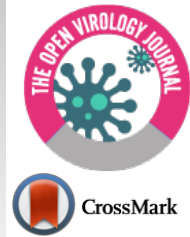




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LETTER

Iota-Carrageenan as an Antiviral Treatment for the Common Cold

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Abstract:

Introduction:

The common cold syndrome of acute upper respiratory tract viral infection is the most common disease among mankind and is an extremely common illness in children. There is a great need for a safe and effective antiviral treatment with minimal side effects. The challenge in developing a treatment is the numerous and varied respiratory viruses that cause this common illness and the need for a treatment with good tolerability and safety.

Explanation:

All respiratory viruses must reach the cell surface by passing through respiratory fluid and mucus, and this common feature may allow for the development of antivirals that capture viruses during this transit.

This article discusses how large polyanionic molecules such as iota-carrageenan may trap positively charged respiratory viruses. Iota-carrageenan is a large polysaccharide molecule which is neither absorbed from the respiratory tract nor metabolised. It, therefore, does not have any pharmacological properties. Iota-carrageenan nasal spray has been shown to reduce the titres of respiratory viruses and to reduce the severity of symptoms in placebo-controlled clinical trials, including children and adults. The results of four clinical trials are presented.

Conclusion:

Iota-carrageenan is a good candidate as a safe and effective non-specific antiviral treatment for common cold, and more research is justified on polyanionic molecules like carrageenans as antivirals.

Keywords: Electrical charge, Iota-carrageenan, Common cold, Rhinovirus, Upper respiratory tract infection, Heparan sulphate, Antiviral.

Article History

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1. INTRODUCTION

Acute upper respiratory tract viral infections such as common cold are probably the most common viral diseases of mankind. Common cold is caused by a wide range of viruses such as rhinoviruses, coronaviruses, influenza viruses, Respiratory Syncytial Viruses (RSV), parainfluenza viruses, adenoviruses, enteroviruses, metapneumoviruses and unknown viruses which may be responsible for 20-30% of infections [1]. With such a wide range of viruses responsible for the common cold syndrome, it is not surprising that there is a great unmet need for a safe and well-tolerated antiviral treatment for this most common disease.

A major issue in developing an antiviral treatment for the common cold is that focussing on one group of viruses such as

rhinoviruses, which may on occasion account for at least 50% of colds [2], means that the treatment would only be effective in treating 50% of colds, and this would not be acceptable as a freely available treatment to the general public. Antiviral treatments aimed at blocking the viral receptor or host cell receptor are unlikely to be of benefit in treating common cold as they are developed to act specifically on only one group of viruses.

The common cold, therefore, presents a formidable challenge for the development of antiviral treatments because of the diverse viruses responsible for this disease. One common factor shared by all the common cold viruses is that they must somehow reach their specific host cell receptor by moving down through a relatively great depth of respiratory fluid and mucus and that they must achieve this journey without any means of self-propulsion. This article will discuss how common cold viruses may utilise their electrical charge to reach the host cell surface and how this mechanism may be

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confounded by large polyanionic molecules such as iota-carrageenan.

2. IMPORTANCE OF ELECTRICAL CHARGE ON VIRUSES AND CELLS

Respiratory viruses are trapped and washed away in a protective layer of respiratory mucus as part of the normal respiratory defence against infection by mucociliary clearance. Respiratory mucus and fluid are some 10 micrometres in depth [3] and compared to the size of respiratory viruses such as a rhinovirus, which is some 30 nanometres in size [4]. This presents a formidable barrier to infection. In order to infect cells lining the respiratory tract, the viruses must contact the host cell and interact with a receptor that triggers penetration of the host cell membrane. The initial movement of the virus towards the cell is dependent on Brownian motion, which knocks the virus in random directions, and eventually, the virus comes close enough to the cell to be attracted to the cell surface by other factors such as the electrostatic attraction of the virus to large charged molecules on the surface of the cell [5, 6]. Naked respiratory viruses such as rhinoviruses must attach to a specific receptor on epithelial cells in order to uncoat and invade cells, whereas many enveloped viruses fuse with cellular membranes in order to penetrate the cell [7]. The initial encounter between a virus and its host cell is not with a virus-specific receptor but with the ubiquitous glycoprotein attachment factors such as Heparan Sulphate Proteoglycans (HSP) on the cell surface [8]. In general, the surface of mammalian cells presents a negative electric field due to the

