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The Effect of Opuntia Cactus Extract on Hospitalized Moderate COVID-19 Infection: A Randomized Controlled Trial

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Abstract

Background: Due to the high load of the COVID-19 pandemic and its extraordinary mortality rate and some antiviral effects of cactus compounds reported in the literature, the present study aimed to assess the effect of *Opuntia cactus* on patients with COVID-19 infection and symptoms of disease.

Methods: This is a randomized controlled trial study. Patients with COVID-19 infection who were referred to Imam Ali hospital, located in Karaj, Iran, were randomly divided into intervention and control groups. All patients received a standard treatment regimen based on the latest guidelines. Patients in the intervention group received 250 mL of *Opuntia* extract syrup daily. In addition to standard treatment, the control group received only the standard regimen. Patients' symptoms including coughing, dyspnea, myalgia, headache, weakness, etc., were estimated daily and compared between the two groups.

Results: Fifty-two patients participated in the study. The average length of hospital stays was significantly shorter in the intervention group; also, blood oxygen saturation below 93%, fever, anosmia, coughing, headache, dizziness, myalgia, dyspnea, chest pain, and anorexia were significantly less frequent in the intervention group compared to the control group ($P<0.05$).

Conclusion: *Opuntia cactus* extract can improve the condition of COVID-19 patients due to symptomatic improvement in patients and decreased hospital stays. Moreover, the duration of most signs and symptoms significantly decreased in the patient group. More clinical trials are also necessary to approve this.

Keywords: COVID-19, Pandemic, Opuntia cactus, Herbal medicine

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Introduction

After the emergence of the COVID-19 virus from China, no one could anticipate this disease might threaten human life to such an extent, killing up to a million people by October 2020, based on official reports worldwide (1,2). Many efforts have been made to find an effective therapeutic regimen or vaccine, but there are no definite results so far (3-5).

Natural compounds and derivatives of *Opuntia polyacantha* have been shown to have biological-related activities including anti-inflammatory, antioxidant, hypoglycemic, antimicrobial, and neuroprotective properties (6,7). Evidence suggests that *O. polyantha*'s polysaccharides can enhance monocyte/macrophage function (8). Alcoholic extracts of cacti have been shown to have anti-inflammatory, anti-glycemic, and anti-viral properties (9). Besides, *O. cactus* extract can reduce the expression of nitric oxide by macrophage cells, making it a good choice as a complementary source in diseases with oxidative stress (10). *O. polyacantha* extract has been revealed to produce 35 ROS, nitric oxide, and interleukin-6. Induction of nitric oxide, cyclooxygenase-2 (COX-2), and some inflammatory cytokines plays a vital role in inflammation caused by oxidative stress (6,11-13).

The fruits and stems of many *Opuntia* species have been used in popular traditional medicine to treat burns, ulcers, edema, bronchial asthma, hypertension, indigestion, and type II diabetes (6). Various benefits of cactus compounds are suggested in traditional medicine. Meanwhile, these benefits have a scientific basis thanks to numerous experimental models devoted to the evaluation of cactus compounds for the treatment of various diseases. Therapeutic potentials of cactus compounds have been suggested for metabolic syndrome (including type 2 diabetes and obesity), nonalcoholic fatty liver disease, rheumatism, cerebral ischemia, cancers, and viral and bacterial infections (9).

Given the high burden of the COVID-19 pandemic and

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its high mortality rate and some antiviral effects of cactus compounds mentioned in the literature, the present study aimed to assess the effects of *O. cactus* in patients with COVID-19 infection in terms of symptoms relief or decreasing the hospital stay time, compared to controls.

Materials and Methods

This study is a double-controlled blinded randomized controlled trial. Twenty-five patients with COVID-19 infection, who were referred to the Imam Ali hospital, Karaj, Iran, were randomly divided into intervention and control groups. A written informed consent was obtained from all patients before enrolment. All the study steps were performed according to the declaration of Helsinki. All patients were ensured that the anonymity and confidentiality of their information would be maintained and they were free to leave the study at any stage without affecting their usual standard of care.

