



Therapeutic activity of fucoidan and carrageenan as marine algal polysaccharides against viruses

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Abstract

Marine resources are today a renewable source of various compounds that are used in numerous industries. In recent years, considerable attention has been focused on diverse algae or their metabolites to develop several novel bioactive substances. Algae derivatives are defined as a food or part of food that has health benefits and prevention or treatment of disease. Algal sulfated polysaccharides have a high potential as a source of functional ingredients with a wide range of applications in the food and pharmaceutical industries. Fucoidan and carrageenan, as two main seaweed sulfated polysaccharides, possess numerous biological properties. These polysaccharides are highly valuable in food and healthy immune system diet and also can be applied in the pharmaceutical field. They have shown antiviral activity against SARS-CoV-2 causes COVID-19 infection by preventing virus entry into the cell or interfering with viral replication. Thus, they may provide some novel ingredients for the production of healthy functional foods, antiviral supplement formulations, or algal-based treatments for viral respiratory diseases, especially anti-COVID-19 and recommend solutions to this global health problem in the future. This article provides a review of recent researches on immune-boosting food ingredients, the antiviral activity of algae bioactive compounds, fucoidan, and carrageenan, in particular against SARS-CoV-2.

Keywords Seaweed · Fucoidan · Carrageenan · Antivirus activity · Functional foods · SARS-CoV-2

Introduction

Diet and food as a source of nutrients have a crucial effect on human body function and health (Bilandžić et al. 2014). Thus, incorporating specific foods into the diet may strengthen a person's immune response and prevent or delay chronic diseases (Kamyari et al. 2021). Since oxidative

stress is involved in several diseases, the consumption of food products with antioxidant and anti-inflammatory ingredients can improve human health and the immune system. Usually, healthy foods contain omega-3 fatty acids, vitamins, minerals, and, dietary fibers (Arshad et al. 2020; Iddir et al. 2020).

Edible seaweeds have become a good source of food and alternative bioactive compounds with many industrial applications in food, cosmetics, and pharmaceuticals (Khalid et al. 2018). Algal bioactive compounds have attracted much attention in the development of functional foods and nutraceutical industries. Many reports have been published about isolated compounds from seaweeds with biological activities, demonstrating their ability to produce metabolites that can be used in functional foods, marine-based drugs and health products (Alam et al. 2021). Moreover, the industrial application of the carbohydrate isolated from macroalgae including agar and carrageenan is well known (Khalid et al. 2018). Polysaccharides are the most important compounds present in seaweeds and are well documented for their biological activities. Some seaweeds that have a large amount of polysaccharides are *Ascophyllum*, *Porphyra*,

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and *Palmaria* species. The important polysaccharides are ulvan from green seaweeds, fucoidan, alginate, and laminarin from brown seaweeds, agar, and carrageenan from red macroalgae. Two main seaweed sulfated polysaccharides, fucoidan and carrageenan possess several biological activities such as anti-cancer, anti-coagulant, antioxidant, anti-inflammation, anti-hyperglycemia, and immunoregulatory activities (Moosavi-Nasab et al. 2020; Pangestuti and Kim 2014; Wang et al. 2019). Recently, studies have been focused on novel pharmaceuticals bioactive substances from algae, in particular those with antiviral attributes which may be useful for protection against COVID-19 (Alam et al. 2021).

SARS-CoV-2, the causative agent of COVID-19 infection, is a positive-sense, single-stranded RNA (+ ssRNA) virus with 26–32 kilobase length. Coronavirus attacks the respiratory system and primarily locates at the nasal cavity and nasopharynx and according to the last studies, the disease severity is depending on high viral load and a long virus-shedding period (Bansal et al. 2020; Tsukagoshi et al. 2021). Because of the lower availability of vaccines and definitive treatment, a helpful way to strengthen the immune system against coronavirus is eating a diet high in immune-boosting nutrients that can be an active role in maintaining health and wellness (Singh et al. 2020). Indeed, foods and their ingredients can improve the body's immune system against viruses. There are some possible bioactive compounds with the antiviral activity which can be useful against coronavirus via prevention of the viral spike (S) protein binding to host cell receptor, viral RNA replication or inhibition of protease activity and limitation of angiotensin I converting enzyme 2 (ACE2) activity (Galanakis et al. 2020). There are some important nutrients and natural ways to stimulate the immune system with foods; thus, several studies suggested the consumption of healthy foods or drinks with immune-boosting and taking essential vitamins such as vitamin A, B and C (Singh et al. 2020).

Particularly, due to virus mutation, cause the world to face "infecting outburst" crisis that virus infection worldwide spreads, improving the immune system with healthy foods is crucial. Thus, in this study, the role of fucoidan and carrageenan on immune-boosting and their antiviral activity, in particular, anti-SARS-CoV-2 activity will be reviewed which are applicable in functional foods, supplements, and pharmaceutical industries.

Algae as nutraceutical/functional foods

Bioactive compounds are the primary or secondary metabolites with pharmacological effects on metabolism and health in general (Torregrosa-Crespo et al. 2018). Seaweeds or their extracts are rich in metabolites such as proteins, vitamins, polyunsaturated fatty acids, and antioxidants that could be

mined to produce several valuable ingredients for a wide range of commercial industries.

Several studies have reported that algae bioactive compounds possess biological activities. Thus, the utilization of algae for the recovery of functional substances, nutraceuticals, and pharmaceuticals for incorporation into highly value-added products and functional foods has attracted much attention (Bhattacharjee 2016; Moosavi-Nasab et al. 2019; Rengasamy et al. 2020). The use of seaweeds as a food source has been traced back to the fourth century in many parts of Asia and their medicinal uses are even mentioned since prehistoric times. Seaweeds are increasingly used for their seaweed-derived food hydrocolloids (Ale and Meyer 2013). The most common traditional utilization of algal polysaccharides is their use as a source of the texturing ingredient in food industries. However, they have been studied as an important bioresource in the recovery of marine functional ingredients, because they exhibit several biological and physiological characteristics with health benefits (Mišurcová et al. 2014) such as antioxidant and anti-inflammatory (Moosavi-Nasab et al. 2020), antidiabetic and anti-obesity (Oliyai et al. 2020; Oliyai et al. 2021), and anticancer (Liu et al. 2019), etc.