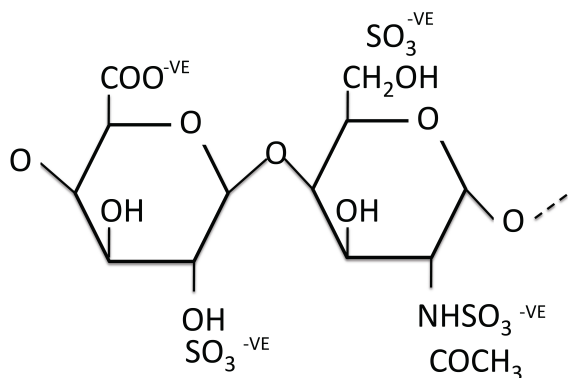


Fig. (1). Structure of heparan sulphate, illustrating the disaccharide repeating units (dimers) with two negatively charged sulphate groups. (-VE means negatively charged).

ubiquitous HSP molecules on the cell surface and this electrical property of cells can be utilised by positively charged viruses to direct the virus towards the cell surface and closer to any specific receptor on the cell surface. Heparan Sulphate Proteoglycans (HSP) are found on the cell surface of all tissues and in the extracellular matrix where they interact with numerous ligands such as cytokines, chemokines, enzymes, and growth factors [9, 10]. HSP are glycoproteins containing one or more covalently attached Heparan Sulphate chains (HS) with 40-300 sugar residues [10]. The HS chain is made up of linked dimers of sugar molecules, as illustrated in Fig. (1), and the sulphate and other groups along the chain give HS a high

electronegative charge to make it one of the most highly negatively charged polymers in nature [10].

3. CARRAGEENAN

Carrageenan is a general term used to describe sulphated polysaccharides extracted from edible seaweeds. Carrageenan is widely used in the food industry for its thickening and gel-like properties in food products such as ice cream and sauces. It is also used to formulate syrups, and in cosmetics and processed meat [11]. The *in vitro* antiviral activity of carrageenan was first described in 1958 when carrageenan was shown to exert a marked inhibitory effect on the growth of influenza B virus and mumps virus in embryonated chicken eggs [12]. Since the discovery of the antiviral activity of carrageenan in 1958 carrageenan has been shown to have *in vitro* antiviral activity for a wide range of viruses such as hepatitis A virus [13], herpes simplex virus [14], rhinovirus [15], papillomavirus [16], dengue virus [17], various enveloped viruses such as cytomegalovirus, vesicular stomatitis virus and human immunodeficiency virus [18], porcine reproductive and respiratory syndrome virus [19] and influenza A virus [20].

The term carrageenan covers a range of sulphated polysaccharides and oligosaccharides, but the three commercially important carrageenans are iota-, kappa- and lambda- carrageenans. These carrageenans are composed of disaccharide repeating units (dimers), with the kappa, iota and lambda dimers having one, two and three sulphate ester groups respectively resulting in correspondent calculated sulphate contents of 20%, 33% and 41% (w/w) [21]. Iota-carrageenan applied as a nasal spray has been shown in human clinical trials to have efficacy as an early treatment for the common cold and to have antiviral activity against common cold and influenza viruses [15, 22 - 25].

4. CARRAGEENAN AS AN ANTIVIRAL FOR HUMAN VIRAL DISEASE

The antiviral activity of a seaweed extract containing carrageenan was first discovered by chance in 1958 by Gerber *et al.* [12] at the Squibb Institute for Medical Research in New Jersey, USA. The investigators were searching for new antiviral compounds using the chick embryo as a screening model, and influenza B and mumps virus as test viruses. The results of the studies were erratic as they were using 0.25% agar as a vehicle for the viruses and they suspected that the vehicle had more antiviral activity than any of the antivirals they were testing. They went on to study the antiviral effects of carrageenan extracted from seaweeds (agar) and demonstrated that the carrageenan had a marked inhibitory effect on the replication of influenza B and mumps viruses. They demonstrated that significant protection against fatal influenza B infection of the chick embryo was obtained even when the treatment with carrageenan was delayed for as long as 24 hours after the inoculation with the virus [12]. It is surprising that after the clear demonstration of *in vitro* antiviral activity of carrageenan in 1958, there were no immediate follow-up animal or human studies to develop an antiviral treatment for human use and it was some 50 years later before any human treatment was investigated.

