Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The antiviral activity of iota-, kappa-, and lambda-carrageenan against COVID-19: A critical review

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ABSTRACT

Objective: There is no specific antiviral treatment available for coronavirus disease 2019 (COVID-19). Among the possible natural constituents is carrageenan, a polymer derived from marine algae that possesses a variety of antiviral properties. The purpose of this review was to summarize the evidence supporting carrageenan subtypes' antiviral activity against the emerging severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19.

Methods: PubMed/MEDLINE and Google Scholar searches were conducted for publications using the terms 'carrageenan', 'iota carrageenan', 'kappa carrageenan', lambda-carrageenan', 'coronavirus', 'common cold', 'rhinovirus', and 'SARS-CoV-2′ search was also done in grey literature to increase our understanding. A search for the word "carrageenan" was also carried out. Most of the publications were discussed in narrative.

Results: Carrageenan has been shown to have potent antiviral activity against both coronaviruses (coronavirus NL63, SARS-CoV-2) and non-coronaviruses such as dengue virus, herpes simplex virus, cytomegalovirus, vaccinia virus, vesicular stomatitis virus, sindbis virus, human immunodeficiency virus, influenza virus, human papillomavirus, rabies virus, junin virus, tacaribe virus, African swine fever, bovine herpes virus, suid herpes virus, and rhinovirus. No *in vivo* study has been conducted using carrageenan as an anti-SARS-CoV-2 agent. The majority of the *in vivo* research was done on influenza, a respiratory virus that causes common cold together with coronavirus. Thus, various clinical trials were conducted to determine the transferability of these *in vitro* data to clinical effectiveness against SARS-CoV-2. When combined with oral ivermectin, nasally administered iota-carrageenan improved outcome in COVID-19 patients. It is still being tested in clinics for single-dose administration.

Conclusion: Though the carrageenan exhibited potent antiviral activity against SARS-CoV-2 and was used to treat COVID-19 under emergency protocol in conjunction with oral medications such as ivermectin, there is no solid evidence from clinical trials to support its efficacy. Thus, clinical trials are required to assess its efficacy for COVID-19 treatment prior to broad application.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first appeared in late December 2019 in China's Hubei Province, has had a negative impact on the majority of affected countries' national healthcare systems.[1–3] SARS-CoV-2 infection is primarily a respiratory infection.[4,5] However, numerous other organs may also be impacted,[6–8] with numerous unknown consequences.[9–11] Furthermore, the COVID-19 Global cases database indicated that over 136 million confirmed COVID-19 cases had been reported as of April 12, 2021, resulting in 2, 949,409 deaths.[12] The virus spreads quickly in through the world because of its high reproductive number R_0, which is estimated to be $3.25 \leq R0 \leq 3.4$, which means that one infected person can spread the virus to up to three unvaccinated people.[13] The SARS-CoV-2 virus is a member of the *Coronaviridae* family and the *Betacoronavirus* genus.[14,15] SARS-CoV shares 79.6% of its sequence with the virus.[16]

Numerous COVID-19 drug candidates have been proposed, each with a distinct mechanism of action,[14,17–19] including the use of convalescent plasma and interferon, as well as inhibitors of the interleukin 6 receptor, which have the potential to suppress the cytokine storm.[14,20,21] Chloroquine and its hydroxy-form, both of which inhibit viral entry via endocytosis, endosomal acidification, and angiotensin converting enzyme 2 glycosylation, were used to treat COVID-19 [14,22], as well as

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ivermectin, which inhibits viral protein nuclear transport.[18,23] Additionally, antiviral agents that inhibit proteases (e.g., remdesivir) and nucleotide or nucleoside analogs that inhibit viral RNA synthesis have been repurposed for the treatment of SARS-CoV-2 infection.[14,17] Remdesivir has been approved by FDA.[24,25] Corticosteroids, however, have also been shown to be effective against severe and potentially fatal COVID-19 infection and recently have been approved by the World Health Organization.[26,27] Additional sources of drug candidates must be investigated, including natural sources such as carrageenan. Carrageenan is a naturally occurring component of marine algae[28,29] and thus may be a viable alternative source of COVID-19 emergency treatment, as previous research has demonstrated that carrageenan is actively used to treat viruses that cause the common cold.[30–32] Thus, the purpose of this review was to synthesize evidence from *in vitro*, *in vivo*, and clinical trials in order to provide comprehensive information about the possibility of treating COVID-19 patients with carrageenan derived from marine algae.

