

1 **Carrageenan containing over-the-counter nasal and oral sprays inhibit**

2 **SARS-CoV-2 infection of airway epithelial cultures**

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17 # equal contribution

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19 **Running head:** Nasal and oral sprays against SARS-CoV-2

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21 **Key words:** carrageenan, virus transmission, virucidal, virus inhibition, sulfated  
22 polysaccharides

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36

37 **Abstract**

38 Pharmaceutical interventions are urgently needed to prevent SARS-CoV-2 infection and  
39 transmission. As SARS-CoV-2 infects and spreads via the nasopharyngeal airways, we  
40 analyzed the antiviral effect of selected nasal and oral sprays on virus infection *in vitro*. Two  
41 nose sprays showed virucidal activity but were cytotoxic precluding further analysis in cell  
42 culture. One nasal and one mouth spray suppressed SARS-CoV-2 infection of TMPRSS2-  
43 Vero E6 cells and primary differentiated human airway epithelial cultures. The antiviral  
44 activity in both sprays could be attributed to polyanionic ι- and κ-carrageenans. Thus,  
45 application of carrageenan containing nasal and mouth sprays may reduce the risk of  
46 acquiring SARS-CoV-2 infection and may limit viral spread, warranting further clinical  
47 evaluation.

48

49 **Introduction**

50 The coronavirus disease 2019 (COVID-19) causing agent, severe acute respiratory syndrome  
51 coronavirus 2 (SARS-CoV-2), emerged at the end of 2019 and quickly spread within the  
52 human population around the globe (57). Manifestations range from mild common cold  
53 symptoms to severe lung injury, multi-organ dysfunctions and eventually death, especially in  
54 the elderly or patients suffering from co-morbidities (18). Measures to confine the spread of  
55 the virus include lock-down strategies which severely affect socio-economic structures.  
56 SARS-CoV-2 is mainly transmitted via respiratory droplets and aerosols exhaled from  
57 infected individuals and subsequent exposure of the respiratory mucosa of an uninfected  
58 individual (19, 35, 54). Agents reducing viral loads in the throat and nasal cavity or protecting  
59 mucosal tissue from initial infection, may prevent infection and reduce virus spread between  
60 individuals (30, 48). Sprays applied to the nasal and oral mucosa to soothe symptoms, reduce  
61 disease duration and increase viral clearance of respiratory infections caused by viruses such

62 as rhino-, influenza- or common cold coronaviruses have been approved and are available as  
63 over-the-counter medicine. Some contain decongestant compounds like xylometazoline (16),  
64 tramazoline, or oxymetazoline (39) to reduce symptoms of nasal congestion (9). This effect is  
65 supported by moisturizing or gel forming mucoprotective substances such as dexpanthenol  
66 (39) and hydroxypropyl methylcellulose (42, 51). Additionally, sulfated polysaccharides such  
67 as carrageenans are included as broad-spectrum antiviral agents (12–14, 27, 31).

68 As SARS-CoV-2 infects the nasopharyngeal airways, we here analyzed one oral and five  
69 nasal sprays (Table 1) for their virucidal and antiviral activity against SARS-CoV-2. All  
70 sprays are commercially available and do not require prescription. Two of the sprays exert  
71 direct virucidal activity at high concentrations but also elicited cytotoxic effects. Two  
72 carrageenan-containing sprays inhibited SARS-CoV-2 infection of immortalized cells and,  
73 more importantly, fully-differentiated human airway epithelial cells resembling a crucial entry  
74 portal of the virus, with little to no effect on cell viability. Thus, application of these sprays  
75 may help to prevent from acquiring SARS-CoV-2 or suppress viral replication in the nasal  
76 epithelia in infected individuals, which may result in attenuated disease and reduced  
77 transmission rates. Further evaluation of antiviral nose sprays in clinical studies is warranted.

78

## 79 **Results**

80 To address whether commercially available, topically applied pharmaceuticals affect SARS-  
81 CoV-2, we first determined the virucidal activity of five nasal (products **A**, **C-F**) and one oral  
82 (product **B**) spray (Table 1). To this end, high titers of the SARS-CoV-2 isolate  
83 France/IDF0372 were incubated for 30 minutes in 90 % (v/v) PBS or products **A** to **F**.  
84 Remaining infectivity was determined by measuring the tissue culture infectious dose 50  
85 (TCID<sub>50</sub>) on Vero E6 cells. Incubation with products **A**, **B**, **E** and **F** resulted in similar  
86 infectious titers as incubation in PBS, showing that these sprays have no direct virucidal

87 activity (Fig. 1A). Products **C** and **D** inactivated SARS-CoV-2 infectivity entirely, however,  
88 also affected cell viability (observed by light microscopy) so that the detection limit increased  
89 to  $2 \times 10^3$  TCID<sub>50</sub>/ml (Fig. 1A, black lines), corresponding to a reduction of the viral titer by at  
90 least 99.5 %.

