SYSTEMATIC REVIEW ARTICLE

Natural Derived Nasal Spray; A Proposed Approach for COVID-19 Disease Control

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Abstract: Considering the importance of COVID-19 disease pandemic, emerged by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in line with other studies to find appropriate prevention or treatment methods for this virus infection by proposing the use of natural derived ingredients as an approach for COVID-19 disease control was our study objective. Here we reviewed previous studies on natural derived nasal sprays and found that some known natural derived ingredients have antiviral properties, so their topical use as a nasal spray is effective in reducing the symptoms of respiratory infections. Moreover, such nasal sprays also have the potential of decreasing viral load, including titer of coronaviruses, in the nasal cavity. It seems that the use of carrageenan or other herbal ingredients in the nasal spray may block the SARS-CoV-2 virus from entering the lung cells of an affected person and can also prevent virus transmission to other susceptible persons. Further, noticing what we know about the novel 2019 coronavirus so far, we suggested carrageenan that has an unspecific physical antiviral activity and some other natural derived ingredients as a choice in coping with SARS-CoV-2 virus infection.

Keywords: Acute respiratory infections, COVID-19, SARS-CoV-2, natural derived ingredients, nasal sprays, carrageenan.

BACKGROUND

Acute respiratory infections are the most common illnesses that people around the world experience during their lifetime. Among these, viral infections, including influenza and the common cold, are the most prevalent ones[1]. Moreover, the problem that nowadays the world is facing, COVID-19 disease, is also a respiratory infection caused by coronaviruses. Acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) are other coronavirus outbreaks [2].

Common cold, as a viral disease that affects the upper respiratory system, is the most common infection among viral illnesses in human beings with ordinary symptoms like blocked nose (congestion), rhinorrhea, and sneezing [3]. Studies on the cause of respiratory illnesses have discovered rhinoviruses, coronaviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, adenoviruses, enteroviruses, and metapneumovirus as known involved viruses [4, 5]. The common cold pathogenesis consists of a multifaceted interaction between viruses and the host's inflammatory response. The host's response can vary for each respiratory virus. Two main clinical symptoms of the common cold, blocked nose and rhinorrhea, are caused by vasodilation and increased vascular permeability resulting from a viral infection of the nasal mucosa and cholinergic stimulation effects on the mucous gland to increased secretion and sneezing [6].

Although nowadays, a wide variety of medications are recommended for common cold treatment, considering serious potential side effects, there are no definitely effective drugs for prevention or treatment [4]. Several attempts to find effective prophylactic or therapeutic treatments, including natural derived ingredients, vitamins, zinc, and others, have been made, but their debatable results are unreliable [5].

Because of the upper respiratory tract and nasal cavity involvement in the common cold, the use of local nasal sprays may be effective in improving symptoms and treating the disease. Furthermore, the prevention of common cold infection through the nasal spray demonstrates the effectiveness, safety, and satisfaction of the patient [4].

Several chemical nasal sprays include decongestant sprays, antihistamine sprays, steroid nasal sprays, etc. The ordinary use of these sprays reduces the symptoms of the common cold and allergic rhinitis. Decongestant sprays such as ephedrine, oxymetazoline, and xylometazoline reduce the congestion and help patients in breathing by constricting

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swollen blood vessels and tissues, but they are effective only for a few days and do not have an antiviral effect on viral common cold [3, 7]. Antihistamine sprays such as azelastine and olopatadine affect H1 brain cells by crossing the blood-brain barrier, eventually lead to sedation [8, 9]. Corticosteroid nasal sprays such as beclomethasone dipropionate, fluticasone propionate, fluticasone furoate, mometasone furoate, triamcinolone acetonide, and budesonide bind to intracellular glucocorticoid receptors in the cytoplasm of inflammatory cells and inhibit inflammation by down-regulating the inflammatory responses [7, 10]. In some cases, fighting against viral diseases with chemical drugs may be highly effective, but it may also cause severe adverse effects in human beings [11, 12]. It should also be considered that the prescription of nasal decongestants for children is not recommended[13]. Other nasal sprays, such as saline nasal spray, which is used to lavage the nasal cavity, are worth mentioning. It can help reduce inflammatory mediators in nasal secretions, remove pathogens, and improve ciliary function by decreasing mucosal concentration and increasing moisture in the nose [14]. Ipratropium bromide, sodium cromoglycate, and zinc nasal sprays are also frequently used, but their efficacy is controversial [3, 7, 12, 15].