Carrageenan was shown in the years after 1958 to have antiviral activity against a wide range of viruses *in vitro* and there was increasing interest in the use of carrageenan as a treatment for HPV from 2006 when carrageenan used in sexual lubricants and lubricated condoms was shown to be a potent inhibitor of HPV infection *in vitro* [16]. This led to proposals for a human clinical trial in 2010 and the interim analysis of this trial suggests that using a carrageenan-based lubricant gel can reduce the risk of genital HPV infections in women [26].

In 2007 at around the same time that clinical trials were being discussed based on the effects of carrageenan on HPV, interest was also developing at Marinomed Biotech AG (Marinomed), a company in Vienna Austria, on a clinical trial on the efficacy of carrageenan as a nasal spray for the early treatment of a common cold. *In vitro* studies in Austria conducted by Marinomed, demonstrated that iota-carrageenan was a potent inhibitor of rhinovirus infection of cultured HeLa cells [15]. Following the positive results of *in vitro* antiviral studies on rhinovirus, Marinomed contacted the author to conduct the first clinical trial on the antiviral effects of carrageenan at the Common Cold Centre based in Cardiff University, UK. The results of this pilot study were published in 2010 [22] and despite the small number of patients involved in the pilot study (17 in the carrageenan treated group and 18 in the placebo group), the study reported a significant reduction in the symptoms of the common cold ($p = 0.046$) and a reduction in mixed viral load in nasal lavage ($p = 0.009$) when iota-carrageenan as an intranasal spray (0.12% solution in saline) was used as an early treatment of common cold (within 48 hours of symptom onset) [22]. The results of this pilot study on iota-carrageenan nasal spray are now supported by three larger studies on the early treatment of common cold involving hundreds of adults and children [24, 25, 27].

5. PROPOSED MECHANISM OF ACTION OF IOTA-CARRAGEENAN AS AN ANTIVIRAL

Iota-carrageenan is a highly negatively charged long-chain polysaccharide made up of dimers similar in structure and electrical charge to HS as illustrated in Fig. (2). Both HS and iota-carrageenan have negatively charged sulphate groups along the chain and these provide most of the dense electrical charge of the polyanionic molecules. Iota-carrageenan mimics the HS that the virus is first attracted to on the surface of the cell and can, therefore, trap the virus and prevent infection, as illustrated in Fig. (3a and 3b). In the early stage of infection, newly released viruses infect adjacent epithelial cells and magnify the infection and increase the viral titre as illustrated in Fig. (3a). When iota-carrageenan is present in the early stages of infection, it acts like airway mucus to trap viruses, as the mucins in airway mucus have a high sialic acid content and this together with the high sulphate content results in a strongly negatively charged surface which may attract any positively charged surface of an airway virus [28]. The long, negatively charged iota-carrageenan molecule attracts and traps the newly released positively charged viruses and prevents them from infecting adjacent nasal epithelial cells, as illustrated in Fig. (3b). The iota-carrageenan and trapped viruses will be transported by mucociliary clearance to the nasopharynx and then swallowed, and the viruses will be destroyed in the acid

environment of the stomach.

The antiviral efficacy of polyanionic molecules such as iota-carrageenan is dependent on early intervention at the first sign of symptoms, in order to prevent the spread and magnification of infection along the respiratory mucosa, and that is why nasal spray treatments, as discussed below, are used in clinical trials within 24-48 hours of the onset of symptoms.

6. WHY IOTA-CARRAGEENAN IS AN IDEAL TREATMENT FOR THE COMMON COLD

Iota-carrageenan nasal spray is an ideal early treatment for the common cold because of several characteristics; safety, tolerability, lack of interaction with any other medications, and a non-specific antiviral action against different groups of viruses.

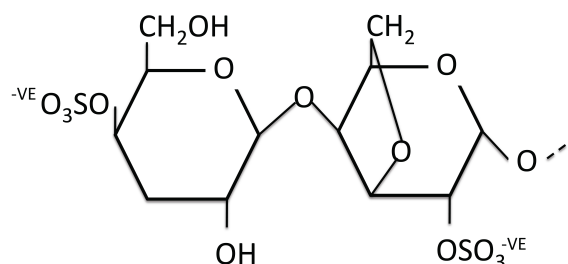


Fig. (2). Structure of iota-carrageenan, illustrating the disaccharide repeating units (dimers) with two negatively charged sulphate groups. (-VE means negatively charged).

