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

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Nasal spray
Carrageenan
Iota-carrageenan
Clinical trial

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 papilomavirus, 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 vitro 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 \(3.25 \leq R_0 \leq 3.4\), 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 \(\text{Coronaviridae}\) family and the \(\text{Betacoronavirus}\) 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
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.\(^{14,27}\) 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\(^{26,28}\) 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 Gigartinaeae and Solieriaeae families,\(^{36,37}\) as well as the Porcellariaceae, Solieriaeae, Phyllophoraceae, and Hypneaeae families.\(^{33,36}\) 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.\(^{37}\) The US Food and Drug Administration (21 CFR 172.620) has generally recognized its polymer as safe for topical application and consumption.\(^{42}\) Carrageenan, as a biomolecule, possesses a variety of biological properties, including\(^{43–45}\) antioxidant,\(^{46}\) anti-bacteria,\(^{47}\) anticoagulant,\(^{48,49}\) and immunomodulator.\(^{51,52}\) Numerous reports indicate that carrageenan is also an antiviral, including against respiratory viruses.\(^{53–58}\)

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,\(^{54}\) a 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).\(^{50}\) 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\(^{52}\). The inhibition of the host cell could be achieved at a concentration of 3000 μg/ml.\(^{50}\)

Carrageenan works by inhibiting enveloped RNA or DNA viruses, preventing them from attaching to or entering host cells.\(^{52,59–61}\) Like other sulphated polysaccharides including heparin, dextran sulphate,
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       | IC$_{50}$ = 0.37            | 56         |
|            | DENV-2 RNA virus | Vero       | IC$_{50}$ = 50                | 61         |
|            | DENV-3 RNA virus | Vero       | IC$_{50}$ = 6.3              | 61         |
|            | DENV-4 RNA virus | Vero       | IC$_{50}$ = 0.5               | 61         |
|            | HSV-1 DNA virus | Vero       | IC$_{50}$ = 1.9             | 95         |
|            | HSV-2 DNA virus | Vero       | IC$_{50}$ = 1.6             | 95         |
|            | HSV-3 DNA PRK virus | Vero | IC$_{50}$ = 3.7        | 56         |
|            | HSV-4 DNA PRK virus | Vero | IC$_{50}$ = 2            | 56         |
|            | CMV DNA virus | HEL        | IC$_{50}$ = 2.8            | 56         |
|            | Vaccinia DNA virus | PRK | IC$_{50}$ = 36           | 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 virus | HEK-293T | IC$_{50}$ = 15.89        | 97         |
|            | RABVs SAD-L16 virus | Vero | IC$_{50}$ = 2.2          | 97         |
|            | RABVs SAD-L16 virus | SK-N-SH | IC$_{50}$ = 19.93       | 97         |
|            | RABVs SAD-L16 virus | BSR     | IC$_{50}$ = 57.70        | 97         |
|            | TACV RNA virus | Vero       | IC$_{50}$ = 0.3           | 57         |
|            | ASV DNA virus | Vero       | IC$_{50}$ = 0.2           | 57         |
| Iota-      | DENV-1 RNA virus | Vero       | IC$_{50}$ = 150          | 58         |
|            | DENV-2 RNA virus | Vero       | IC$_{50}$ = 0.4          | 61,69      |
|            | DENV-3 RNA virus | HepG2     | IC$_{50}$ = 0.14         | 61         |
|            | DENV-3 RNA virus | Vero       | IC$_{50}$ = 4.1          | 61         |
|            | DENV-4 RNA virus | HepG2     | IC$_{50}$ = 0.63         | 61         |
|            | DENV-4 RNA virus | Vero       | IC$_{50}$ = 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$_{50}$ = 0.39         | 71         |

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. They specifically interact with the viral envelope of glycoprotein gp120 and inhibit the interaction of the virus with CD4. Their negative charges shield off the positively charged amino acids...
at the viral envelope (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. Its kappa-form is also reported to be strong and effective against human enterovirus 71 by preventing replication during viral adsorption.