Moreover, the therapeutic potential of medicinal plants is confirmed and can be an important source of novel drugs [16]. Plants and natural derived extracts with antiviral activity might be an alternative method for chemical compounds in upper respiratory tract infections' treatment [11]. In other words, the link among botanical therapeutics, naturally derived pharmaceuticals, and multi-component botanical drugs and health have been shown by findings. It was also confirmed that these products would be useful agents in treatment and prevention [17].

OBJECTIVE

Due to the COVID-19 disease pandemic and efforts to find appropriate ways to cope with this virus, in this review, we tried to propose an effective method to reduce the severity of this disease by collecting data from previous clinical trials and animal studies on the effect of treating various viral infections of the upper respiratory tract with herbal nasal sprays.

CARRAGEENAN

Investigations showed that the most examined natural derived ingredient for upper respiratory tract viral infections' treatment is carrageenan [4, 5, 13, 18-20]. Carrageenan is a high-molecular sulphated galactose polymer and an indigestible polysaccharide derived from Rhodophyceae red algae (seaweeds). It is generally used in food preparations, cosmetic and pharmaceutical industries. It has gelling and emulsifying properties[21]. Carrageenan is used in three copolymer forms as Iota, Kappa, and Lambda, due to the number and location of sulphate moieties on the hexose scaffold structure that have different degrees of solubility and gelling properties. Carrageenan compounds are listed in the US Food and Drug Administration as "Generally Recognized as Safe" (GRAS) products for consumption and topical applications [4, 13, 18].

There is some evidence that shows that carrageenan formerly had been used as a home remedy to cure colds[21]. Evidence revealed that carrageenan has antiviral activity against some animal viruses. It seems that carrageenan has the ability to reduce the immune responses *via* lowering a viral load by forming a barrier on the mucosal surface and inhibiting the interface between the virus and cellular surface. In consequence, it could interfere with the mechanism of the cells' infection. However, it should be noted that antiviral success depends on the type of polymer, virus, and host cells [4, 13, 18].

In 2010, in a study on efficacy and safety of an iota-carrageenan nasal spray in patients with common cold symptoms, 35 patients with early symptoms of common cold received Iota-carrageenan in a randomized, double-blind placebo-controlled exploratory trial. The results showed a significant reduction in the symptoms of the common cold and the viral load in nasal lavages. Furthermore, pro-inflammatory mediators FGF-2, Fractalkine, GRO, G-CSF, IL-8, IL-1a, IP-10, IL-10, and IFN-a2 were reduced in subjects using iota-carrageenan. Moreover, this method did not show any side effects [4].

In another double-blind, randomized placebo-control study by Fazekas *et al*. in 2012 on children with acute symptoms of common cold, clearance of disease time, viral load, and secondary infections with other respiratory viruses were reduced in the iota-carrageenan group compared with 0.9% sodium chloride solution (as placebo) group. This finding confirms the beneficial effects of iota-carrageenan in the treatment of the common cold. Failure to significantly reduce symptoms of the disease in this study could be due to the inability of children with an average age of 5 years to express their discomforts [13].

In a randomized, double-blind placebo-controlled trial, Ludwig *et al*. in 2013 investigated the difference of carrageenan-supplemented nasal spray and saline solution on 211 patients suffering from early symptoms of the common cold in decreasing symptoms and viral load in nasal fluids. As expected, local administration of carrageenan with nasal spray reduced the duration of cold symptoms and viral load in the nasal fluids of patients. In this study, viral load determination showed that the prevalence of rhinovirus or coronavirus infection was in more than 80% of the cases [5].

Koenighofer *et al*. analyzed individual patient data of two randomized controlled trials in 2014 to study the therapeutic effectiveness of carrageenan nasal spray in acute common cold. The findings presented a significant reduction in duration of disease, and fewer relapses and virus clearance have been observed in 126 carrageenan-treated patients. In both trials, virus-confirmed common cold was caused by three main virus subtypes: human rhinovirus, human coronavirus, and influenza A virus. The remarkable point is that carrageenan nasal spray showed the majority antiviral efficacy in the human coronavirus-infected population. The study data suggested that carrageenan is directly bound to the virus and prevented attachments of the virus to the cells, so carrageenan nasal spray exerts effects in an unspecific physical mode on all different viruses [19].