6.1. Safety

Common cold is the most common diseases of mankind and is especially common in infants and children. Any treatment for common cold must have a good safety profile as the benefits of treating a self-limiting disease of short duration must be balanced against any risks posed by the treatment. Iota-carrageenan is a large polysaccharide molecule which is neither absorbed from the respiratory tract nor metabolised. It works against respiratory viruses by its physical properties and electrical charge, and as a nasal spray is licensed for use as a medical device rather than as a medicine. Iota-carrageenan does not have any pharmacological properties and, therefore, does not have any toxicology or known side effects on treatment. The safety of iota-carrageenan is demonstrated from the results of four placebo-controlled clinical trials which reported that there were no significant differences in adverse events between the verum and placebo-treated groups and those adverse events were mainly related to symptoms of respiratory viral infection [22, 24, 25, 27]. There are no long-term safety studies on the nasal spray, but it has been marketed across Asia and Europe for several years with no indication of any safety issues. Carrageenans, including iota-carrageenan, are widely used in the food, pharmaceutical and cosmetic industries and are Generally Recognised As Safe (GRAS) [29]. The safety of iota-carrageenan administered as a nasal spray or nebulised (0.12%) has been studied in rabbits and rats and no absorption of the carrageenan was reported and the data did not show any local intolerance or toxicity of the iota-carrageenan [29]. It is important to note that the dose of iota-carrageenan

given intranasally is very small compared to the large amounts of carrageenans that may be ingested in many foods, and the controversy that surrounds the safety of carrageenans in foods [30] does not apply to the topical use of a nasal spray.

6.2. Tolerability

Common cold is an acute disease that can be treated by self-medication at home. Any treatment for common cold with significant side effects will not be tolerated by the patient. Iota-carrageenan nasal spray does not have any side effects apart from those associated with the use of a nasal spray and it does not cause any nasal irritation or nasal sensation.

6.3. Interaction with Other Medicines and Treatment

Iota-carrageenan works as a medical device by its physical properties and therefore does not have any known interaction with any other concomitant treatments for the common cold or any other disease. If patients are using other nasal treatments such as saline, corticosteroids, bronchodilators, *etc.*, it is best to use the iota-carrageenan nasal spray at least an hour before or after the other treatment, in order to avoid diluting the treatment and any interaction.

6.4. Non-Specific Antiviral Against a Wide Range of Viruses

Common cold is caused by a wide range of RNA and DNA respiratory viruses and any treatment that works specifically against one type of virus is unlikely to be effective in treating the majority of cases of the common cold. *In vitro* and *in vivo* studies have shown that iota-carrageenan has efficacy in reducing the viral load of a wide range of RNA and DNA based viruses such as rhinoviruses [15] hepatitis A [13] and influenza viruses [23].

6.5. Efficacy of Iota-Carrageenan Nasal Spray as a Treatment for the Common Cold

Iota-carrageenan nasal spray has been shown to reduce the

titres of respiratory viruses and to reduce the severity of symptoms in placebo-controlled clinical trials, including children and adults [22, 24, 25, 27]. A summary of some of the results of clinical trials is illustrated in Table 1.

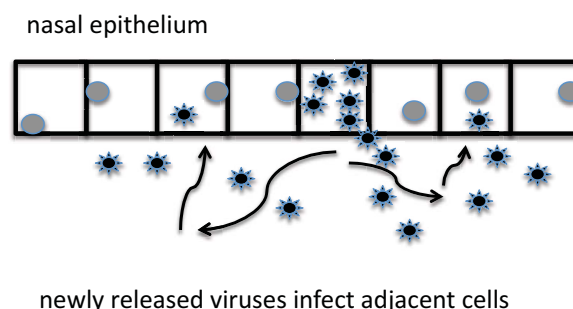


Fig. (3a). In the early stage of infection, newly released viruses infect adjacent epithelial cells and magnify the infection and increase the viral titre.