2. Methods

PubMed/MEDLINE and Google Scholar searches for articles were conducted using the title and abstract terms 'carrageenan', 'iota carrageenan', 'kappa carrageenan', lambda carrageenan', 'coronavirus', and 'SARS-CoV-2'. ClinicalTrials.gov and isrctn.com databases were also searched for recent clinical trials evaluating the efficacy of carrageenan for COVID-19. The publications till April 21, 2021 were then classified and analyzed according to their type of study: *in vitro*, *in vivo*, or clinical trials.

3. Results

3.1. Carrageenan: an overview

Carrageenan is a soluble sulphate galactose polymer derived from the marine alga Rhodophyceae. Its constituents are found in the algae's outer cell wall and intracellular matrix.[33] The galactan backbone of the polymer is synthesized in the Golgi bodies of the cell, while the sulfation step occurs in the cell wall via a sulfotransferase pathway.[33–35] Carrageenan bioactives are polydisperse and have a wide range of molecular weights. It is primarily found in the *Gigartinaceae* and *Solieriaceae* families,[36,37] as well as the *Furcellariaceae*, *Solieriaceae, Phyllophoraceae*, and *Hypneaceae* families.[33,38] Carrageenan is commonly used as an emulsifier, stabilizer, thickener, and gelling agent in topical products, cosmetics, and food preparations due to its emulsifying, stabilizing, thickening, and gelling properties.[39–41] There are three major subtypes of carrageenan: kappa (Fig. 1a), iota (Fig. 1b), and lambda (Fig. 1c), which differ in their location and number of sulphate moieties on the hexose scaffold skeleton and contain one, two, or three negatively charged sulphate ester groups per disaccharide repeating unit, respectively.[42] The US Food and Drug Administration (21 CFR 172.620) has generally recognized its polymer as safe for topical application and consumption.[43] Carrageenan, as a biomolecule, possesses a variety of biological properties, including,[44,45] antioxidant,[46] anti-bacteria,[47] anticoagulant,[48–50] and immunomodulator.[51,52] Numerous reports indicate that carrageenan is also an antiviral, including against respiratory viruses.[53–55]

3.2. In vitro evidence

A study published in 1987 found that iota-carrageenan, a sulphated polysaccharide derived from marine red algae, effectively inhibited several viruses in cultured cells, including African swine fever (ASF), encephalomyocarditis virus (EMC), herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), semliki forest virus (SFV), and Vaccinia.[53] Therefore, it was without effect against adenovirus type 5, measles, polio type 1 and vesicular stomatitis virus.[53] A year later, a