91 We next explored whether the sprays may inhibit SARS-CoV-2 infection. For this, the  
92 products were titrated on TMPRSS2-expressing Vero E6 cells which were subsequently  
93 infected with SARS-CoV-2. Viral infection was determined 2.5 days later by MTS assay (33).  
94 Simultaneously, cell viability in the presence of the products but absence of virus was  
95 determined by quantifying intracellular ATP concentrations. Final cell culture concentrations  
96 of products D-F that exceeded  $\sim 2$ -5 % (v/v) resulted in massive cell death precluding any  
97 reliable conclusion regarding antiviral activity (Fig. 1B). Product C, which was virucidal (Fig.  
98 1A), was also cytotoxic (half-maximal cytotoxic concentration, CC<sub>50</sub>  $\sim 4.4 \pm 0.15$  %) but  
99 reduced viral infection with a half-maximal inhibitory concentration (IC<sub>50</sub>) value of  $1.3 \pm 0.7$   
100 %, corresponding to a selectivity index (SI) of 3.3. The non-virucidal products A (a nasal  
101 spray) and B (a mouth spray) inhibited SARS-CoV-2 infection with IC<sub>50</sub> values of  $\sim 1.3 \pm 0.8$   
102 % (v/v; corresponding to a  $\sim 77$ -fold dilution of product A) and  $\sim 3.1 \pm 1.7$  % (v/v,  
103 corresponding to  $\sim 32$ -fold dilution of product B). Product A did not affect Vero E6 cell  
104 viability at concentrations up to 50 % (2-fold dilution) whereas product B reduced cell  
105 viability with a CC<sub>50</sub> values of  $\sim 19.3$  % ( $\sim 5$ -fold dilution, SI  $\sim 6.2$ ).

106 Products **A** and **B** contain carrageenans (Table 1), which are sulfated polysaccharides isolated  
107 from red seaweeds previously shown to exert antiviral activity (4, 13, 15, 17, 20, 24). Product  
108 **A** contains  $\iota$ -carrageenan (1.2 mg/ml) and  $\kappa$ -carrageenan (0.4 mg/ml), and product **B**  $\iota$ -  
109 carrageenan only (1.2 mg/ml). To evaluate whether these polyanions exert antiviral activity  
110 against SARS-CoV-2, we analyzed purified  $\iota$ - and  $\kappa$ -carrageenan as well as  $\iota$ -carrageenan  
111 only, without the additives of the products (Fig. 1C). Both carrageenan solutions reduced

112 SARS-CoV-2 infection with  $IC_{50}$  values of  $21\pm 13$   $\mu\text{g/ml}$  and  $33\pm 28$   $\mu\text{g/ml}$ , and did not affect  
113 cell viability at concentrations up to 160 and 120  $\mu\text{g/ml}$ , respectively (Fig. 1C). The antiviral  
114 activities of both carrageenan preparations are similar to those of products **A** and **B** with  
115 calculated  $IC_{50}$  values of  $20\pm 13$   $\mu\text{g/ml}$  and  $37\pm 20$   $\mu\text{g/ml}$ , respectively. Thus,  $\iota$ - and  $\kappa$ -  
116 carrageenans inhibit SARS-CoV-2 infection and are responsible for the antiviral activity in  
117 products **A** and **B**.

118 We next tested whether products **A** and **B** may also prevent SARS-CoV-2 infection of  
119 physiologically relevant target cells. For this, we generated from two donors fully  
120 differentiated human airway epithelial cultures (HAEC) which morphologically and  
121 functionally resemble the entry site for SARS-CoV-2 (19, 53). Cultures were exposed at the  
122 air-liquid-interface to either PBS, or a 2-fold dilution (50% (v/v)) of product **A** or **B**, and were  
123 then inoculated with SARS-CoV-2. One, two and three days later, cultures were stained for  
124 nuclei (DAPI) and SARS-CoV-2 spike protein as described (40), and then imaged by confocal  
125 microscopy (Fig. 2). At day 2, infected HAECs from both donors stained clearly positive for  
126 viral spike protein when treated with PBS. The signal intensities (Fig. 2A, B) and the number  
127 of infected cells (Fig. 2C, D) further increased at day 3, demonstrating productive infection.  
128 Products **A** and **B** blocked SARS-CoV-2 infection entirely (Fig. 2A, C) in HAECs from donor  
129 1, whereas a few spike positive cells could be detected in HAECs from donor 2 (Fig. 2B, D).  
130 Thus, SARS-CoV-2 infection of fully differentiated airway epithelial cell cultures can be  
131 efficiently reduced by carrageenan-containing nasal and mouth sprays.