Algae as a source of anti-viral bioactive compounds

Recently, the overexploitation of the natural resource with antiviral substances has received more attention. There are numerous researches that recommended the antiviral activity of algal substances such as seaweed polysaccharides (Chi et al. 2020; Diogo et al. 2015; Elizondo-Gonzalez et al. 2012; Gomaa and Elshoubaky 2016), phlorotannins (Park et al. 2013), cyanovirin-N (Rui et al. 2008), proteins such as lectin (Hwang et al. 2020; Lee 2019; Mu et al. 2017), phyco-biliproteins (Abd El Hamid et al. 2019), and cyanobacteria such as *Spirulina* with the potential of using for stimulating the immune system and acting as antivirus against COVID-19 by inhibition of TNF- α secretion during cytokine storm therapy (El-Sheekh and Abomohra 2020; Singh et al. 2020; Tzachor et al. 2021). There is little information about the anti-COVID 19 activity of the other algal bioactive compounds. Mostly, sulfated polysaccharides, in particular, fucoidan and carrageenan, were investigated. However, it has recently been reported that the *Spirulina* (Ratha et al. 2020) and *Spirulina* peptides (MubarakAli et al. 2021) possess the inhibitory effect on COVID-19 by binding to the spike protein. Moreover, phlorotannins are promising antiviral compounds. For instance, dieckol, isolated from *Ecklonia cava*, showed the SARS-CoV 3CLpro trans-/cis-cleavage inhibitory activity against in silico model (Ugur et al. 2021).

Algal sulfated polysaccharides

Seaweeds are rich in sulfated polysaccharides, which are valuable additives or ingredients because of their biological attributes. Sulfated polysaccharides are complex groups of polymers with an average molecular weight of 20,000–200,000 Da (Je et al. 2021) and are commonly found in different species of three major groups of seaweeds such as red, green, and brown algae. The chemical structure of sulfated polysaccharides is variable and dependent on seaweed species (Manlusoc et al. 2019). The main sulfated polysaccharides found in seaweeds include agar and carrageenan from red algae, fucoidan from brown algae, and ulvan from green seaweeds (Ngo and Kim 2013). The antiviral potential of sulfated polysaccharides, in particular, fucoidan and carrageenan, has been acknowledged in the past decade. Fucoidan is a non-toxic sulfated polysaccharide and has been approved by Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS) category and can be used in food ingredients at levels up to 250 mg/day (Citkowska et al. 2019). Carrageenan also is an important water-soluble sulfated polysaccharide from red seaweeds (Rhodophyta) which can be marketed as a green product and has been used extensively in foods, cosmetics, and pharmaceuticals. Carrageenan and its derivatives have unique characteristics such as biocompatibility and biodegradability and possess reactive functional groups that make them useful in different areas of applications that are mainly related to their anionic nature (Khan et al. 2020; Pacheco-Quito et al. 2020; Pangestuti and Kim 2014).

Fucoidan

Fucoidan, as one of the most abundant seaweed sulfated polysaccharides, is localized in the cell walls and extracellular of brown seaweeds (Phaeophyceae) such as *Fucus*, *Ascophyllum*, *Saccharina*, and *Sargassum*. This polysaccharide is widely distributed in more than 265 genera and 2040 species of marine invertebrates such as sea cucumbers (Moosavi-Nasab et al. 2020; Zayed and Ulber 2020). The structure and composition of the purified fucoidan are mostly influenced by the extraction techniques used or the seaweed species. It is reported that the antiviral activity of fucoidan is mostly related to the molecular weight and sulfated groups (Wang et al. 2020; Zayed et al. 2020). From the structural point of view, fucoidan is the most abundant naturally occurring sulfated polysaccharide composed of (1–3)- and (1–4)-linked α -L-fucopyranose units and has sulfate groups at the C-2, C-4, or both positions (Fig. 1). The main repeating unit of the fucoidan chain could be altered by the insertion of different monosaccharide units such that mannose, galactose, glucose, xylose, etc. Depending on its source, fucoidan exists in different heterogeneous forms

which differ in their arrangement of the sulfated group, molecular weight, and monosaccharide composition (Fernando et al. 2020; Jayawardena et al. 2019) affecting the fucoidan biological activities (Jayawardena et al. 2019). Moreover, the fucose content is dependent on the origin of algae, the time of harvest, and the species of algae (Jin et al. 2013). According to different extraction methods, the molecular weight of fucoidan products can be divided into low molecular weight (< 10 kDa), middle molecular weight (10–10,000 kDa), and high molecular weight (> 10,000 kDa) (Van Weelden et al. 2019). In addition, structure–activity relationships of bioactivities of polysaccharides are crucial because their biological activities greatly depend on their structural properties such as molecular weight and chain conformation. Thus, the modifications can exert their effect obtaining better functions with a wide range of utilization in the production of functional foods (Xu et al. 2018). Therefore, several modifications of original fucoidan such as fractionation, depolymerization and over-sulfation were evaluated through enzymatic, chemical, or physical methods (Zayed and Ulber 2020). Furthermore, seaweed species, environmental factors affecting the growth of the seaweeds and harvesting quality, processing extraction, and storage are critical for final fucoidan attributes (Flórez-Fernández et al. 2020; Zhao et al. 2018). Usually, the bioactivities of fucoidan are related to its chemical structural make-up of monosaccharides' composition and substituted functional groups which are differentiated by methylation analysis, Fourier-transform infrared spectroscopy, and Nuclear magnetic resonance (Fernando et al. 2020). Fucoidan has shown a broad spectrum of biological properties (Fig. 2) including antimicrobial (Poveda-Castillo et al. 2018), anti-coagulant (Guan et al. 2020), antioxidant (Koh et al. 2019), anti-inflammatory (Ni et al. 2020a, b), anti-virus (Sun et al. 2018), wound healing (Park et al. 2017), bone regeneration (Kim et al. 2018), and immunomodulatory activities beneficial for the pharmaceutical, cosmeceutical, nutraceutical, and functional food industries (Fernando et al. 2020). In addition, fucoidan has been shown the anticarcinogenic properties in breast and colon cancer cells (He et al. 2019), PC-3 and U-145 prostate cancer cells (Boo et al. 2013; Choo et al. 2016), lung cancer (Wu et al. 2020). Moreover, the antiviral attributes of fucoidan (Alboofetileh et al. 2019; Krylova et al. 2020; Ponce et al. 2019) make it of great interest to isolate from various brown macroalgae.

Carrageenan

Carrageenan is a water-soluble sulfated polysaccharide derived from red macroalgae including *Chondrus*, *Hypnea*, *Gigartina*, *Euclima*, *Agardhiella*, *Furcellaria*, *Iridaea*, *Sarconema*, and *Solieria* and has a linear chain of partially sulfated galactans (Pacheco-Quito et al. 2020).