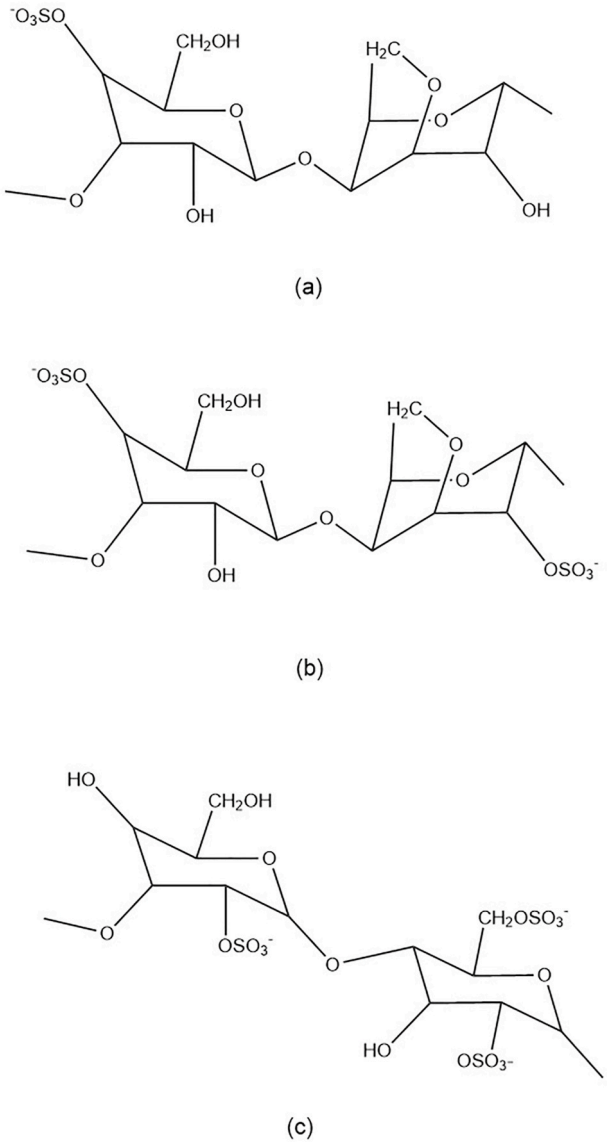

Fig. 1. Representation of the stereo-chemically fundamental carrageenan repeating sequence. (a) Kappa-carrageenan consisted of 4-*O*-Sulfato-beta-D-galactopyranosyl unit and 3,6-Anhydro-alpha- D-galactopyranosyl unit, (b) iota-carrageenan consisted 4-*O*-Sulfato-beta-D-galactopyranosyl unit and 3,6-Anhydro-2-0-sulfato-alpha-D-galactopyranosyl unit, (c) lambda-carrageenan consisted of 2-*O*-Sulfato-beta-D-galactopyranosyl unit and 2,6-Di-*O*-sulfato-alpha-D-galactopyranosyl unit.

study using other types of polyanionic carrageenan including kappa and lambda also showed antivirus properties to HSV-1, HSV-2, cytomegalovirus (CMV), vaccinia, sindbis, and human immunodeficiency virus type 1 (HIV-1).[56] The half-maximal inhibitory concentration (IC_{50}), a concentration of a molecule required to inhibit virus-induced cytopathogenicity by 50%, varied between 0.3 and 12 μg/ml and 0.2–1.9 μg/ml, for kappa-and lambda-carrageenan, respectively (as shown in Table 1). In 1990, researchers discovered that kappa-carrageenan inhibited arenavirus replication in Vero cells in a potent and selective manner, including junin (IC_{50} = 0.3 g/ml) and tacaribe (IC_{50} = 0.2 g/ml), whereas its sulphated polysaccharide was not inhibitory to host cell proliferation even at a concentration of 200 g/ml[57] The inhibition of the host cell could be achieved at a concentration of 3000 μg/ml.[58]

Carrageenan works by inhibiting enveloped RNA or DNA viruses, preventing them from attaching to or entering host cells.[32,59–61] Like other sulphated polysaccharides including heparin, dextran sulphate,

Table 1
Carrageenan (kappa-, iota-, and lambda-) efficacy against some viruses *in vitro*, including SARS-CoV-2.

