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Using polyphenol rich *Cistus creticus* and other plant extracts containing nasopharyngeal spray may provide an additional tool in the preventive and symptomatic armamentarium against mild upper respiratory tract infections

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Abstract

Reducing the risk of acquiring upper respiratory tract infections is a significant health issue with severe ecological consequences. Vaccinations against respiratory tract infections (influenza, COVID-19, pertussis, pneumococcus) provide an unreplaceable role in the prevention. However, other personal and social measurements are promoted to reduce symptoms and decrease transmission and unfavourable outcomes. Polyphenol-containing *Cistus creticus* extract, alongside other polyphenol-rich ingredients, was shown to be beneficial in treating upper respiratory tract infections. However, clinical data about the prophylactic impact of the nasopharyngeal application of the polyphenol-rich cistus extract is scarce. A retrospective study was designed to evaluate its potential role in preventing disease and decreasing the burden of symptoms.

Keywords: *Cistus creticus*, polyphenols, URTI, prevention, quality of life

Introduction

Upper respiratory tract infections constitute one of the major global health problems resulting in high morbidity and mortality in developed and developing countries **[1]**. In recent years, comprehensive scientific research aimed to clarify the pathomechanism of upper respiratory tract infections, focusing on COVID-19 diseases caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to find and develop optimized prophylactic and therapeutic strategies for this emerging disease-causing pandemic. Antiviral treatments like redeliver, ritonavir-boosted nirmatrelvir, molnupiravir, and immunomodulatory therapies including corticosteroids, tocilizumab, and baricitinib form cornerstones of the risk-stratified strategy of the management. **[2,3]** Several studies focused on the paramedical and holistic additional adjuvant treatment options of upper respiratory tract infections, such as vitamins, essential mineral nutrients, and recently polyphenol-rich fitotherapeutical compounds, with controversial results. However, in terms of prophylaxis, there needs to be more data and a lack of studies with good quality. Therefore, validation of these adjuvant compounds is challenging **[4-6]**.

With its high concentration of polyphenols, a native medicinal plant from the Mediterranean Basin, *Cistus creticus*, was shown to have a pleiotropic beneficial effect both *in vitro* and *in vivo* for treating upper respiratory tract infections, including mild COVID-19 involving any upper respiratory tract. Additionally, polyphenols, the most critical component of the cistus creticus complex, can bind to the polybasic region of proteins. In this way, it inhibits the area responsible for the un—fusion activity of the hemagglutinin of the influenza virus and the S protein of the SARS-CoV-2 virus. Binding to the given protein region prevents the virus from entering the host cell and prevents infection. **[7-11]**. This study was designed to assess the beneficial effects of cistus extract-containing products in the clinical course of upper respiratory tract infections.

Methods

Study design

A single-center retrospective comparative study was conducted among consecutive adult (age ≥ 18 years) asymptomatic, healthy, at baseline SARS-CoV-2 PCR hostile persons who were defined as close contact according to whom definitions of SARS-CoV-2 infected patients receiving diagnostic and medical care in the Complex

Medical Centre private clinic in Budapest, Hungary. Verbal and written consent was obtained from each patient before participation in standard care procedures offered by the clinic. The study period was between February 2021 and May 2021. The private clinic has provided care for COVID-19 outpatients since the start of the pandemic. Close contacts of SARS-CoV-2 PCR-positive patients were offered medication, including receiving *Cistus creticus extract* containing nasopharyngeal spray (patented name Virostop) to use three times a day added to standard of care (symptomatic treatment). A Group of close contacts who did not opt to use the spray received standard care according to the physician's decision.

The study was performed under ethical and IRB approval (IV/7423-3/2021/EKU; Medical Research Council, Hungary).

Cistus creticus extract composition

Cistus creticus Acrocephalus extra., 100 mg/ml; *Echinacea purpura* extra., 240 mg/ml; Salvia officinalis extra., 45 mg/ml; Citrus bioflavonoid complex, 20 mg/ml; Acerola dried ext. 120 mg/ml (the patented name is Virostop).