In a study which was conducted in 2015, the synergic activity of zanamivir and carrageenan in intranasal use against influenza A virus was evaluated *in-vitro* and *in-vivo*. Findings showed that both compounds were effective individually, but they show significantly more efficacy when used synergically. This combination can be a strategy to protect against newly emerging pandemic viruses throughout the time of identification, manufacturing, and vaccine research [20].

The most recent study by Graf *et al*. in 2018 as *in vitro* and *in vivo* experiments has been done to develop an effective nasal spray containing xylometazoline hydrochloride and iota-carrageenan for the symptomatic relief of rhinitis and sinusitis. The study results demonstrated that Iota-carrageenan does not affect the vasoconstrictive ability of xylometazoline HCl, and it also saves its efficacy and antiviral effectiveness in coping with human rhinovirus (hRV) 1a, hRV8, and human coronavirus OC43. They showed that the physical antiviral activity of carrageenan is based on creating a viscous layer at the mucosa that traps viruses and inhibits both primary and secondary infection [18].

Finally, the advantage of this compound is the disappearance of symptoms caused by a reduction in immune response and viral load in the common cold, without any side effects on nasal tissue, blood vessels, and glands. Thus, carrageenan is safe enough to use in the treatment or prevention of the common cold in adults and children [4, 19]. Due to the high prevalence of coronaviruses among viral common cold agents, it seems that it may also be useful in the treatment of a new emerging coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

OTHER NATURAL DERIVED INGREDIENTS

Aside from carrageenan, a mixture of three plant-derived components, including Euphorbium resinifera, Pulsatilla pratensis, and Luffa operculata have been investigated. Euphorbium compositum®SN, TheraMax, which contains both green tea and elderberry extracts, and Artemisia abrotanum L. are other plant extract-derived antiviral compounds with no toxicity and side effect [11, 22, 23].

Euphorbium compositum®SN is a homeopathic combination. In a study conducted by Glatthaar-Saalmüller *et al*. in 2001, the antiviral effect of Euphorbium compositum®SN on influenza A virus, respiratory syncytial virus (RSV), human rhinovirus (HRV), and herpes simplex virus type 1 (HSV-1) was investigated in an *in-vitro* model. The results of this analysis revealed an antiviral effect on these viruses. Also, Euphorbium compositum plant-derived components, E. resinifera and Pulsatilla pratensis, showed antiviral activity against RSV and low toxicity [11].

Remberg *et al*., in a study on Artemisia abrotanum L. derived nasal spray, showed that this traditional medicine could control allergic rhinitis symptoms through its anti-allergic and anti-inflammatory reactions [23].

In another study by *Smee et al*. in 2011 on green tea and elderberry extracted composition, TheraMax demonstrated antiviral activity probably through blocking virus adsorption against eight strains of influenza A and B which have been shown *in-vitro* and *in-vivo* [22]. Characteristics of these studies are summarized in Tables **1** and **2**.

There are multiple plant-derived intranasal compounds that can be suggested for the treatment of viral respiratory infections. However, according to the previous studies, the effect of plant-derived intranasal compounds on the prevention of viral respiratory infections in healthy or high-risk exposed people has not been widely practiced in clinical trials.

CORONAVIRUS OUTBREAKS

In the last two decades, the world has faced the emergence of three coronaviruses that have been globally spread and raised concerns. Coronaviruses are single-stranded, positive-sense RNA, enveloped, and nonsegmented viruses [24]. In 2003, in China, an untreatable and rapidly spreading respiratory illness with unknown etiology emerged. It turned out to be caused by an uncommon coronavirus whose sequence was significantly different from the known human coronaviruses at that time. The virus was eventually named SARS-CoV. Almost a decade later, in 2014, the new MERS-CoV coronavirus, which caused respiratory disease, appeared in the Middle East [24-26].

Recently, in December 2019, it was reported to the World Health Organization (WHO) that a group of patients with pneumonia of an unknown source had been observed in China. One week later, the novel coronavirus 2019 (SARS-CoV-2) was isolated from these patients. So far, the novel virus has infected more people than both of its predecessors, and therefore more deaths are expected [24].

COVID-19 DISEASE

Coronavirus disease (COVID-19) is an infection caused by SARS-CoV-2, which primarily involves the human respiratory system. The first cases were reported in December 2019 in Wuhan City, China. SARS-CoV-2 is highly transmittable and a pathogenic viral infection. So it is a great global public health concern now [27].