Type	Virus	Group	Cell lines	IC_{50} or EC_{50} (μg/ml)	References
Kappa-	DENV-1	RNA virus	Vero	EC_{50} = >50	[61]
	DENV-2	RNA virus	Vero	EC_{50} = 1.8	[61]
	DENV-3	RNA virus	Vero	EC_{50} = 6.3	[61]
	DENV-4	RNA virus	Vero	EC_{50} = >50	[61]
	HSV-1	DNA virus	Vero	IC_{50} = 1.9	[95]
	HSV-2	DNA virus	Vero	IC_{50} = 1.6	[95]
	HSV-1	DNA virus	PRK	IC_{50} = 3.7	[56]
	HSV-2	DNA virus	PRK	IC_{50} = 2	[56]
	CMV	DNA virus	HEL	IC_{50} = 2.8	[56]
	Vaccinia	DNA virus	PRK	IC_{50} = 36	[56]
	VSV	RNA virus	PRK	IC_{50} = 0.3	[56]
	VSV	RNA virus	HeLa	IC_{50} = 7	[56]
	VSV	RNA virus	Vero	IC_{50} = 7	[56]
	Sindbis virus	RNA virus	Vero	IC_{50} = 7	[56]
	HIV-1	RNA virus	MT-4	IC_{50} = 12	[56]
	H1N1	RNA virus	MDCK	IC_{50} = 32.1	[69]
	HPV16	DNA virus	HeLa	IC_{50} = 0.044	[96]
	RABVs SAD-L16	RNA virus	HEK-293T	IC_{50} = 15.89	[97]
	RABVs SAD-L16	RNA virus	NA	IC_{50} = 22.10	[97]
	RABVs SAD-L16	RNA virus	SK-N-SH	IC_{50} = 19.93	[97]
	RABVs SAD-L16	RNA virus	BSR	IC_{50} = 57.70	[97]
	JV	RNA virus	Vero	IC_{50} = 0.3	[57]
	TACV	RNA virus	Vero	IC_{50} = 0.2	[57]
	ASF	DNA virus	Vero	EC_{50} = 150	[58]
	H1N1	RNA virus	MDCK	EC_{50} = 89.57	[98]
Iota-	DENV-1	RNA virus	Vero	EC_{50} = 40.7	[61]
	DENV-2	RNA virus	Vero	EC_{50} = 0.4	[61,99]
	DENV-2	RNA virus	C6/36 HT	EC_{50} = 7	[99]
	DENV-2	RNA virus	HepG2	EC_{50} = 0.14	[61]
	DENV-3	RNA virus	Vero	EC_{50} = 4.1	[61]
	DENV-3	RNA virus	HepG2	EC_{50} = 0.63	[61]
	DENV-4	RNA virus	Vero	EC_{50} = 8.2	[61]
	HPV16	DNA virus	HeLa	IC_{50} = 0.006	[96]
	H1N1	RNA virus	MDCK	IC_{50} = 0.39	[71]
	H3N2	RNA virus	MDCK	IC_{50} = 0.92	[71]
	H5N1	RNA virus	MDCK	IC_{50} = 10.14	[71]
	H7N7	RNA virus	MDCK	IC_{50} = 118.48	[71]
	SSPL	RNA virus	ACE2-HEK293 cells	IC_{50} = 2.6	[75]
	SARS-CoV-2 (western blot)	RNA virus	Vero	IC_{50} = 0.046	[75]
	SARS-CoV-2 (PCR)	RNA virus	Vero	IC_{50} = 1.54	[75]
	hCoV OC43	RNA virus	Vero	IC_{50} = 0.33	[75]
Lambda-	DENV-1	RNA virus	Vero	EC_{50} = >50	[61]
	DENV-2	RNA virus	Vero	EC_{50} = 0.15	[61]
	DENV-2	RNA virus	HepG2	EC_{50} = 0.22	[61]
	DENV-3	RNA virus	Vero	EC_{50} = 2	[61]
	DENV-3	RNA virus	HepG2	EC_{50} = 0.14	[61]
	DENV-4	RNA virus	Vero	EC_{50} = 4.2	[61]
	BoHV-1	DNA virus	MDBK	IC_{50} = 0.52	[100]
	SuHV-1	DNA virus	MDBK	IC_{50} = 10.42	[100]
	HSV-1	DNA virus	PRK	IC_{50} = 1.6	[56]
	HSV-2	DNA virus	PRK	IC_{50} = 1.5	[56]
	HSV-1	DNA virus	Astrocytes	IC_{50} = 1.6	[67]
	HSV-2	DNA virus	Astrocytes	IC_{50} = 0.9	[67]
	HSV-1	DNA virus	Vero	IC_{50} = 0.4	[67]
	HSV-2	DNA virus	Vero	IC_{50} = 0.4	[67]
	CMV	DNA virus	HEL	IC_{50} = 0.3	[56]
	Vaccinia	DNA virus	PRK	IC_{50} = 16	[56]
	VSV	RNA virus	PRK	IC_{50} = 0.2	[56]
	VSV	RNA virus	HeLa	IC_{50} = 4	[56]
	VSV	RNA virus	Vero	IC_{50} = 2	[56]
	Sindbis virus	RNA virus	Vero	IC_{50} = 2	[56]
	HIV-1	RNA virus	MT-4	IC_{50} = 1.9	[56]
	H1N1	RNA virus	MDCK	IC_{50} = 0.04	[70]
	H3N2	RNA virus	MDCK	IC_{50} = 0.3	[54]
	Influenza B	RNA virus	MDCK	IC_{50} = 1.4	[54]
	SARS-CoV-2	RNA virus	Vero	EC_{50} = 0.9	[54]
	HPV16	DNA virus	HeLa	IC_{50} = 0.010	[96]
	ASF	DNA virus	Vero	EC_{50} = 25	[58]