In vitro tissue culture studies with Cistus creticus extra., Echinaceae purpureae extra., Salvia officinalis extra., Citrus bioflavonoid complex herbal preparations gave a virus inhibitory selectivity index (SI) of 8-16 (significant values) against seasonal influenza A(H1N1) PDM, A(H3N2), B, and against SARS CoV-2 virus. The investigated combination of Cistus creticus Acrocephalus extra., Echinaceae purpureae extra., Salvia officialis extra., Citrus bioflavonoid complex (patented name Virostop) resulted in two times higher antiviral in vivo inhibition effect than Cistus creticus extra. Alone. **(14)**

Subject eligibility, data collection, and outcomes

All adult (> 18 years of age at the time of examination) outpatients attending the clinic with upper respiratory tract symptoms were offered to invite their close contact with negative SARS-CoV-2 PCR (case definition as per WHO) in the study. Collected data were basic demographics, comorbidities, comedication, lifestyle factors, the severity of symptoms, and quality of life scores based on the standardized Wisconsin Upper Respiratory Symptom Survey (WURSS24) test a validated questionnaire designed to assess the quality of life and symptoms of acute viral respiratory tract infections. All close contacts of SARS-CoV-2 positive patients receiving care at the clinic were offered to participate in the study and were asked to complete the test battery every second day (day 2, 4, 6, 8, 10, and final evaluation of day 12). Detection of SARS-CoV-2 in pharyngeal wash samples was performed by RT-PCR amplification of SARS-CoV-2 N-gene fragments, based on WHO guidelines on days 0 and 10 (±2). SARS-CoV-2 immunoglobulins (Ig), including IgA, were also determined to identify seroconversion, particularly in asymptomatic persons. Data were collected from the institute's electronic patient management framework program.

The primary outcome was the SARS-CoV-2 positivity in the two groups (cistus extract users and standard of care). The secondary endpoint was a composite of standardized symptomatic scores.

Statistics

Descriptive statistics included the number of cases (n) with percentages (%) for categorical variables, whereas, for continuous variables, mean, standard deviation, minimum, median, and maximum were described. Age was compared by a two-sample Wilcoxon test, while a chi-square test between treatment groups reached the distribution of gender. The number and frequency of concomitant medication use were calculated by synchronous medication category and treatment group. The ratio of patients who used the given concomitant medication was compared by chi-square test for each concurrent medication category. The effect of treatment on symptoms and derived scores were analysed using repeated measures ANOVA. Fisher's exact test compared the ratio of patients with positive PCR results on Day 10. Day (time point), treatment group, time point, treatment group interaction, and use of NSAID were included in the model as fixed factors. Residual plots investigated goodness-of-fit. For all statistical tests, a 2-tailed p-value of < 0.05 determines statistical significance. The electronic patient management framework program carried out data collection, and with Microsoft Office Excel 2016, tests were calculated using SAS 9.4, and graphical representations were prepared using the R 4.1.1 version.

Results

There were 182 subjects involved in the study, 108 (59.3 %) in the standard-of-care plus cistus extract group and 74 (40.7 %) in the standard-of-care group. There were no statistically significant differences between the treatment groups in gender distribution and age **(Table 1)**.

Table 1. Basic demographics according to treatment groups, n=182

	Female gender (n, %)	Age (median, IQR)
SOC + cistus creticus extract	74 (68.5 %)	40 (28-50)
SOC	46 (62.2 %)	41.5 (31-51)

Chi-square test for gender: p=0.3741; Wilcoxon-test for age: p= 0.4824
IQR: interquartile range; SOC: standard of care

At the time of the second PCR (day 10±2 of treatment), none of the patients using cistus extract as prophylaxis became PCR positive, whereas 4 in the standard of care group (p=0.026, **Table 2).**

Table 2. SARS-CoV-2 PCR results at day 10 (±2) according to treatment groups, n=182			
Treatment Group	PCR result	N	%
SOC + cistus extract	Negative	108	100
	Positive	**0**	**0**
	Subtotal	108	
SOC	Negative	70	94.6
	Positive	**4**	**5.4**
	Subtotal	74	
Total		182	
Fisher's exact test: p=0.026			
PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOC: standard of care			

Although the number of examined elements is low, the result is statistically significant (0 versus 4 PCR positivity), so further studies are recommended.