Inclusion criteria were 18-60-year-old patients who needed hospitalization, with approved COVID-19 infection by either chest CT scan or Reverse transcription polymerase chain reaction (RT-PCR) by a nasopharyngeal swab, with a disease onset of less than eight days. Exclusion criteria were respiratory rate of more than 30 per minute, blood oxygen saturation below 94%, severe renal impairment, severe liver disease, and receiving medications other than the standard protocol and supportive care. All patients received a standard treatment regimen based on the latest guidelines of the Iranian Ministry of Health (lopinavir/ritonavir). The permuted block randomization technique was used for grouping. The R software was used for randomization and matching between allocation of the patients to the two groups. Patients in the intervention group received 250 mL *O. cactus* extract syrup (as mentioned further below) on a daily basis, and the control group received standard protocol and 250 mL Aloe vera syrup (Barij Essence Pharmaceutical Company, Iran) daily. Both interventions were administered in identical Plastic syrup bottles. Patients' symptoms, including coughing, dyspnea, myalgia, gastrointestinal symptoms, headache, weakness, and anosmia, were evaluated and documented on a daily basis by physical examination. Blood oxygen saturation was also routinely checked. *Opuntia* extract was first obtained by rinsing the greenhouse-cultivated prickly pear cladodes, removing the spines with a sharp blade, and cutting the spineless cladodes into smaller pieces. Then, 150 g of cut cladodes were mixed with 250 mL of tap water using an electric mixer. Lastly, the mixture was passed through a fine mesh strainer with middle-sized openings and stored for later use.

Statistical analysis

Qualitative data was described using frequency and percentage, and quantitative data using normal and standard deviation. Student's *t* test was used to check the average difference between two independent groups, and the χ^2 test was used for qualitative variables. In addition, the paired *t* test or Wilcoxon test was used to examine the mean difference in each group before and after the treatment. Analysis of covariance (ANCOVA) or the generalized estimating equations (GEE) test (for duplicated data) was used to evaluate the effects of intervention. Moreover, STATA software (StataCorp, version 14) was used for data analysis.

Results

Fifty-two patients participated in the study. There were 26 patients in the intervention group (11 males (42. 3%) and 15 females (57. 7%)) and 26 in the control group (7 males (26.9%) and 19 females (73.1%)). There was no meaningful statistical difference between the two groups regarding gender distribution ($P=0.244$). The mean age in the intervention group was 51.15 ± 13.94 years and in the control group was 57.04 ± 13.60 years, without a statistically significant difference ($P=0.13$; Table 1).

Qualitative variables including the frequency of myalgia, chest pain, anorexia, nausea, and vomiting were less frequent in the intervention group ($P<0.05$). Persistence of symptoms for more than 14 days was less common 1in the intervention group as well ($P<0.05$). The mean length of hospital stay, duration of blood oxygen saturation below 93%, fever, anosmia, coughing, headache, dizziness, myalgia, dyspnea, chest pain, and anorexia were significantly shorter in the intervention group compared to the control group ($P<0.05$; Table 2).

To evaluate the effect of *Opuntia* extract on improving blood oxygenation, its effect on oxygen saturation and the duration of oxygen saturation below 93% was investigated by linear regression. The mean durations of blood oxygen saturation below 93%, hospital stay, headache, and myalgia were significantly meaningful in the intervention group (Table 2).

Discussion

After the emergence of the COVID-19 pandemic, no one could anticipate this disease might threaten human life to such an extent, killing up to a million people by October 2020, based on official reports around the world.

At that time, after nearly a year of its appearance, there was no approved vaccine or a definitive therapeutic regimen. Several attempts have been made to find potential treatment options using herbal medicine. Here we sought to assess the efficacy of a cactus extract on clinical symptoms of COVID-19 in a randomized controlled trial. This seems to be the first study to report the efficacy of *O. cactus* on COVID-19 infection in the literature.

As shown in the present study, *O. cactus* extract can alleviate myalgia, chest pain, anorexia, nausea, and

Table 1. Demographic characteristics of the study participants

Variable		Mean ± SD/frequency (prevalence)			*P* value
		Control	Intervention	Total	
Gender	Male	7 (26.9%)	11 (42.3%)	18 (34.6%)	0.244*
	Female	19 (73.1%)	15 (57.7%)	34 (65.4%)	
	Total	26 (50%)	26 (50%)	52 (100%)	
Age (y)	-	57.04 ± 13.6	51.15 ± 13.94	54.10 ± 13.96	0.130**
Underlying disease	Yes	19 (73.1%)	12 (46.2%)	31 (59.6%)	0.089*
	No	7 (26.9%)	14 (53.8%)	21 (40.4%)	

*χ^2 test, ** Independent *t* test.