and pentosan polysulfate, carrageenan was also shown to inhibit the first step of the replication cycle of HIV-1 virus adsorption to $CD4^+$ T-cell membrane.[56,62,63] They specifically interact with the viral envelop of glycoprotein gp120 and inhibit the interaction of the virus with CD4.[64-66] Their negative charges shield off the positively charged amino acids

at the viral envelop (Fig. 2). The natural kappa-carrageenan from red seaweed *Gigartina skottsbergii* showed anti HSV with the IC_{50} ranging from 0.9 to 1.6 and 0.4 μg/ml for mouse astrocytes and Vero cells, respectively.[67] Its kappa-form is also reported to be strong and effective against human enterovirus 71 by preventing replication during viral adsorption.[68]

It became apparent that carrageenan has a broad spectrum of antiviral properties. Kappa-, iota-, and lambda-carrageenan are also reported to have shown antiviral activity through several viruses causing human respiratory disease which mostly belong to RNA viruses including influenza, rhinovirus and coronavirus (Table 1). A report showed that the derivative of kappa-carrageenan called kappa-carrageenan oligosaccharide (CO-1) with a molecular weight of 2000 Da was reported to be effective at inhibiting the replication of influenza A (H1N1) in MDCK cells with the half-maximal effective concentration (EC_{50}). The effective concentration required to inhibit virus-induced cytopathogenicity by 50%, was 32.1 μg/ml.[69] The inhibition of H1N1 was also shown in iota-carrageenan by inhibition of direct binding to its virus particles with an EC_{50} varied from 0.04 to 0.20 μg/ml.[70] Its iota-form also inhibits H1N1, H3N2, H5N1 and H7N7 with IC_{50} of 0.39, 0.92, 10.14 and 118.48 μg/ml, respectively.[71] In addition, lambda-carrageenan was effective in inhibiting both influenza A and B with EC_{50} varying between 0.3 and 1.4 μg/ml.[54] The size of the molecule matters to the effectiveness of the inhibition. Carrageenan's low molecular weight has the potential to effectively inhibit virus particles.[69] Varying chain lengths might be attributed to the water solubility properties and the abilities to internalize the host-cells.[69,72,73] Thus, in 2008, a study reported that carrageenan showed antiviral properties against HRVs or human rhinoviruses in HeLa cells.[32] Additionally, iota-carrageenan inhibits replication of HRV serotypes 1A, 8, 14, 16, 83, 84 on primary human nasal epithelial (HNep) cells.[32] Iota-carrageenan also showed inhibitory properties against hCoV OC43, a member of beta-coronaviridae that is a frequent cause of respiratory illness,[74] with IC_{50} of 0.33 μg/ml.[75] A study published recently found that kappa-carrageenan inhibits emerging SARS-CoV-2 (MOI of 0.05) in Vero cells, with an EC_{50} value of 0.9 g/ml.[54] SARS-CoV-2 entry process was inhibited Its kappa-form.[54] Another study showed that iota-carrageenan neutralized SARS-CoV-2 Spike pseudotyped lentivirus (SSPL) at MOI of 0.1 in a dose-dependent manner with IC_{50} of 2.58 μg/ml.[75] Additionally, Prieschl-Grassauer and her colleague compared the effectiveness of iota-, kappa-, and lambda using SSPL at 10 and 100 μg/ml. Thus, they found that iota-form effectively inhibited the virus at 10 μg/ml while kappa-and lambda-form were only active at 100 μg/ml.[75] To get more deep-insight, SARS-CoV-2 isolated from a 61-year-old patient and was amplified in Vero B4 cells and its inhibitory activities were conducted using iota-carrageenan. The IC_{50} ranged from 0.046 to 1.54 g/ml.[75] The activity of iota-form against SARS-CoV-2 was also studied using Vero E6 and showed less inhibition compared with Vero B4. [76,77] A study using two commercial pharmaceutical products, namely viruseptin nasal contained 1.2 mg/ml iota-and 0.4 mg/ml kappa-carrageenan (A) and viruseptin oral contained 1.2 mg/ml iota-form (B), showed inhibitory activity against SARS-CoV-2 at IC_{50} of 20 and 37 μg/ml, respectively.[78] Without additives, in the pure form of carrageenan, A and B inhibited SARS-CoV-2 at IC_{50} of 21 and 33 μg/ml, respectively.[78] Thus, the result is quite similar between products with additives and in pure form. Another research group investigated the inhibitory effect of iota-carrageenan on SARS-CoV-2 in Vero E6 and discovered a similar trend: at 600, 60, and 6 g/ml, with a xylitol concentration of 50 mg/ml, can indeed reduce over 4.25 log 10 copies/ml viruses compared to control.[79]