The majority of patients using cistus extract had upper respiratory tract symptoms at baseline (72.2 %) compared to the standard of care group, where signs were present in 37.8% of the cases ($p < 0.001$). However, from day 4 to day 12, the difference between groups disparities **(Table 3)**

Table 3. Effect of treatment on symptom evolution, n=182															
		Baseline		**Day 2**		**Day 4**		**Day 6**		**Day 8**		**Day 10**		**Day 12**	
Treatment	**Presence of >2 symptoms**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
SOC	No	59	79.73	25	34.25	17	24.64	14	20.59	13	37.14	15	45.45	13	54.17
	Yes	15	20.27	48	65.75	52	75.36	54	79.41	22	62.86	18	54.55	11	45.83
SOC + cistus extract	No	40	37.04	21	19.44	25	23.36	32	29.91	17	23.61	28	40.58	43	66.15
	Yes	68	62.96	87	80.56	82	76.64	75	70.09	55	76.39	41	59.42	22	33.85
Chi-square test		**p<0.0001**		**p=0.0248**		p=0.8466		p=0.1723		p=0.1437		p=0.6409		p=0.2988	
SOC: standard of care															

A composite score of Wisconsin Upper Respiratory Symptom Survey 24 evaluation revealed that the severity of symptoms was perceived as significantly less disturbing from day 4 to day 12 **(Figure 1)**. At the same time, the frequency of use of concomitant non-steroid anti-inflammatory medications did not show a difference between the two groups (n= 28, 25.9 % versus n=18, 24.3 %, p=0.8071; **Table 4).**