COVID-19 illness starts with the most common symptoms fever, cough, and fatigue; other revealed symptoms are sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia. Clinically chest CT scan presented as pneumonia, but there were also abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that lead to patient loss [28].

Transmission of infection is through coughing and sneezing large droplets by symptomatic or asymptomatic patients. Inhalation of these droplets or the connection of nose, mouth, and eyes with contaminated surfaces will lead to infection. Spread *via* aerosolization/fecal-oral routes is another possible way. However, there is no evidence of fetus infection, but the postnatal transmission is reported. It is noteworthy that the bacterial load in the nasal cavity is more frequent than in the throat. But no difference between symptomatic and asymptomatic people in viral load level has been found[29]. The pathogenesis mechanism of COVID-19 is not fully known yet, but its similarity to SARS-CoV and MERS-CoV will help us to have a reasonable hypothesis [30]. It seems that, like similar coronaviruses, SARS-CoV-2 spike(s) glycoprotein binds to the cell membrane receptors and enters the host cells [27].

As a result of the rapid spread of the COVID-19 disease among human beings, laboratory diagnosis methods of SARS-CoV-2 infection are important for early diagnosis and

Table 1. Characteristics of human studies.

Author	Type of study	Disease	Viruses	Intervention	Virus load Detection Method	Result
P. Remberg *et al*. 2004 [23]		Allergic rhinitis		Artemisia abrotanum L.		-Symptoms↓
Ron Eccles *et al*. 2010 [4]	Randomized, double-blind, placebo-controlled	Common cold	Influenza virus type A and B, respiratory syncytial virus type A and B, rhinoviruses (major/minor group viruses), parainfluenza virus types 1/2/3/4, human metapneumovirus, and coronavirus types OC43 and 229E	Iota-Carrageenan	Quantitative Real-time PCR	-Viral load ↓ -Symptoms↓ - Proinflammatory mediators↓
Tamas Fazekas *et al*. 2012 [13]	Randomized, double-blind, placebo-controlled	Common cold	Influenza virus type A and B, respiratory syncytial virus, rhinovirus, parainfluenzavirus (PIV1, PIV2, PIV3), human metapneumovirus, and coronaviruses	Iota-Carrageenan	Quantitative Real-time PCR	-Viral load ↓ -Disease clearance time ↓ -Secondary infection ↓
Martin Ludwig *et al*. 2013 [5]	Randomized, double-blind, placebo-controlled	Common cold	Influenza virus type A and B, respiratory syncytial virus, rhinovirus, parainfluenza viruses (PIV1, PIV2, PIV3), human metapneumovirus and coronavirus type OC43 and 229E,	Carrageenan	Quantitative Real-time PCR	-Viral load ↓ -Symptoms↓
Martin Koenighofer *et al*. 2014 [19]	Individual patient data analysis of two randomized controlled trials	Common cold	Influenza virus types A and B, respiratory syncytial virus, human rhinovirus, parainfluenza viruses (PIV1, PIV2, PIV3), human metapneumovirus, and coronavirus types OC43 and 229E.	Carrageenan	Quantitative Real-time PCR	-Viral load ↓ -Symptoms↓ -Disease clearance time ↓ -Disease relapse↓

necessary actions, and for this purpose, virus culture, immunological assay, and nucleic acid testing have been suggested [31].

An immunological assay is a serology test that detects the presence of SARS-CoV-2 antibodies. It is valuable when the RT-PCR test has not been done on negative cases or confirmed COVID-19-positive cases. There is a doubt about the utility of these immunological assays' test results for public health management purposes. Antibody tests can only be useful for detecting previous SARS-CoV-2 infections if used at least 15 or more days after infection and have a lower value in the first week of COVID-19 sickness exposure [32].

The gold standard method for SARS-CoV-2 detection is reverse transcription-quantitative polymerase chain reaction (RT-qPCR) [33], and currently, the most used targets for RT-qPCR are conserved regions of Orf1Ab(open reading frames1Ab), N (nucleocapsid), S (spike), and E (envelope protein) genes [34, 35].

The real-time RT-PCR tests sensitivity and specificity are not 100%. The main concern is the risk of false-negative and false-positive. False-negative results may occur by viral load difference in anatomic sites of patients and sampling procedures, lack of laboratory practice standard, personnel skill, mutations in the primer and probe-target regions, or mismatches between the primers and probes and the target sequences [36]. Several problems like contamination during sampling, contamination by PCR amplicons, contamination of reagents, cross-reactions with other viruses or genetic material could also lead to false-positive results[37].