132

### 133 **Discussion**

134 As SARS-CoV-2 primarily enters the human body via infection of nasal epithelial cells (50,  
135 54), we here evaluated whether nasal sprays may exert antiviral activity against this novel  
136 pathogen. We found that carrageenan-containing products **A** (a nose spray) and **B** (a mouth  
137 spray) inhibit SARS-CoV-2 infection of human airway epithelial cultures, which represent a

138 physiologically relevant entry site for SARS-CoV-2. Both over-the-counter products were  
139 applied as two-fold dilution at the air-liquid interface of the epithelia, and at these  
140 concentrations both products efficiently blocked SARS-CoV-2 infection of HAECs derived  
141 from two donors. The limited availability of these primary epithelia did not allow for testing  
142 of further dilutions of the sprays and hence to determine IC<sub>50</sub> values. However, dose-response  
143 inhibition studies performed in a cell line showed that a ~77-fold dilution of product **A**  
144 suppressed SARS-CoV-2 half-maximally, and a 10- to 20-fold dilution by more than 80 %,  
145 suggesting that application of the spray into the nostrils might reach local concentrations on  
146 nasal epithelia that are sufficient to block SARS-CoV-2 infection.

147

148 Products **C** and **D** showed virucidal effects upon incubation of virus in 90% (v/v) of the  
149 compounds. This virucidal effect is likely mediated by the ingredients xylometazoline  
150 hydrochloride and dexpanthenol (45) (present in product **D**), or the additive benzalkonium (2)  
151 (present in products **C** and **D**), all of which have previously been described as virucidal (2,  
152 45). Similar antiviral activities against SARS-CoV-2 were also reported for povidone-iodine  
153 containing sprays (present in product **D**), probably because of the disinfectant properties (1).  
154 Upon application of diluted nose sprays, antiviral activity was lost for product **D** but not for  
155 product **C**, which showed an IC<sub>50</sub> value of  $1.3 \pm 0.7$  % (v/v). However, both sprays  
156 diminished cell viability at concentrations exceeding 5 % (v/v) in cell culture, possibly due to  
157 the ingredient benzalkonium, a known cytotoxic preservative in both sprays (5, 8, 26). Also,  
158 the micro-gel containing products **E** and **F** were cytotoxic under conditions tested precluding  
159 any conclusions regarding a possible anti-SARS-CoV-2 effect. It should be mentioned,  
160 however, that the cytotoxic effects of products **C-F** obtained in our *in vitro* cell cultures  
161 assays do not reflect toxicity *in vivo*, since all sprays analyzed are tested for safety in humans.  
162 Furthermore, we emphasize that a repeated administration of nasal sprays (or respective

163 drops) containing decongestants may have harmful effects on the mucosa, which may  
164 inadvertently foster infection (25, 41, 44).

165

166 Carrageenan containing products **A** and **B** inhibited SARS-CoV-2 infection of Vero E6 cells  
167 with  $IC_{50}$  values of  $1.3 \pm 0.8$  % (corresponding to  $20 \pm 13$   $\mu\text{g/ml}$  of  $\iota$ - $\kappa$ -carrageenan) and  $3.1 \pm 1.7$   
168 % (corresponding to  $37 \pm 20$   $\mu\text{g/ml}$ ). The anti-SARS-CoV-2 activity of purified  $\iota$ - $\kappa$ -  
169 carrageenans were in the same range, showing that these polymers are the responsible  
170 antiviral factors in products **A** and **B**. Carrageenans have previously been reported to have  
171 broad antiviral activity against e.g. influenza A, Dengue, hepatitis A, rhino- and common cold  
172 coronaviruses in cell culture and some clinical studies (15, 20, 27, 29), and application of  
173 carrageenan-containing nose sprays to combat SARS-CoV-2 has been suggested (21, 43, 47).  
174 Four preprint articles support our findings and show that a mixture of gellan and  $\lambda$ -  
175 carrageenan (36) or  $\iota$ -carrageenan inhibit SARS-CoV-2 infection (3, 24, 38). The antiviral  
176 effect of carrageenans is most likely based on decreased viral attachment to and entry into  
177 target cells.  $\iota$ -carrageenan has been shown to interfere with papilloma or rhinovirus binding  
178 and entry due to its sulphated polysaccharide characteristics that mimic cellular heparan  
179 sulfates or aggregates viral particles (4, 17). Viral binding by  $\iota$ -carrageenan has also been  
180 shown for influenza A and human coronavirus OC43 (29, 37). Thus,  $\iota$ - and  $\kappa$ -carrageenan,  
181 which only differ in the number and location of sulphate moieties on the hexose scaffolds,  
182 potentially inhibit SARS-CoV-2 by a similar mechanism. This is supported by a recent study  
183 that confirmed inhibition and suggested SARS-CoV-2 aggregation by  $\iota$ -carrageenan (49).