3.3. *In vivo evidence*

In 1993, an *in vivo* study was carried out using ICR mice (abbreviated from Institute of Cancer Research mice) that had been infected with cytomegalovirus and treated intraperitoneally with various doses of iota-carrageenan.[80] Iota-carrageenan at 0.5 mg confers a greater protective effect on mice infected with murine cytomegalovirus via a host-mediated mechanism.[80] In 1999, an *in vivo* study was conducted using HSV-2-infected female Swiss Webster mice with a single dose (10 mg/ml) of lambda- and iota-carrageenan.[81] Post-exposure revealed that lambda-carrageenan provides significant protection ($p < 0.05$) against

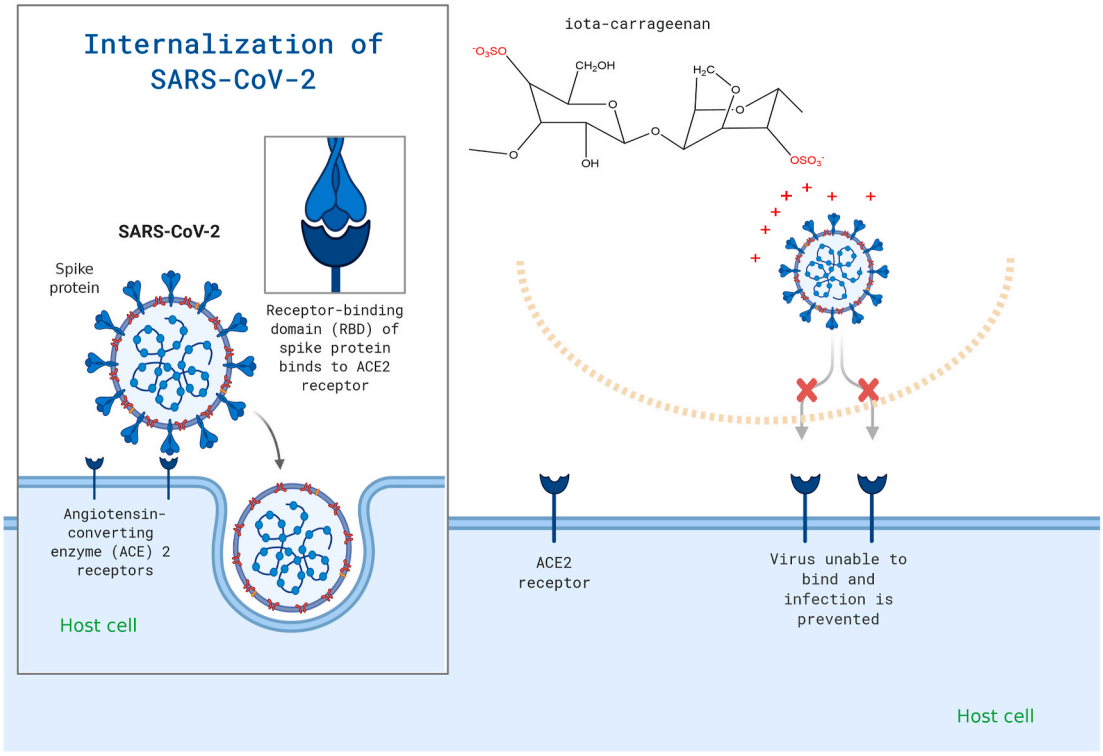

Fig. 2. Carrageenan may be used to specifically target the viral attachment of SARS-CoV-2.

disease caused by intravaginal HSV-2 challenge.[81] However, that is not the case for the iota-form.[81] Therefore, a single dose of kappa-carrageenan protected 9 of 10 BALB/c mice infected with HSV-2 intravaginally.[82] Another study showed that iota-carrageenan provides significant protection to BALB/cAnNCr mice-challenged HPV16 pseudovirus by either mechanical-or chemical disruption.[83]