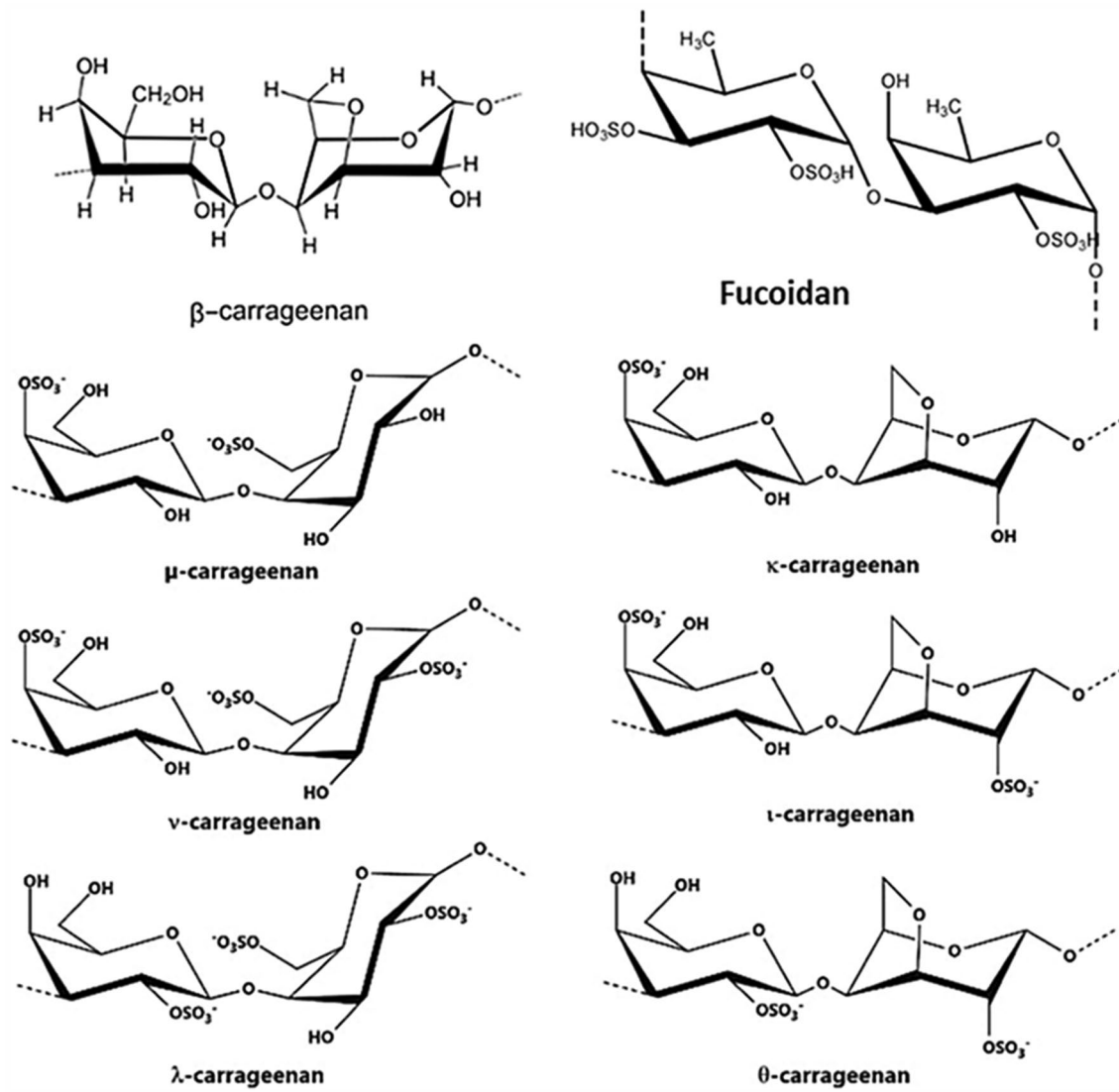
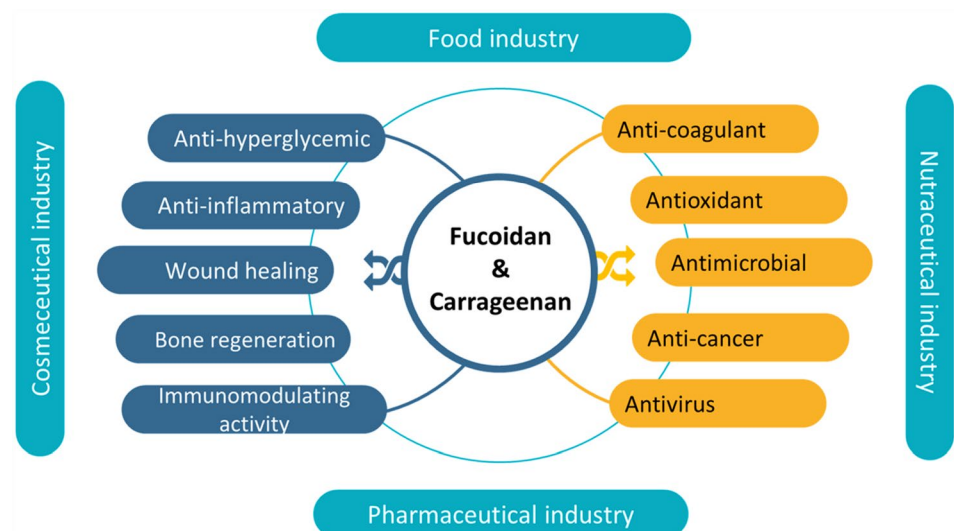


Fig. 1 The structure of fucoidan and carrageenans

Fig. 2 Biological properties of fucoidan and carrageenan



Its molecular weight is typically between a low molecular weight of 20–40 KDa and a high molecular weight of 200–800 KDa depending on the source of algae and preparation (McKim et al. 2019). Based on carrageenan solubility in potassium chloride, it is derived into various types such as kappa (κ), iota (ι), lambda (λ), mu (μ), nu (ν), teta (θ), and beta (β) carrageenan (Fig. 1) of which kappa, iota and lambda are three main carrageenans with the wide range of application in several industries (Geonzon et al. 2020).

κ -carrageenan commercially is extracted from *Kappaphycus alvarezii*, whereas λ -carrageenan is derived from the genera *Gigartina* or *Chondrus*. *Euचेuma denticulatum* is the commercial source for ι carrageenan extraction (Khotimchenko et al. 2020). The chemical structure of carrageenan is made up of repeating units of D-galactose and 3,6-anhydro-galactose (3,6-AG) linked together. α -1,3 and β -1,4-glycosidic and carrageenan forms are different in degree and position of sulfate groups and galactose linkages (McKim et al. 2019). Different types of carrageenans usually possess a sulfated degree of about 22–35% and make them strongly anionic which influences solubility temperature and gel strength. The kappa form is characterized by a repeating unit of 4-sulfate- β -D-galactopyranosyl (1–4)-3,6-anhydro- α -D-galactose-linked (1–3) with ester sulfate and 3,6-AG value of about 25 to 30% and 28 to 35%, respectively. While iota-carrageenan contains a higher ester sulfate level (28–30%) and lower a 3,6-AG content (25–30%) compared with kappa form. Among all, lambda carrageenan contains the highest degree of ester sulfate about 32–39% and has no content of 3,6-AG (Necas and Bartosikova 2013).