184

185 Carrageenan containing products **A** and **B** do not contain potentially harmful decongestants.  
186 Furthermore, clinical trials showed that  $\iota$ -carrageenan containing sprays have a good safety  
187 profile and resulted in symptomatic benefit, reduced duration of symptoms, and reduced viral  
188 loads in adult and pediatric patients with common cold symptoms (12–14, 27, 31). Thus,

189 application of product A may be advisable as prophylactic agent to protect from acquiring  
190 SARS-CoV-2, or at the very early stage of viral infection, because it may reduce viral spread  
191 and viral loads in the nasal cavity. Notably, development of severe COVID-19 is always  
192 associated with viral dissemination from the upper into the lower respiratory tract. Thus,  
193 reducing viral infectivity in the nasal cavity by antiviral nasal sprays or in the oral cavity by  
194 oral sprays and rinses (34) early in infection may attenuate disease outcome (29), viral spread  
195 or transmission. It has to be considered that sprays applied to the nasal or oral cavity will not  
196 be evenly distributed as a protective film but are instead confined to some areas (11, 23, 28).  
197 Moreover, the deposited substance will be cleared by mucociliary (23, 42, 46) or salivary  
198 clearance (7, 22, 32). Thus, the protective effect might be temporally restricted, and not  
199 replace the effect of wearing a protective mask. Nonetheless, whilst providing only some  
200 protection, application of the sprays on already infected areas might prevent local spread of  
201 the virus potentially reducing viral loads and thus symptoms or transmission to another  
202 individuum.

203

204 In conclusion,  $\iota$ - $\kappa$ -carrageenan containing sprays might be useful repurposed pharmaceuticals  
205 for prevention and treatment of SARS-CoV-2/COVID-19 and animal and clinical studies are  
206 urgently required to evaluate efficacy in both settings. Finally, it should also be considered to  
207 improve the current formulations by combination of carrageenans with other anti-SARS-CoV-  
208 2 agents, e.g. gelating agents (36), molecular tweezers (52), peptides (55, 56) or neutralizing  
209 antibodies (10, 16).

210

## 211 **Material and Methods**

212 *Reagents.*

213 Viruseptin nasal and oral sprays were obtained from Häsla Pharma GmbH, Nasic from  
214 Klosterfrau Berlin GmbH, Rhinospray from Sanofi-Aventis, and Wick Erste Abwehr and  
215 Wick Sinex Avera from Wick Pharma, Procter & Gamble GmbH. I- and  $\kappa$ -carrageenan were  
216 purchased from Sigma.

217

#### 218 *Cell culture.*

219 All cells were cultured in Dulbecco's modified Eagle's medium (DMEM, Gibco) containing  
220 100 units/ml penicillin, 100  $\mu$ g/ml streptomycin, 2 mM L-glutamine. Vero E6 (*Cercopithecus*  
221 *aethiops* derived epithelial kidney) medium was supplemented with 2.5% heat-inactivated  
222 fetal calf serum (FCS), 1 mM sodium pyruvate, and 1x non-essential amino acids. Caco-2  
223 (human epithelial colorectal adenocarcinoma) cells (kindly provided by Holger Barth) were  
224 supplemented with 10% FCS. Tmprss2-expressing Vero E6 cells (kindly provided by the  
225 National Institute for Biological Standards and Control (NIBSC), #100978) were  
226 supplemented with 10% FCS and 1 mg/ml geneticin.