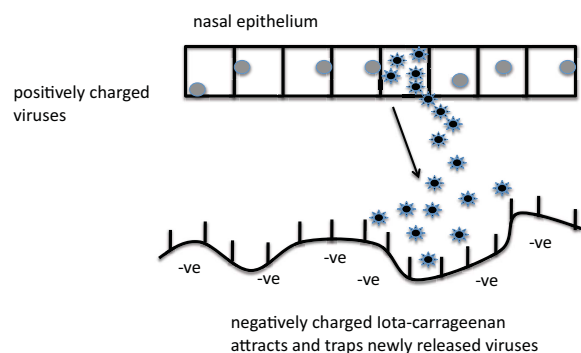


Fig. (3b). Mechanism of action of iota-carrageenan as an antiviral for the treatment of a common cold. The long, negatively charged iota-carrageenan molecule attracts and traps the newly released positively charged viruses and prevents them from infecting adjacent nasal epithelial cells. The iota-carrageenan and trapped viruses will be transported by mucociliary clearance to the nasopharynx and then swallowed, and the viruses will be destroyed in the acid environment of the stomach. (-VE means negatively charged).

Table 1. Summary of clinical trials on the iota-carrageenan nasal spray as a treatment for the common cold.

Publication	Patients	Treatment	Antiviral	Symptomatology
Eccles <i>et al.</i> (2010) A double-blind placebo-controlled trial [22]	n = 35 Adults mean age 19.6 years	0.12% iota-carrageenan nasal spray, 3 times a day for four days	Nasal lavage was analyzed by real-time RT-PCR for the presence of viral genomes. Viral load in the respiratory virus-positive patients increased by almost sixfold, whereas it decreased by 92% in the iota-carrageenan treatment group ($p < 0.009$).	Carrageenan treated group had a reduction in total symptom scores between days 2-4 of the trial ($p=0.046$)
Fazekas <i>et al.</i> (2012) Double-blind placebo-controlled trial [24]	n = 153 children aged between 1-18 years, mean age 5 years	0.12% iota-carrageenan nasal spray, 3 times a day for seven days	Topical application of the iota-carrageenan spray reduced viral loads in nasal secretions to a significantly higher degree than placebo after 3 to 5 days of treatment ($p = 0.026$)	A non-significant reduction in total symptom scores between days 2-7 of trial

(Table 1) cont.....

Publication	Patients	Treatment	Antiviral	Symptomatology
Ludwig <i>et al.</i> (2013) Double-blind placebo-controlled trial [27]	n = 211 adults mean age 33 years	0.12% iota-carrageenan nasal spray, 3 times a day for seven days	Viral titers in nasal fluids showed a significantly greater decrease in carrageenan treated patients in the intention-to-treat population (p = 0.024) and in the per-protocol population (p = 0.018) between days 1 and 3/4.	Significant reduction in total symptom scores in later days of cold (p=0.048)
Eccles <i>et al.</i> (2015) Double-blind placebo-controlled trial [25]	n = 200 adults mean age 20 years	0.12% iota-carrageenan nasal spray, 4 times a day for four days	Non-significant trend for a reduction in viral titres in the iota-carrageenan group compared to the placebo group.	Significant reduction in total symptom scores between days 2-4 of the trial (p = 0.0364)

Eccles *et al.* (2010) conducted the first double-blind, randomised, placebo-controlled clinical trial on an iota-carrageenan (0.12%) nasal spray in Cardiff, United Kingdom. The study was a small study involving 35 adults (mean age 19.6 years) with early symptoms of the common cold (<48 hours onset of symptoms). The nasal spray was administered into each nasal passage three times a day for four days. Nasal lavage was obtained on day 1 (before treatment) and day 3 or 4 (during treatment). The results reported that the pre-defined primary efficacy variable showed a significant difference (p < 0.046) between placebo and iota-carrageenan treatment groups for the total symptom score (day 2-4) with the iota-carrageenan treatment group having lower symptom scores than placebo. Nasal lavage was analyzed by real-time RT-PCR for the presence of viral genomes. Viral load in the respiratory virus-positive patients increased by almost sixfold, whereas it decreased by 92% in the iota-carrageenan treatment group (p < 0.009).

Fazekas *et al.* (2012) conducted a double-blind, randomised, placebo-controlled trial similar to the design of the trial conducted by Eccles *et al.* (2010) on 153 children aged between 1-18 years (mean age 5 years) with early symptoms of the common cold (<36 hours onset of symptoms) in Vienna, Austria. The nasal spray was administered into each nasal passage three times a day for seven days. The primary efficacy variable was the difference in total symptom scores between days 2-7, but this did not reach any statistically significant difference between treatment groups, perhaps because the children and their parents had difficulty in assessing symptom scores due to the young age of the children. However, the trial did report a significant reduction in viral load (p = 0.026), reduced time to clearance of the disease symptoms (7.6 in the iota-carrageenan treatment group versus 9.4 days in the placebo group, p = 0.038).