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. 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. 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. 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. 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. Varying chain lengths might be attributed to the water solubility properties and the abilities to internalize the host-cells. Thus, in 2008, a study reported that carrageenan showed antiviral properties against HRVs or human rhinoviruses in HeLa cells. Additionally, iota-carrageenan inhibits replication of HRV serotypes 1A, 8, 14, 16, 83, 84 on primary human nasal epithelial (HNep) cells. iota-carrageenan also showed inhibitory properties against hCoV OC43, a member of beta-coronaviridae that is a frequent cause of respiratory illness, with IC_{50} of 0.33 μg/ml. 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. SARS-CoV-2 entry process was inhibited its kappa-form. 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. 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. 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. The activity of iota-form against SARS-CoV-2 was also studied using Vero E6 and showed less inhibition compared with Vero B4. 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. 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. 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.

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. Iota-carrageenan at 0.5 mg confers a greater protective effect on mice infected with murine cytomegalovirus via a host-mediated mechanism. 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. Post-exposure revealed that lambda-carrageenan provides significant protection (p < 0.05) against...
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 Helps 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 (Iverzat) | 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 Inhalation Inhalation in Hospitalized COVID-19 Patients | Inhalation of Carrageol® (contains 1.2 mg/ml iota-carrageenan) three times daily | recruiting      | –     | Austria    |
| NCT04681001       | Prophylactic treatment with carrageose nasal spray to prevent SARS-CoV-2, COVID-19, infections in health care workers | Nasal spray of Coldamars 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 ivmevercin regimen as in the previous study. 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). The treated group also had a significantly lower number of infected healthcare care workers. 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, with numerous co-administration with ivmevercin 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.

Funding

The author wishes to express his gratitude to Program for Prioritas Nasional Ilmu Pengetahuan Kebumian, the Indonesian Institute of Sciences (MALSAI/5942. SDB.002).

Declaration of competing interest

None declared.

References

1. Chakraborty I, Maity P. COVID-19 outbreak: migration, effects on society, global environment and prevention. Sci Total Environ. 2020;728:138882.
2. Greene CJ, Burleson SL, Crosby JC, Heimann MA, Pfitz DC. Coronavirus disease 2019: international public health considerations. Journal of the American College of Emergency Physicians. 2020;1:70–77.
3. Nairn F, Abdnin RS, Bahar MA, et al. SARS-CoV-2 infection and implications for vaccine development. Hum Vaccines Immunother. 2020;16:3061–3073.
4. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. J Am Med Assoc. 2020;323:2085–2086.
5. Hou YJ, Okada K, Edwards CE, et al. SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. Cell. 2020;182:429–446, e414.
6. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Trav Med Infect Dis. 2020;30:101623.
7. Robba C, Bartagni D, Peloso P, Rocco PR. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. Expert Rev Respir Med. 2020;14:865–868.
8. Pons S, Fodil S, Azzoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care. 2020;24:1–8.
9. Syahrul S, Maliga HA, Ibawunmi M, et al. Hemorrhagic and ischemic stroke in patients with coronavirus disease 2019: incidence, risk factors, and pathogenesis—a systematic review and meta-analysis. F1000Research. 2021;10.
10. Mutiaukwa E, Fabrizi A, Mamada SS, et al. Anoxia and dyspnea in SARS-CoV-2 infection: incidence and effects on COVID-19 severity and mortality, and the possible pathobiology mechanisms—a systematic review and meta-analysis. F1000Research. 2021;10.
11. Yunis F, Fabrizi A, Mamada SS, et al. Global prevalence of prolonged gastrointestinal symptoms in COVID-19 survivors and potential pathogenesis: a systematic review and meta-analysis. F1000Research. 2021;10:301.
12. Worldometers. COVID-19 coronavirus pandemic. https://www.worldometers.info/coronavirus/;2020/;2021.
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72 Ji J, Wang LC, Wu H, Luan HM. Bio-function summary of marine oligosaccharides.

68 Chiu Y-H, Chan Y-L, Tsai L-W, Li T-L, Wu C-J. Prevention of human enterovirus 71 infection by kappa carrageenan.

67 Carlucci M, Scolaro L, Damonte E. Inhibitory action of natural carrageenans on influenza A virus and severe acute respiratory syndrome coronavirus 2. Sci Rep. 2021;11:1–12.