Until now, there is not any approved guideline for COVID-19 treatment, so treatments are more supportive and symptomatic. Common precautions are maintaining hydration and nutrition, controlling fever, improving respiration and blood oxygen levels. Low to medium dose of corticosteroids, antibiotics/antifungals for co-infections, antiviral drugs which have been used based on the experience with SARS and MERS such as ribavirin and lopinavir/ritonavir, intravenous immunoglobulin, interferons, chloroquine, and plasma of patients recovered from COVID-19, are some probably efficient medications that are currently in use [29].

As mentioned previously, studies show that coronaviruses are one of the main causes of viral respiratory infections. Nowadays, the prevalence of SARS-CoV-2 has increased the interest of researchers in these viruses. In studies that have been done on SARS-CoV-2 until now, the prevalence and pathogenesis mechanisms of this virus are similar to the other coronaviruses. After the transition to nose and mouth, the SARS-CoV-2 virus attaches to the surface of respiratory cells

Table 2. Characteristics of animal and *in vitro* studies.

Author	Type of study	Disease	Viruses	Intervention	Animal tests	Cells tests
Christine Graf *et al.* 2018 [18]	Animal model (rabbit) and *In vitro* (The human cervical epithelial carcinoma cell line (HeLa) and Vero (embryonic African green monkey kidney) cells)	Rhinitis and sinusitis	Human rhinoviruses (hRV1a and hRV8) and human coronavirus OC43	Xylometazoline hydrochloride and iota-carrageenan	2-Week local tolerance and toxicity study in rabbits	Cytopathic effect reduction assay, Hemagglutination inhibition (HAI) assay, Hen's egg test on the chorioallantoic membrane (HET-CA M), and Permeation studies utilizing bovine respiratory mucosa of the nasal cavity
Martina Morokutti-Kurz *et al.* 2015 [20]	Animal model (C57BL/6 mice) and *In vitro* (Madin-Darby canine kidney (MDCK) cells)	Influenza A infections	Influenza virus A strains (H1N1(09)pdm, H3N2, H5N1, H7N7)	Zanamivir and Kappa-carrageenan and iota-carrageenan		Evaluation of anti-influenza activity in a semi-liquid plaque assay
B. Glatthaar-Saalmüller *et al.* 2001 [11]	*In vitro* (Madin-Darby canine kidney (MDCK) cells/MDCK, HEp-2 and HeLa cell cultures)	Rhinitis and sinusitis	Influenza virus A, respiratory syncytial virus, human rhinovirus, and herpes simplex virus type 1	Euphorbium compositum		Hemagglutination assays, enzyme immunoassays, plaque assays, and analyses of the *in vitro* cytotoxicity (MTT assay)
Donald F Smee *et al.* 2001 [22]	Animal model (BALB/c mice) and *In vitro* (Madin–Darby canine kidney cell)	influenza virus infections	Influenza virus A and B(influenza A/NWS/33 (H1N1))	TheraMax		

and enters them into the host body, eventually leading to proliferation and pathogenesis. Studies have shown that most of the viral load is in the nasal cavity of the virus carrier, even when he/she is symptomatic or asymptomatic [29].

Therefore, previous strategies may be effective in preventing and treating COVID-19 disease [38]. According to the previous studies, we found that some natural derived ingredients have a restrictive effect on viral common cold. Therefore, they may also be effective on SARS-CoV-2. One of these compounds is carrageenan, which has been shown to play a limited role in the replication and pathogenesis of respiratory viruses, especially coronavirus [19].

CONCLUSION

Due to the new emergence of SARS-CoV-2, extensive research works and experimental trials are needed to find effective and rational treatment and prevention strategies. But based on evidence considering safety, carrageenan nasal sprays may also be helpful along with other medications for the treatment of COVID-19. In addition, this spray may also be used to prevent transmission in healthy people in the long term. Moreover, now that there is no definitive cure for COVID-19 disease so far, the use of carrageenan or other herbal ingredients nasal spray may block the SARS-CoV-2 virus from entering the lungs of an affected person and prevent the disease from emerging or exacerbating. It also can prevent virus transmission to other susceptible persons, healthcare providers, those with underlying medical conditions, including immunodeficiency disorders, cardiovascular disease, diabetes, chronic respiratory disease, organ transplants, cancer, patient exposures, asymptomatic COVID-19 carriers, and older adults. This proposed approach could be investigated in further studies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict interests.