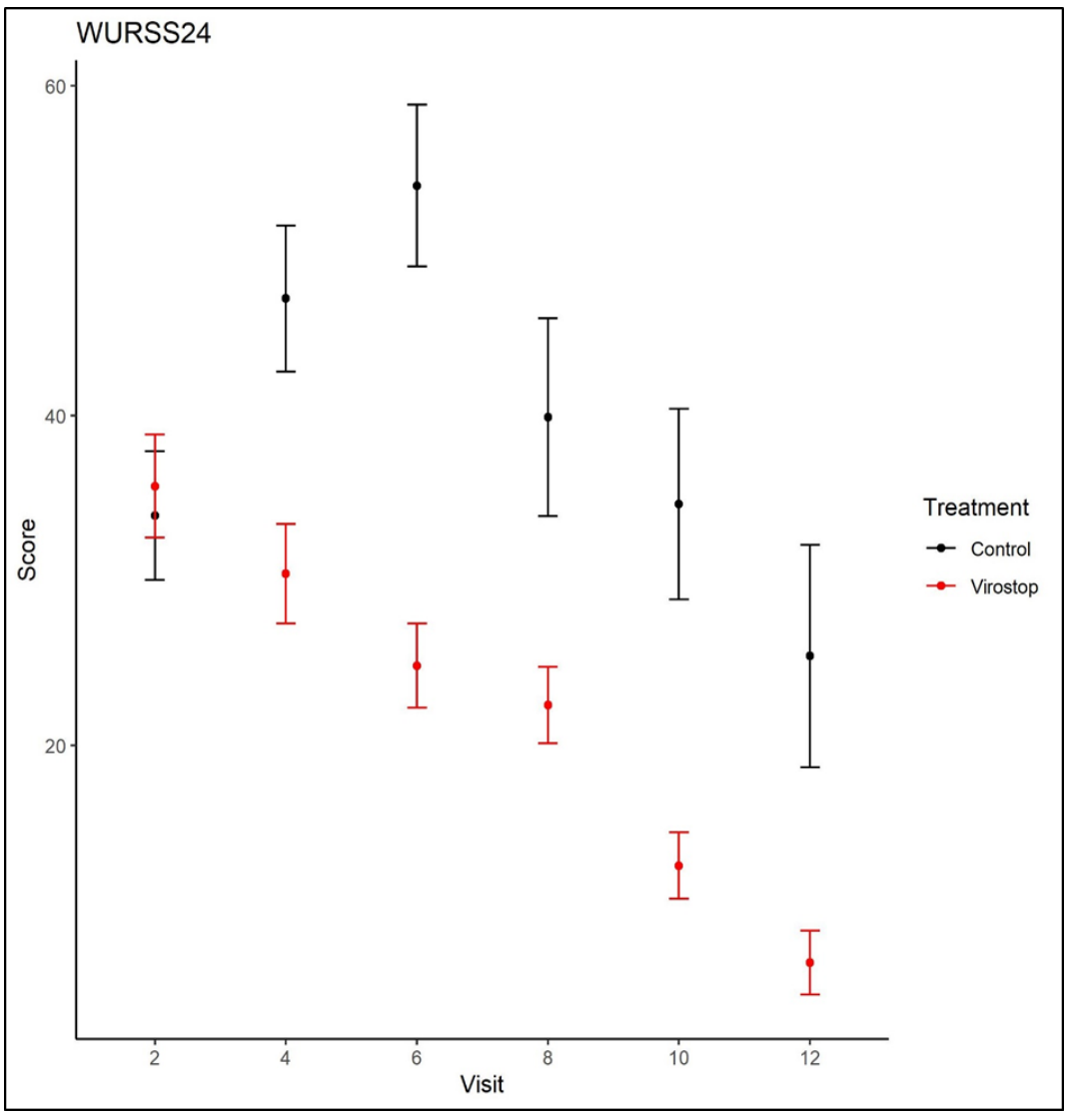

Figure 1: Difference in composite score of patient-reported symptom severity using Wisconsin Upper Respiratory Symptom Survey 24 (WURSS-24) according to treatment group

SOC: standard of care, WURSS24: Wisconsin Upper Respiratory Symptom Survey 24

Table 4: Use of concomitant non-steroid anti-inflammatory medications, n=182			
Treatment	NSAID	N	%
SOC	No	56	75.68
	Yes	18	24.32
SOC + cistus extract	No	80	74.07
	Yes	28	25.93
Chi-square: p=0.8071			
NSAID: non-steroid anti-inflammatory medications			

SARS-CoV-2 IgA positivity was detected in 19 cases (16.7 %) in the cistus extract-using group and 7 (6.1 %) in the control group among 114 tested persons, and two further patients seroconverted in the cistus extract group at second testing. However, the PCR positivity was 0 % in the users of Cistus extract, and immunological protection developed in more cases than in the control group. Based on these, while the virus could not be detected in these volunteers by PCR, a significantly better immune response was developed among the product users. Hypothetically this may be due to a possible reason that the Cistus mixture reduced the amount of virus in patients to such an extent that PCR could no longer detect the infectious virus, but at the same time, the immune system recognized the virus and produced a specific antibody against in the given patient.

Discussion

A single-center retrospective study was performed to evaluate the potential beneficial preventive effects of cistus extract alongside other polyphenol-rich plant extracts in the clinical course of respiratory tract infections. In this study, examining 182 SARS-CoV-2 PCR negative patients at baseline, we found that in the group of persons using cistus extract (patented name Virostop) added to standard-of-care, the frequency of nasopharyngeal SASR-CoV-2 positive PCR positivity was significantly lower. A further finding was that patient-reported symptomatic scores were more favourable among the cistus extract users.