In previous *in vitro* studies, all carrageenan subtypes showed antiviral activity against influenza virus (Table 1). Thus, several researchers investigated combined therapy of carrageenan with available influenza drugs on the market, including prodrug oseltamivir and zanamivir, an active drug. A study using the combination of iota-carrageenan with oseltamivir led to significantly enhanced survival of mice-infected H1N1 in comparison with the respective mono-therapies.[70] The combination of kappa-and iota-carrageenan for the treatment of lethally H7N7 infected C57Bl/6 mice showed better therapeutic effect ($p < 0.0004$) compared to the use of iota-form alone ($p < 0.1507$).[71] Moreover, the combination of kappa and iota-carrageenan with 3 mg/kg BW/day zanamivir used for treatment of H7N7 infected C57Bl/6 mice revealed synergistically elevated survival of mice in comparison of both mono--therapies.[71] However, no reports on the *in vivo* study using kappa-, iota-, or lambda carrageenan have been published recently. Therefore, the evident from molecular docking showed that carrageenan exhibited promising inhibitory action by showing a binding energy score of-8.4 kcal/mol against SARS-CoV-2 M^{pro} at two crucial residues, namely Cys 145 and His 41 .[84]

3.4. Clinical evidence

The common cold is caused by a variety of respiratory viruses, including human rhinoviruses (HRV), coronaviruses, human enteroviruses (HEV), parainfluenza viruses, respiratory syncytial virus (RSV), and influenza viruses. On the other hand, HRVs are the most common cause of respiratory tract infection in all age groups.[30,85] In 2008, under the European clinical trial registry number 2007-007577-23, double blind randomized clinical trials were conducted to evaluate the efficacy and safety of iota-carrageenan in treating patients with the common cold.[86] Around 35 adult patients in the United Kingdom with early symptoms of the common cold received 0.12% iota-carrageenan in saline solution three times daily for up to four days, in comparison to a placebo. Its administration has been shown to decrease viral load in nasal lavages ($p = 0.009$) and symptoms of the common cold ($p = 0.046$). Additionally, several pro-inflammatory mediators such as IFN-2, IL-8, IL-10, IL-1, IP-10, GRO, G-CSF, Fractalkine, and FGF-2 are produced.[86] Likewise, this study also used a large sample size of adult patients ($n = 211$) in Austria from 2010 to 2011 and was registered as ISRCTN80148028 [87]. The results indicated that administering iota-nasal carrageenan's spray significantly decreased the duration of symptoms ($p = 0.037$) and viral titers in nasal fluids ($p = 0.024$).[87] Additional large-scale studies were conducted in the United Kingdom (NCT01944631)[88] and Austria (NCT04533906), both of which show a similar trend to two previous studies (Table 2).

Furthermore, a randomized double-blind trial involving 153 children was conducted between 2009 and 2010 under the registration number ISRCTN52519535 to determine the efficacy of 12% iota-carrageenan in saline solution.[31] The report concluded that there is no statistically significant difference in total symptom score between the treated and placebo groups.[31] As a result, between the treated and placebo groups, significant differences in clearance disease ($p = 0.038$), lower incidence of secondary infections by other respiratory viruses ($p = 0.046$), and viral load reduction ($p = 0.026$) were observed.[31] Thus, these studies showed that treatment with iota-carrageenan nasal spray is safe and effective for children and adults experiencing early symptoms of the common cold.[31]

As iota-carrageenan inhibited SARS-CoV-2 *in vitro* with an IC_{50} of 1.54 g/ml (as shown in Table 1), this effect was mediated by the interaction of positively charged domains on the glycoprotein envelope involved in binding to protein glycans on the host cell surface (Fig. 2). SARS-CoV-2 S-protein is slightly more positively charged compared to S-spike protein of SARS-CoV due to the addition of four positively charged residues and the elimination of five negatively charged residues.[89] Moreover, it was effective at treating common colds caused by both rhinoviruses and coronaviruses.[85,87] Thus, the transferability of these *in vitro* data into clinical effectiveness for COVID-19 could be performed and evaluated.