62 Nakashima H, Yoshida O, Baba M, De Clercq E, Yamamoto N. Anti-HIV activity of dextran sulfate sodium.

64 Mitsuya H, Looney DJ, Kuno S, Ueno R, Wong-Staal F, Broder S. Dextran sulfate sodium, a sulfated oligosaccharide, is a potent and selective anti-HIV agent in vitro.

54 Jang Y, Shin H, Lee MK, et al. Antiviral activity of lambda-carrageenan against African swine fever virus.

49 de Araújo CA, Noseda MD, Cipriani TR, Gonçalves AG, Duarte MER, Ducatti DR. Immuomodulation and antitumor activity of λ-carrageenan oligosaccharides. Curr Lett. 2006;243:228–234.

52 Cicinskas E, Kalitnik AA, Karetin YA, Ram MSGM, Achary A, Kravchenko AO. Immunomodulating properties of carrageenan from tichocarpus crinitus. Inflammation. 2005;28:1–10.

56 Baba M, Snoeck R, Pauwels R, de Clercq E. Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stomatitis virus, and human immunodeficiency virus.

Antimicrob Agents Chemother. 1988;32:1742–1745.

60 Andrieu G, De Clercq E. Inhibitory effect of selected antiviral compounds on arenavirus replication in vitro. Antivir Res. 1990;14:287–299.

58 García-Villan D, Gil-Fernández C. Antiviral activity of sulfated polysaccharides against African swine fever virus. Antivir Res. 1991;15:139–148.

59 Baba M, Nakajima M, Schols D, Pauwels R, Balzarini J, De Clercq E. Pentosan polysulfate, a sulfated oligosaccharide, is a potent and selective anti-HIV agent in vitro. Antivir Res. 1988;9:335–343.

50 dos Santos-Fidencio GC, Gonçalves AG, Duarte MER, Ducatti DR. Effects of carboxyl group on the anticoagulant activity of oxidized carrageenans.

54 Jang Y, Shin H, Lee MK, et al. Antiviral activity of lambda-carrageenan against African swine fever virus.

56 Baba M, Snoeck R, Pauwels R, de Clercq E. Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stomatitis virus, and human immunodeficiency virus.

Antimicrob Agents Chemother. 1988;32:1742–1745.

59 Baba M, Nakajima M, Schols D, Pauwels R, Balzarini J, De Clercq E. Pentosan polysulfate, a sulfated oligosaccharide, is a potent and selective anti-HIV agent in vitro. Antivir Res. 1988;9:335–343.

64 Mitsuya H, Looney DJ, Kuno S, Ueno R, Wong-Staal F, Broder S. Dextran sulfate sodium, a sulfated oligosaccharide, is a potent and selective anti-HIV agent in vitro.

50 dos Santos-Fidencio GC, Gonçalves AG, Duarte MER, Ducatti DR. Immuomodulation and antitumor activity of λ-carrageenan oligosaccharides. Curr Lett. 2006;243:228–234.

52 Cicinskas E, Kalitnik AA, Karetin YA, Ram MSGM, Achary A, Kravchenko AO. Immunomodulating properties of carrageenan from tichocarpus crinitus. Inflammation. 2005;28:1–10.

56 Baba M, Snoeck R, Pauwels R, de Clercq E. Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stomatitis virus, and human immunodeficiency virus.

Antimicrob Agents Chemother. 1988;32:1742–1745.

59 Baba M, Nakajima M, Schols D, Pauwels R, Balzarini J, De Clercq E. Pentosan polysulfate, a sulfated oligosaccharide, is a potent and selective anti-HIV agent in vitro. Antivir Res. 1988;9:335–343.

64 Mitsuya H, Looney DJ, Kuno S, Ueno R, Wong-Staal F, Broder S. Dextran sulfate sodium, a sulfated oligosaccharide, is a potent and selective anti-HIV agent in vitro.

50 dos Santos-Fidencio GC, Gonçalves AG, Duarte MER, Ducatti DR. Immuomodulation and antitumor activity of λ-carrageenan oligosaccharides. Curr Lett. 2006;243:228–234.