The far most important tool to provide protection and decrease unfavourable outcomes against upper respiratory tract infections constitutes the uptake of available vaccinations against respiratory viruses and bacteria, including pneumococcus, influenza, and SARS-

CoV-2. There are, however, potential adjunctive measurements to moderate the risk of infection, ease subjective symptom severity, and improve quality of life. The polyphenol-rich extract of *Cistus creticus* expressed in vitro effect against the H7N7 influenza virus, which findings were confirmed in mice resulting in the prevention of clinical deterioration and histopathological signs of pneumonia **[8,9]**. A recent study of molecular docking mechanisms of eleven flavonoids of Cistus pollen extract showed high interaction affinity against SARS-CoV-2 spike receptor binding domain/angiotensin-converting enzyme II (ACE II), suggesting potential in prevention and treatment **[12]**. In our study, a cohort of SARS-CoV-2 PCR hostile persons received standard care with or without cistus extract. None of the subjects taking cistus extract became SARS-CoV-2 PCR positive on day 10, compared to 4 in the other group, which constituted a significant difference and motivated further studies to map this preventive effect.

An important finding from the clinical field by *Kalus et al*. in a prospective, randomized trial was that patients taking cistus extract reported a more significant reduction of symptoms using a standardized score. Another study comparing cistus extract with green tea products involving 300 patients found that the improvement of symptoms was significantly faster among patients using cistus extract **[10, 11]**. Of note, more patients among cistus extract users have developed IgA positivity with an overall more rapid recovery than in the control group, suggesting an essential potential protective role of the cistus extract. This observation claims to design further targeted research.

Limitations

There are some limitations of this study that worth to be mentioned. First, this is a retrospective study based on prospectively collected data, making generalizability difficult. Second, a complete picture of comorbidities was unavailable because persons involved in the study were mainly healthy contacts at baseline and not registered as patients, where the panel of comorbidities is well listed. Third, patients provided self-reports every second day. However, a decrease in the activity to 80 % was observed. Fourth, no laboratory parameters were detected in this cohort of contact persons.

In summary, there is accumulating data that early administration of polyphenols in upper respiratory tract infections may express an additional effect on decreasing viral burden and potentially reducing the length of symptoms **[10,13]**. This study provides a different pivot in the research of flavonoid-rich polyphenolic cistus extract and underlines its role in preventing and improving symptoms of patients suffering from upper respiratory tract infections.

Conclusion

Besides vaccination and other preventive measurements, additional use of *Cistus creticus* extract containing nasopharyngeal spray improves symptoms and may add extra protection during upper respiratory tract virus infections, including SARS-CoV-2. Further randomized controlled trials are needed to confirm these findings, but it should be emphasized that this retrospective study took place in Hungary during the third pandemic wave. This wave was the most serious (the mortality rate was 25 and 10 percent higher in the 40-49 and 50-59 age groups, respectively, compared to the second wave). The viral RNA sequence examinations showed several virus variants: Alpha B 1.1.7.; Delta B.1617; and Gamma P.1 were detectable based on National Public Health Center during the study period.

Declarations

Conflict of interest: The authors declare no conflicts of interest regarding this article.

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Institutional Review Board Ethical Approval Number: (IV/7423- 3 /2021/EKU)

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Appendix

Supplementary material to Figure 1.

Difference in composite score of patient-reported symptom severity using Wisconsin Upper Respiratory Symptom Survey 24 (WURSS-24) according to treatment group.

WURSS24 – standard of care + cistus extract group						
Day	**N**	**Mean**	**SD**	**Min**	**Median**	**Max**
2	108	35.731481	32.446824	0	24	125
4	107	30.420561	31.191749	0	15	120
6	107	24.841121	26.540162	0	13	107
8	72	22.444444	19.788949	0	15.5	79
10	69	12.710145	16.717463	0	8	92
12	65	6.8307692	15.624069	0	3	114

WURSS24 – standard of care group						
Day	**N**	**Mean**	**SD**	**Min**	**Median**	**Max**
2	73	33.931507	33.367203	0	29	134
4	69	47.115942	36.775366	0	46	137
6	68	53.955882	40.469422	0	57	131
8	35	39.914286	35.46114	0	29	99
10	33	34.636364	33.249829	0	21	97
12	24	25.416667	33.000549	0	9	114

WURSS24-Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
trt	1	179	53.60	<.0001
day	5	639	9.09	<.0001
trt*day	5	639	4.86	0.0002