227

#### 228 *Generation of air-liquid interface cultures of human airway epithelial cells.*

229 Differentiated air-liquid interface (ALI) cultures of human airway epithelial cells (HAECs)  
230 were generated from primary human basal cells isolated from airway epithelia as recently  
231 described (53). Cells were isolated from tissue obtained from a male and a female donor in the  
232 age range 25-50 years. All experiments were performed with approval of the ethics committee  
233 of Medical School Hannover (Project no. 2701-2015). In short,  $3.5 \times 10^4$  cells were seeded  
234 onto the apical side of collagen-coated, 6.5 mm Transwell filters (Corning Costar) in 200  $\mu$ l  
235 apical and 600  $\mu$ l basolateral growth medium. After 48 h the apical medium was replaced and  
236 after 72 - 96 h, upon confluency, completely removed (air-lifting). Then, the basolateral  
237 medium was replaced by differentiation medium, consisting of DMEM-H and LHC Basal  
238 (1:1) (Thermo Fisher) supplemented with Airway Epithelial Cell Growth Medium

239 Supplement Pack and was replaced every 2 days. Air-lifting defined day 0 of ALI culture and  
240 experiments were performed at day 25 to 28. To avoid mucus accumulation on the apical side,  
241 cells were washed apically with PBS for 30 min every three days from day 14 onwards.

242

243 *Virus strain and virus propagation.*

244 Viral isolate BetaCoV/France/IDF0372/2020 (#014V-03890) was obtained through the  
245 European Virus Archive global. Virus was propagated by inoculation of 70% confluent Caco-  
246 2 cells in 75 cm<sup>2</sup> cell culture flasks in medium containing 15 mM HEPES. Three days post  
247 inoculation when a strong cytopathic effect (CPE) was visible supernatants were harvested.  
248 Supernatants were centrifuged for 5 min at 1,000×g to remove cellular debris, aliquoted and  
249 stored at –80 °C. Infectious virus titer was determined as plaque forming units as previously  
250 described (6).

251

252 *TCID<sub>50</sub> endpoint titration.*

253 To determine the tissue culture infectious dose 50 (TCID<sub>50</sub>), 20,000 Vero E6 cells were  
254 seeded per 96 well. 10 µl SARS-CoV-2 was mixed with 90 µl PBS or compound and  
255 incubated for 30 min at room temperature. Then, the mixture was titrated 5-fold and 18 µl of  
256 each dilution was used for inoculation in triplicates in total 180 µl. Cells were incubated for 6  
257 days and monitored for CPE. TCID<sub>50</sub>/ml was calculated according to Reed and Muench and  
258 detection limits determined by minimal applied virus dilution or cytotoxicity of the present  
259 compound.

260

261 *SARS-CoV-2 infection assay.*

262 To assess infection rate, virus-induced cell death was determined by quantifying cell viability  
263 via MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-  
264 tetrazolium) assay. To this end, 18,000 TMPRSS2-expressing Vero E6 cells were seeded in

265 96 well plates. The next day, the respective compound of interest was added and the cells  
266 inoculated with the desired multiplicity of infection (MOI) of SARS-CoV-2 in a total volume  
267 of 180  $\mu$ l. After 2.5 days, when CPE was visible, 36  $\mu$ l of CellTiter 96® AQueous One  
268 Solution Reagent (Promega G3580) was added to the medium and incubated for 3 h at 37°C.  
269 Then, optical density (OD) was recorded at 620 nm using an Asys Expert 96 UV microplate  
270 reader (Biochrom). All values were corrected for the background signal derived from  
271 uninfected cells and untreated controls were set to 100% infection.

272

### 273 *Cell viability assay.*

274 Cytotoxicity of the compounds was assessed using a cell viability assay measuring ATP levels  
275 in cells lysates with a commercially available kit (CellTiter-Glo®, Promega). Experiments  
276 were performed corresponding to the respective infection assays in the absence of the  
277 compound.