Carrageenan is generally utilized as a gel-forming, thickening, stabilizing agent in foods (Pangestuti and Kim 2014), green edible films (da Rosa et al. 2020; Farhan and Hani 2020; Huang et al. 2020; Roy and Rhim 2020), and the encapsulating agent in biomedical applications (Chen et al. 2019; Yew et al. 2020). In addition, carrageenan has achieved the potential therapeutic interest in diseases due to a vast number of biological targets including antioxidant (Rafiquzzaman et al. 2016), anti-hyperglycemic (Sokolova et al. 2014), anti-tumor (Chen et al. 2018; Khotimchenko et al. 2020), anti-cancer (Liu et al. 2019), anticoagulant (Groult et al. 2019), immunomodulating properties (Cicin-skas et al. 2020) and antiviral (Song et al. 2020) properties are illustrated in Fig. 2. Also, several in vitro and in vivo studies have reported that red seaweed polysaccharides can act as prebiotics and effectively regulate the composition of gut microorganisms because several microbial communities are able to digest these dietary fibers. Carrageenan derived from *Kappaphycus alvarezii* exhibited a positive influence on the population of beneficial bacteria such as *Bifidobacterium* (Qiu et al. 2022).

Antiviral mechanism of fucoidan and carrageenan

Different types of fucoidan and carrageenans extracted from brown and red algae possess substantial antiviral activity. Reports are available in either native or chemically modified forms of sulfated polysaccharides against a broad assortment of viruses including influenza A (IAV) and B (IBV), herpes simplex virus (HSV-1 and HSV-2), hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV), and human papillomavirus (HPV). Table 1 describes the antiviral dose and properties of fucoidan. The amount of fucoidan used is varied in different studies.

Algae sulfated polysaccharides have shown their efficacy, particularly strongly toward pathogenic viruses in different phases of virus infection. Indeed, the special structure attributes of sulfated polysaccharides cause antiviral properties via obstruction at different phases of the life cycle of a virus. Virus entry is the initial stage of infection that is the first target of antiviral treatments. Sulfated polysaccharides can cease the virus infection by inhibiting virus adsorption and penetration to the host cell (beginning of the viral cycle). This mechanism of antiviral activity of sulfated polysaccharides occurs by two pathways including (a) directly interacting with the positively charged regions on the surface of the viral envelope and inhibiting of the virus infection ability and killing the virus directly, (b) blocking virus interaction with the receptors via their polyanionic features and preventing to adhere thereto, thus, making them capable of deactivating viruses (Chen et al. 2020; Iravani and Varma 2021). Indeed, polysaccharides should bind to amino acids at the surface of the virus. Thus charge density and structural flexibility of polysaccharides are crucial for interaction with virus S glycoprotein (Song et al. 2020). Partly low-cost preparation and cytotoxicity, a wide range of antiviral activities, and the safety of seaweed sulfated polysaccharides make them superior as a novel drug (Dinesh et al. 2016).

Numerous studies recommend fucoidan as an alternative form of treatment or prophylaxis in cases of viral infection (Table 1). Different source of fucoidan extract from *Undaria pinnatifida* (Hayashi et al. 2013; Richards et al. 2020; Synytsya et al. 2014), *Kjellmaniella crassifolia* (Wang et al. 2017), *Laminaria japonica* (Makarenkova et al. 2010) has been found to be quite active against IAV via inhibiting virus binding to host cell and replication. Furthermore, inactivation of HIV and prevention of cell-to-cell virus spread by two high molecular weight fucoidans isolated from *Saccharina cichorioides* (α -L-fucan) and *S. japonica* (galactofucan) have been found.

Table 1 The antiviral activity of fucooidan and carrageenan in virus infections

Sulfated polysaccharide	Source	Dose/IC ₅₀ (µg mL ⁻¹)	Disease and Effect of treatment	Selected References
Fucooidan	<i>Undaria pinnatifida</i>	In vivo study with 5 mg day ⁻¹ twice a day for 14 days	Anti-IAV activity Positive effect on production of antigen-specific antibody	Hayashi et al. (2013), Richards et al. (2020), Synnysya et al. (2014)
	<i>Kjellmaniella crassifolia</i>	250 µg mL ⁻¹	Inhibition of virus attachment and blocking virus penetration	Wang et al. (2017)
	<i>Laminaria japonica</i>	50–500 µg mL ⁻¹		Makarenkova et al. (2010)
	<i>Saccharina cichorioides</i> , <i>S. japonica</i>	0.001–100 µg mL ⁻¹	Anti-HIV activity Prevention of attachment and cell-to-cell virus spread	Prokofjeva et al. (2013)
	<i>Sargassum mcclurei</i> , <i>Sargassum polycystum</i> and <i>Turbinara ornate</i>	IC ₅₀ value 0.33–0.7 µg mL ⁻¹	Anti-HCV activity Inhibits virus replication	Thuy et al. (2015)
	<i>Sargassum swartzii</i>	1.56 and 6.25 µg mL ⁻¹		Dinesh et al. (2016)
	<i>Cladosiphon okamuranus Tokida</i>	0.83 g day ⁻¹	Anti-HSV activity	Mori et al. (2012)
	<i>Scytosiphon lomentaria</i>	IC ₅₀ value 0.76–1.34 µg mL ⁻¹	Anti-HSV activity The galactofucan fractions of fucooidan showed the antiviral activity because of the low uronic acid and high sulfate esters content	Ponce et al. (2019)
	<i>Sargassum henslowianum</i>	IC ₅₀ value 0.89 and 0.82 µg mL ⁻¹	Inhibition of virus attachment	Sun et al. (2020)
	<i>Fucus evanescens</i>	In vitro study with 0.25–250 µg mL ⁻¹ In vivo study with 10 mg kg ⁻¹ day ⁻¹	Antivirus activity against HSV, ECHO-1, and HIV-1 Inhibiting virus replication	Krylova et al. (2020)
Carrageenan	Commercial carrageenan	Iota carrageenan	Anti- IAV	Leibbrandt et al. (2010)
	Commercial carrageenan	kappa carrageenan and sulfated derivatives In vivo study with 40 mg kg ⁻¹ d ⁻¹	Inhibition virus replication	Wang et al. (2012)
	Commercial carrageenan	Kappa, acetylated and sulfated derivatives In vivo study with 30 mg kg ⁻¹ day ⁻¹		Tang et al. (2013)
	Commercial carrageenan	Lambda carrageenan IC ₅₀ 1–20 ng mL ⁻¹	Anti- HPV potential Inhibition of virus attachment and blocking virus penetration	Rodríguez et al. (2014)
	<i>Gigartina skottsbergii</i>	Lambda carrageenan IC ₅₀ 0.52 and 10.42 for BoHv-1 and SuHV-1, respectively	BoHV-1 and SuHV-1 Inhibition of virus attachment and blocking virus penetration	Diogo et al. (2015)
	<i>Stenogramme interrupta</i>	Kappa/itoa and lambda carrageenan 0.65–2.88 µg mL ⁻¹	Anti-HSV activity Inhibition of virus attachment and blocking virus penetration	Cáceres et al. (2000)
	<i>Gigartina skottsbergii</i>	Lambda carrageenan 10 mg mL ⁻¹	Interfere with protein binding to the heparan sulfate co-receptor in host tissues	Carlucci et al. (2004)
	<i>Gigartina atpurpurea</i>	Kappa and lambda carrageenan 0.2–0.8 µg mL ⁻¹		Harden et al. (2009)
	<i>Solieria chordalis</i>	Iota carrageenan 3.2–54.4 µg mL ⁻¹		Boulho et al. (2017)
	<i>Solieria filiformis</i>	Iota carrageenan 4.5–11.7 µg mL ⁻¹		Ana et al. (2021)