Table 2. Descriptive analysis of variables between the two groups

Variable		Mean ± SD/frequency (prevalence)			*P* value
		Control	Intervention	Total	
ICU admission	No	21 (80.8%)	26 (100%)	47 (90.4%)	0.051
	Yes	5 (19.2%)	0	5 (9.6%)	
Signs and symptoms more than 14 days	No	4 (15.4%)	26 (100%)	30 (57.8%)	<0.001
	Yes	22 (84.6%)	0 (0%)	22 (42.3%)	
Hospital stay (days)		10.04 ± 4.28	3.85 ± 2.29	6.94 ± 4.62	<0.001
Blood O_2 Sat. below 93% duration (days)		6.58 ± 3.48	1.77 ± 0.99	4.08 ± 3.47	<0.001
Fever duration (days)		2.80 ± 1.81	1.00	2.06 ± 1.64	0.012
Anosmia duration (days)		20.50 ± 6.02	10.83 ± 2.93	16.36 ± 6.89	0.004
Coughing duration (days)		11.80 ± 2.88	5.68 ± 1.36	8.60 ± 3.79	<0.001
Headache duration (days)		9.86 ± 4.31	3.17 ± 1.19	6.77 ± 4.68	<0.001
Dizziness duration (days)		7.94 ± 4.74	3.23 ± 1.42	5.83 ± 4.31	<0.001
Myalgia duration (days)		7.87 ± 4.84	3.20 ± 2.30	6.45 ± 4.72	<0.001
Chest pain duration (days)		8.12 ± 4.50	3.00 ± 2.38	6.63 ± 4.60	0.002
Anorexia duration (days)		11.44 ± 3.75	4.80 ± 1.85	8.49 ± 4.51	<0.001

vomiting in the case group, compared to controls. It also decreased the mean length of hospitalization, the duration with oxygen saturation below 93%, duration of fever, anosmia, cough, headache, dizziness, myalgia, dyspnea, chest pain, and anorexia.

Despite this fact, clinical trials on the effects of herbal plants on viral infection are not as deliberate as the standard pharmaceutical field (14). Liu et al reported that adding traditional herbal medicine to standard drugs could improve symptoms of SARS infection. They also reported that herbal medicine could boost pulmonary infiltrations and reduce the consumption of corticosteroids in SARS patients (15).

Moreover, the Chinese government focused on their traditional medicine to control the COVID-19 pandemic. More than fifty clinical trials have been performed in China regarding the effect of traditional medicine (such as QingYi-4, Xin Guan-1 Formula and Xin Guan-2 Formula, Lian Hua Qing Wen capsules, and Tan Re Qing injections) in the treatment of COVID-19 infection, and some other trials tried to evaluate the effect of herbal medicine in combination with modern medicine (16,17).

Cactus extract has been reported to have antibacterial (18), antiviral (19), antidiabetic (20), anti-ulcer, cardioprotective (21), hepatoprotective (22), neuroprotective (23), anti-inflammatory (24), antitumoral, and antioxidant effects (18,25). In addition, *Opuntia dillenii* methanolic extract has been shown to have antiviral properties against reovirus-1, Sindbis virus, HSV 1 and 2, parainfluenza virus, feline coronavirus, vesicular stomatitis virus, coxsackievirus, respiratory syncytial virus, and Punta Toro virus (26). Moreover, Gentile et al showed antiviral properties of *O. ficus-indica* against some DNA and RNA viruses (27).

These effects are probably due to potential preventive effects, especially boosting the immune responses or direct immunomodulatory properties of polysaccharides or direct antiviral mechanisms of action. The anti-coronaviral activities of polyphenols and pelargonium have been reported in some investigations (28, 29). Quercetin, kaempferol, and cryptotanshinone were shown to have anti-SARS-CoV properties which are found in cacti as well (30). Moreover, some other antiviral mechanisms including viral penetration inhibition, replication inhibition, or inhibiting the SARS-3CL-pro activity have been suggested (17).

There were some limitations in the present study. First, as we had to perform the study in the shortest possible time, the sample size was quite small, while it is acceptable to assess the effects of the cactus extract on COVID-19 infection for the first time. Also, patients with severe diseases were excluded. In addition, people younger than 18 years old or older than 60 were excluded from the study. Patients with many underlying diseases were also excluded. We suggest performing larger trials with longer follow-ups on different groups of patients with COVID-19 infection to illuminate the effect of Opuntia cactus extract on COVID-19 infection.

Conclusion

Opuntia cactus extract could reduce myalgia, chest pain, anorexia, nausea, and vomiting in patients with COVID-19 infection, probably due to its antioxidant, anti-inflammatory, or direct anti-viral properties. Further studies are required to evaluate these preliminary promising findings.

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Authors' Contribution

Conceptualization: Zeinab Siami.
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Funding acquisition: Zeinab Siami.
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Project administration: Zeinab Siami.
Resources: Zeinab Siami.
Software: Zeinab Siami.
Supervision: Zeinab Siami.
Validation: Zeinab Siami.
Visualization: Zeinab Siami.
Writing–original draft: Zeinab Siami.
Writing–review & editing: Zeinab Siami.

Competing Interests

None.

Ethical Approval

The study protocol was approved by the Ethics Committee of the Alborz University of Medical Sciences. The clinical trial was registered at the website of the Iranian Registry of Clinical Trials (identifier: IRCT20200504047298N2)(https://en.irct.ir/trial/47675).

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