278

### 279 *Effect of product A and B on SARS-CoV-2 infection of HAECs.*

280 Immediately before infection, the apical surface of HAECs were washed three times with 200  
281  $\mu$ l PBS to remove accumulated mucus. Next, 50  $\mu$ l PBS or product, and 50  $\mu$ l SARS-CoV-2  
282 (MOI 0.07) were added to the apical surface and incubated for 2 h at 37°C before inoculum  
283 was removed and cells washed three times with PBS. After one, two, and three days, cells  
284 were fixed for 30 min in 4% paraformaldehyde in PBS and permeabilized for 10 min with  
285 0.2% saponin and 10% FCS in PBS (perm/staining buffer). Cells were washed twice with  
286 PBS and stained with for SARS-CoV-2 spike protein (ab252690, abcam) diluted 1:300,  
287 respectively, in staining buffer over night at 4°C. After two PBS-washes, cells were stained  
288 with AlexaFluor488-labelled anti-rabbit anti-rat secondary antibody, respectively (all 1:500;  
289 Thermo Scientific) and DAPI + phalloidin AF 405 (1:5,000; Thermo Scientific) for 1 h at  
290 room temperature. Images were taken on an inverted confocal microscope (Leica TCS SP5)

291 using a 40x lens (Leica HC PL APO CS2 40x1.25 OIL). Images for the blue (DAPI) and  
292 green (AlexaFluor488) channel were taken using appropriate excitation and emission settings  
293 that were kept constant for all the acquisitions. For quantification, randomly chosen locations  
294 in each filter were selected and z-stacks acquired. A maximum z-projection was performed  
295 and anti-SARS-CoV-2 positive cells per area (0.15 mm<sup>2</sup>) visually identified and counted.

296  
297 **Data availability:** All data are available upon request to qualified researcher.

298

299 **Funding:** This project has received funding through a Collaborative Research Centre grant of  
300 the German Research Foundation (316249678 – SFB 1279) and from the European Union’s  
301 Horizon 2020 research and innovation programme under grant agreement No 101003555  
302 (Fight-nCoV) to JM and ANZ. JAM is indebted to the Baden-Württemberg Stiftung for the  
303 financial support of this research project by the Elite Program for Postdocs. DS, CC, TW, LW  
304 and RG are part of and RG is funded by a scholarship from the International Graduate School  
305 in Molecular Medicine Ulm. JM and MF further acknowledge funding by the Ministry for  
306 Science, Research and the Arts of Baden-Württemberg, Germany, and the German Research  
307 Foundation (458685747 - Fokus-Förderung COVID-19).

### 308 **Acknowledgments**

309 We would like to thank Daniela Krnavek and Nicola Schrott for technical assistance.

310 **Competing interests:** All authors declare to have no competing interest.

311

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501

## 502 **Figure Legends**

503 **Fig. 1. Effect of nasal and oral sprays as well as carrageenans on SARS-CoV-2.** A) SARS-CoV-2  
504 was incubated for 30 min in 90 % PBS or products A-F. The remaining infectious titer was determined  
505 by TCID<sub>50</sub> analysis on Vero E6 cells. Values shown are means ± SD derived from three independent  
506 experiments, each performed in technical triplicates. Black lines indicate detection limits that increase  
507 upon cytotoxicity of the respective compound which was observed by light microscopy. B) and C)  
508 TMPRSS2-expressing Vero E6 cells were treated with indicated concentrations of product A-F (B) or  
509 carrageenans (C) and infected with SARS-CoV-2. Infection rates were determined 2.5 days later by  
510 MTS assay (blue squares). For determination of toxicity, cells were treated with indicated  
511 concentrations of compounds in the absence of virus, and cellular ATP was measured by CellTiter-Glo  
512 assay 2.5 days later (black triangles). Values shown in B and C are means ± SEM derived from two  
513 (Product C, D, E and F) or three (Product A, B, ι- and κ-carrageenan, and ι-carrageenan) independent  
514 experiments, each performed in technical triplicates.

515

516 **Fig. 2. Product A and B inhibit SARS-CoV-2 infection of primary human airway epithelial**  
517 **cultures (HAEC).** A, B) HAEC derived from donor 1 (A) and 2 (B) were exposed to PBS or 50 %  
518 (v/v) of product A or B, and then infected with SARS-CoV-2. After 2 hours, virus and compound  
519 mixture were removed and cells washed in PBS to restore air-liquid interface. After 1, 2 and 3 days,

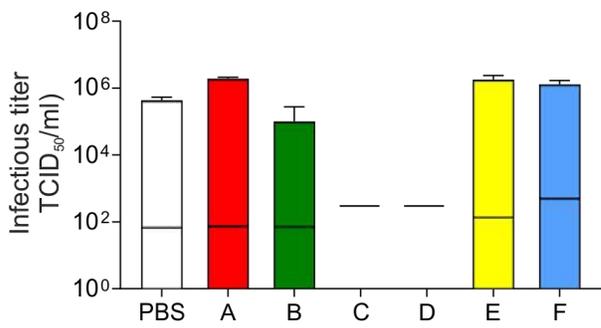
520 filters were fixed and stained for SARS-CoV-2 spike protein (green) and cell nuclei (blue) and imaged  
521 by confocal microscopy. Shown are merged images. Scale bars represent 100  $\mu\text{m}$ . *n.a.*, not available.  
522 **C, D)** Number of infected cells per area were obtained by counting SARS-CoV-2 infected cells within  
523 microscopic images. Data represent analysis of 3-5 images per timepoint and condition and are means  
524  $\pm$  standard deviation.