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REFERENCES

[1] Monto, A.S. Epidemiology of viral respiratory infections. *Am. J. Med.*, **2002**, *112*(6)(Suppl. 6A), 4S-12S. http://dx.doi.org/10.1016/S0002-9343(01)01058-0 PMID: 11955454

[2] Chen, Y.; Liu, Q.; Guo, D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J. Med. Virol.*, **2020**, *92*(4), 418-423.
http://dx.doi.org/10.1002/jmv.25681 PMID: 31967327

[3] van Driel, M.L.; Scheire, S.; Deckx, L.; Gevaert, P.; De Sutter, A. What treatments are effective for common cold in adults and children? *BMJ*, **2018**, *363*, k3786.
http://dx.doi.org/10.1136/bmj.k3786 PMID: 30305295

[4] Eccles, R.; Meier, C.; Jawad, M.; Weinmüllner, R.; Grassauer, A.; Prieschl-Grassauer, E. Efficacy and safety of an antiviral Iota-Carrageenan nasal spray: a randomized, double-blind, placebo-controlled exploratory study in volunteers with early symptoms of the common cold. *Respir. Res.*, **2010**, *11*(1), 108.
http://dx.doi.org/10.1186/1465-9921-11-108 PMID: 20696083

[5] Ludwig, M.; Enzenhofer, E.; Schneider, S.; Rauch, M.; Bodenteich, A.; Neumann, K.; Prieschl-Grassauer, E.; Grassauer, A.; Lion, T.; Mueller, C.A. Efficacy of a carrageenan nasal spray in patients with common cold: a randomized controlled trial. *Respir. Res.*, **2013**, *14*, 124.
http://dx.doi.org/10.1186/1465-9921-14-124 PMID: 24219370

[6] Heikkinen, T.; Järvinen, A. The common cold. *Lancet*, **2003**, *361*(9351), 51-59.
http://dx.doi.org/10.1016/S0140-6736(03)12162-9 PMID: 12517470

[7] Whittaker, C. Nasal sprays: a short review. *S. Afr. Pharm. J.*, **2011**, *78*(7), 21-23.

[8] Simon, M.W. The Efficacy of Azelastine in the Prophylaxis of Acute Upper Respiratory Tract Infections. *Pediatr. Asthma Allergy Immunol.*, **2003**, *16*(4), 275-282.
http://dx.doi.org/10.1089/088318703322751327

[9] Meltzer, E.O.; Hampel, F.C.; Ratner, P.H.; Bernstein, D.I.; Larsen, L.V.; Berger, W.E. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, &. *Immunology*, **2005**, *95*(6), 600-606.

[10] Hayward, G.; Thompson, M.J.; Perera, R.; Del Mar, C.B.; Glasziou, P.P.; Heneghan, C.J. Corticosteroids for the common cold. *Cochrane Database Syst. Rev.*, **2015**, (10), CD008116. PMID: 26461493

[11] Glatthaar-Saalmuller, B; Fallier-Becker, P. Antiviral action of Euphorbium compositum and its components. *Forschende Komplementarmedizin und klassische Naturheilkunde = Research in complementary and natural classical medicine.*, **2001**, *8*(4), 207-12.
http://dx.doi.org/10.1159/000057223

[12] Corey, JP; Houser, SM; Ng, BA Nasal congestion: a review of its etiology, evaluation, and treatment. *Ear, nose, & throat journal.*, **2000**, *79*(9), 690-3.
http://dx.doi.org/10.1177/014556130007900908

[13] Fazekas, T.; Eickhoff, P.; Pruckner, N.; Vollnhofer, G.; Fischmeister, G.; Diakos, C.; Rauch, M.; Verdianz, M.; Zoubek, A.; Gadner, H.; Lion, T. Lessons learned from a double-blind randomised placebo-controlled study with a iota-carrageenan nasal spray as medical device in children with acute symptoms of common cold. *BMC Complement. Altern. Med.*, **2012**, *12*, 147.
http://dx.doi.org/10.1186/1472-6882-12-147 PMID: 22950667

[14] Tano, L.; Tano, K. A daily nasal spray with saline prevents symptoms of rhinitis. *Acta Otolaryngol.*, **2004**, *124*(9), 1059-1062.
http://dx.doi.org/10.1080/00016480410017657 PMID: 15513550