Iota-carrageenan could be administered directly to patients infected with COVID-19 via nasal spray in conjunction with an oral antiviral such as ivermectin. Ivermectin was found to have significant antiviral activity against SARS-CoV-2 in three clinical trials: NCT04343092 (Effectiveness of ivermectin as adjunct therapy in COVID-19 management),[90] NCT04422561 (Prophylactic ivermectin in COVID-19 contacts),[91,92] and NCT04381884 (Ivermectin effect on SARS-CoV-2 replication in patients with COVID-19).[92]

In 2020, a clinical trial involving 229 participants was conducted at Eurnekian Public Hospital in Buenos Aires, Argentina under the registry number NCT04425850 (Table 2) to determine the efficacy of a topical treatment with iota carrageenan (nasal and buccal) and ivermectin (buccal). No adverse events were observed in the treated COVID-19 patients over a 30-day period.[93] In 2021, a randomized controlled 1-1 clinical trial under registration NCT04701710 was conducted to prioritize health personnel infected with SARS-CoV-2 ($n = 232$) at

Table 2
A list of clinical trials involving carrageenan for the common cold and SARS-CoV-2 infection that have been registered on ClinicalTrials.gov.

Identifier number	Title	Intervention	Status	Phase	Location
NCT01944631	Iota-carrageenan nasal spray in common cold	Four times daily for 4–10 days, nasal spray containing 1.20 g/l iota-carrageenan in saline	completed	4	UK
NCT04533906	Study to Investigate if Sucking a Coldamaris Lozenge Elutes Sufficient Iota-carrageenan to Inactivate Usual Common Cold Viruses	Sucking iota-carrageenan containing lozenge	completed	NA	Austria
NCT04425850	Usefulness of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19 (IVERCAR)	Ivermectin nasal spray and Iota carrageenan nasal spray (used as buccal drops 5 times a day). Application to the nose and oral cavity on a topical basis.	completed	NA	Argentina
NCT04701710	Prophylaxis Covid-19 in healthcare agents by intensive treatment with ivermectin and iota-carrageenan (Ivercar-Tuc)	Ivermectin 2 drops of 6 mg equals 12 mg every 7 days orally, and iota-carrageenan 6 sprays daily for 4 weeks	completed	2	Argentina
NCT04793984	Efficacy and Safety Evaluation of Inhaleen Inhalation in Hospitalized COVID-19 Patients	Inhalation of Carragelose® (contains 1.2 mg/ml iota-carrageenan) three times daily	recruiting	–	Austria
NCT04681001	Prophylactic treatment with carragelose nasal spray to prevent SARS-CoV-2, COVID-19, infections in health care workers	Nasal spray of Coldamaris pro. (contains 1.2 mg/ml iota-carrageenan) into nostrils and mouth	recruiting	–	Austria
NCT04590365	Iota-carrageenan nasal spray COVID-19 prophylaxis for healthcare professionals (ICE-COVID)	Coldamaris plus nasal and throat spray (Iota-carrageenan 0.12% in 0.5% saline)	recruiting	–	UK

Argentina's Public Healthcare Centre, using the same iota-carrageenan and ivermectin regimen as in the previous study.[94] The result indicated that the number of subjects diagnosed with COVID-19 was significantly lower in the treated group, at 3.4%, than in the control group, at 21.4% ($p = 0.0001$).[94] The treated group also had a lower prevalence of mild to moderate COVID-19 presentation compared to the control group.[94] This intensive preventive treatment with iota-carrageenan and ivermectin was able to significantly reduce the number of infected health care workers.[94] The study using iota-carrageenan in a single dose is still ongoing under the register numbers NCT04793984, NCT04681001, and NCT04590365. Therefore, the results of these ongoing clinical trials are required to provide conclusive evidence of iota-carrageenan's efficacy in patients with COVID-19. Additionally, there is a dearth of data on carrageenan, particularly regarding drug–drug, drug–gene, and drug–disease interactions. This information is critical in predicting potential adverse events that may occur during treatment.

4. Conclusion

Numerous carrageenan subtypes, including kappa-, iota-, and lambda-, inhibit SARS-CoV-2 infection *in vitro* by interfering with virus adsorption and internalization. The antiviral activity of iota-carrageenan as a single dose administered nasally is being studied in several clinical trials, whereas its co-administration with ivermectin was studied in two clinical trials and demonstrated improvement in outcome for COVID-19 patients. However, large-scale clinical trials should be conducted to demonstrate the efficacy of iota-carrageenan and its kappa-and lambda-subtypes in the treatment of COVID-19 patients.

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Declaration of competing interest

None declared.

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