The scientific names of species for algae should be italic

These two fractions were the most effective inhibitors at a concentration of 0.001–100 $\mu\text{g mL}^{-1}$ and did not exert cytotoxicity at concentrations up to 100 $\mu\text{g mL}^{-1}$ (Prokofjeva et al. 2013). A similar anti-HIV activity was observed by fucoidan extracted from *Sargassum mcclurei*, *Sargassum polycystum*, and *Turbinara ornate* with a mean IC_{50} value of 0.33–0.7 $\mu\text{g mL}^{-1}$ (Thuy et al. 2015) and two fucoidan fractions FF1 (45 kDa) and FF2 (30 kDa) isolated from *Sargassum swartzii* with no toxicity up to 1000 $\mu\text{g mL}^{-1}$ (Dinesh et al. 2016). It has been proposed that the fucoidan derived from *Kjellmaniella crassifolia* inactivates virus particles via binding to neuraminidase and block the release of viral particles. The viral neuraminidase protein is responsible for IAV entry into the host cells and the release process of the virus from the cells. Thus, the inhibition of the cellular EGFR pathway and neuraminidase is a useful therapeutic pathway for IAV disease. Fucoidan inhibits the EGFR pathway via interfering with the activation of EGFR, PKC α , NF- κ B, and Akt (Wang et al. 2017). Furthermore, fucoidan derived from *Cladosiphon okamuranus Tokida* has a positive effect on HCV treatment at 0.83 g day^{-1} and interference virus replication. Direct antiviral activity of fucoidan is related to its interaction with the virus envelope glycoprotein. Moreover, fucoidan indirectly inhibits anti-HCV activity by reducing the RNA replication and serum α -interferon (IFN α levels in FLR3-1 replicon cells and serum alanine aminotransferase levels (Mori et al. 2012). Li et al. (2017) found that fucoidan from *Fucus vesiculosus* has an HBV replication suppressive effect by limiting the HBsAg and ABeAg expression and secretion. Moreover, fucoidan has a positive effect on inhibition of HBV DNA replicative intermediates in a dose-dependent manner. Indeed, fucoidan exhibits the anti-HBV activity and virus replication via activation of MEK-ERK pathway and treatment with 100 $\mu\text{g/ml}$ of fucoidan enhanced the level of phosphorylated ERK in hepatocytes. Fucoidan also promotes the type I interferon response by activation of interferon regulatory factor 3 (IRF3) and IRF7.

A recent study revealed that fucoidan extracted from *Scytosiphon lomentaria* showed anti-HSV-1 and anti-HSV-2 with no cytotoxicity up to 1000 $\mu\text{g mL}^{-1}$ ($\text{CC}_{50} > 1000 \mu\text{g mL}^{-1}$). Indeed, the galactofucan fractions of fucoidan offer antiviral activities against the herpes simplex virus. Galactofucan exhibits antiherpetic property with high selectively against HSV and its activity is due to the low uronic acid and high sulfate ester content of galactofucan (Ponce et al. 2019). Given the lack of antiviral activity of uronic acid, fractions with higher content of sulfate groups exhibit stronger anti-HSV activity (Sun et al. 2020). In parallel to this investigation, two fractions of fucoidan SHAP-1 and SHAP-2 isolated from *Sargassum henslowianum* have shown inhibition toward the HSV-1 on Vero- cells with

the IC_{50} value 0.89 and 0.82 $\mu\text{g mL}^{-1}$, respectively. They claimed that the SHAP-1 and SHAP-2 interfere at the first phase of infection and destructive virus adsorption to the host cell surface. Indeed, sulfate ester content and galactofucan fractions are key factors in the virucidal activity of fucoidan. In addition, depending on the number and position of the sulfate groups, sulfated polysaccharides exhibit different levels of antiviral activity. The backbone of fucoidan consists of α -(1 \rightarrow 3)-linked L-Fucp with sulfate groups on the C-2 and C-4 positions that are responsible for the high anti-HSV activity of SHAP-1 and SHAP-2 (Sun et al. 2020). Recently, native and enzymatic modified fucoidans from *Fucus evanescens* were evaluated for antiviral activity against HSV-1, HSV-2, enterovirus (ECHO-1), and HIV-1 in Vero and human MT-4 cell lines. The in vitro assay revealed the beneficial effects of both types of fucoidan against HSV-1, HSV-2, ECHO-1, and HIV-1 by inhibiting virus replication in different phases of pretreatment of cells, pretreatment of the virus, simultaneous treatment, and treatment of infected cells. These studies suggested that the main target for antiviral action of fucoidan is virus adsorption. Treatment with fucoidans causes increase in the resistance to virus infection (preventive effect), directly affects virus particles (virucidal effect), and inhibits the early stage of virus replication (virus-inhibiting effect). Indeed, the primary mechanism of antiviral properties of fucoidan is due to the interaction of sulfated groups of fucoidan with positively charged virus capsid protein and hinders the attachment of the virus to the host cell, consequently suppressing the entry process of the virus. However, both types of fucoidans exhibited potential antiviral activity by downregulation replication of the DNA-containing HSV-1 and HSV-2 (Krylova et al. 2020). Thus, the higher degree of sulfation exhibits more interaction points for inactivating viruses.

Carrageenan has also been used to treat various viral diseases and several studies have described the in vitro or in vivo antiviral activity of carrageenans (Table 1). The antiviral activity of carrageenan is attributed to several factors including the sulfate group distribution in the repeating galactose units, molecular weight, and the interaction with other biomolecules such as proteins and creating complexes with new colloidal entities which causes the inhibition or promotion of carrageenan bioactivity. It has been reported that the low molecular weight of carrageenans has a higher solubility and can easily penetrate cell membranes and, therefore, are more effective in antiviral activity. Sugar composition with the lowest molecular weight may have a synergist influence on the antiviral activity of carrageenan. Furthermore, carrageenan has an influence on different phases of viral infection processes based on its structural diversity and complexity (Ana et al. 2021). Leibbrandt et al. (2010) revealed that the viral infection by influenza A PR8/34 H1N1 virus in a mouse model was reduced upon exposure

