herpes virus (Jang et al., 2021), and dengue virus (Talarico and Damonte, 2007).

Iota-(ι-)carrageenan's antiviral activity has also been well documented, especially against respiratory viruses (Morokutti-Kurz et al., 2017). Likewise, it seems to contribute to neutralize SARS-CoV-2, particularly because of positively charged regions on the glycoprotein envelope and protein aggregation in host cells surface (Hassanzadeh et al., 2020).

Additionally, galactans show good antiviral activity against herpes simplex virus (HSV), dengue virus, hepatitis A virus and HIV (preventing the interaction between HIV gp120 and the CD4+ T-cell receptor) (Ahmadi et al., 2015).

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 (Hardouin et al., 2016), for instance by preventing the infection and replication of vesicular stomatitis virus (Chi et al., 2016), reducing the formation of syncytia in measles virus (Morán-Santibañez et al., 2016), inhibiting cell-to-cell fusion in Newcastle disease virus (Aguilar-Briseño et al., 2015), or downregulating protein synthesis in HSV (Lopes et al., 2017).

2.3. Antiviral Activity of Sulfated Brown Macroalgae Polysaccharides

Due to its abundance in these algae species, fucoidan is the most commonly studied polysaccharide, having already 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 (Dinesh et al. 2016; Jiao et al., 2012).

3. Conclusion

Comparing the algae species referred herein, 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 higher extension. Independently of algae source, sulfated polysaccharides showed activity against various DNA and RNA viruses. The associated antiviral mechanisms as well as corresponding effectiveness appear to 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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