1 **Table 1: Overview and composition of tested products A-F.**

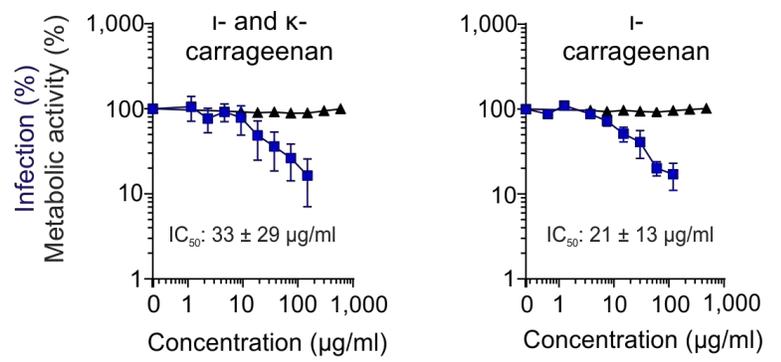
Product	Trade name	Active agent	Additives
A	Viruseptin (nasal)	ι- and κ-carrageenan (1.2 and 0.4 mg/ml)	sodium chloride
B	Viruseptin (oral)	ι-carrageenan (1.2 mg/ml)	sodium chloride, xylitol, cherry flavor
C	Nasic (nasal)	xylometazoline hydrochloride (0.1%), dexpanthenol (5%)	benzalkonium chloride, monopotassium phosphate, disodium phosphate dodecahydrate
D	Rhinospray (nasal)	tramazoline hydrochloride (1.264 mg/ml)	sodium chloride, citric acid, benzalkonium chloride, menthol, cineol, camphor racemic, sodium hydroxide, magnesium sulfate, magnesium chloride, calcium chloride, sodium hydrogen carbonate, povidone-iodine glycerol 85%, hyromellose
E	Wick Erste Abwehr (nasal)	hydroxypropyl methylcellulose	succinic acid, disodium succinate, pyroglutamic acid
F	Wick Sinex Avera (nasal)	oxymetazoline hydrochloride (0.5 mg/ml)	sorbitol, trisodium citrate, polysorbat 80, benzyl alcohol, citric acid, benzalkonium chloride, acesulfame potassium, menthol, cineol, sodium edetate, aloe dry extract, L-carvone