to treatment with iota-carrageenan nasal spray. Similarly, Wang et al. (2012) confirmed the antiviral activity of kappa carrageenan against IAV with an inhibition rate of 45–47% at a dose of 40 mg kg⁻¹ day⁻¹ which has a similar concentration of Ribavirin (39.9% inhibition rate). They confirmed carrageenan oligosaccharide with 1–3 kDa molecular weight and sulfated content of 0.8–1.0 mol mole⁻¹ possesses appropriate inhibition of IAV replication in vitro and in vivo. In parallel with this observation, the low molecular weight of kappa carrageenans (3, 5 and 10 kDa) and its acetylated and sulfated derivatives (acetylated degree of 1.0 and sulfation degree of 2.4) showed an inhibitory effect against influenza virus A/FM1/47 (H1N1). As the in vivo study using FM 1-induced pulmonary oedema model exhibited that acetylation significantly enhanced their inhibition activity against influenza virus and both types of kappa carrageenan showed higher antiviral activity compared with Ribavirin at the dose of 30 mg kg⁻¹ daily. Considering that the low molecular weight of carrageenans has a better water solubility, they can be a promising substance against the influenza virus (Tang et al. 2013). The inhibitory effect of κ-carrageenan against H1N1 viruses mainly is in inhibiting the HA binding to Madin-Darby canine kidney cells (MDCK), internalization, downregulation of mRNA, and protein expression without affecting adsorption. The low molecular weight kappa-carrageenan prevents the mRNA transcription via interfering with the polymerase activity while the high molecular weight κ-carrageenan directly blocks the virus attachment to the host cell. However, the antiviral activity of carrageenan is influenced by the sulfation level, molecular weight, the serotype of the virus, and the host cells (Shao et al. 2015). Lambda carrageenan had also been reported for its potent anti-HPV potential in vitro with IC₅₀ 1–20 ng mL⁻¹ and in vivo study (Rodríguez et al. 2014). Similarly, Diogo et al. (2015) reported the potent antiviral efficacy of lambda carrageenan isolated from *Gigartina skottsbergii* against laboratory strains bovine herpesvirus type 1 (BoHV-1) and suid herpesvirus type 1 (SuHV-1). Moreover, the carrageenan derivatives were found to have better antiviral activity.

Some investigations reported anti-HSV-1 activity of kappa/iota and lambda-carrageenan from *Stenogramme interrupta* (Phyllophoraceae) (Cáceres et al. 2000), anti-HSV-2 activity of lambda carrageenans from *Gigartina skottsbergii* (Carlucci et al. 2004), and *Gigartina atpurpurea* (Harden et al. 2009) by the interaction between virus-sulfated polysaccharides and interfering with the attachment of virions to host cells. Cell-to-cell fusion and transmission of HSV-1 infection were also blocked by iota-carrageenan from *Solieria chordalis* at 3.2–54.4 µg mL⁻¹ concentrations without any cytotoxicity (Boulho et al. 2017). Recently, carrageenan-rich enzymatic extracts from *Solieria filiformis* were screened for antiviral activity against HSV-1 and exhibited significant anti-HSV-1 activity at the effective

concentration (EC₅₀) of 4.5 µg mL⁻¹ without toxic effects on cells in in vitro study. These mechanisms of anti-viral activity of carrageenans are mainly related to negatively charged groups of structure that are linked to the positive charges of virus envelop and inhibit the virus attachment to the cell surface and penetration (Ana et al. 2021). Carrageenans inhibit virus infection at different steps of the viral life, from inhibition of initial viral adsorption and entry to the host cell to blocking viral replication. Moreover, carrageenans can suppress the DNA replication of the enveloped virus (HSV-1) significantly rather than non-enveloped RNA virus (ECHO-1). According to the chemical structure of carrageenan, conformation, 3,6-anhydrogalactose, and sulfate group content show different antiviral activity. For instance, carrageenan structure in the configuration of a chaotic coil has more flexibility and provides better attachment to certain viral envelope glycoproteins, which are necessary for the binding the virus to the host cell (Krylova et al. 2022).

Treatment and or prevention of SARS-CoV-2

In the past years, researchers have developed vaccines and medicine such as remdesivir, favipiravir, simeprevir, various monoclonal antibodies, paxlovid, and molnupiravir to prevent the infection or propagation of SARS-CoV-2 (Zhang et al. 2022). Moreover, in vitro anti-SARS-CoV-2 activity of ivermectin, an antiparasitic agent, is reported (Caly et al. 2020). Also, the clinical trials of anti-hepatitis C virus (HCV) activity of Sofosbuvir showed that Sofosbuvir was effective against patients infected with SARS-CoV-2 via RdRp Inhibiting mechanism (Sayad et al., 2020). Despite that the treatment is crucial, especially in the first days, the development of novel drugs for the prophylactic approach is necessary (Zhang et al. 2022). Although the efficacy of these medicines is confirmed, their adverse effects remain unclear. Therefore, promising antiviral bioactive compounds from natural sources need to be developed as safe agents.

Several studies reported that the diverse structure of sulfated polysaccharides has a crucial role in boosting the host antiviral response by interfering with virus attachment, adsorption, and its replication process (Hans et al. 2021). Carrageenans (kappa-, iota- and lambda- carrageenan) are commercially available in the market and used in food products and pharmaceuticals (Pacheco-Quito et al. 2020). Moreover, fucoidan derived from *Undaria pinnatifida* is a commercially available dietary supplement (Richards et al. 2020). Recently, some studies have developed novel nasal sprays formulated with carrageenan, and their clinical investigations suggested their effective antiviral activity in particular against COVID-19. According to the clinical trial studies, lambda-carrageenan nasal spray can decrease the risk of SARS-CoV-2 infection (Moakes et al. 2021).

Anti-SARS-CoV-2 activity

Two main mechanisms of antiviral action of natural compounds include inhibition of interfering virus entry and replication (Fig. 3). First, S glycoprotein is the main antigen on the surface of coronavirus and involves virus attachment and mediating the membrane and membrane fusion to enter a cell. Thus, the antiviral compounds should inhibit the S protein attachment to the host receptor in a dose-dependent manner. Second, the virus proteases such as 3CLpro and PLpro, RdRP, or RNA replicas participate in virus transcription and replication. Therefore, the inhibition of CoV-2 protein such as N and M protein can suppress and block the virus replication (Xian et al. 2020).

SARS-CoV-2 like other viruses circulating in wildlife for human infection initially should encounter humans and a cellular receptor allowing the virus to bind. Recently, it was shown that the SARS-CoV-2 spike protein, binds to the human ACE2 (Bian and Li 2020). The ACE2 is an integral membrane glycoprotein that is known for the highest expression in most tissues such as the kidneys, endothelium, lungs, and heart. According to the structural database of ACE2, besides inhibiting SARS-CoV-2, the inhibition of the ACE2 protein is absolutely necessary to reduce the operability of the host receptor of SARS-CoV-2. If the ACE2 protein is inhibited, it suggests that coronavirus is prevented and treated (Ni et al. 2020a, b).