Ludwig *et al.* (2013) conducted a double-blind, randomised, placebo-controlled trial on 211 patients (mean age 33 years) with early symptoms of the common cold (< 48 hours onset of symptoms) in Vienna, Austria. The nasal spray was administered into each nasal passage three times a day for seven days. In patients showing a laboratory-confirmed cold virus infection and adherence to the protocol, alleviation of symptoms was 2.1 days faster in the carrageenan group in comparison to placebo (p = 0.037). Viral titers in nasal fluids showed a significantly greater decrease in carrageenan treated patients in the intention-to-treat population (p = 0.024) and in the per-protocol population (p = 0.018) between days 1 and 3/4.

Eccles *et al.* (2015) conducted a double-blind, randomised,

placebo-controlled trial on 200 patients (mean age 20 years) with early symptoms of the common cold (< 48 hours onset of symptoms) in Cardiff, United Kingdom. The nasal spray was administered into each nasal passage four times a day for a mandatory four days, with an option to continue treatment up to a maximum duration of 10 days. The primary end-point was the difference between treatment groups for total symptom scores between days 2-4 and this reached statistical significance (p = 0.0364) when one patient was excluded from analysis due to probably misunderstanding the symptom scoring. Only 45% of the patients tested positive for a respiratory virus, but in these patients, there was a non-significant trend for a reduction in viral titres in the iota-carrageenan group compared to the placebo group.

Clinical trials on patients with the common cold are difficult because of the acute nature of the disease and because patients often self-medicate or present too late for treatment and must be excluded from entry into trials that are studying the early treatment of a common cold. Like any clinical trial, the four clinical trials on iota-carrageenan can be criticised as being either a small pilot study [22], not achieving statistical significance on the primary outcome measure [25], or only showing effects on viral titre and not on symptoms [24, 27]. But when the four trials are considered together, they provide evidence that an iota-carrageenan nasal spray can reduce viral titres, and also reduce symptom severity in common cold.

7. SOURCE OF IOTA-CARRAGEENAN USED IN NASAL SPRAYS

The iota-carrageenan used in nasal sprays for the treatment of common cold is pharma grade iota-carrageenan, Gelcarin 379NF obtained from DuPont. This source of iota-carrageenan is mainly produced from the seaweed *Echeuma denticulatum*, which is sometimes named *Echeuma spinosum*. The polymer contains mainly >90% iota-carrageenan and, to a much lesser extent <10% kappa-carrageenan but does not contain any lambda-carrageenan [31].

CONCLUSION

Common cold is caused by a wide range of respiratory viruses and any antiviral treatment for this common disease must work on some mechanism of viral activity that is common to all of these viruses. All respiratory viruses must pass through the physical barrier of mucus and respiratory fluid in order to reach the cell surface and this article proposes that the viruses may utilise their positive electrical charge in order to reach the negatively charged cell surface. Polyanionic molecules such as iota-carrageenan may present a way of trapping the viruses as

they move towards the surface of the cell. The lack of any pharmacological or toxicological activity in large polyanionic molecules such as iota-carrageenan due to their lack of absorption or metabolism makes them a safe topical antiviral treatment. The efficacy and safety of an iota-carrageenan nasal spray have been studied in four clinical trials to date, and the results of these trials provide some support the efficacy and safety of iota-carrageenan as an early treatment for common cold. Further research is needed on polyanionic compounds like iota-carrageenan for the treatment of common cold.

Search Strategy and Selection Criteria

Relevant publications were found by searching PubMed during July2018-January 2020. The main search terms were “carrageenan”, “iota-carrageenan” “common cold”, “URTI”, “heparan sulphate”. The bibliographies of key articles were used to identify other relevant articles. Key articles were used in cited reference searches on the Web of Science database.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICTS OF INTERESTS

The author acts as a consultant to the pharmaceutical industry, including companies involved in marketing carrageenan containing treatments but does not have any financial interest in any company. This writing of this review was not supported by any grant or funds from any organisation. No data from any depository was used in the writing of this review.

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