2

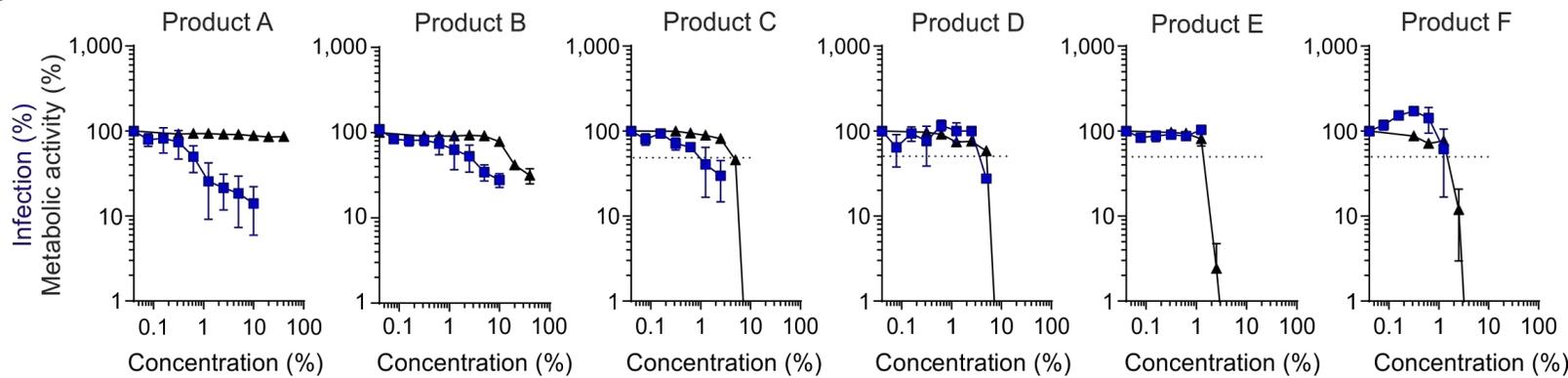
A



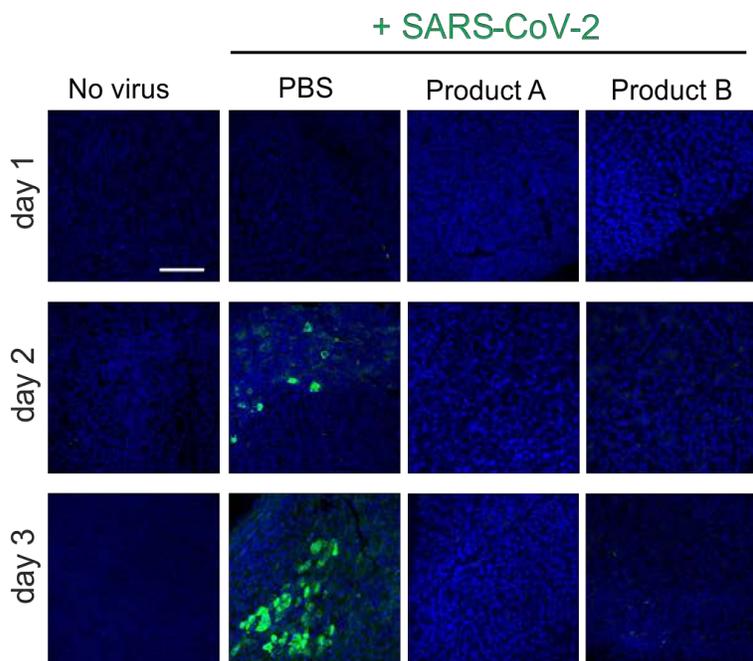
C



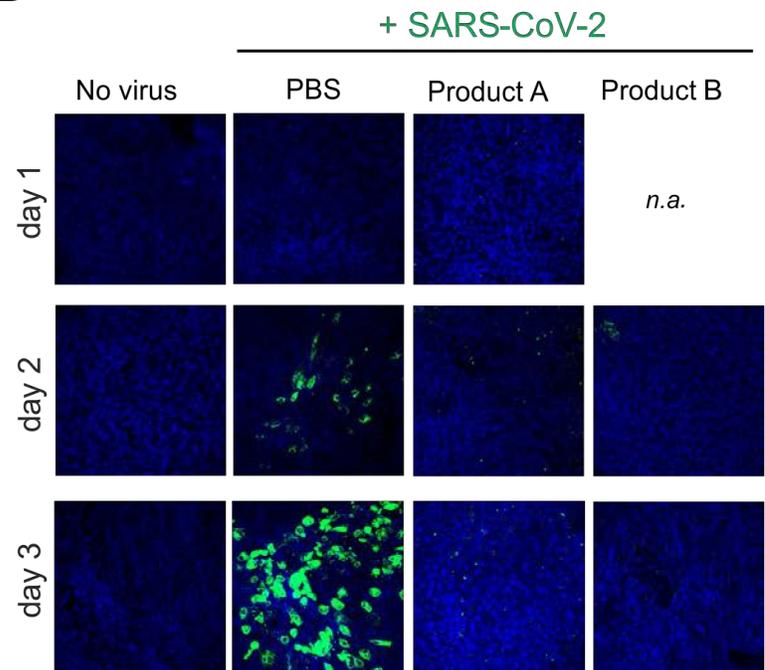
B



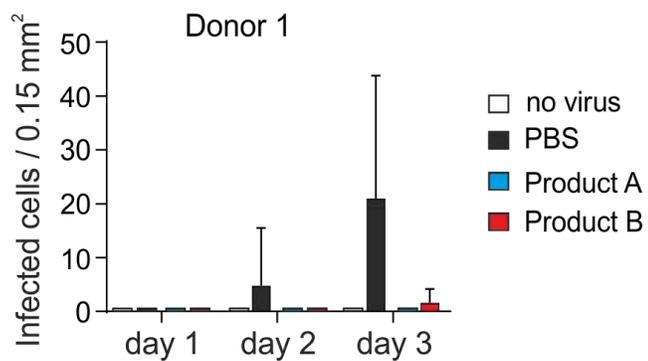
A



B



C



D