Some reports have been conducted to investigate the inhibitory activity of fucoidan against HSV1 (Wozniak et al. 2015), IAV (Synytsya et al. 2014), HPIV1 (Sun et al. 2018) and HIV (Dinesh et al. 2016). It is supposed that the sulfate groups in fucoidan structure play a key role in the protective effect against SARS-CoV-2 and these fucoidan-structure polyanions act as receptors for viruses,

subsequently, limiting the connection of the positive part of virus capsid to the host cell receptor, thus inhibiting virus entry and cease the cycle of infection as shown in Table 2 (Dimitrova-Shumkovska et al. 2020).

Kwon et al. (2020) explained the potential of fucoidan fractions to inhibit SARS-CoV-2 attachment and entry. SARS-CoV-2 entry is initiated by the binding of viral S-protein to cell surface receptors. Their results indicated that RPI-27 (MW \approx 100 kDa) and RPI-28 (MW \approx 12 kDa), two complex sulfated polysaccharides (fucoidans), were derived from *Saccharina japonica* functions against SARS-CoV-2. Indeed, RPI-27 with EC₅₀ values of $8.3 \pm 4.6 \mu\text{g}/\text{m}$ was more effective than the antiviral drug remdesivir at $11.4 \mu\text{M}$ in Vero-CCL81 cells. Vero-CCL81 cell was capable to express ACE-2. RPI-28 caused about 75% inhibition of SARS-CoV-2 particle attachment. Indeed, RPI-27 and RPI-28 provide multiple binding groups with virus envelop, thus these two fractions showed a stronger protective effect compared with other polysaccharides tested. Highly branched fucoidan fractions (RPI-27 and RPI-28) contained several binding ligands in chemical structure. However, RPI-27 had higher antiviral activity rather than RPI-28 because RPI-27 possessed higher molecular weight and exhibited more multiple interaction points with the S-protein of the virus (Kwon et al. 2020). According to Song et al. (2020), in an in vitro model of SARS-CoV-2 infection of Vero E6 cells, fucoidan and iota carrageenan demonstrated inhibitory activity at concentrations of $\geq 15.6 \mu\text{g mL}^{-1}$ and $\geq 125 \mu\text{g mL}^{-1}$, respectively. Moreover, the inhibitory property could be related to the sulfate content and among these two sulfated polysaccharides, fucoidan with a higher sulfate group (22.8%) was stronger than iota-carrageenan (10.4%). However, gel-forming iota-carrageenan caused virus aggregation.

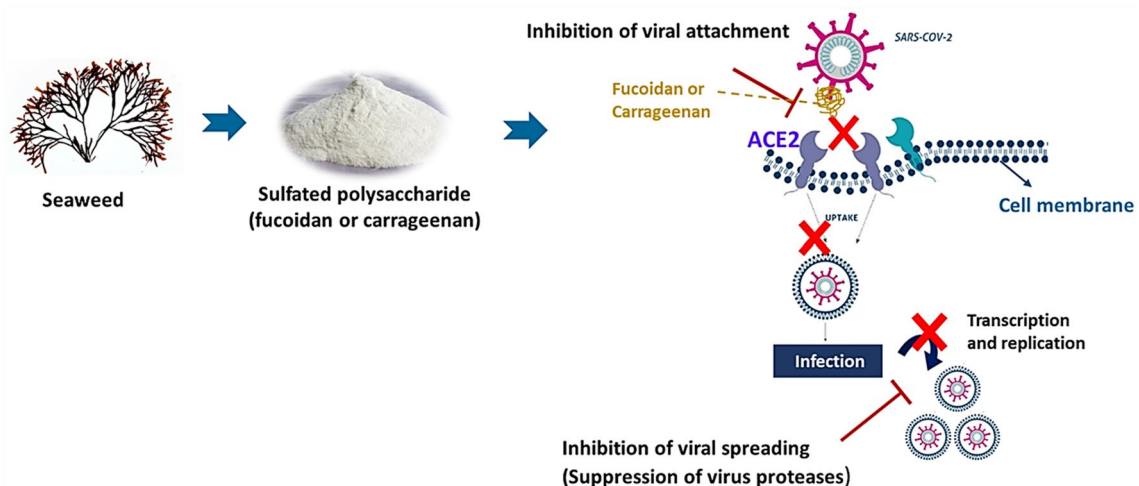


Fig. 3 Antiviral activity of seaweed polysaccharides

Table 2 Anti-SARS-CoV-2 activity of fucoidan and carrageenan

Sulfated polysaccharide	Cell line	Dose ($\mu\text{g mL}^{-1}$)	Mechanism/Results	References
Fucoidan fractions (RPI-27 and RPI-28)	Vero-CCL81	EC ₅₀ values of RPI-27 (8.3 $\mu\text{g mL}^{-1}$)	Inhibiting of viral attachment via binding to the S-protein of SARS-CoV-2	Kwon et al. (2020)
Extracted from <i>Saccharina japonica</i>		RPI-28 (1.2 μM), Remdesivir (11.4 μM)	Fucoidan was more effective than remdesivir	
Commercial fucoidan, iota carrageenan and sea cucumber sulfated polysaccharide (SCSP)	Vero E6 cells	Fucoidan concentration $\geq 15.6 \mu\text{g mL}^{-1}$	Inhibition of virus attachment via binding to S protein of virus	Song et al. (2020)
		Iota-carrageenan concentration $\geq 125 \mu\text{g mL}^{-1}$	Virus aggregation by iota-carrageenan	
			SCSP had highest sulfation degree and inhibitory effect	
			Fucoidan was stronger than iota-carrageenan	
Commercial iota-, kappa- and lambda-carrageenan	SARS-CoV-2 Spike Pseudotyped Lentivirus	Iota carrageenan (10 and 100 $\mu\text{g mL}^{-1}$)	Inhibiting of virus entry and replication	Morokuti-Kurz et al. (2020)
Nasal spray formulated with iota carrageenan and xylitol	Vero E6 cell culture	Kappa- and lambda-carrageenan (100 $\mu\text{g mL}^{-1}$)	Iota carrageenan was more effective than others	
		Iota carrageenan (at least concentration 6 $\mu\text{g mL}^{-1}$) xylitol (50 mg mL^{-1})	Inhibiting of virus entry and replication	Bansal et al. (2020)
Nasal spray formulated with lambda-carrageenan	Madin-Darby canine kidney (MDCK) cells BALB/c mice	EC ₅₀ value of 0.9 $\mu\text{g mL}^{-1}$	Combination of carrageenan and xylitol was more effective	Jang et al. (2021)
Nose and mouth sprays formulated with iota- and kappa- carrageenan	TMPRSS2-Vero E6 cells	Iota carrageenan (1.2 mg mL^{-1}) Kappa-carrageenan (0.4 mg mL^{-1})	Prevention of virus entry and production	Schütz et al. (2021)
Nasal spray formulated with iota-carrageenan and sodium chloride	Calu-3, a human respiratory model cell line	Iota carrageenan (1.7 mg mL^{-1}) and sodium chloride (9 mg mL^{-1})	Decreased viral attachment and entry into target cells because the sulfated polysaccharide mimics cellular heparin sulfates or aggregates viral particles	Varese et al. (2021)
			Inhibiting of viral entry and production	