[15] Hulisz, D. Efficacy of zinc against common cold viruses: an overview. *J Am Pharm Assoc (2003)*, **2004**, *44*(5), 594-603.
http://dx.doi.org/10.1331/1544-3191.44.5.594.Hulisz PMID: 15496046

[16] Atanasov, A.G.; Waltenberger, B.; Pferschy-Wenzig, E.M.; Linder, T.; Wawrosch, C.; Uhrin, P.; Temml, V.; Wang, L.; Schwaiger, S.; Heiss, E.H.; Rollinger, J.M.; Schuster, D.; Breuss, J.M.; Bochkov, V.; Mihovilovic, M.D.; Kopp, B.; Bauer, R.; Dirsch, V.M.; Stuppner, H. Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnol. Adv.*, **2015**, *33*(8), 1582-1614.
http://dx.doi.org/10.1016/j.biotechadv.2015.08.001 PMID: 26281720

[17] Raskin, I.; Ribnicky, D.M.; Komarnytsky, S.; Ilic, N.; Poulev, A.; Borisjuk, N.; Brinker, A.; Moreno, D.A.; Ripoll, C.; Yakoby, N.; O'Neal, J.M.; Cornwell, T.; Pastor, I.; Fridlender, B. Plants and human health in the twenty-first century. *Trends Biotechnol.*, **2002**, *20*(12), 522-531.
http://dx.doi.org/10.1016/S0167-7799(02)02080-2 PMID: 12443874

[18] Graf, C.; Bernkop-Schnürch, A.; Egyed, A.; Koller, C.; Prieschl-Grassauer, E.; Morokutti-Kurz, M. Development of a nasal spray containing xylometazoline hydrochloride and iota-carrageenan for the symptomatic relief of nasal congestion caused by rhinitis and sinusitis. *Int. J. Gen. Med.*, **2018**, *11*, 275-283.
http://dx.doi.org/10.2147/IJGM.S167123 PMID: 30013382

[19] Koenighofer, M.; Lion, T.; Bodenteich, A.; Prieschl-Grassauer, E.; Grassauer, A.; Unger, H.; Mueller, C.A.; Fazekas, T. Carrageenan nasal spray in virus confirmed common cold: individual patient data analysis of two randomized controlled trials. *Multidiscip. Respir. Med.*, **2014**, *9*(1), 57.
http://dx.doi.org/10.1186/2049-6958-9-57 PMID: 25411637

[20] Morokutti-Kurz, M.; König-Schuster, M.; Koller, C.; Graf, C.; Graf, P.; Kirchoff, N.; Reutterer, B.; Seifert, J.M.; Unger, H.; Grassauer, A.; Prieschl-Grassauer, E.; Nakowitsch, S. The Intranasal Application of Zanamivir and Carrageenan Is Synergistically Active against Influenza A Virus in the Murine Model. *PLoS One*, **2015**, *10*(6), e0128794.
http://dx.doi.org/10.1371/journal.pone.0128794 PMID: 26053018

[21] Necas, J.; Bartosikova, L. Carrageenan: a review. *Vet. Med. (Praha)*, **2013**, *58*(4)
http://dx.doi.org/10.17221/6758-VETMED

[22] Smee, D.F.; Hurst, B.L.; Wong, M.H. Effects of TheraMax on influenza virus infections in cell culture and in mice. *Antivir. Chem. Chemother.*, **2011**, *21*(6), 231-237.
http://dx.doi.org/10.3851/IMP1744 PMID: 21730370

[23] Remberg, P.; Björk, L.; Hedner, T.; Sterner, O. Characteristics, clinical effect profile and tolerability of a nasal spray preparation of Artemisia abrotanum L. for allergic rhinitis. *Phytomedicine*, **2004**, *11*(1), 36-42.
http://dx.doi.org/10.1078/0944-7113-00350 PMID: 14971719

[24] Guarner, J. *Three emerging coronaviruses in two decades: the story of SARS, MERS, and now COVID-19*; Oxford University Press US, **2020**.
http://dx.doi.org/10.1093/ajcp/aqaa029

[25] Oboho, I.K.; Tomczyk, S.M.; Al-Asmari, A.M.; Banjar, A.A.; Al-Mugti, H.; Aloraini, M.S.; Alkhaldi, K.Z.; Almohammadi, E.L.; Alraddadi, B.M.; Gerber, S.I.; Swerdlow, D.L.; Watson, J.T.; Madani, T.A. 2014 MERS-CoV outbreak in Jeddah--a link to health care facilities. *N. Engl. J. Med.*, **2015**, *372*(9), 846-854.
http://dx.doi.org/10.1056/NEJMoa1408636 PMID: 25714162

[26] Skowronski, D.M.; Astell, C.; Brunham, R.C.; Low, D.E.; Petric, M.; Roper, R.L.; Talbot, P.J.; Tam, T.; Babiuk, L. Severe acute respiratory syndrome (SARS): a year in review. *Annu. Rev. Med.*, **2005**, *56*, 357-381.
http://dx.doi.org/10.1146/annurev.med.56.091103.134135 PMID: 15660517

[27] Shereen, M.A.; Khan, S.; Kazmi, A.; Bashir, N.; Siddique, R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *J. Adv. Res.*, **2020**, *24*, 91-98.
http://dx.doi.org/10.1016/j.jare.2020.03.005 PMID: 32257431

[28] Rothan, H.A.; Byrareddy, S.N. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J. Autoimmun.*, **2020**, *109*, 102433.
http://dx.doi.org/10.1016/j.jaut.2020.102433 PMID: 32113704

[29] Singhal, T. A review of coronavirus disease-2019 (COVID-19). *Indian J. Pediatr.*, **2020**, *87*(4), 281-286.
http://dx.doi.org/10.1007/s12098-020-03263-6 PMID: 32166607

[30] Li, X.; Geng, M.; Peng, Y.; Meng, L.; Lu, S. Molecular immune pathogenesis and diagnosis of COVID-19. *J. Pharm. Anal.*, **2020**, *10*(2), 102-108.
http://dx.doi.org/10.1016/j.jpha.2020.03.001 PMID: 32282863

[31] Mathuria, J.P.; Yadav, R.; Rajkumar, Laboratory diagnosis of SARS-CoV-2 - A review of current methods. *J. Infect. Public Health*, **2020**, *13*(7), 901-905.
http://dx.doi.org/10.1016/j.jiph.2020.06.005 PMID: 32534946

[32] Deeks, JJ; Dinnes, J; Takwoingi, Y; Davenport, C; Spijker, R; Taylor-Phillips, S Antibody tests for identification of current and

past infection with SARS-CoV-2. Cochrane Database of Systematic Reviews. **2020**, *2020*(6)

[33] Falzone, L.; Musso, N.; Gattuso, G.; Bongiorno, D.; Palermo, C.I.; Scalia, G.; Libra, M.; Stefani, S. Sensitivity assessment of droplet digital PCR for SARS-CoV-2 detection. *Int. J. Mol. Med.,* **2020**, *46*(3), 957-964.
http://dx.doi.org/10.3892/ijmm.2020.4673 PMID: 32705153

[34] Iglói, Z.; Leven, M.; Abdel-Karem Abou-Nouar, Z.; Weller, B.; Matheeussen, V.; Coppens, J.; Koopmans, M.; Molenkamp, R. Comparison of commercial realtime reverse transcription PCR assays for the detection of SARS-CoV-2. *J. Clin. Virol.,* **2020**, *129*, 104510.
http://dx.doi.org/10.1016/j.jcv.2020.104510 PMID: 32570045

[35] Wang, H.; Li, X.; Li, T.; Zhang, S.; Wang, L.; Wu, X.; Liu, J. The genetic sequence, origin, and diagnosis of SARS-CoV-2. *Eur. J. Clin. Microbiol. Infect. Dis.,* **2020**, *39*(9), 1629-1635.
http://dx.doi.org/10.1007/s10096-020-03899-4 PMID: 32333222

[36] Tahamtan, A.; Ardebili, A. *Real-time RT-PCR in COVID-19 detection: issues affecting the results*; Taylor & Francis, **2020**.

[37] Surkova, E.; Nikolayevskyy, V.; Drobniewski, F. False-positive COVID-19 results: hidden problems and costs. *Lancet Respir. Med.,* **2020**, *8*(12), 1167-1168.
http://dx.doi.org/10.1016/S2213-2600(20)30453-7 PMID: 33007240

[38] Cascella, M.; Rajnik, M.; Cuomo, A.; Dulebohn, S.C.; Di Napoli, R. *Features, Evaluation and Treatment Coronavirus (COVID-19)*; StatPearls, **2020**.