This efficient blockage of the SARS-CoV-2 spike protein binding to ACE-2 receptor by carrageenan was further confirmed. Morokutti-Kurz, Graf, Grassauer, and Prieschl-Grassauer (2020) described the *in vitro* anti-SARS-CoV-2 activities of carrageenan. They suggested that the iota-carrageenan is a safe compound for the treatment of coronavirus infection because their study revealed the iota-carrageenan interference in SARS-CoV-2 Spike Pseudotyped Lentivirus (SSPL) entry with an IC_{50} value of $2.6 \mu\text{g mL}^{-1}$. Moreover, the same result was obtained against various Rhino- and Coronaviruses. Iota-carrageenan not only exhibited the inhibitory activity against SSPL at $10 \mu\text{g mL}^{-1}$, but also was active at $100 \mu\text{g mL}^{-1}$ concentration. While kappa-carrageenan and lambda-carrageenan were only active at $100 \mu\text{g mL}^{-1}$. Nevertheless, iota-carrageenan had stronger antiviral activity rather than the others (Morokutti-Kurz et al. 2020). Mechanistically, a binding competition between anionic groups of sulfated polysaccharides and cationic regions of virus envelope glycoprotein was proposed as a potential mode of action for SARS-CoV-2 inhibition by carrageenan (Jang et al. 2021).

In addition, the algal-derived nasal spray can be a promising self-administered antiviral spray. *In vitro* study against in Vero cell culture showed the effective reduction in SARS-Cov-2 infection by iota carrageenan at least concentration of $6 \mu\text{g mL}^{-1}$, while antiviral activity could promote by the combination of 5% $m V^{-1}$ xylitol (Bansal et al. 2020). Similarly, Jang et al. (2021) reported potent antiviral activity, the efficacy of lambda-carrageenan against laboratory strains of IAV and IBV viruses, and primary isolation of SARS-CoV-2 with an EC_{50} value of $0.3\text{--}1.4 \mu\text{g mL}^{-1}$ and $0.9 \mu\text{g mL}^{-1}$, respectively. Regarding its cytotoxicity, the CC_{50} concentration for lambda-carrageenan was safe up to $300 \mu\text{g mL}^{-1}$. According to the analysis, lambda-carrageenan treatment induced gene expression reduction of viral proteins and prevention of virus production in Vero cell culture. Interestingly, lambda-carrageenan is composed of (1,3)-linked α -D-galactose-2-sulfated and (1,4)-linked β -D-galactose-2,6,-disulfat units. Lambda-carrageenan is more soluble in cold water compare with kappa- and iota-carrageenan due to its higher sulfate content (32–39% of ester sulfate degree). Thus lambda-carrageenan is a promising antiviral seaweed polysaccharide applicable in nasal spray formulation (Jang et al. 2021).

In order to harness the SARS-Cov-2 inactivating power of algal sulfated polysaccharides, new nasal and oral sprays were formulated by carrageenan. Hui (2020) suggested the povidone-iodine and carrageenan-containing sprays as a promising candidate for chemoprophylaxis and suppression of the coronavirus outbreak. In parallel with this observation, Schütz et al. (2021) applied two types of nose and mouth sprays formulated by iota- and kappa- carrageenan with 1.2 mg mL^{-1} and 0.4 mg mL^{-1} concentration, respectively.

Both types of sprays exhibited the anti-COVID-19 activity because of their polyanionic structure properties. Therefore, using carrageenan-based sprays could be useful to eradicate the COVID-19 pandemic.

Similarly, the *in vitro* respiratory epithelium model treated with nasal spray formulated with iota-carrageenan (1.7 mg mL^{-1}) and sodium chloride showed adequate inhibition against SARS-CoV-2 (Varese et al. 2021).

Clinical trial

There are a few clinical trials about the anti-SARS-CoV-2 activity of carrageenan and fucoidan, while these two sulfated polysaccharides are suitable for anti-COVID-19 researches. The clinical trials of a nasal spray containing carrageenan showed the practical therapeutic against COVID-19. Héctor et al. (2020) showed a decreased coronavirus spread in humans after carrageenan nasal spray administration. A randomized controlled clinical trial was conducted in 2020 in 229 healthy personals (females and males < 40 and > 40–55 years) with no COVID-19 symptoms; some groups consumed one carrageenan spray (containing 0.17 g of carrageenan) into a nostril and the other groups consumed four sprays into the oral cavity after utilization of one drop of ivermectin (0.6 mg mL^{-1}) five times a day for 14 days. This study showed an appropriate dosage of ivermectin and carrageenan and improvement in protection in the subjects treated with ivermectin and carrageenan combination, suggesting the importance of consuming carrageenan spray with such an antiviral drug by coronavirus patients. Furthermore, Figueroa et al. (2021) found that iota-carrageenan spray possesses an inhibitory effect against SARS-CoV-2. Clinically, 394 hospital personnel were classified into two treatment groups who administrated iota-carrageenan (1.7 g L^{-1}) and placebo four times daily for 21 days. The lower infection rate in the carrageenan treatment group (1%) compared with placebo ones (5%) explained that iota-carrageenan was active against COVID-19. This valuable information proved the potential of carrageenan against COVID-19 and nasal sprays containing carrageenan are approved and available in some countries.

Despite carrageenan being approved by FDA and recognized as safe food additive, some investigations revealed that carrageenan has an adverse effect on the immune system and blood coagulation because of its sulfate groups. In addition, it is reported that exposure of human intestinal epithelial cells to the carrageenan ($1\text{--}10 \text{ mg/l}$) for 1–8 days caused cell death in both primary cells and a cell line (Liu et al. 2015). Furthermore, a considerable amount of research has been conducted on different biological activities and therapeutic potential of fucoidan for the treatment of disease. However, it is difficult to absolutely confirm the beneficial effects of fucoidan because of the different findings in various studies.

Therefore, more investigations are needed to evaluate the side effects of fucoidan on human health in various study models.

Conclusion

It is noteworthy that several recent works have stated that numerous poly sulfated compounds are considered for their inhibitory potential for the virus attachment and replication. In the past decade, sulfated polysaccharides were mainly derived from seaweeds because of their antiviral properties. Several studies confirmed that various fucoidan and carrageenan preparations have been shown to exhibit a wide spectrum of antiviral activity and propose a potential approach to the use of natural seaweed metabolites to tackle the current pandemic SARS-CoV-2. Moreover, seaweed-derived functional foods can provide health benefits by reducing the risk of diseases and enhancing the immune body system, thus improving the quality of life. Thus, promoting the utilization of a healthy diet containing seaweeds or the production of functional foods will be suggested. Considering the role of structural properties of fucoidan and carrageenan, they are highly valuable in face masks and other medical and hygiene materials. Therefore, more attention should be paid to the scale-up of production and application of fucoidan as a novel algal-based medicine.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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